Evidence Table 1: Overall summary of studies addressing the relation of initial liver biopsy results to outcomes of treatment for chronic hepatitis C

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Studies with multivariate analyses					
Studies comparing peg-IFN + RBV with IFN alpha 2b + RBV					
Manns, 2001	United States Canada Europe Argentina	1530	ALT >34 for women and >43 for men, detectable HCV in serum, nl Cr, initial liver bx w/ CHC in past year, tx naïve, WBC <13, neutrophil >1.5, Hgb 12 for women and 13 for men, plts >100,000, nl Bili, nl Alb	HIV+, immune suppression, depression, other psychiatric illness, decompensated liver disease, comorbidities: cardiovascular, neurologic or hematologic, no contraception, AFP >50 mg/L, DM	To assess the safety and efficacy of two different regimens of Peg IFN and RBV compared w/ IFN alpha 2b and RBV and identify predictors and response for peg IFN alpha 2b.
Studies comparing IFN + RBV with IFN alone					
Berg, 2000	Germany	185	El ALT, any previous treatment, HCV+, detectable HCV in serum	Psychiatric illness, acute or chronic IDU, HBV+, decompensated liver disease, acute or chronic EtOH, immune suppression, plts <100,000, depression, HIV+, severe concurrent diseases, Hgb <11 g/dL, pregnancy	To examine if 12 wk combination therapy is more effective in improving initial and SVR compared w/ IFN monotherapy in untreated pts. Pts who achieved a virologic response were treated w/ IFN alpha monotherapy for an additional 40 wks and then SVR was evaluated 24 wks after end of tx

Evidence Table 1: Overall summary of studies addressing the relation of initial liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Studies comparing IFN + RBV with IFN alone					
Mangia, 2001	Italy	192	Detectable HCV in serum, ALT available for 6 mos, initial liver bx	DM, HBV+, decompensated liver disease: ascites, bleeding varices, and encephalopathy, pregnancy, depression, EtOH, HIV+, plts <100,000, autoimmune disorder, significant medical illness, IFN monotherapy, WBC <3500, Hgb <12 for females and <13 for males, other psychiatric illness	To compare the efficacy of a high dose regimen of IFN alpha2b (5 mu tiw) for 12 mos alone or in combination w/ RBV for the tx of naïve pts w/ CHC. Secondary aims were to evaluate the effects of baseline features on the response to therapy and to determine a reliable point in time during tx to predict non response.
McHutchison, 2000	United States	1712			To evaluate racial differences in response to therapy in pts w/ CHC, and potential contributing factors that might account for such differences

Evidence Table 1: Overall summary of studies addressing the relation of initial liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Saracco, 2001	Europe	594	HCV+, detectable HCV in serum, initial liver bx w/i prior 2 yrs, nonresponse to previous therapy, IFN monotherapy, age >18 and <65	Concomitant significant medical illness, IDU, HBV+, decompensated liver disease, relapse after previous therapy: >=1 course of IFN, pregnancy, depression, HIV+, cardiovascular comorbidity: ischemic cardiovascular disease, neurologic comorbidity: seizures, hematologic comorbidity: hemolytic anemia or hemophilia, abnl uric acid, obesity-induced liver disease, nonresponse to previous therapy: IFN and ribavirin combination therapy, other comorbidities: Wilson's disease, hemochromatosis, or autoimmune hepatitis, IFN + RBV, WBC <3000, neutrophil <500, Hgb <10 g/dL, plts <70,000, GI comorbidity, alpha-1antitrypsin deficiency	To assess if higher than standard doses of IFN given w/ RBV for prolonged periods of administration improved the rate of sustained response in previous IFN-alone nonresponders. The study compares the efficacy and safety of 3 mu and five mu of IFN plus 1000 mg daily RBV for either 6 or 12 mos

Evidence Table 1: Overall summary of studies addressing the relation of initial liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Studies comparing peg-IFN with IFN alpha2b					
Lindsay, 2001	United States Europe Australia	1299	U/S: no mass lesion, detectable HCV in serum, initial liver bx w/i 1 yr of enrollment, AFP w/i nl limits, ALT el >= 1 time w/i 6 mos of enrollment, WBC >4, neutrophil >1.8, Hgb >12 in females and > 13 in males, plts > 130	Hemophilia, breast feeding, illicit drug use, HBV+, HCC, pregnancy, HIV+, active IDU, hemochromatosis, alpha-1-antitrypsin deficiency, Wilson's disease, EtOH, NASH, any antiviral therapy, hemoglobinopathy, other medical conditions that could interfere with participation, any prior tx, autoimmune hepatitis	To evaluate the efficacy of pegIFN alpha 2b compared w/ IFN alpha 2b in tx-naïve pts w/ CHC
Studies comparing peg-IFN with IFN alpha2a					
Zeuzem, 2000	Germany	120	HCV+, age >18 and <70 yrs, presence of fibrosis: CHC on liver bx, initial liver bx w/i 1 yr, el ALT for >=6 mos before tx, WBC >2500, plts >70,000	EtOH >50 g/d of ethanol, IDU w/i previous year, GI comorbidity, immune suppression: organ transplant or autoimmune disorder, psychiatric illness, HIV+, HBV+, cardiovascular comorbidity, pregnancy, neurologic comorbidity, malignancy comorbidity, anaphylactic allergy to IFN, other comorbidities: liver disease from another cause OR renal disease OR rheumatologic disease, other viral infections: systemic bacterial or fungal infection, lactation, IFN + RBV, IFN monotherapy, amantadine, hematologic comorbidity	To compare the efficacy, safety, and health related quality of life of IFN alpha alone or in combination w/ amantadine for tx of CHC.

Evidence Table 1: Overall summary of studies addressing the relation of initial liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Studies comparing different doeses of IFN					
Ascione, 1998	Europe	80	Positive HCV antibodies, ALT 2x nl for 1 yr, initial liver bx: chronic active liver damage or persistent CHC, age 18-60 yrs	Chronic disease that could affect life expectancy, active IDU, homosexual men, HBV+, HCC, pregnancy or absence of contraceptive use in women of childbearing age, immune suppression, GI comorbidity: Fe, copper, alpha-1-antitrypsin deficiency or previous liver decompensation, Alb <3.0 g/L, esophageal varices F2-F3, decompensated DM, any previous therapy, WBC <3000, plts <100,000, Bili >51 µMol/L, HIV+	To see if doubling the dose of IFN improved long-term response. To evaluate efficacy of the tx regimens in cirrhotic pts
Kumada, 1996	Japan	54	ALT >70 IU/L for 6 mos, initial liver bx determination of CHC, presence of cirrhosis, presence of fibrosis, detectable HCV in serum, positive HCV antibodies	Drug-induced liver disease, Wilson's disease, EtOH liver disease, PBC, autoimmune hepatitis, chronic HBV+	To describe the relationship between the therapeutic effect of IFN in CHC pts and various factors including: dosage, age, gender, disease durration, +/- blood transfusion, pre-tx ALT levels, pre-tx liver histology (HAI score), HCV-RNA concentration, and HCV genotype.

Evidence Table 1: Overall summary of studies addressing the relation of initial liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Payen, 1998	France	247	Abnl ALT for 6 mos, initial liver bx IFN monotherapy: 3 mu IFN, tiw for 6 mos, HCV+, detectable HCV in serum	Adverse reaction to previous therapy: grade 3 or 4 by WHO classification, HBV+, presence of cirrhosis, age <18 yrs, HIV+, Fe deposition in liver, women of childbearing age not using contraceptives, severe associated disease, pregnancy	To compare the efficacy of IFN alpha2b regimens in pts w/ CHC who relapsed after an initial 6 mos IFN tx
Studies comparing IFN + amantidine with IFN alone					
Zeuzem, 2000a	Canada Europe Australia	531	HCV+, detectable HCV in serum: RNA >2000 copies per mL, el ALT on >=2 occasions in previous 6 mos, initial liver bx w/ hepatitis, liver bx findings consistent with CHC, adults	Malignancy, decompensated liver disease, HBV+, immune suppression, depression, other psychiatric illness, HIV+, hepatitis A infection, other comorbidities: seizure, neurologic OR cardiovascular, AFP >25 ng/mL, chronic pulmonary disease, autoimmune disorder, unwillingness to practice contraception, severe retinopathy, IFN monotherapy, neutrophil <1500, plts <90,000, Cr 1.5x UL of nl	To compare the efficacy and safety of peg-IFN alpha-2a administered once per wk w/ the efficacy and safety of IFN alpha-2a tiw for 48 wks.

Evidence Table 1: Overall summary of studies addressing the relation of initial liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Studies of IFN + colchicine					
Angelico, 2000	Italy	65	Age: 18-65, ALT >1.5x nl, Ishak score > 1 or < 5 on initial liver bx, detectable HCV in serum,	HBV+	To determine whether the combination of colcichine and IFN alpha is more effective than IFN alpha alone in treating non-cirrhotic pts w/ CHC
Studies with univariate analyses					
Studies of IFN alone					
Saracco, 1997	Italy	164	HCV+, initial liver bx, ALT abnl x 6 mos before entry	Current or past drug addiction,HBsAg+, presence of cirrhosis, HIV+, liver disease of any other etiology	To assess the effects of prolonged tx w/ different doses of IFN alpha 2b on relapse rate of pts w/ CHC. To determine factors predictive of sustained response
Shiffman, 2000	United States	95	WBC >2500, nl PT, nl Bili, HCV+, detectable HCV in serum, plts >90,000	HIV+, active IDU, HBV+, hepatitis delta infection, EtOH "on a regular basis," immune suppression, other viral infections, any other cause of hepatitis, chronic renal failure, pregnancy	To see if pts w/ nl ALT levels and CHC responded to IFN as well as those w/ el ALT levels and if predictors of sustained response could be applied to them as well.
Villa, 2001	Italy	30	Consecutively seen in clinic, ALT 2x nl for 6 mos, HBV+, HCV+	IFN tx, peg-IFN + RBV tx	To determine the outcome of medium to high doses of IFN therapy in pts w/ HBV-HCV.

Evidence Table 1: Overall summary of studies addressing the relation of initial liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Studies of IFN + RBV					
Di Bisceglie, 2001	United States	124	Initial liver bx w/i 12 mos of rx, IFN monotherapy >=36 mu, detectable HCV in serum, positive HCV antibodies		To see if nonresponders to IFN alone would respond to a combination of IFN/RBV for either 24 or 48 wks
Studies of IFN + RBV					
Shiffman, 2000a	United States	140	ALT, IFN monotherapy, pregnancy, nonresponse to previous therapy: IFN monotherapy	IFN monotherapy: max dose 6 mu IFN alpha-2a, OR max dose 9 mg IFN alphacon, OR max dose 3 mu IFN alpha-2b, any other type of liver disease, IDU, EtOH	To determine whether combination IFN/RBV was effective in tx of IFN monotherapy nonresponders. To determine subgroups who did not respond.
Studies of IFN + amantidine					
Mangia, 2001a	Italy	200	Detectable HCV in serum, initial liver bx, el ALT for 6 mos	EtOH, current IDU, depresson, other psychiatric illness, HBV+, decompensated liver disease, plts < 100,000, HIV+, DM, significant medical illness, WBC < 3,500, immune suppression	To assess the efficacy and safety of IFN+amantadine compared to IFN monotherapy in naïve pts w/ CHC
Studies with stratified analyses					
Studies of different types of IFN					
Villa, 1996	Italy	60	Age >18 and <65 yrs, ALT >2x UL of		Wilson's disease, autoimmune
A prospective double blinded,					

Evidence Table 1: Overall summary of studies addressing the relation of initial liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
			nl for >= 6 mos	disorder, alpha-1-antitrypsin deficiency, HIV+, immune suppression: immunosuppressive therapy w/i past 6 mos, decompensated liver disease, presence of cirrhosis: Child's grade B or C, HBV+, EtOHism, plts <100,000, WBC, IFN monotherapy	randomized study comparing IFN beta w/ recombinant IFN and leukocyte-derived IFN alpha. The outcomes measured were histological, biochemical, and virological responses.
Studies comparing peg-IFN with IFN					
Heathcote, 2000	United States Canada	271	ALT, initial liver bx	AFP >100 ng/mL, plts <75,000, WBC <500, IFN monotherapy, presence of any other liver disease, comorbidities: malignancy, GI, neurologic, or cardiovascular, HIV+, depression, psychiatric illness, decompensated liver disease	To compare the efficacy and safety of two doses of peg-IFN alpha-2a, given once wkly, w/ the safety and efficacy of a standard regimen of unmodified IFN alpha-2a in pts w/ HCV and cirrhosis or fibrosis.

Evidence Table 2: Characterstics of patients in studies addressing the relation of liver biopsy results to outcomes of treatment for chronic hepatitis C

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Studies with multivariate analyses										
Studies comparing peg-IFN + RBV with IFN alpha 2b + RBV										
Manns, 2001	RCT									
		IFN: peg-IFN2b, 1.5 mg/kg, qw, 48 wks RBV: 800 mg qd, 48 wks	511	43 63		Kno	7.9	S3 29	1 2,3 4,5,6	68.10 28.96 3.13
		IFN (initial): peg-IFN2b, 1.5 mg/kg, qw, 4 wks IFN (maintenance): peg-IFN2b, 0.5 mg/kg, qw, 44 wks RBV: 1000-1200 mg qd, 48 wks	514	44 66		Kno	7.9	S3 30	1 2,3 4,5,6	67.90 29.96 2.33
		IFN: alpha-2b, 3 mu tiw, 48 wks RBV: 1000-1200 mg qd, 48 wks	505	43 67		Kno	7.8	S3 28	1 2,3 4,5,6	67.92 28.91 3.17

Evidence Table 2: Characterstics of patients in studies addressing the relation of liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Studies comparing IFN + RBV with IFN alone										
Berg, 2000	RCT									
		IFN: alpha-2a, 6 mu tiw, 12 wks	93	42		HAI	S 1.5		70	
		RBV: 7 mg/kg, bid, 12 wks		57					15.2	
									1a	24.73
									1a/b	1.08
									1b	47.31
									2a	2.15
									2a/c	1.08
									2b	3.23
									3a	18.28
									4	2.15
		IFN: alpha-2a, 6 mu tiw, 12 wks	92	42		HAI	S 1.5		82	
				55					14.7	
									1a	20.65
									1a/b	1.09
									1b	54.35
									2a	2.17
									2a/c	1.09
									2b	1.09
									3a	17.39
									4	2.17

Evidence Table 2: Characterstics of patients in studies addressing the relation of liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Mangia, 2001	RCT									
		IFN: alpha-2b, 5 mu tiw, 12 mos	96	49		Sch		A>1 19.8		
				72		Sch		A0,1 80.2	8	
						Sch		S1,2 93.8	1b	53.13
						Sch		S3 6.2	2a	33.33
									3	9.38
									other	4.17
		IFN: alpha-2b, 5 mu tiw, 12 mos	96	46		Sch		A>1 26.0		
		RBV: 1000-1200 mg qd, 12 mos		61		Sch		A0,1 74.0	7	
						Sch		S1,2 89.6	1b	41.67
						Sch		S3 10.4	2a	35.42
									3	17.71
									other	5.21
McHutchison, 2000	RCT									
		IFN (210 pts): alpha-2b, 3 mu tiw,	1600	43		HAI	7.1			
		24 wks		65		Kno	S 1.5		17	
		IFN (461 pts): alpha-2b, 3 mu tiw, 24				Kno		S3 1.1	1	65.06
		wks				Kno		S4 0.2	non- 1	34.94
		IFN (464 pts): alpha-2b, 3 mu tiw, 48								
		wks								
		IFN (465 pts): alpha-2b, 3 mu tiw, 48								
		wks								
		RBV (461 pts): 1000/1200 mg qd,								
		24 wks								
		RBV (464 pts): 1000/1200 mg qd,								

Evidence Table 2: Characterstics of patients in studies addressing the relation of liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
		48 wks								
		IFN (12 pts): alpha-2b, 3 mu tiw, 24 wks	53	46 68		HAI Kno	7.8 S 1.7		18	
		IFN (13 pts): alpha-2b, 3 mu tiw, 48 wks				Kno Kno		S3 47.2 S4 11.3	1 non-1	96.23 3.77
		IFN (13 pts): alpha-2b, 3 mu tiw, 48 wks								
		IFN (15 pts): alpha-2b, 3 mu tiw, 24 wks								
		RBV (13 pts): 1000/1200 mg qd, 48 wks								
		RBV (15 pts): 1000/1200 mg qd, 24 wks								
		IFN (1 pts): alpha-2b, 3 mu tiw, 24 wks	27	45 81		Kno Kno	S 1.5	S4 40.7	21	
		IFN (13 pts): alpha-2b, 3 mu tiw, 24 wks							1 non-1	59.26 40.74
		IFN (6 pts): alpha-2b, 3 mu tiw, 48 wks								
		IFN (7 pts): alpha-2b, 3 mu tiw, 48 wks								
		RBV (13 pts): 1000/1200 mg qd, 24 wks								
		RBV (7 pts): 1000/1200 mg qd, 48 wks								

Evidence Table 2: Characterstics of patients in studies addressing the relation of liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
		IFN (12 pts): alpha-2b, 3 mu tiw, 48 wks	32	45 75		HAI HAI	7.9	40.6	21	
		IFN (5 pts): alpha-2b, 3 mu tiw, 48 wks				Kno Kno	S3	6.2	1 non- 1	78.13 21.88
		IFN (7 pts): alpha-2b, 3 mu tiw, 24 wks				Kno	S4	88		
		IFN (8 pts): alpha-2b, 3 mu tiw, 24 wks								
		RBV (12 pts): 1000/1200 mg qd, 48 wks								
		RBV (8 pts): 1000/1200 mg qd, 24 wks								

Evidence Table 2: Characterstics of patients in studies addressing the relation of liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Saracco, 2001	RCT									
		IFN: alpha-2b, 3 mu tiw, 12 mos	139	46	12	ISH	A 2.6			
		RBV: 1000 mg qd, 12 mos		66		ISH	S 6.2			
									1	66.91
									2	16.55
									3	9.35
									4	7.19
		IFN: alpha-2b, 5 mu tiw, 12 mos	162	44	9	ISH	A 2.5			
		RBV: 1000 mg qd, 12 mos		75		ISH	S 6.4			
									1	60.49
									2	19.14
									3	13.58
									4	6.79
		IFN: alpha-2b, 3 mu tiw, 6 mos	142	46	15	ISH	A 2.8			
		RBV: 1000 mg qd, 6 mos		77		ISH	S 6.2			
									1	67.61
									2	14.79
									3	14.08
									4	3.52
		IFN: alpha-2b, 5 mu tiw, 6 mos	151	45	7	ISH	A 2.6			
		RBV: 1000 mg qd, 6 mos		78		ISH	S 6.0			
									1	68.87
									2	13.25
									3	11.26
									4	6.62

Evidence Table 2: Characterstics of patients in studies addressing the relation of liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Studies comparing peg-IFN with IFN alpha-2b										
Lindsay, 2001	RCT									
		IFN: peg-IFN2b, 0.5 ng/kg, qw, 48 wks	315	43.1 59 C: 90.1	3	HAI HAI	A 6.8 S 1.4		18.5 1 2 3 other	 67.30 11.11 16.83 4.76
		IFN: peg-IFN2b, 1.0 ng/kg, qw, 48 wks	297	43.7 63 C: 90.9	3	HAI HAI	A 6.9 S 1.4		20.4 1 2 3 other	 67.00 10.10 17.85 5.05
		IFN: peg-IFN2b, 1.5 ng/kg, qw, 48 wks	304	42.9 63 C: 94.0	4	HAI HAI	A 6.7 S 1.3		19.2 1 2 3 other	 73.36 10.53 13.49 2.63
		IFN: alpha-2b, 3 mu tiw, 48 wks	303	42.6 68 C: 89.1	4	HAI HAI	A 7.1 S 1.4		18.6 1 2 3	 71.62 9.24 17.49

Evidence Table 2: Characterstics of patients in studies addressing the relation of liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
									other	1.65
Studies comparing peg-IFN with IFN alpha-2a										
Zeuzem, 2000	RCT									
		Amantadine: 100 mg, Twice a day, 48 wks	60	42.1 62						
		IFN (initial): alpha-2a, 6 mu tiw, 24 wks IFN (maintenance): alpha-2a, 3 mu, tiw, 24 wks							1 2 3 4	70.00 5.00 21.67 1.67
		IFN (initial): alpha-2a, 6 mu tiw, 24 wks IFN (maintenance): alpha-2a, 3 mu, tiw, 24 wks	60	41.6 60					1 2 3 4	66.67 5.00 25.00 1.67
Studies comparing different doeses of IFN										
Ascione, 1998	RCT									
		IFN (initial): alpha-2b, 3 mu tiw, 12 mos	40	53				S3, A2 3 7.5	5.74 1b 2a	 62.50 37.50
		IFN (initial): alpha-2b, 6 mu tiw, 12 mos	40	70					5.44	

Evidence Table 2: Characterstics of patients in studies addressing the relation of liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
									1b	67.50
									2a	32.50
Kumada, 1996	RCT	IFN (initial): natural IFN, 5 mu, bid, 20 wks	27	56.1 56		HAI HAI	10.2	CPH I 22.2	6.7	
		IFN (initial): natural IFN, 5 mu, qd, 2 wks				HAI		CPH II a 63.0	1b 1b+2a	44.44 3.70
		IFN (initial): natural IFN, 5 mu, qw, 12 wks				HAI		CPH II b 14.8	2a 2a+2b	44.44 3.70
		IFN (initial): natural IFN, 5 mu tiw, 4 wks							2b	3.70
		IFN (maintenance): natural IFN, 5 mu, bid, 20 wks								
		IFN (maintenance): natural IFN, 5 mu, qd, 2 wks								
		IFN (maintenance): natural IFN, 5 mu, qw, 12 wks								
		IFN (maintenance): natural IFN, 5 mu tiw, 4 wks								

Evidence Table 2: Characterstics of patients in studies addressing the relation of liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
		IFN (initial): natural IFN, 10 mu, bid, 20 wks	27	53.4 67				CPH II b 18.5	6.9	
		IFN (initial): natural IFN, 10 mu, qd, 2 wks				HAI HAI	9.1	CPH I 25.9	1b 1b+2a	77.78 0.00
		IFN (initial): natural IFN, 10 mu, qw, 12 wks				HAI		CPH II a 55.6	2a 2a+2b	11.11 0.00
		IFN (initial): natural IFN, 10 mu, tiw, 4 wks							2b	11.11
		IFN (maintenance): natural IFN, 10 mu, bid, 20 wks								
		IFN (maintenance): natural IFN, 10 mu, qd, 2 wks								
		IFN (maintenance): natural IFN, 10 mu, qw, 12 wks								
		IFN (maintenance): natural IFN, 10 mu tiw, 4 wks								

Evidence Table 2: Characterstics of patients in studies addressing the relation of liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Payen, 1998	RCT									
		IFN: alpha-2b, 3 mu tiw, 6 mos	75	45.6		HAI	7.2			
				92					8.83	
				C: 98.6					1	5.33
									1a	10.67
									1b	28.00
									2	13.33
									3	16.00
									other	8.00
		IFN: alpha-2b, 3 mu tiw, 12 mos	91	44.1		HAI	7.6			
				71					9.47	
				C: 100					1	3.30
									1a	3.30
									1b	29.67
									2	15.38
									3	23.08
									other	5.49
		IFN: alpha-2b, 10 mu tiw, 6 mos	81	42.1		HAI	8			
				70					9.08	
				C: 100					1	2.47
									1a	3.70
									1b	33.33
									2	9.88
									3	28.40
									other	6.17

Evidence Table 2: Characterstics of patients in studies addressing the relation of liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Studies comparing IFN + amantidine with IFN alone										
Zeuzem, 2000a	RCT									
		IFN (initial): peg-IFN2a, 180 µg, qw, 48 wks	267	40.5 67 C: 86.1, B: 2.24, A: 8.98, O: 2.62		HAI	8.6	A1 65.0 A2 30.0 A3 3.3 S1 88.4 S3 7.1	1a 1b 2 3 4 not specified	29.96 32.96 9.36 25.47 1.87 0.37
		IFN (initial): alpha-2a, 6 mu tiw, 12 wks IFN (maintenance): alpha-2a, 3 mu, tiw, 36 wks	264	41 67 C: 84.8, B: 1.89, A: 9.84, O: 3.40		HAI	3.4	A1 60.0 A2 40.0 A3 0.0 S1 84.8 S3 4.9	1a 1b 2 3 4 not specified	31.44 29.55 12.88 23.86 1.14 1.14

Evidence Table 2: Characterstics of patients in studies addressing the relation of liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Studies of IFN + colchicine										
Angelico, 2000	RCT									
		IFN (initial): alpha-2a, 6 mu tiw, 6 mos		34 46 59					6.9	
		IFN (maintenance): alpha-2a, 3 mu, tiw, 6 mos							1b non 1b not specified	61.76 32.35 5.88
		Colcichine (initial): 1 mg, 6x/wk, 3 yrs	31	49 58					7.5	
		IFN (initial): alpha-2a, 6 mu tiw, 6 mos							1b non 1b not specified	64.52 25.81 9.68
		IFN (maintenance): alpha-2a, 3 mu, tiw, 6 mos								

Evidence Table 2: Characterstics of patients in studies addressing the relation of liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Studies with univariate analyses										
Studies of IFN alone										
Saracco, 1997	RCT									
		IFN (initial): alpha-2b, 3 mu tiw, 3 mos IFN (maintenance): alpha-2b, 3 mu, tiw, 21 mos	54	45.4 61					1b	55.56
		IFN (initial): alpha-2b, 3 mu tiw, 3 mos IFN (maintenance): alpha-2b, 6 mu, tiw, 21 mos	34	48.5 65					1b	44.12
		IFN (initial): alpha-2b, 3 mu tiw, 3 mos IFN (maintenance): alpha-2b, 6 mu, tiw, 3 mos	65						1b	161.54
		IFN (initial): alpha-2b, 3 mu tiw, 3 mos IFN (maintenance): alpha-2b, 6 mu, tiw, 18 mos	11							

Evidence Table 2: Characterstics of patients in studies addressing the relation of liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Shiffman, 2000	RCT									
		IFN (initial): alpha-2a, 6 mu, qd, 3 mos		47 47	43				21	68.1
		IFN (initial)1: alpha-2a, 6 mu tiw, 3 mos IFN (maintenance): alpha-2a, 3 mu, tiw, 12 mos		C: 59.5					1	74.47
		IFN (initial): alpha-2a, 6 mu tiw, 6 mos		48 52	43.4				10	62.2
		IFN (maintenance): alpha-2a, 3 mu, tiw, 12 mos		C: 45.8					1	75.00
Villa, 2001	RTnc									
		IFN: 6 mu tiw, 6 mos	14	34 71		HAI HAI	A 1.9 S 11.6			
									1a	7.14
									1b	78.57
									2a	14.29
		IFN: 9 mu tiw, 6 mos	16	33 75		HAI HAI	A 1.7 S 11.9			
									1a	31.25
									1b	43.75
									2a	25.00

Evidence Table 2: Characterstics of patients in studies addressing the relation of liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Studies of IFN + RBV										
Di Bisceglie, 2001	RCT									
		IFN: alpha-2b, 3 mu tiw, 24 wks	63	43		Sch		A0 20.6	90	
		RBV: 1000-1200 mg qd, 24 wks		70		Sch		A1 30.2		
				C: 96.8		Sch		A2 25.4	1	74.60
						Sch		A3 23.8	2	19.05
									3	6.35
		IFN: alpha-2b, 3 mu tiw, 48 wks	61	46		Sch		A0 18.0	100	
		RBV: 1000-1200 mg qd, 48 wks		57		Sch		A1 21.3		
				C: 98.3		Sch		A2 41.0	1	86.89
						Sch		A3 19.7	2	9.84
									3	3.28

Evidence Table 2: Characterstics of patients in studies addressing the relation of liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Shiffman, 2000a	RCT									
		IFN (initial): alpha-2b, 5 mu tiw, 3 mos IFN (maintenance): alpha-2b, 5 mu, tiw, 3 mos	48	44.5 60 C: 50, B: 50	21	Kno	7.3		1	89.58
		IFN (initial): alpha-2b, 3 mu tiw, 3 mos IFN (maintenance): alpha-2b, 5 mu, tiw, 3 mos RBV: 1000-1200 mg, divided dose, twice daily, 9 mos	42	43.6 69 C: 69.0, B: 30.9	19	Kno	7		1	88.10
		IFN: alpha-2b, 5 mu tiw, 6 mos RBV: 1000-1200 mg, divided dose, twice daily, 9 mos	50	42.9 66 C: 64, B: 36	14	Kno	6.4		1	90.00

Evidence Table 2: Characterstics of patients in studies addressing the relation of liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Studies of IFN + amantidine										
Mangia, 2001a	RCT									
		IFN (initial): alpha-2a, 6 mu tiw, 12 mos	101	48 70		HAI HAI		S0-3 48.5 S1-3 51.5	7.1	
									1	59.41
									2a	25.74
									3	10.89
									4	3.96
		Amantadine (initial): 100 mg, bid, 12 mos	99	46 62		HAI HAI		S0-3 36.4 S1-3 63.6	7.1	
		IFN (initial): alpha-2a, 6 mu tiw, 12 mos							1	52.53
									2a	34.34
									3	7.07
									4	6.06
Studies with stratified analyses										
Studies of different types of IFN										
Villa, 1996	RCT									
		IFN (maintenance): alpha-2a, 3 mu, tiw, 6 mos	21	45 71	33			S3, A2 66.7	185	
		IFN (maintenance): natural IFN, 3 mu tiw, 6 mos	20	46 70	35			S3, A2 65.0	171	
		IFN (maintenance): beta IFN, 3 mu, tiw, 6 mos	19	41 79	16			S3, A2 84.2	153	

Evidence Table 2: Characterstics of patients in studies addressing the relation of liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)

Evidence Table 2: Characterstics of patients in studies addressing the relation of liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Studies comparing peg-IFN with IFN										
Heathcote, 2000	RCT									
		IFN: alpha-2a, 3 mu tiw, 48 wks	88	46.9 70 C: 87.5, B: 5.68, A: 3.40, O: 3.40	76	HAI	12.8		104.1 1a 1b 2 3 4 not specified	 31.82 21.59 13.64 30.68 0.00 2.27
		IFN: peg-IFN2a, 90 mg, qw, 48 wks	96	47.2 74 C: 90.6, B: 1.04, A: 2.08, O: 6.25	79	HAI	12.7		104.1 1a 1b 2 3 4 not specified	 28.13 32.29 7.29 27.08 2.08 3.13
		IFN: peg-IFN2a, 180 mg, qw, 48 wks	87	47.1 72 C: 86.2, B: 5.74, A: 2.29, O: 5.74	79	HAI	13.4		123.3 1a 1b 2 3 4 not specified	 37.93 17.24 16.09 22.99 1.15 4.60

Evidence Table 3: Methodologic quality of studies addressing the relation of initial liver biopsy results to outcomes of treatment for chronic hepatitis C

Author, Year	Representativeness[a]	Bias[b]	Description[c]	Outcomes[d]	Statistics[e]	Conflict[f]	Total[g]
Studies with multivariate analyses							
Studies comparing peg-IFN + RBV with IFN alpha 2b + RBV							
Manns, 2001	100	50	0	80	83	50	63
Studies comparing IFN + RBV with IFN alone							
Berg, 2000	90	0	0	85	83	0	86
Mangia, 2001	80	50	0	60	100	0	58
McHutchison, 2000	25	--	--	40	83	50	49
Saracco, 2001	88	100	0	70	100	0	64
Studies comparing peg-IFN with IFN alpha2b							
Lindsay, 2001	90	100	0	85	100	50	75
Studies comparing peg-IFN with IFN alpha2a							
Zeuzem, 2000	100	100	0	60	100	50	87
Studies comparing different doeses of IFN							
Ascione, 1998	100	0	0	80	100	50	56
Kumada, 1996	90	100	0	75	83	0	70
Payen, 1998	75	100	0	85	83	50	81

Evidence Table 3: Methodologic quality of studies addressing the relation of initial liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Year	Representativeness[a]	Bias[b]	Description[c]	Outcomes[d]	Statistics[e]	Conflict[f]	Total[g]
Studies comparing IFN + amantidine with IFN alone							
Zeuzem, 2000a	100	50	0	70	100	100	90
Studies of IFN + colchicine							
Angelico, 2000	75	100	0	85	100	100	87
Studies with univariate analyses							
Studies of IFN alone							
Saracco, 1997	70	100	0	75	83	0	66
Shiffman, 2000	88	50	0	80	100	100	89
Villa, 2001	90	50	0	35	67	100	48
Studies of IFN + RBV							
Di Bisceglie, 2001	75	50	0	85	67	50	76
Shiffman, 2000a	100	100	0	60	83	50	69
Studies of IFN + amantidine							
Mangia, 2001a	88	50	0	85	100	50	91

Evidence Table 3: Methodologic quality of studies addressing the relation of initial liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Year	Representativeness[a]	Bias[b]	Description[c]	Outcomes[d]	Statistics[e]	Conflict[f]	Total[g]
Studies with stratified analyses							
Studies of different types of IFN							
Villa, 1996	60	0	0	60	33	50	31
Studies comparing peg-IFN with IFN							
Heathcote, 2000	100	100	0	70	83	50	88

[a] ***Representativeness***: The total maximum for this section was 10 points. This included setting and population described and start and end date specified (2 points); detailed description of inclusion and exclusion criteria or statement that all potential trainees enrolled (2 points); information about excluded or not-participating patients (2 points); appropriateness of the spectrum of disease included in the study sample (2 points); and description of key patient characteristics at enrollment (2 points).

[b] ***Bias and Confounding***: The total maximum score was 2 points. This included whether there was an independent, blind comparison of initial liver biopsy to outcomes.

[c] ***Description of Biopsy***: The total maximum score was 2 points. This included description of the technique and size of liver biopsy.

[d] ***Outcomes and Followup:*** The total maximum score was 10 points. This included description of complications, side effects and adverse reactions (2 points); sufficient description of criteria for determining outcomes (2 points); reporting on the numbers and reasons for withdrawals from the study or losses to followup (2 points); proportion of patients who withdrew from the study or were lost to followup (2 points); and sufficiency of the planned length of followup (2 points).

[e] ***Statistical Quality and Interpretation***: The total maximum score was 6 points. This included whether magnitude of difference between groups and an index variability was stated (2 points); whether analyses and statistical tests were clearly identified (2 points); and appropriate handling of crossovers and/or dropouts in the analysis (2 points).

[f] ***Conflict of Interest***: The total maximum score was 2 points. This included whether the study reported the source of funding and the role played by the funding entity.

[g] ***Total Score*** is the mean of the percentage scores from the categories, Representativeness, Bias and Confounding, Description of Biopsy, Outcomes and Followup, and Statistical Quality and Interpretation.

Evidence Table 4: Results of studies addressing the relation of initial liver biopsy results to outcomes of treatment for chronic hepatitis C

Author, Yr	Rx Group	Outcome	Histological Variable(s)	Multivariate: Adj. Parameter Estimate Relating to SVR	Multivariate: Adj. p-value	Other Significant Independent Variables
Studies comparing peg-IFN + RBV with IFN alpha 2b + RBV						
Manns, 2001	A IFN (maintenance): pegIFN2b, 1.5 mg/kg, once wkly, 48 wks	SVR	Absence of cirrhosis	NR**	NR	Weight, age, HCV viral load, HCV genotype other than 1b
			Absence of bridging fibrosis or cirrhosis	NR	<.01	
	RBV (maintenance): 800 mg qd, 48 wks					
	B IFN (initial): pegIFN2b, 1.5 mg/kg, once wkly, 4 wks					
	IFN (maintenance): pegIFN2b, 0.5 mg/kg, once wkly, 44 wks					
	RBV (maintenance): 1000-1200 mg qd, 48 wks					
	C IFN (maintenance): alpha-2b, 3 mu tiw, 48 wks					
Studies comparing IFN + RBV with IFN alone						
Berg, 2000	A IFN: alpha-2a, 6 mu tiw, 12 wks	SVR	Histologic activity, grade and stage	NR	NR	HCV genotype GGT levels
	RBV: 7 mg/kg, bid, 12 wks					
	B IFN: alpha-2a, 6 mu tiw, 12 wks					

Evidence Table 4: Results of studies addressing the relation of initial liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Yr	Rx	Group	Outcome	Histological Variable(s)	Multivariate Adj. Parameter Estimate Relating to SVR	Multivariate Adj. p-value	Other Significant Independent Variables
Mangia, 2001	A	IFN (maintenance): alpha-2b, 5 mu tiw, 12 mos	SVR	Histologic grade	NR[b]	NS	Genotype, IFN-ribavirin tx
	B	IFN (maintenance): alpha-2b, 5 mu tiw, 12 mos		Histologic stage	NR[c]	NS	
		RBV (maintenance): 1000-1200 mg qd, 12 mos		Histologic stage	NR[d]	NS	
McHutchison, 2000	A	IFN (210 pts): alpha-2b, 3 mu tiw, 24 wks	SVR	Degree of fibrosis	NR[**]	NR	IFN-ribavirin tx, gender, genotype, baseline viral load, compliance
		IFN (461 pts): alpha-2b, 3 mu tiw, 24 wks					
		IFN (464 pts): alpha-2b, 3 mu tiw, 48 wks					
		IFN (465 pts): alpha-2b, 3 mu tiw, 48 wks					
		RBV (461 pts): 1000/1200 mg qd, 24 wks					
		RBV (464 pts): 1000/1200 mg qd, 48 wks					

Evidence Table 4: Results of studies addressing the relation of initial liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Yr	Rx Group		Outcome	Histological Variable(s)	Multivariate Adj. Parameter Estimate Relating to SVR	Multivariate Adj. p-value	Other Significant Independent Variables
	B	IFN (12 pts): alpha-2b, 3 mu tiw, 24 wks					
		IFN (13 pts): alpha-2b, 3 mu tiw, 48 wks					
		IFN (13 pts): alpha-2b, 3 mu tiw, 48 wks					
		IFN (15 pts): alpha-2b, 3 mu tiw, 24 wks					
		RBV (13 pts): 1000/1200 mg qd, 48 wks					
		RBV (15 pts): 1000/1200 mg qd, 24 wks					
	C	IFN (1 pts): alpha-2b, 3 mu tiw, 24 wks					
		IFN (13 pts): alpha-2b, 3 mu tiw, 24 wks					
		IFN (6 pts): alpha-2b, 3 mu tiw, 48 wks					
		IFN (7 pts): alpha-2b, 3 mu tiw, 48 wks					
		RBV (13 pts): 1000/1200 mg qd, 24 wks					
		RBV (7 pts): 1000/1200 mg qd, 48 wks					

Evidence Table 4: Results of studies addressing the relation of initial liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Yr	Rx Group	Outcome	Histological Variable(s)	Multivariate Adj. Parameter Estimate Relating to SVR	Multivariate Adj. p-value	Other Significant Independent Variables
	D IFN (12 pts): alpha-2b, 3 mu tiw, 48 wks					
	IFN (5 pts): alpha-2b, 3 mu tiw, 48 wks					
	IFN (7 pts): alpha-2b, 3 mu tiw, 24 wks					
	IFN (8 pts): alpha-2b, 3 mu tiw, 24 wks					
	RBV (12 pts): 1000/1200 mg qd, 48 wks					
	RBV (8 pts): 1000/1200 mg qd, 24 wks					

Evidence Table 4: Results of studies addressing the relation of initial liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Yr	Rx	Group	Outcome	Histological Variable(s)	Multivariate: Adj. Parameter Estimate Relating to SVR	Multivariate: Adj. p-value	Other Significant Independent Variables
Saracco, 2001	A	IFN (maintenance): alpha-2b, 3 mu tiw, 12 mos	SVR	Grade ≥5.2	OR: 1.0 (0.73 - 1.45)	0.8	Age ≤44, genotype 2 or 3, tx with 5 mu IFN-ribavirin for 12 mos
				Stage ≥2.3	OR: 0.93 (0.34 - 2.56)	0.8	
		RBV (maintenance): 1000 mg qd, 12 mos		Cirrhosis	OR: 0.5 (0.14 - 1.77)	0.2	
	B	IFN (maintenance): alpha-2b, 5 mu tiw, 12 mos					
		RBV (maintenance): 1000 mg qd, 12 mos					
	C	IFN (maintenance): alpha-2b, 3 mu tiw, 6 mos					
		RBV (maintenance): 1000 mg qd, 6 mos					
	D	IFN (maintenance): alpha-2b, 5 mu tiw, 6 mos					

Evidence Table 4: Results of studies addressing the relation of initial liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Yr	Rx Group	Outcome	Histological Variable(s)	Multivariate Adj. Parameter Estimate Relating to SVR	Multivariate Adj. p-value	Other Significant Independent Variables
Studies comparing peg-IFN with IFN alpha-2b						
Lindsay, 2001	A IFN (initial): pegIFN2b, 0.5 ng/kg, once wkly, 48 wks B IFN (initial): pegIFN2b, 1.0 ng/kg, once wkly, 48 wks C IFN (initial): pegIFN2b, 1.5 ng/kg, once wkly, 48 wks D IFN (initial): alpha-2b, 3 mu tiw, 48 wks	SVR	HAI score	OR 2.2, 95% CI (1.1 - 4.8)	NS	HCV genotype other than 1, HCV RNA $\leq 2x10^6$ copies/mL
Studies comparing peg-IFN with IFN alpha-2a						
Zeuzem, 2000	A Amantadine: 100 mg, Twice a day, 48 wks IFN (initial): alpha-2a, 6 mu tiw, 24 wks IFN (maintenance): alpha-2a, 3 mu tiw, 24 wks B IFN (initial): alpha-2a, 6 mu tiw, 24 wks	SVR	Fibrosis at baseline	NR	NS	HCV genotype

Evidence Table 4: Results of studies addressing the relation of initial liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Yr	Rx Group	Outcome	Histological Variable(s)	Multivariate Adj. Parameter Estimate Relating to SVR	Multivariate Adj. p-value	Other Significant Independent Variables
Studies comparing different doses of IFN						
Ascione, 1998	A IFN: alpha-2b, 3 mu tiw, 12 mos	SBR	Liver histology (chronic hepatitis v. cirrhosis)	NR	NR	
	B IFN: alpha-2b, 6 mu tiw, 12 mos					

Evidence Table 4: Results of studies addressing the relation of initial liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Yr	Rx Group		Outcome	Histological Variable(s)	Multivariate Adj. Parameter Estimate Relating to SVR	Multivariate Adj. p-value	Other Significant Independent Variables
Kumada, 1996	A	IFN (initial): natural IFN, 5 mu, bid, 20 wks	SVR	HAI score	0.0018 [a]	0.98	HCV RNA concentration, genotype non 1b
		IFN (initial): natural IFN, 5 mu, once wkly, 12 wks					
		IFN (initial): natural IFN, 5 mu, qd, 2 wks					
		IFN (initial): natural IFN, 5 mu tiw, 4 wks					
		IFN (maintenance): natural IFN, 5 mu, bid, 20 wks					
		IFN (maintenance): natural IFN, 5 mu, once wkly, 12 wks					
		IFN (maintenance): natural IFN, 5 mu, qd, 2 wks					
		IFN (maintenance): natural IFN, 5 mu tiw, 4 wks					
	B	IFN (initial): natural IFN, 10 mu, bid, 20 wks					
		IFN (initial): natural IFN, 10 mu, once wkly, 12 wks					
		IFN (initial): natural IFN, 10 mu, qd, 2 wks					
		IFN (initial): natural IFN, 10 mu tiw, 4 wks					

Evidence Table 4: Results of studies addressing the relation of initial liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Yr	Rx Group		Outcome	Histological Variable(s)	Multivariate Adj. Parameter Estimate Relating to SVR	Multivariate Adj. p-value	Other Significant Independent Variables
Payen, 1998	A	IFN (maintenance): alpha-2b, 3 mu tiw, 6 mos	SVR	Pre-treatment Knodell index	mean 0.76 95% CI (0.61-0.95)	0.015	High level ALT, low viral load, viral genotype = 3, tx for 12 mos
	B	IFN (maintenance): alpha-2b, 3 mu tiw, 12 mos					
	C	IFN (maintenance): alpha-2b, 10 mu tiw, 6 mos					
Zeuzem, 2000a	A	IFN (initial): pegIFN2a, 180 ug, once wkly, 48 wks	SVR	Absence of cirrhosis or bridging fibrosis	NR	0.03	Tx with peg-IFN alpha 2a, age, smaller body surface, decreased HCV RNA, increased ALT quotient, HCV genotype other than 1
	B	IFN (initial): alpha-2a, 6 mu tiw, 12 wks IFN (maintenance): alpha-2a, 3 mu tiw, 36 wks					
Studies of IFN + colchicine							
Angelico, 2000	A	IFN (initial): alpha-2a, 6 mu tiw, 6 mos IFN (maintenance): alpha-2a, 3 mu tiw, 6 mos	Bio-chemical response [e]	Low stage pre-treatment, Low grade pre-treatment	NR NR	0.036 0.49	Colchicine tx
	B	Colcichine (initial): 1 mg, 6x/wk, 3 yrs IFN (initial): alpha-2a, 6 mu tiw, 6 mos					

Evidence Table 4: Results of studies addressing the relation of initial liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Yr	Rx Group	Outcome	Histological Variable(s)	Multivariate Adj. Parameter Estimate Relating to SVR	Multivariate Adj. p-value	Other Significant Independent Variables
	IFN (maintenance): alpha-2a, 3 mu tiw, 6 mos					

[a] Estimate of Cox Proportional Hazard
[b] Based on analysis of total study population
[c] Based on analysis of Group A
[d] Based on analysis of Group B
[e] Similar results were found for SVR, data not presented
* P < 0.05
** Text reported that the statistic was significant but did not report the p-value

Evidence Table 5: Overall summary of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Extracellular matrix					
Casaril, 2000	Italy	183	HCV+	Other viral infections: autoimmune hepatitis, HIV+, HCC, decompensated liver disease, IDU, Fe overload w/i 2y, chronic inflammatory disease, EtOH	To investigate the relationship between serum iron load and fibrosis as measured by liver bx and serum tests.
Di Costanzo, 1996	Italy	68	Abnl ALT for > 3 yr, initial liver bx w/compatible histology, HCV+	Large esophageal varices, other causes of liver disease, any disease that increases collagen metabolism, pulmonary fibrosis, rheumatic disease, decompensated liver disease	To evaluate whether assays for connective tissue polypeptides may be clinically useful in predicting primary response to IFN therapy
Fortunato, 2001	Italy	103	Laboratory-confirmed hepatitis C, initial liver bx	Liver disease of any other etiology, HBV+, alcoholism, IFN, any previous therapy	To determine if a multivariate function based on 6 biochemical serum markers can destinguish chronic hepatitis from cirrhosis

Evidence Table 5: Overall summary of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Fukuda, 1998	Japan	36	Congenital coagulation disorder, referred to the Hemophilia Group		To determine whether serum fibrosis markers predict liver bx results in hemophiliacs
Fukuzaki, 2000	Japan	78		IFN therapy, other chronic liver disease	To observe changes in HA, serum type IV collagen 7S region, and P-III-P in pts with complete, biochemical, or no response to IFN tx
Gabrielli, 1997	Italy	139	ALT 2x UL of nl for 6 mos, initial liver bx showing CHC, positive HCV antibodies	Comorbidity: autoimmune or renal disease, malignancy comorbidity, IDU, other illicit drug use, EtOH >80 g/d	To correlate serum levels of laminin and type III procollagen w/ histology
Giannini, 2001	Italy	109	ALT >1.5x UL of nl for 6 mo, HCV+	IFN monotherapy, autoimmune disease, any extrahepatic disease, HIV+, HBV+, EtOH	To assess the usefulness of serum P-III-P as a marker of hepatic fibrogenesis in pts w/ CHC
Guechot, 1994	Not specified	176	HCV+, serum alkaline phosphatase 2x nl, anti-mitochondrial antibodies titer > 1/100	EtOH >50g/day, HBV+, pulmonary fibrosis, rheumatic disorders,	To determine the diagnostic value of aminoterminal propeptide of type III procollagen level and hyluronan levels in serum as markers of fibrosis
Guechot, 1996	France	326	Initial liver bx: findings consistent with CHC infection, detectable HCV	Rheumatic disease, pulmonary fibrosis, other chronic liver disease,	To determine the diagnostic accuracy of HA and type III

Evidence Table 5: Overall summary of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
			in serum, HCV+	HBV+	procollagen amino terminal peptide
Ikeda, 2000	Japan	205	Initial liver bx, detectable HCV in serum, HCV+	HCC, HBV+	To use common laboratory data to discriminate between chronic hepatitis and cirrhosis.
Ishibashi, 1996	Japan	121	ALT 1.5 UL of nl, detectable HCV in serum, HCV+	IFN, any previous therapy, serum autoimmune markers, presence of cirrhosis, HBV+, EtOH	To evaluate the effect of IFN tx on serum markers of fibrosis
Jeffers, 1995	United States	86	HCV+, initial liver biopsy, ALT el x 6 mos	Heavy EtOH, HBV+, negative autoantibodies, hepatotoxic drugs, other liver disease	To correlate the level of P-III-P w/ HCV-RNA concentration, ALT and histologic severity of disease
Kasahara, 1997	Japan	98	ALT el for >= 6 mo, initial liver bx showing CHC, detectable HCV in serum, positive antibodies	EtOH, autoimmune hepatitis, HIV+,	To determine if MMPs MMP-1, and MMP-2, and tissue inhibitors of MMPs, TIMP-1, and TIMP-2, are associated w/ bx findings.
Lichtinghagen, 1999	Germany				To examine the expression, concentration and activity of MMP-1, -2, -7 and -9 in liver and serum of pts w/ CHC, HCV cirrhosis and healthy controls. To evaluate those parameters as

Evidence Table 5: Overall summary of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
					markers of hepatic fibroproliferation.
Lichtinghagen, 2000	Germany	80	Initial liver bx	Malignancy: assessed with chest x-rays, abdominal U/S, AFFP, CEA, and CA 19-9	To assess if levels (or ratios) of MMP-2 and -9, in relation to their tissue inhibitors, are associated w/ stage of HCV induced liver disease. (Levels were assessed for both circulating and expressed proteins in polymorphonuclear and mononuclear leukocytes.)
Lichtinghagen, 2001	Germany	46			To evaluate the correlation between hepatic mRNA expression of MMP-2, -7, -9, TIMP-1, -2, and -3 w/ disease activity of CHC.
Lo Iacono, 1998	Spain, Italy	52	Abnl ALT, detectable HCV in serum, HCV+, age 18-60 yrs	Other viral infections: non-organ-specific auto-antibodies, HIV+, decompensated liver disease: "clinically advanced cirrhosis," screened HBV antibodies, IDU, EtOH >80 g/d	To investigate the basal levels of circulating adhesion molecules and follow changes w/ IFN therapy.
McHutchison, 2000a	United States	486	HCV+, initial liver bx > 1cm length,	EtOH, chronic liver disease of any	To determine whether serum HA

Evidence Table 5: Overall summary of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
	Canada		or 3 portal triads	other etiology	was a reliable predictor of cirrhosis and fibrosis
Murawaki, 1999	Japan	176	Initial liver bx	Antiviral therapy, EtOH	To elucidate the clinical usefulness of the serum MMP-2 concentration in chronic viral liver disease.
Murawaki, 2001	Japan	165	Initial liver bx, HCV+, plts, ALT, collagen, other serological markers, detectable HCV in serum	Presence of fibrosis, presence of cirrhosis, decompensated liver disease, peg-IFN monotherapy, peg-IFN + RBV, EtOH, IFN monotherapy, anti-retroviral therapy for HIV, IFN, IFN + RBV	Compare ROC serum IV-C and plt count for predicting fibrosis stage.
Murawaki, 2001a	Japan	169	Abnl ALT, detectable HCV in serum	Antiviral therapy, extrahepatic illnesses, presence of cirrhosis, EtOH	To assess the usefulness of serum fibrotic markers for diagnosing fibrotic staging and necroinflammatory grading in CHC.
Ninomiya, 1998	Japan	49	Informed consent, ALT el for >= 6 mo, initial liver bx, detectable HCV in serum, HCV+	Drug-induced liver disease, autoimmune hepatitis, HBV+, EtOH	1. To evaluate HA as a marker of fibrosis. 2. To investigate the effect of IFN tx on fibrosis.
Ohashi, 1998	Japan	62	Initial liver bx, CHC w/o any other		To clarify the effect of IFN tx on

Evidence Table 5: Overall summary of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
			liver disease		the serum markers of hepatic fibrosis and hepatic histological features.
Plevris, 2000	United Kingdom	221	Initial liver bx	IFN tx	To evaluate serum HA as a marker of liver cirrhosis in pts w/ chronic liver disease
Serejo, 2001	Portugal	117	Detectable HCV in serum	Drug-induced liver disease, immune suppression-induced liver disease, HBV+, alcoholic liver disease	To assess clinical significance of serum P-III-P in assessing its ability to act as a marker for fibrogenins in pts treated w/ alpha IFN.
Ueno, 2001	Japan	52	ALT, initial liver bx, detectable HCV in serum, HCV+	Routine medication use, high levels of antinuclear, antibody or antimitochondrial antibody, HBV+, excessive EtOH	To compare hepatic histological changes w/ serum fibrosis markers before and after IFN tx alpha. To investigate the usefulness of serum fibrosis markers in the long-term followup of pts w/ CHC.
Verbaan, 1997	Sweden	109	Initial liver bx, HCV+	IFN tx	To evaluate how well serum levels of P-III-P, IV-C and IgG correlate w/ histological features
Walsh, 1999	United	38		Wilson's disease, alph-1-antitrypsin,	To evaluate the association of

Evidence Table 5: Overall summary of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
	Kingdom			hemochromatosis, HBV+, excessive EtOH	P-III-P (measured by two commercially available tests) and liver fibrosis
Walsh, 1999a	United Kingdom	52	Detectable HCV in serum, initial liver bx	EtOH, HBV+, decompensated liver disease, immune suppression, Wilson's disease, alpha-1-antitrypsin deficiency, hemochromatosis, significant extrahepatic disease	To determine the sensitivity/specificity of MMP-2, TIMP-1, TIMP-2 in detecting advanced liver disease (ISHAK >/= F3 and HAI > 6)
Walsh, 2000	Europe	42	CHC via blood, transfusion, HIV-	HBsAg+, absence of liver autoantibodies, nl caeruloplasmin, alpha-1-antitrypsin deficiency, hemochromatosis, EtOH	To correlate laminin and IV-C w/ liver bx findings
Wong, 1998	United Kingdom	130	Detectable HCV in serum, initial liver bx	EtOH, HBV+, HCC, immune suppression, HIV+, liver disease of any other etiology, primary fibrosis, rheumatic disorders	To show that serum HA is a good marker for fibrosis in CHC pts.
Yamada, 1996	Japan	35	ALT el for >6 mo, initial liver bx showing CHC, detectable HCV in serum, HCV+	Any antiviral therapy, IFN + RBV, peg-IFN monotherapy, peg-INF + RBV, inflammatory connective tissue diseases, autoantibodies, presence of cirrhosis, HBV+ habitual EtOH	To examine the effect of IFN on serum HA levels. To determine the correlation between serial serum levels of HA and liver bx findings.

Evidence Table 5: Overall summary of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Yamada, 1998	Japan	36	Detectable HCV in serum, HCV+	Any previous therapy, connective tissue disorder, other viral infections: autoantibodies, HBV+, habitual EtOH	To see if serum P-III-P, IV-C and HA correlated w/ stage of liver fibrosis in pts w/ HCV, and to evaluate the effects of IFN therapy on these numbers
Cytokines/cytokine receptors					
Izzo, 1996	Italy	297	AFP, U/S, detectable HCV in serum for >5 yrs, HCV+	Malignancy, HIV+, immune suppression, HCC, decompensated liver disease, HBV+	To determine whether sIL-2R are el in pts w/ CHC and whether these levels correlate w/ histological severity of hepatic injury
Nutt, 2000	United States	70	ALT, initial liver bx, detectable HCV in serum, positive HCV antibodies	GI comorbidity: other chronic liver diseases, HIV+, HBV+	To compare liver histology of HCV+ w/ nl ALT to HCV+ w/ el ALT
Zylberberg, 1999	France, Belgium	154	Detectable HCV in serum, HCV+	Antiviral or immunomodulatory therapy for >= 6 mo, hemodialysis, HIV+	To investigate the relationship between sTNF-alpha receptors and disease activity w/ fibrosis.
Enzymes					
Anderson, 2000	Canada	133	HCV+, ALT el for >= 6 mo	Liver pathology not available, other chronic liver disease	To evaluate the clinical utility of ALT and AST in CHC pts.

Evidence Table 5: Overall summary of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Assy, 2000	Canada	79	HCV+	Other previous or concurrent liver disease, drug-induced hepatitis, hemochromatosis, HIV+, HBV+	To assess the predictive values of age, gender, route of transmission, steatosis, EtOH, and ALT and AST on liver bx findings
Barbaro, 1996	Italy	156	HCV+, detectable HCV in serum	Hypertension, chronic, EtOH, HBV+, pregnancy, metabolic liver disease, autoimmune hepatitis, age <18 yrs, diabetes, CD4 <400, hepatotoxic drugs w/i 6 mo, any previous antiviral therapy, WBC <2500, neutrophil <1000, Hgb <10, Bili >3 x nl, PT >5 over control, Cr >2 x nl, other viral hepatitis	To evaluate the association between glutathione and HIV status, HCV replication, and liver bx findings.
Choi, 1999	United States	38	Serological markers: ALT and HCV-RNA, HCV+		To determine whether ALT levels and histopathological changes in liver bx specimens correlate w/ HCV disease progression or response to IFN tx.

Evidence Table 5: Overall summary of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Enzymes					
Goldstein, 1999	United States	81	Bx w/ >3 portal tracts, AFP, initial liver bx, detectable HCV in serum, positive HCV antibodies	Yolk sac carcinoma, HIV+, HCC, HBV+, EtOH >60 g/d for >5 yrs	To show a relationship between AFP, ALT, inflammation and fibrosis, and hepatocyte MIB-1 scores.
Gordon, 2000	United States	1744	HCV+, detectable HCV in serum, ALT abnl x 6 mos prior to study		To see if pretreatment ALT levels correlate w/ histologic features and whether these values influence response to tx
Haber, 1995	United States	90	HCV+, liver bx slides on file	Difficulty making firm HCV diagnosis	To determine the relationship between serum aminotransferase levels and histological grade in HCV
Healey, 1995	United Kingdom	42	HCV+, Detectable HCV in serum, initial liver bx, >= 3 serial transminases of serum alanine aminotransferase		To determine the correlation between liver histology and serum transaminases in hepatitis C infection
Imbert-Bismut, 2001	France	339	Initial liver bx, detectable HCV in serum, HCV+	Inadequate liver bx, other liver disease, HIV+, HBV+	To assess the predictive value of basic serum biochemical markers for diagnosis of liver fibrosis in pts w/ CHC
Imperiale, 2000	United States	177	ALT measured w/i 4 mo of liver bx, initial liver bx between 1993 and	GI comorbidity: primary biliary cirrhosis or primary sclerosing	To evaluate the AST/ALT ratio in ability to diagnose cirrhosis in

Evidence Table 5: Overall summary of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
			1998, detectable HCV in serum, HCV+	cholangitis, Wilson's disease and alpha-1-antitrypsin, autoimmune suppression as cause of liver disease, HBV+	pts w/ CHC infection.
Jamal, 1999	United States	275	ALT in 4 consecutive determinations either all nl or all el, detectable HCV in serum, HCV+, HCV genotype	IFN monotherapy, hemochromatosis, autoimmune disease, immune suppression, HCC, HBV+ <18 yrs	To describe the clinical and histological features of pts w/ CHC and nl ALT levels.
Kobayashi, 2000	Japan	61	Initial liver bx, IFN monotherapy for 6 mos, positive HCV antibodies		To assess the correlation between serial changes in ALT levels and histological outcome 5 yrs after tx of pts w/ CHC w/ IFN for 6 mos.
	Taiwan	93	ALT >=1.5 x nl for >6 mo, HCV+	Renal dialysis, HIV+, HBV+,	To study the relationship
Luo, 1998				metabolic liver disease, hepatotoxic drugs, homosexuality, IDU, EtOH >60 g/d	between ALT levels, histology, serum HCV-RNA and HCV genotypes in pts w/ CHC.
	United States	44	Adequate size of liver bx, other	HBV+	To evaluate whether ALT level
McCormick, 1996			serological markers: ALT w/i 4 wk of liver bx, initial liver bx, nl serum Fe, negative AMA, nl ceruloplasmin, detectable HCV in serum		or HCV-RNA levels can predict histological measures in pts w/ CHC.

Evidence Table 5: Overall summary of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Michielsen, 1997	Belgium	51	ALT el for >6 mo, initial liver bx, detectable HCV in serum, CAH	Pts w/persistently nl AST/ALT levels	To determine if a correlation exists between el AST and/or ALT, and histological disease in pts w/ CHC
Ono, 1999	Japan	435	HCV+	HCC: diffuse, HCC or portal vein invasion	To evaluate the stage of liver fibrosis using routine clinical blood biochemistry tests
Park, 2000	Australia	153	El ALT for >= 6 mo w/i 4 mo of bx, initial liver bx: CHC or cirrhosis, presence of fibrosis, HCV+	Antiviral treatment at time of bx, liver disease w/any other etiology, EtOH >20 g/d currently or w/i 5 yrs	To see if AST/ALT ratio greater than one predicted cirrhosis accurately in pts w/ HCV
Poynard, 1997	France	500	Initial liver bx consistent w/ CHC, HCV+	HBV+, any IFN tx, other liver disease	To assess the predictive value of (1)social and clinical factors (age, gender, infection duration, delay between biologic determination and bx, homosexuality, transmission via blood transfuction, transmission by IDU, body weight, ethnicity) and (2) biologicial factors (AST/ALT, GGT, serum bili, serum albumin, PT, WBC, plts, serum Hgb, serum creatinine) for the presence of histologic activity or fibrosis.

Evidence Table 5: Overall summary of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Sheth, 1998	United States	139	Biochemical determinations w/i 4 mo of liver bx, ALT el for 6 mo, HCV+		To evaluate whether the ratio of AST to ALT predicts cirrhosis and fibrosis stage in pts w/ CHC infection
Shima, 2000	Japan	36	CHC on initial liver bx	Detectable HCV in serum after prior tx and 3 yrs following tx, metabolic disease, autoimmune hepatitis, HBV+, alcohol abuse	To evaluate the relationship between serum total bile acid and liver inflammation and fibrosis in IFN treated pts
Stanley, 1996	United Kingdom	100	HCV+		To examine liver histology in pts w/ nl an abnl ALT and chronic HCV infection
Tsushima, 1999	Japan	53	Detectable HCV in serum, HCV+		To evaluate the association of plasma TGF-B1 w/ liver fibrosis.
Yeo, 2001	United States	60	ALT between nl and 2X nl, positive HCV antibodies		To examine the relationship between HCV-RNA levels and severity of disease in pts w/ chronic HCV
Viral markers					
Adinolfi, 1998	Italy	36	ALT el for >= 6 mo, detectable HCV in serum, positive HCV antibodies	IFN or immunosuppressive therapy, malignancy comorbidity, immune suppression, presence of cirrhosis, HBV+, excessive alcohol intake	To evaluate the relationship between HCV-RNA levels in serum, liver, and periportal blood mononuclear cells and the degree of liver injury in CHC pts

Evidence Table 5: Overall summary of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Iijima, 2000	Japan	135	>= 5 yrs f/u of liver bx, HCV core protein, initial liver bx, detectable HCV in serum, HCV+	IFN tx, any antiviral therapy, malignancy, HIV+, immune suppression, cirrhosis, HBV+, EtOH >80 g/d, age >60 yrs	To determine if HCV viremia correlates w/ degree of fibrosis
Kao, 1996	Taiwan	94	ALT >62 for >1 yr, initial liver bx, detectable HCV in serum, HCV+	Lamivudine for HBV, anti-retroviral therapy for HIV, IFN, any previous therapy, drug-induced hepatitis, immune suppression, HBV+, IDU, EtOH	To clarify the relationship between serum HCV titer and histological severity
Papatheodoridis, 1997	Greece	112	Detectable HCV in serum	HBV+, HIV+, autoantibodies, alcoholic liver disease, therapy in previous 6 mos	To investigate the significance of IgM anti core antibody associations with HCV genotype and liver disease necroinflammatory action
Puoti, 1999	Italy	59	Signed consent, ALT nl 3 times at 2-mo intervals for >= 6 mo, detectable HCV in serum, HCV+	Abnl ferritin, plts <100,000, any previous therapy, HBV+, EtOH >60 g/d for men and >40 g/d for women	To see if HCV carriers w/ nl ALT levels show a correlation between serum HCV-RNA titers and liver histology which could be used as a non-invasive means to separate healthy carriers from those w/ liver damage.

Evidence Table 5: Overall summary of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Miscellaneous					
Bayati, 1998	United States	200	Initial liver bx	EtOH >60 g/d for >5 yrs	To determine the relation between AFP and liver histology in pts w/ CHC.
Chu, 2001	Taiwan	115	ALT 1.5x nl for >6 mos, U/S w/o evidence of HCC, detectable HCV in serum, positive HCV antibodies	Renal dialysis, exposure to hepatotoxic medications, metabolic liver disease, HCC, decompensated liver disease, HBV+, IDU, EtOH >60 g/d	To assess the prevalence of el AFP in pts w/ CHC and to evaluate the clinical, virologic and histopathological significance.

Evidence Table 6: Characteristics of patients in studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Extracellular matrix									
Casaril, 2000	CC								
		A: CHC Pts	102	42.5 54		Sch			
		B: Healthy subjects w/ nl liver function tests and negative viral studies	81	44.2 58		Sch			
Di Costanzo, 1996	CohP								
		A: Responders to IFN alpha	22	47.1 77	18	HAI HAI	A 9.5 S 2.2		
		B: Nonresponders to IFN alpha	46	50.3 72	41	HAI HAI	A 9.1 S 2.7		
Fortunato, 2001	XS								
		A: Pts w/ chronic HCV infection	54						
		B: Pts w/ cirrhosis from HCV infection	49						
Fukuda, 1998	CohR								
		O: Hemophilia Pts who had liver bx before IFN tx	36	31 94					

Evidence Table 6: Characteristics of patients in studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Fukuzaki, 2000										
		A: Complete response: ALT 2x nl	23	46		HAI			78	
		range (<40 U/l) during tx and maintained for 24 wks and HCV RNA- at 42 wks post tx		39						
									1b/2a	39.13
									2b	56.52
		B: Biochemical response: ALT 2x nl	9	53					75	
		range (<40 U/l) during tx and maintained for 24 wks and HCV RNA+ at 42 wks post tx		78						
									1b/2a	55.56
									2b	44.44
		C: No response	46	53					105	
				37						
									1b/2a	91.30
									2b	6.52
Gabrielli, 1997										
		A: Pts w/ chronic HCV infection	99	50		Sch				
				64						
		B: Healthy controls	40							
Giannini, 2001	CS									
		O: Pts w/ chronic HCV infection	109	44		HAI/Tri	S 0.9			
				74		HAI/Tri	A 6.5			

Evidence Table 6: Characteristics of patients in studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Guechot, 1994	CC								
		A: Pts in cohort of ursodiol for PBC trial	78	9					
		B: Pts in trial of alpha-IFN for viral hepatitis C treatment	58	71					
		C: Healthy controls	40	25					
Guechot, 1996	XS								
		O: HCV+ pts	326	43.6	16	HAI		A0 13.5	
				55		HAI		A1 52.8	
						HAI		A3 17.5	
						HAI		A4 16.2	
Ikeda, 2000	CS								
		O: 205 consecutive Pts w/ CHC	205	56					
				55					
Ishibashi, 1996	CohP								
		A: Complete responders to IFN tx	49						
		B: Relapsers after IFN tx	36						
		C: Nonresponders to IFN tx	36						

Evidence Table 6: Characteristics of patients in studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Jeffers, 1995	XS								
		A: Pts w/ mild CAH	34			HAI			114
		B: Pts w/ moderate-severe CAH	25						169
		C: Pts w/ cirrhosis	27						160

Evidence Table 6: Characteristics of patients in studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Kasahara, 1997	CohP									
		A: IFN tx, sustained response	26	52.2		HAI	8.8			
				54						
									1b	53.85
									2a	34.62
									2b	3.85
									not specified	0.00
		B: IFN tx, transient response	21	51.7		HAI	8.2			
				62						
									1b	90.48
									2a	0.00
									2b	4.76
									not specified	9.52
		C: IFN tx, no response	51	55.3		HAI	9.2			
				43						
									1b	92.16
									2a	5.88
									2b	1.96
									not specified	0.00

Evidence Table 6: Characteristics of patients in studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Lichtinghagen, 1999	CS								
		A: Pts w/ CHC presenting to OP clinic				MHAI			
		B: Nl serum and plasma from healthy blood donors							
		C: Livers explanted, but unable to transplant							
		D: Cirrhotic liver from transplant pts							
Lichtinghagen, 2000	CohR								
		A: Healthy controls	20			MHAI			
		B: HCV+ Pts w/ chronic hepatitis	40						
		C: HCV+ Pts w/ cirrhosis	20						

Evidence Table 6: Characteristics of patients in studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Lichtinghagen, 2001	CS									
		A: Pts w/ CHC	29			MHAI				
		B: Pts w/ CHC and cirrhosis	7							
		C: Nl controls	10							
Lo Iacono, 1998										
		O: CHC virus Pts w/ recurring IFN tx	52	40.8 63		HAI Sch	A 4.4 S 1.6			
									1b	73.08
									non-1b	26.92
McHutchison, 2000a	CohR									
		O: Pts w/ CHC enrolled in a tx study	486					A0 22.2	132	
		for CHC		73				A1 49.2 A3 12.5 A4 16.0		

Evidence Table 6: Characteristics of patients in studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Murawaki, 1999	CC								
		A: Pts w/ minimal chronic hepatitis.	24	49		HAI			
				83					
		B: Pts w/ mild chronic hepatitis.	21	51					
				62					
		C: Pts w/ moderate chronic hepatitis.	17	49					
				53					
		D: Pts w/ liver cirrhosis	35	58					
				74					
		E: Pts w/ hepatocellular carinoma.	55	65					
				69					
		F: Control Pts w/ no liver disease.	24	46					
				58					
Murawaki, 2001	CS								
		O: Pts HCV+ w/liver bx (fibrosis <	165	53		Met/Des		S0 9.0	
		F4)		67		Met/Des		S1 78.0	
						Met/Des		S2 40.0	
						Met/Des		S3 38.0	
Murawaki, 2001a	CohP								
		O: Pts w/ chronic HCV w/o cirrhosis	169	53		Des			
				66					

Evidence Table 6: Characteristics of patients in studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Ninomiya, 1998	CohP									
		A: IFN tx, complete response	16	44.9		HAI	A 3.0			
				56		HAI	S 10.8			
		B: IFN tx, partial response	25	42.3		HAI	A 3.2			
				64		HAI	S 9.5			
		C: IFN tx, no response	8	52.6		HAI	A 3.5			
				75		HAI	S 10.9			
Ohashi, 1998	CohP									
		A: Pts who completely responded to IFN.	27	48.8		HAI				
				56						
									1a	0.00
									1b	25.93
									2a	25.93
									2b	11.11
									mixed	7.41
									not specified	11.11
		B: Pts who did not respond to IFN.	35	54.2						
				66						
									1a	0.00
									1b	57.14
									2a	8.57
									2b	5.71
									mixed	0.00
									not specified	2.86

Evidence Table 6: Characteristics of patients in studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Plevris, 2000	CohP								
		A: Pts w/ liver disease caused by HCV infection	69			HAI			
		B: Pts w/ liver disease caused by alcohol							
		C: Pts w/ autoimmune liver disease							
		D: Pts w/ primary bilary cirrhosis							
		E: Pts w/ cryptogenic liver disease							

Evidence Table 6: Characteristics of patients in studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Serejo, 2001	CohP									
		A: Pts who were sustained	44	35.9		HAI	A 7.5	A0-A1 50.0	1	38.64
		responders.		64				A2 50.0	mixed	13.64
								A3 0.0	other	20.45
		B: Pts who were relapsers.	35	39.9		HAI	A 6.9	A0-A1 65.7	1	40.00
				51				A2 34.3	mixed	25.71
								A3 0.0	other	17.14
		C: Pts who were nonresponders.	38	45.5		HAI	A 11.1	A0-A1 34.2	1	42.11
			68					A2 28.9	mixed	7.89
								A3 36.8	other	23.68

Evidence Table 6: Characteristics of patients in studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Ueno, 2001	CohP								
		A: Complete responders w/ bx done	12	47		Met	A 1.6		71
		<2 yrs after tx.		50		Met	S 1.4		
		B: Nonresponders w/ bx done <2	24	48		Met	A 2.0		77
		yrs after tx		71		Met	S 1.1		
		C: Complete responders w/ bx done	10	51		Met	A 2.5		71
		>2 yrs after tx		60		Met	S 1.1		
		D: Nonresponders w/ bx done >	6	51		Met	A 1.5		94
		2 yrs after tx		67		Met	S 1.3		
Verbaan, 1997	CohR								
		O: Pts w/ CHC infection	109	46		HAI			
				66					
Walsh, 1999									
		A: Pts w/ CHC infection	33			MHAI			
		B: Healthy controls	5						
Walsh, 1999a	CohP								
		A: CHC w/ liver bx	43			MHAI			
				67					
		B: Healthy controls	19						

Evidence Table 6: Characteristics of patients in studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Walsh, 2000	XS								
		A: Pts w/ chronic HCV infection	37						
				65					
		B: Healthy controls	5						
				80					
Wong, 1998	CS								
		O: CHC virus Pts	130	37					
				72					
Yamada, 1996	CohP								
		A: Pts who were complete	9			Oth			
		responders to IFN tx.							
		B: Pts who were partial responders	14						
		to IFN tx.							
		C: Pts who were nonresponders to	12						
		IFN tx.							
Yamada, 1998	CohP								
		O: Japanese Pts w/ CHC and	36	31		Des			
		hemophilia		94					

Evidence Table 6: Characteristics of patients in studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Cytokines/cytokine receptors										
Izzo, 1996	CC									
		A: Pts w/ chronic HCV infection	123	53.9						
				67						
		B: Healthy HBV and HCV- controls	174							
Nutt, 2000	CS									
		A: HCV+ consecutive Pts w/ liver	35	44		HAI	A 4			
		bx and nl ALT on >/= 2 occasions		80						
		B: HCV+ consecutive Pts w/ liver bx	35	46		HAI	A 7			
		and el ALT		91						
Zylberberg, 1999	CC									
		A: Pts w/ CHC	60	48						
				68						
									1	60.00
									2	6.67
									3	20.00
									Other	13.33
		B: Pts w/ chronic HBV	34	41						
				76						
		C: Healthy control Pts								

Evidence Table 6: Characteristics of patients in studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Enzymes									
Anderson, 2000	CohR								
		O:	133	45.6					
				70					
Assy, 2000	CohR								
		O: Pts w/ chronic HCV infection	79	43.5		Des	S 1.5		
			59			HAI	A 3.5		
Barbaro, 1996	CC								
		A: Pts+ for HIV and HCV infection	55	17		HAI		S0 3.6	
				82		HAI		S1 3.6	
						HAI		S2 47.3	
						HAI		S3 38.2	
						HAI		S4 7.3	
		B: HCV+ pts	50	30		HAI		S0 4.0	
				94		HAI		S1 6.0	
						HAI		S2 42.0	
						HAI		S3 42.0	
						HAI		S4 6.0	
		C: Healthy controls	51	30					
				69					
Choi, 1999	CS								
		O: Pts w/ CHC infection	38	44		Oth			

Evidence Table 6: Characteristics of patients in studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
				39					
Goldstein, 1999	XS								
		O: CHC Pts given AFP, ALT testing, and liver bx	81						
Gordon, 2000	CohP								
		A: ALT <1.3 x nl in pts w/ HCV	105	40.9		MHAI			
		B: ALT >1.3 x nl in pts w/ HCV	1639	42.9					
Haber, 1995	CS								
		O: Pts w/ serologically confirmed	90	40.9		HAI			
		HCV		69					14.5
Healey, 1995	CohR								
		A: HCV+ normal AST	19	38.9		HAI			
				42					
		B: HCV+ abnormal AST	23	35.7					
				61					

Evidence Table 6: Characteristics of patients in studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Imbert-Bismut, 2001	XS								
		A: CHC Pts tested in first yr	205	47		Met		A0 25.4	108
		period		53				A1 41.5	
								A2 30.7	
								A3 2.4	
								S0 17.6	
								S1 44.4	
								S2 19.5	
								S3 8.8	
								S4 9.8	
		B: CHC Pts tested in second yr, as	134	48				A0 12.7	122
		confirmatory group		84				A1 59.7	
								A2 24.6	
								A3 3.0	
								S0 14.9	
								S1 40.3	
								S2 20.9	
								S3 7.5	
								S4 16.4	
Imperiale, 2000	CohR								
		O: A cohort of Pts w/ HCV.	177	42.3		Oth			
				36					

Evidence Table 6: Characteristics of patients in studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Jamal, 1999	CC									
		A: HCV Pts w/ nl ALT levels.	75	44		MHAI	S 1.4			
				60					21	
				C: 46.6, O: 53.3						
		B: HCV Pts w/ abnl ALT levels.	200	44						
				58					20	
				C: 42, O: 58						
Kobayashi, 2000	CohR									
		O: consecutive Pts treated w/	61	47		MHAI			96	
		alpha-IFN for 6 mos w/ f/u of 5 yrs		77						
									1b	86.89
									other	13.11
Luo, 1998										
		O: 93 Pts w/ CHC.	93	53		Oth	A 1.3			
				72			A 2.3			
							A 2.6		1b	38.71
								S1-S2 39.8	2a	13.98
								S3 47.3	2b	11.83
								S4 12.9	mixed	3.23
						HAI	S 1.5		not specified	3.23

Evidence Table 6: Characteristics of patients in studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
McCormick, 1996	CohR	O: Pts w/ CHC who were either treated or untreated and were biopsied.	44	77		HAI			
Michielsen, 1997	CS	O: CHC Pts	51	47 53		HAI/Oth			
Ono, 1999	XS	O: Pts w/ chronic HCV infection	435	58 73		Des			
Park, 2000	CohR	O: Pts w/ CHC	153	46.5 64		Sch			20
Poynard, 1997	XS	O: Pts w/ chronic HCV infection	500	49.1 58 C: 97.2, O: 0.8		Met			

Evidence Table 6: Characteristics of patients in studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Sheth, 1998	CohR									
		A: Ratio of AST to ALT >/= 1 in Pts w/ CHC				Oth				
		B: Ratio of AST to ALT </= 1 in Pts w/ CHC								
Shima, 2000	CohP									
		O: Pts w/ chronic HCV infections w/	36	56		HAI		<10 77.8		
		sustained response to IFN tx		67		HAI		>11 22.2		
Stanley, 1996	CS									
		A: Pts w/ chronic HCV infection and nl ALT	15	38.9		Oth				
									1a	20.00
									3a	13.33
		B: Pts w/ chronic HCV infection and el ALT	85	38.2						
									1a	29.41
									3a	29.41
Tsushima, 1999	CohR									
		A: Pts receiving IFN tx.	43	51.8 74		Oth				
		B: Pts not receiving IFN tx.	10	57.6 80						

Evidence Table 6: Characteristics of patients in studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Yeo, 2001	CS									
		O: Pts w/ chronic HCV infection	60			HAI				
				47 C: 80, B: 20						
									1a	43.33
									1b	31.67
									2a/b	8.33
									unknown	18.33
Viral markers										
Adinolfi, 1998	XS									
		O: HCV+ Pts undergoing liver bx	36	53	25	HAI		A1 25.0		
		and HCV-RNA levels		64		HAI		A2 33.3		
						HAI		A3 16.7	1b	52.78
									2a/c	33.33
									3a	5.56
									4	2.78
									mixed	5.56
Iijima, 2000	CS									
		O: CHC Pts not receiving antiviral	135	49.5		HAI/Des				
		therapy		70						

Evidence Table 6: Characteristics of patients in studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Kao, 1996	XS									
		A: Pts w/ chronic persistent	34	43		Oth			131	
		hepatitis		59					1b	64.71
		B: Pts w/ CAH and/or liver cirrhosis	30	51					162	
				67					1b	66.67
		C: Pts w/ HCC	30	65					74	
				73					1b	80.00
Papatheodoridis, 1997										
		O: Pts w/ chronic HCV	112	43.7		HAI				
				69						
									1a	7.14
									1b	24.11
									2a	5.36
									3a	18.75
									4a	2.68
Puoti, 1999	CohP									
		O: Anti-HCV+ Pts w/ persistently nl	59	47.5		HAI	A 0.8			
		ALT		34		HAI	S 4.0			

Evidence Table 6: Characteristics of patients in studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Miscellaneous										
Bayati, 1998	CS									
		A: Pts w/ a nl AFP level of <10.	125	52.5	46	Des				
				56					22.5	
		B: Pts w/ a high AFP level of >/= 10.	75	57.7	68					
				48					26.4	
Chu, 2001	XS									
		A: Chronic HCV Pts w/ el AFP	33	57 36		HAI/Sch				
									1b	72.73
									non-1b	21.21
		B: Chronic HCV Pts w/ nl AFP	82	49 29						
									1b	45.12
									non-1b	43.90

Evidence Table 7: Methodologic quality of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy

Author, Year	Representativeness[a]	Bias[b]	Description[c]	Outcomes[d]	Statistics[e]	Conflict[f]	Total[g]
Extracellular matrix							
Casaril, 2000	70	50	0	0	100	0	44
Di Costanzo, 1996	60	100	50	75	100	50	77
Fortunato, 2001	50	100	100	50	100	50	80
Fukuda, 1998	50	50	0	100	25	0	45
Fukuzaki, 2000	50	0	0	0	67	0	29
Gabrielli, 1997	60	100	100	50	100	50	82
Giannini, 2001	70	100	100	50	100	0	84
Guechot, 1994	40	0	50	33	100	0	45
Guechot, 1996	60	50	50	50	67	0	55
Ikeda, 2000	90	0	50	100	50	0	58
Ishibashi, 1996	50	0	50	50	100	0	50
Jeffers, 1995	70	100	0	100	75	0	69
Kasahara, 1997	70	100	50	25	67	0	62
Lichtinghagen, 1999	20	0	0	0	33	0	11
Lichtinghagen, 2000	30	100	0	33	100	50	53

Evidence Table 7: Methodologic quality of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Representativeness[a]	Bias[b]	Description[c]	Outcomes[d]	Statistics[e]	Conflict[f]	Total[g]
Lichtinghagen, 2001	30	100	0	50	100	50	56
Lo Iacono, 1998	80	100	50	56	67	50	71
McHutchison, 2000a	100	50	50	50	100	0	70
Murawaki, 1999	50	50	0	50	100	50	50
Murawaki, 2001	50	100	50	50	100	50	70
Murawaki, 2001a	50	100	50	0	100	50	60
Ninomiya, 1998	60	50	0	25	67	50	40
Ohashi, 1998	80	50	0	50	100	0	56
Plevris, 2000	30	100	100	50	100	0	76
Serejo, 2001	50	100	0	50	100	0	60
Ueno, 2001	80	100	100	25	67	50	74
Verbaan, 1997	90	100	100	83	67	50	88
Walsh, 1999	50	50	0	67	100	50	53
Walsh, 1999a	50	100	0	50	100	0	60
Walsh, 2000	50	50	0	50	100	0	50
Wong, 1998	80	50	0	100	100	0	66
Yamada, 1996	60	100	0	50	100	0	62

Evidence Table 7: Methodologic quality of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Representativeness[a]	Bias[b]	Description[c]	Outcomes[d]	Statistics[e]	Conflict[f]	Total[g]
Yamada, 1998	60	50	50	50	100	0	62
Cytokines/cytokine receptors							
Izzo, 1996	80	0	50	25	67	50	44
Nutt, 2000	60	100	0	100	75	0	67
Zylberberg, 1999	60	100	0	25	67	0	50
Enzymes							
Anderson, 2000	70	0	0	0	100	50	34
Assy, 2000	70	100	0	50	100	50	64
Barbaro, 1996	60	100	100	25	100	0	77
Choi, 1999	40	50	0	50	75	0	43
Goldstein, 1999	60	100	50	50	100	0	72
Gordon, 2000	83	50	0	50	100	0	57
Haber, 1995	100	100	0	100	100	50	80
Healey, 1995	60	100	50	25	17	0	50
Imbert-Bismut, 2001	90	100	50	50	100	50	78
Imperiale, 2000	75	50	0	50	100	0	55

Evidence Table 7: Methodologic quality of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Representativeness[a]	Bias[b]	Description[c]	Outcomes[d]	Statistics[e]	Conflict[f]	Total[g]
Jamal, 1999	75	100	0	50	100	0	65
Kobayashi, 2000	75	100	50	50	100	0	75
Luo, 1998	60	100	100	50	100	0	82
McCormick, 1996	50	50	0	50	75	0	45
Michielsen, 1997	70	100	0	50	100	0	64
Ono, 1999	90	100	50	50	100	0	78
Park, 2000	50	50	0	50	100	0	50
Poynard, 1997	50	100	0	50	100	50	60
Sheth, 1998	80	50	0	50	100	0	56
Shima, 2000	60	100	0	50	100	0	62
Stanley, 1996	88	100	50	50	100	0	78
Tsushima, 1999	63	100	100	33	100	0	79
Yeo, 2001	70	100	0	67	100	100	67
Viral markers							
Adinolfi, 1998	60	0	0	50	50	50	32
Iijima, 2000	80	100	0	25	100	50	61

Evidence Table 7: Methodologic quality of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Representativeness[a]	Bias[b]	Description[c]	Outcomes[d]	Statistics[e]	Conflict[f]	Total[g]
Kao, 1996	80	50	0	50	100	50	56
Papatheodoridis, 1997	88	100	0	50	100	0	68
Puoti, 1999	70	100	50	50	100	0	74
Miscellaneous							
Bayati, 1998	63	50	0	50	75	0	48
Chu, 2001	90	100	100	50	100	50	88

Evidence Table 7: Methodologic quality of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Representativeness[a]	Bias[b]	Description[c]	Outcomes[d]	Statistics[e]	Conflict[f]	Total[g]

[a] ***Representativeness***: The total maximum for this section was 10 points. This included setting and population described and start and end date specified (2 points); detailed description of inclusion and exclusion criteria or statement that all potential trainees enrolled (2 points); information about excluded or not-participating patients (2 points); appropriateness of the spectrum of disease included in the study sample (2 points); and description of key patient characteristics at enrollment (2 points).

[b] ***Bias and Confounding***: The total maximum score was 2 points. This included whether there was an independent, blind comparison with a reference standard.

[c] ***Description of Biopsy***: The total maximum score was 2 points. This included description of the technique and size of liver biopsy.

[d] ***Outcomes and Followup:*** The total maximum score was 8 points. This included description of complications, side effects and adverse reactions (2 points); sufficient description of criteria for determining outcomes (2 points); reporting on the numbers and reasons for withdrawals from the study or losses to followup (2 points); and proportion of patients who withdrew from the study or were lost to followup (2 points).

[e] ***Statistical Quality and Interpretation***: The total maximum score was 6 points. This included whether magnitude of difference between groups and an index variability was stated (2 points); whether analyses and statistical tests were clearly identified (2 points); and appropriate handling of crossovers and/or dropouts in the analysis (2 points).

[f] ***Conflict of Interest:*** The total maximum score was 2 points. This included whether the study reported the source of funding and the role played by the funding entity.

[g] ***Total Score*** is the mean of the percentage scores from the categories, Representativeness, Bias and Confounding, Description of Biopsy, Outcomes and Followup, and Statistical Quality and Interpretation.

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
Extracellular matrix										
Casaril, 2000	A: CHC Pts	102			laminin		Sp: 0.44*			
	B: Healthy subjects w/ nl liver function tests and negative viral studies	81			P-III-P		Sp: 0.30*			
Di Costanzo, 1996	A: Responders to IFN alpha	22	HAI: 2.24		Laminin					
	B: Non-responders to IFN alpha	46	HAI: 2.75		P-III-P					

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
Fortunato, 2001	A: Pts w/ chronic HCV infection	54			Albumin					
					ALP					
	B: Pts w/ cirrhosis from HCV infection	49			ALT					
					Apo A1					
					Apo B					
					AST					
					AST/ALT ratio					
					Cholesterol					
					Direct Bili					
					Fibronectin					
					GPX					
					LDII					
					LDL					
					MnSOD					
					PCHE					
					P-III-P					
					Plts					
					PT					
					Total Bili					
Fukuda, 1998	O: Hemophilia Pts who had liver bx before IFN tx	36			HA		n/s: 0.78*			
					type IV collagen		n/s: 0.38*			

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
Fukuzaki, 2000	A: Complete response: ALT twice normal range (<40 IU/l) durring tx and maintained for 24 wks and HCV RNA- at 42 wks post tx	23			HA IV 7s PIIIP					
	B: Biochemical response: ALT twice normal range (<40 IU/l) durring tx and maintained for 24 wks and HCV RNA+ at 42 wks post tx	9								
	C: No response	46								
Gabrielli, 1997	A: Pts w/ chronic HCV infection	99			Laminin P-III-P	1.8 1.0			51.7 34.4	80 20.6
	B: Healthy controls	40								
Giannini, 2001	O: Pts w/ chronic HCV infection	109	Oth: 0.9	Oth: 6.5	P-III-P		Sp: 0.03*			
Guechot, 1994	A: Pts in cohort of ursodiol for PBC trial	78			HA GroupA HA GroupB				0.51 0.55	0.74 0.92
	B: Pts in trial of alpha-interferon for viral hepatitis C treatment	58			PIII NP GroupA PIII NP GroupB				0.62 0.4	0.77 0.66
	C: healthy controls	40								

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
Guechot, 1996	O: HCV+ pts	326			HA		Pr: 0.58*			
					HA	110		0.92	79.2	89.4
					HA	85		0.86	64.5	91.2
					P-III-P		Pr: 0.34*			
					P-III-P	0.8		0.69	70	63.4
					P-III-P	1.0		0.73	60	74
Ikeda, 2000	O: 205 consecutive Pts w/ CHC	205			gamma globulin	10 x 10^4 / mm^3	n/s: 0.57 [b]			
					gender	10 x 10^4 / mm^3	n/s: -0.21 [b]			
					HA	10 x 10^4 / mm^3	n/s: 0.42 [b]			
					Plts	10 x 10^4 / mm^3	n/s: -0.43 [b]		81.1	89.8
Ishibashi, 1996	A: Complete responders to IFN tx	49	HAI: 1.4	HAI: 6.3	HA		Sp: 0.51*			
					IV-75		Sp: 0.42*			
	B: Relapsers after IFN tx	36	HAI: 1.3	HAI: 6.4	P-III-P		Sp: 0.33*			
	C: Non-responders to IFN tx	36	HAI: 2.1	HAI: 7.7						
Jeffers, 1995	A: Pts w/ mild CAH	34			P-III-P	Abnormal			70	
	B: Pts w/ moderate-severe CAH	25			P-III-P	Abnormal			58	82
	C: Pts w/ cirrhosis	27								
Kasahara, 1997	A: IFN tx, sustained response	26	HAI: 2	HAI: 6.8	MMP-2		Sp: 0.26*			
	B: IFN tx, transient response	21	HAI: 1.7	HAI: 6.5	TIMP-1		Sp: 0.30*			
	C: IFN tx, no response	51	HAI: 2.3	HAI: 7.4						

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
Lichtinghagen, 1999	A: Pts w/ CHC presenting to OP clinic				MMP-1					
					MMP-2					
	B: Nl serum and plasma from healthy blood donors				MMP-7					
	C: Livers explanted, but unable to transplant									
	D: Cirrhotic liver from transplant pts									
Lichtinghagen, 2000	A: Healthy controls	20			MMP-2		Sp: ns			
	B: HCV+ Pts w/ chronic hepatitis	40			MMP-9		Sp: ns			
					Ratio of MMP-2:TIMP-1		Sp: -0.38			
	C: HCV+ Pts w/ cirrhosis	20								
					TIMP-1		Sp: ns			
					TIMP-2		Sp: ns			
Lichtinghagen, 2001	A: Pts w/ CHC	29			MMP-7		Sp: 0.53*	0.75		
	B: Pts w/ CHC and cirrhosis	7			MMP-9		Sp: 0.39*	0.67		
	C: nl controls	10			TIMP-1		Sp: 0.46*	0.76		
					TIMP-2		Sp: 0.34	0.66		
					TIMP-3		ns	0.55		
					TIMP-4		Sp: 0.52*	0.72		
Lo Iacono, 1998	O: CHC virus Pts w/ recurring IFN tx	52	Sch: 1.6	HAI: 4.4	P-III-P	>10.57		0.73	88.9	51.7
					sICAM-1	>520		0.75	63.6	55.9
					sVCAM-1	>1280		0.96	100	85.3

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
McHutchison, 2000a	O: Pts w/ CHC enrolled in a tx study for CHC	486	HAI: 1.5	HAI: 2.4	HA		n/s: 0.54*			
					HA	100			76	82
					HA	110			73	83
					HA	60			88	59
					HA	80			83	72
Murawaki, 1999	A: Pts w/ minimal chronic hepatitis.	24			7S collagen	8.5				85
					HA	100				93
	B: Pts w/ mild chronic hepatitis.	21			IV collagen	150				81
	C: Pts w/ moderate chronic hepatitis.	17			MMP-2	700 ng/mL				89
	D: Pts w/ liver cirrhosis	35								
	E: Pts w/ hepatocellular carinoma.	55								
	F: control Pts w/ no liver disease.	24								
Murawaki, 2001	O: Pts HCV + w/liver bx (fibrosis < F4)	165			Plts	14x10^4/mm^3			68	73
					Plts	16x10^4/mm^3			68	71
					Type IV Collagen	110 ng/ml			71	73
					Type IV Collagen	130 ng/ml			66	75

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
Murawaki, 2001a	O: Pts w/ chroinc HCV w/o cirrhosis.	169			ALT	80			61	66
					HA	50			75	80
					HA	70			50	79
					IV-C7S	6			70	73
					IV-C7S	6.5			63	73
					MMP-2	550			75	70
					MMP-2	575			68	69
					P-III-NP	0.8			74	52
					P-III-NP	0.9			64	59
					TIMP-1	160			79	56
					TIMP-1	170			82	34
Ninomiya, 1998	A: IFN tx, complete response	16	MHAI: 3	MHAI:	HA after treatment		Sp: 0.56*			
	B: IFN tx, partial response	25	MHAI: 3.2	MHAI: 9.5						
	C: IFN tx, no response	8	MHAI: 3.5	MHAI:	HA before treatment		Sp: 0.61*			
					P-III-P after treatment		Sp: 0.51*			
					P-III-P before treatment		Sp: 0.53*			
					Type IV collagen after treatment		Sp: 0.32*			
					Type IV collagen before treatment		Sp: 0.24			

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
Ohashi, 1998	A: Pts who completely responded to IFN.	27			HA					
					IV-C		0.49			
	B: Pts who did not respond to IFN.	35			P-III-P		0.53			
Plevris, 2000	A: Pts w/ liver disease caused by HCV infection	69			HA	100			72	95
					HA	200			67	98
	B: Pts w/ liver disease caused by alcohol				HA	300			47	100
	C: Pts w/ autoimmune liver disease									
	D: Pts w/ primary bilary cirrhosis									
	E: Pts w/ cryptogenic liver disease									
Serejo, 2001	A: Pts who were sustained responders.	44			P-III-P					
	B: Pts who were relapsers.	35								
	C: Pts who were non-responders.	38								
Ueno, 2001	A: Complete responders w/ bx done < 2 years after tx.	12			HA		Sp: 0.29*			
	B: Non-responders w/ bx done < 2 years after tx	24			P-III-P		Sp: 0.33*			
	C: Complete responders w/ bx done more than 2 years after tx	10			type IV collagen		Sp: 0.35*			
	D: Non-responders w/ bx done more than 2 years after tx	6								

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
Verbaan, 1997	O: Pts w/ CHC infection	109			IgG		Sp: 0.43*			
					P-III-P	1.11	Sp: 0.32*		78	56
					type-IV collagen	250	Sp: 0.43*		87	75
Walsh, 1999	A: Pts w/ CHC infection	33			ALT	155		0.51	71	44
	B: Healthy controls	5			CIS P-III-P	0.8 U/mL		0.76*	50	85.7
					Orion P-III-P	4.2 ng/L		0.67	85	37.5
Walsh, 1999a	A: CHC w/ liver bx	43			ALT			0.59	67	52
	B: Healthy controls	19			MMP-2	860		0.67	69	59
					TIMP-1	500		0.73*	94	57
					TIMP-2	102		0.73*	85	47
Walsh, 2000	A: Pts w/ chronic HCV infection	37			ALT			0.54*		
					Laminin	1.26		0.82*	80	85.3
	B: Healthy controls	5			type IV collagen	148		0.85*	80	73.3
Wong, 1998	O: CHC virus Pts	130			ALT				76	48
					AST				48	39
					HA				86	88
Yamada, 1996	A: Pts who were complete responders to IFN tx.	9	Oth: 2.11		HA		Sp: 0.79*			
					P-III-P		Sp: 0.45*			
	B: Pts who were partial responders to IFN tx.	14	Oth: 1.78		type-IV collagen		Sp: 0.42*			
	C: Pts who were non-responders to IFN tx.	12	Oth: 7.08							

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
Yamada, 1998	O: Japanese Pts w/ CHC and hemophilia	36	Desm: 1.9		HA type IV collagen		Sp: 0.78* Sp: 0.38*			
Cytokines/cytokine receptors										
Izzo, 1996	A: Pts w/ chronic HCV infection	123			IL-2R					
	B: Healthy HBV and HCV-controls	174								
Nutt, 2000	A: HCV + consecutive Pts w/ liver bx and nl ALT on >= 2 occasions	35	HAI: 4		ALT					
	B: HCV + consecutive Pts w/ liver bx and elevated ALT	35	HAI: 7							
Zylberberg, 1999	A: Pts w/ CHC	60			sTNF-R55					
	B: Pts w/ chronic HBV	34			sTNF-R75					
	C: Healthy control Pts				TNF-alpha					
Enzymes										
Anderson, 2000	O	133			AST/ALT ratio > 1				31	95
Assy, 2000	O: Pts w/ chronic HCV infection	79	Desm: 1.5	HAI: 3.5	ALT AST		M: 0.51* M: 0.64*			
Barbaro, 1996	A: Pts+ for HIV and HCV infection	55			CD4 plus T-cell count		Pr: 0.02			

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
	B: HCV+ pts C: Healthy controls	50 51			Plasma glutathione		Pr: 0.74*			
Choi, 1999	O: Pts w/ CHC infection	38			ALT HCV RNA					
Goldstein, 1999	O: CHC Pts given AFP, ALT testing, and liver bx	81			AFP ALT					
Gordon, 2000	A: ALT < 1.3 x nl in pts w/ HCV B: ALT > 1.3 x nl in pts w/ HCV	105 1639	MHAI: MHAI:	MHAI: MHAI:						
Haber, 1995	O: Pts w/ serologically confirmed HCV	90	HAI: 3.4		ALT/AST					
Healey, 1995	A: HCV+ normal AST B: HCV+ abnormal AST	19 23			AST					

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
Imbert-Bismut, 2001	A: CHC Pts tested in first year period	205			10 markers in logistic regression, group A			0.86		
	B: CHC Pts tested in second year, as confirmatory group	134								
					10 markers in logistic regression, group B			0.89		
					6 markers in logistic regression, group A			0.82		
					6 markers in logistic regression, group B			0.85		
Imperiale, 2000	O: A cohort of Pts w/ HCV.	177			AST/ALT	>1			56	90
Jamal, 1999	A: HCV Pts w/ nl ALT levels.	75	MHAI: 1.4		ALT					
	B: HCV Pts w/ abnl ALT levels.	200	MHAI:							
Kobayashi, 2000	O: consecutive Pts treated w/ alpha-IFN for 6 mos w/ f/u of 5 years	61			ALT					
Luo, 1998	O: 93 Pts w/ CHC.	93	Oth: 0.5	Oth: 7.7	ALT					

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
					HCV RNA					
McCormick, 1996	O: Pts w/ CHC who were either treated or untreated and were biopsied.	44			ALT HCV titer		Sp: 0.49* Sp: 0.35			
Michielsen, 1997	O: CHC Pts	51			ALT AST		Sp: 0.08 Sp: 0.29*			
Ono, 1999	O: Pts w/ chronic HCV infection	435			ALB Alkaline phosphatase ALT AST GTP LDH Plts PT total Bili WBC	> 4 vs. < 4 1IV 1IV 104 1%				
Park, 2000	O: Pts w/ CHC	153			AST/ALT	1			46.7	95.9

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
Poynard, 1997	O: Pts w/ chronic HCV infection	500			Age					
					AST					
					Bili					
					Body weight					
					Creatinine					
					GGT					
					IDU					
					Index: age, Plts			0.79		
					Plts					
					PT					
Sheth, 1998	A: Ratio of AST to ALT >= 1 in Pts w/ CHC B: Ratio of AST to ALT <= 1 in Pts w/ CHC				AST/ALT	> 1				100
Shima, 2000	O: Pts w/ chronic HCV infections w/ sustained response to IFN tx	36	HAI: 2	HAI: 8	Cholinesterase					
					Plts					
					Total bile acid					
					Zinc sulphate turbidity test					
Stanley, 1996	A: Pts w/ chronic HCV infection and nl ALT	15			ALT	> normal	Sp: ns			
	B: Pts w/ chronic HCV infection and elevated ALT	85								
Tsushima, 1999	A: Pts receiving IFN tx.	43	Oth: 1		ALT/AST					
	B: Pts not receiving IFN tx.	10	Oth: 2							

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
Yeo, 2001	O: Pts w/ chronic HCV infection	60			ALT HCV-RNA Viral genotype	> 100				
Viral markers										
Adinolfi, 1998	O: HCV+ Pts undergoing liver bx and HCV-RNA levels	36			HCV RNA					
Iijima, 2000	O: CHC Pts not receiving antiviral therapy	135			HCV core protein					
Kao, 1996	A: Pts w/ chronic persistent hepatitis	34			HCV titer					
	B: Pts w/ CAH and/or liver cirrhosis	30								
	C: Pts w/ HCC	30								
Papatheodoridis, 1997	O:Pts w/ chronic HCV	112			IgM anti HCV core					
Puoti, 1999	O: Anti-HCV+ Pts w/ persistently nl ALT	59	HAI: 0.8	HAI: 4	HCV RNA		Sp: 0.43*			
Miscellaneous										
Bayati, 1998	A: Pts w/ a nl AFP level of < 10.	125			AFP	17.8				98.6
	B: Pts w/ a high AFP level of >= 10.	75								

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
Chu, 2001	A: Chronic HCV Pts w/ elevated AFP	33			AFP					
	B: Chronic HCV Pts w/ nl AFP	82								

[a] Correlation coefficient: Pr = Pearson's r, Sp = Spearman's ρ, M = Multivariate, n/s = not specified
[b] p-value not reported for correlation coefficient
ns = no correlation coefficient given, but it was mentioned that the value was nonsignificant (p>0.05)
* Correlation coefficient is statistically significant (p<0.05)

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
Extracellular matrix										
Casaril, 2000	A: CHC Pts	102			laminin		Sp: 0.44*			
	B: Healthy subjects w/ nl liver function tests and negative viral studies	81			P-III-P		Sp: 0.30*			
Di Costanzo, 1996	A: Responders to IFN alpha	22	HAI: 2.24		Laminin					
	B: Non-responders to IFN alpha	46	HAI: 2.75		P-III-P					

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
Fortunato, 2001	A: Pts w/ chronic HCV infection	54			Albumin					
					ALP					
	B: Pts w/ cirrhosis from HCV infection	49			ALT					
					Apo A1					
					Apo B					
					AST					
					AST/ALT ratio					
					Cholesterol					
					Direct Bili					
					Fibronectin					
					GPX					
					LDII					
					LDL					
					MnSOD					
					PCHE					
					P-III-P					
					Plts					
					PT					
					Total Bili					
Fukuda, 1998	O: Hemophilia Pts who had liver bx before IFN tx	36			HA		n/s: 0.78*			
					type IV collagen		n/s: 0.38*			

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
Fukuzaki, 2000	A: Complete response: ALT twice normal range (<40 IU/l) durring tx and maintained for 24 wks and HCV RNA- at 42 wks post tx	23			HA IV 7s PIIIP					
	B: Biochemical response: ALT twice normal range (<40 IU/l) durring tx and maintained for 24 wks and HCV RNA+ at 42 wks post tx	9								
	C: No response	46								
Gabrielli, 1997	A: Pts w/ chronic HCV infection	99			Laminin P-III-P	1.8 1.0			51.7 34.4	80 20.6
	B: Healthy controls	40								
Giannini, 2001	O: Pts w/ chronic HCV infection	109	Oth: 0.9	Oth: 6.5	P-III-P		Sp: 0.03*			
Guechot, 1994	A: Pts in cohort of ursodiol for PBC trial	78			HA GroupA HA GroupB				0.51 0.55	0.74 0.92
	B: Pts in trial of alpha-interferon for viral hepatitis C treatment	58			PIII NP GroupA PIII NP GroupB				0.62 0.4	0.77 0.66
	C: healthy controls	40								

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
Guechot, 1996	O: HCV+ pts	326			HA		Pr: 0.58*			
					HA	110		0.92	79.2	89.4
					HA	85		0.86	64.5	91.2
					P-III-P		Pr: 0.34*			
					P-III-P	0.8		0.69	70	63.4
					P-III-P	1.0		0.73	60	74
Ikeda, 2000	O: 205 consecutive Pts w/ CHC	205			gamma globulin	10 x 10^4 / mm^3	n/s: 0.57 [b]			
					gender	10 x 10^4 / mm^3	n/s: -0.21 [b]			
					HA	10 x 10^4 / mm^3	n/s: 0.42 [b]			
					Plts	10 x 10^4 / mm^3	n/s: -0.43 [b]		81.1	89.8
Ishibashi, 1996	A: Complete responders to IFN tx	49	HAI: 1.4	HAI: 6.3	HA		Sp: 0.51*			
					IV-75		Sp: 0.42*			
	B: Relapsers after IFN tx	36	HAI: 1.3	HAI: 6.4	P-III-P		Sp: 0.33*			
	C: Non-responders to IFN tx	36	HAI: 2.1	HAI: 7.7						
Jeffers, 1995	A: Pts w/ mild CAH	34			P-III-P	Abnormal			70	
	B: Pts w/ moderate-severe CAH	25			P-III-P	Abnormal			58	82
	C: Pts w/ cirrhosis	27								
Kasahara, 1997	A: IFN tx, sustained response	26	HAI: 2	HAI: 6.8	MMP-2		Sp: 0.26*			
	B: IFN tx, transient response	21	HAI: 1.7	HAI: 6.5	TIMP-1		Sp: 0.30*			
	C: IFN tx, no response	51	HAI: 2.3	HAI: 7.4						

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
Lichtinghagen, 1999	A: Pts w/ CHC presenting to OP clinic				MMP-1					
					MMP-2					
	B: Nl serum and plasma from healthy blood donors				MMP-7					
	C: Livers explanted, but unable to transplant									
	D: Cirrhotic liver from transplant pts									
Lichtinghagen, 2000	A: Healthy controls	20			MMP-2		Sp: ns			
	B: HCV+ Pts w/ chronic hepatitis	40			MMP-9		Sp: ns			
					Ratio of MMP-2:TIMP-1		Sp: -0.38			
	C: HCV+ Pts w/ cirrhosis	20								
					TIMP-1		Sp: ns			
					TIMP-2		Sp: ns			
Lichtinghagen, 2001	A: Pts w/ CHC	29			MMP-7		Sp: 0.53*	0.75		
	B: Pts w/ CHC and cirrhosis	7			MMP-9		Sp: 0.39*	0.67		
	C: nl controls	10			TIMP-1		Sp: 0.46*	0.76		
					TIMP-2		Sp: 0.34	0.66		
					TIMP-3		ns	0.55		
					TIMP-4		Sp: 0.52*	0.72		
Lo Iacono, 1998	O: CHC virus Pts w/ recurring IFN tx	52	Sch: 1.6	HAI: 4.4	P-III-P	>10.57		0.73	88.9	51.7
					sICAM-1	>520		0.75	63.6	55.9
					sVCAM-1	>1280		0.96	100	85.3

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
McHutchison, 2000a	O: Pts w/ CHC enrolled in a tx study for CHC	486	HAI: 1.5	HAI: 2.4	HA		n/s: 0.54*			
					HA	100			76	82
					HA	110			73	83
					HA	60			88	59
					HA	80			83	72
Murawaki, 1999	A: Pts w/ minimal chronic hepatitis.	24			7S collagen	8.5				85
					HA	100				93
	B: Pts w/ mild chronic hepatitis.	21			IV collagen	150				81
	C: Pts w/ moderate chronic hepatitis.	17			MMP-2	700 ng/mL				89
	D: Pts w/ liver cirrhosis	35								
	E: Pts w/ hepatocellular carinoma.	55								
	F: control Pts w/ no liver disease.	24								
Murawaki, 2001	O: Pts HCV + w/liver bx (fibrosis < F4)	165			Plts	14x10^4/mm^3			68	73
					Plts	16x10^4/mm^3			68	71
					Type IV Collagen	110 ng/ml			71	73
					Type IV Collagen	130 ng/ml			66	75

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
Murawaki, 2001a	O: Pts w/ chroinc HCV w/o cirrhosis.	169			ALT	80			61	66
					HA	50			75	80
					HA	70			50	79
					IV-C7S	6			70	73
					IV-C7S	6.5			63	73
					MMP-2	550			75	70
					MMP-2	575			68	69
					P-III-NP	0.8			74	52
					P-III-NP	0.9			64	59
					TIMP-1	160			79	56
					TIMP-1	170			82	34
Ninomiya, 1998	A: IFN tx, complete response	16	MHAI: 3	MHAI:	HA after treatment		Sp: 0.56*			
	B: IFN tx, partial response	25	MHAI: 3.2	MHAI: 9.5						
	C: IFN tx, no response	8	MHAI: 3.5	MHAI:	HA before treatment		Sp: 0.61*			
					P-III-P after treatment		Sp: 0.51*			
					P-III-P before treatment		Sp: 0.53*			
					Type IV collagen after treatment		Sp: 0.32*			
					Type IV collagen before treatment		Sp: 0.24			

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
Ohashi, 1998	A: Pts who completely responded to IFN.	27			HA					
					IV-C		0.49			
	B: Pts who did not respond to IFN.	35			P-III-P		0.53			
Plevris, 2000	A: Pts w/ liver disease caused by HCV infection	69			HA	100			72	95
					HA	200			67	98
	B: Pts w/ liver disease caused by alcohol				HA	300			47	100
	C: Pts w/ autoimmune liver disease									
	D: Pts w/ primary bilary cirrhosis									
	E: Pts w/ cryptogenic liver disease									
Serejo, 2001	A: Pts who were sustained responders.	44			P-III-P					
	B: Pts who were relapsers.	35								
	C: Pts who were non-responders.	38								
Ueno, 2001	A: Complete responders w/ bx done < 2 years after tx.	12			HA		Sp: 0.29*			
	B: Non-responders w/ bx done < 2 years after tx	24			P-III-P		Sp: 0.33*			
	C: Complete responders w/ bx done more than 2 years after tx	10			type IV collagen		Sp: 0.35*			
	D: Non-responders w/ bx done more than 2 years after tx	6								

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
Verbaan, 1997	O: Pts w/ CHC infection	109			IgG		Sp: 0.43*			
					P-III-P	1.11	Sp: 0.32*		78	56
					type-IV collagen	250	Sp: 0.43*		87	75
Walsh, 1999	A: Pts w/ CHC infection	33			ALT	155		0.51	71	44
	B: Healthy controls	5			CIS P-III-P	0.8 U/mL		0.76*	50	85.7
					Orion P-III-P	4.2 ng/L		0.67	85	37.5
Walsh, 1999a	A: CHC w/ liver bx	43			ALT			0.59	67	52
	B: Healthy controls	19			MMP-2	860		0.67	69	59
					TIMP-1	500		0.73*	94	57
					TIMP-2	102		0.73*	85	47
Walsh, 2000	A: Pts w/ chronic HCV infection	37			ALT			0.54*		
					Laminin	1.26		0.82*	80	85.3
	B: Healthy controls	5			type IV collagen	148		0.85*	80	73.3
Wong, 1998	O: CHC virus Pts	130			ALT				76	48
					AST				48	39
					HA				86	88
Yamada, 1996	A: Pts who were complete responders to IFN tx.	9	Oth: 2.11		HA		Sp: 0.79*			
					P-III-P		Sp: 0.45*			
	B: Pts who were partial responders to IFN tx.	14	Oth: 1.78		type-IV collagen		Sp: 0.42*			
	C: Pts who were non-responders to IFN tx.	12	Oth: 7.08							

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
Yamada, 1998	O: Japanese Pts w/ CHC and hemophilia	36	Desm: 1.9		HA type IV collagen		Sp: 0.78* Sp: 0.38*			
Cytokines/cytokine receptors										
Izzo, 1996	A: Pts w/ chronic HCV infection	123			IL-2R					
	B: Healthy HBV and HCV-controls	174								
Nutt, 2000	A: HCV + consecutive Pts w/ liver bx and nl ALT on >= 2 occasions	35	HAI: 4		ALT					
	B: HCV + consecutive Pts w/ liver bx and elevated ALT	35	HAI: 7							
Zylberberg, 1999	A: Pts w/ CHC	60			sTNF-R55					
	B: Pts w/ chronic HBV	34			sTNF-R75					
	C: Healthy control Pts				TNF-alpha					
Enzymes										
Anderson, 2000	O	133			AST/ALT ratio > 1				31	95
Assy, 2000	O: Pts w/ chronic HCV infection	79	Desm: 1.5	HAI: 3.5	ALT AST		M: 0.51* M: 0.64*			
Barbaro, 1996	A: Pts+ for HIV and HCV infection	55			CD4 plus T-cell count		Pr: 0.02			

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
	B: HCV+ pts C: Healthy controls	50 51			Plasma glutathione		Pr: 0.74*			
Choi, 1999	O: Pts w/ CHC infection	38			ALT HCV RNA					
Goldstein, 1999	O: CHC Pts given AFP, ALT testing, and liver bx	81			AFP ALT					
Gordon, 2000	A: ALT < 1.3 x nl in pts w/ HCV B: ALT > 1.3 x nl in pts w/ HCV	105 1639	MHAI: MHAI:	MHAI: MHAI:						
Haber, 1995	O: Pts w/ serologically confirmed HCV	90	HAI: 3.4		ALT/AST					
Healey, 1995	A: HCV+ normal AST B: HCV+ abnormal AST	19 23			AST					

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
Imbert-Bismut, 2001	A: CHC Pts tested in first year period	205			10 markers in logistic regression, group A			0.86		
	B: CHC Pts tested in second year, as confirmatory group	134								
					10 markers in logistic regression, group B			0.89		
					6 markers in logistic regression, group A			0.82		
					6 markers in logistic regression, group B			0.85		
Imperiale, 2000	O: A cohort of Pts w/ HCV.	177			AST/ALT	>1			56	90
Jamal, 1999	A: HCV Pts w/ nl ALT levels.	75	MHAI: 1.4		ALT					
	B: HCV Pts w/ abnl ALT levels.	200	MHAI:							
Kobayashi, 2000	O: consecutive Pts treated w/ alpha-IFN for 6 mos w/ f/u of 5 years	61			ALT					
Luo, 1998	O: 93 Pts w/ CHC.	93	Oth: 0.5	Oth: 7.7	ALT					

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
					HCV RNA					
McCormick, 1996	O: Pts w/ CHC who were either treated or untreated and were biopsied.	44			ALT HCV titer		Sp: 0.49* Sp: 0.35			
Michielsen, 1997	O: CHC Pts	51			ALT AST		Sp: 0.08 Sp: 0.29*			
Ono, 1999	O: Pts w/ chronic HCV infection	435			ALB Alkaline phosphatase ALT AST GTP LDH Plts PT total Bili WBC	> 4 vs. < 4 1IV 1IV 104 1%				
Park, 2000	O: Pts w/ CHC	153			AST/ALT	1			46.7	95.9

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
Poynard, 1997	O: Pts w/ chronic HCV infection	500			Age					
					AST					
					Bili					
					Body weight					
					Creatinine					
					GGT					
					IDU					
					Index: age, Plts			0.79		
					Plts					
					PT					
Sheth, 1998	A: Ratio of AST to ALT >= 1 in Pts w/ CHC B: Ratio of AST to ALT <= 1 in Pts w/ CHC				AST/ALT	> 1				100
Shima, 2000	O: Pts w/ chronic HCV infections w/ sustained response to IFN tx	36	HAI: 2	HAI: 8	Cholinesterase					
					Plts					
					Total bile acid					
					Zinc sulphate turbidity test					
Stanley, 1996	A: Pts w/ chronic HCV infection and nl ALT	15			ALT	> normal	Sp: ns			
	B: Pts w/ chronic HCV infection and elevated ALT	85								
Tsushima, 1999	A: Pts receiving IFN tx.	43	Oth: 1		ALT/AST					
	B: Pts not receiving IFN tx.	10	Oth: 2							

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
Yeo, 2001	O: Pts w/ chronic HCV infection	60			ALT HCV-RNA Viral genotype	> 100				
Viral markers										
Adinolfi, 1998	O: HCV+ Pts undergoing liver bx and HCV-RNA levels	36			HCV RNA					
Iijima, 2000	O: CHC Pts not receiving antiviral therapy	135			HCV core protein					
Kao, 1996	A: Pts w/ chronic persistent hepatitis	34			HCV titer					
	B: Pts w/ CAH and/or liver cirrhosis	30								
	C: Pts w/ HCC	30								
Papatheodoridis, 1997	O:Pts w/ chronic HCV	112			IgM anti HCV core					
Puoti, 1999	O: Anti-HCV+ Pts w/ persistently nl ALT	59	HAI: 0.8	HAI: 4	HCV RNA		Sp: 0.43*			
Miscellaneous										
Bayati, 1998	A: Pts w/ a nl AFP level of < 10.	125			AFP	17.8				98.6
	B: Pts w/ a high AFP level of >= 10.	75								

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
Chu, 2001	A: Chronic HCV Pts w/ elevated AFP	33			AFP					
	B: Chronic HCV Pts w/ nl AFP	82								

[a] Correlation coefficient: Pr = Pearson's r, Sp = Spearman's ρ, M = Multivariate, n/s = not specified
[b] p-value not reported for correlation coefficient
ns = no correlation coefficient given, but it was mentioned that the value was nonsignificant (p>0.05)
* Correlation coefficient is statistically significant (p<0.05)

Evidence Table 9: Overall summary of randomized controlled trials of current treatment options for chronic hepatitis C

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Studies of current treatment options in naïve patients					
Pegylated interferon/ribavirin combination therapy					
Glue, 2000	France	72	ALT: 1 abnl result w/i past 6 mos, detectable HCV in serum, "adult" age, initial liver bx, nl Bili, nl Alb, nl Cr, nl fasting blood sugar, nl TSH, nl AFP, nl hematologic parameters, nl PT, antibody titers <1:160	IFN + RBV, HBV+, decompensated liver disease, depression, other psychiatric illness, RBV monotherapy, liver disease of other etiology, IFN monotherapy, any clinical trial or investigational drug w/i 30 ds prior, HIV+	To assess the safety, pharmacokinetics, and efficacy of peg-IFN alpha-2b plus RBV in pts w/ CHC
Manns, 2001	United States Canada Europe Argentina	1530	ALT >34 for women and >43 for men, detectable HCV in serum, nl Cr, initial liver bx w/CHC in past year, tx naïve, WBC >13, neutrophil >1.5, Hgb 12 for women and 13 for men, plts >100,000, nl Bili, nl Alb	HIV+, immune suppression, depression, other psychiatric illness, decompensated liver disease, comorbidities: cardiovascular, neurologic or hematologic, no contraception, AFP >50 mg/L, DM	To assess the safety and efficacy of two different regimens of Peg IFN and RBV compared w/ IFN alpha 2b and RBV and identify predictors and response for peg IFN alpha 2b.

Evidence Table 9: Overall summary of randomized controlled trials of current treatment options for chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Pegylated interferon monotherapy					
Heathcote, 2000	United States Canada	271	ALT, initial liver bx	AFP >100 ng/y, plts <75,000, WBC <500, IFN monotherapy, presence of any other liver disease, comorbidities: malignancy, GI, neurologic, or cardiovascular, HIV+, depression, psychiatric illness, decompensated liver disease	To compare the efficacy and safety of two doses of peg-IFN alpha-2a, given once wkly, w/ the safety and efficacy of a standard regimen of unmodified IFN alpha-2a in pts w/ HCV and cirrhosis or fibrosis.
Lindsay, 2001	United States Europe Australia	1299	U/S: no mass lesion, detectable HCV in serum, initial liver bx w/i 1 y of enrollment, AFP w/i nl limits, ALT el >= 1 time w/i 6 mo of enrollment, WBC >4, neutrophil >1.8, Hgb >12 in females and >13 in males, plts > 130,000/mm^3	Hemophilia, breast feeding, illicit drug use, HBV+, HCC, pregnancy, HIV+, active IDU, hemochromatosis, alpha-1-antitrypsin deficiency, Wilson's disease, EtOH, NASH, any antiviral therapy, hemoglobinopathy, other medical conditions that could interfere with participation, any prior tx, autoimmune hepatitis	To evaluate the efficacy of pegIFN alpha 2b compared w/ IFN alpha 2b in tx-naïve pts w/ CHC

Evidence Table 9: Overall summary of randomized controlled trials of current treatment options for chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Reddy, 2001	United States	158	HCV+, detectable HCV in serum, initial liver bx w/i prior 12 mo	Neurologic comorbidity: seizure disorder, IDU, other illicit drug use, presence of bridging fibrosis, presence of cirrhosis, non-response to previous therapy, pregnancy, depression, other psychiatric illness, EtOH in the past 12 mo, any antiviral therapy, cardiovascular comorbidity, other comorbidities: retinopathy, unstable thyroid dysfunction, renal or liver disease from any other cause, WBC <1500, plts 70,000, Cr 1.5x U/L of nl range, any treatment for HCV	To evaluate safety and efficacy of four doses of once-wkly peg-(40 kD) IFN alpha-2a administered for 48 wks, compared w/ 3 mu of IFN alpha-2a tiw. The study intends to establish the most appropriate dose of Peg (40 kD) IFN alpha-2a for larger trials.
Zeuzem, 2000a	Canada Europe Australia	531	HCV+, detectable HCV in serum: RNA >2000 copies per mL, el ALT on >=2 occasions in previous 6 mo, initial liver bx w/ hepatitis, liver bx findings consistent with CHC, adults	Malignancy, decompensated liver disease, HBV+, immune suppression, depression, other psychiatric illness, HIV+, hepatitis A infection, other comorbidities: seizure, neurologic OR cardiovascular, AFP >25 ng/mL, chronic pulmonary disease, autoimmune disorder, unwillingness to practice contraception, severe retinopathy, IFN monotherapy, neutrophil <1500, plts <90,000, Cr 1.5x UL of nl	To compare the efficacy and safety of peg-IFN alpha-2a administered once per wk w/ the efficacy and safety of IFN alpha-2a tiw for 48 wks.

Evidence Table 9: Overall summary of randomized controlled trials of current treatment options for chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Interferon/ribavirin combination therapy					
Berg, 2000	Germany	185	El ALT, any previous treatment, HCV+, detectable HCV in serum	Psychiatric illness, acute or chronic IDU, HBV+, decompensated liver disease, acute or chronic EtOH, immune suppression, plts <100 nl, depression, HIV+, severe concurrent diseases, Hgb <11 g/dL, pregnancy	To examine if 12 wk combination therapy is more effective in improving initial and SVR compared w/ IFN monotherapy in untreated pts. pts who achieved a virologic response were treated w/ IFN alpha monotherapy for an additional 40 wks and then SVR was evaluated 24 wks after end of tx
el-Zayadi, 1999	Egypt	52	Hgb >12, ALT el for 6 mo, U/S w/absence of focal hepatic lesion, initial liver bx, HCV+, HCV genotype 4	Contraindication to IFN, decompensated liver disease, HCV genotype 1, 2, or 3	To asses the efficacy of IFN alpha 2b alone and w/ RBV as initial therapy in male Egyptian pts w/ CHC, genotype 4.
Ferenci, 2001	Austria		Hgb >12 for males and >13 for females, WBC >3000, ALT 1.5x nl for >=6 mos, initial liver bx w/i 1 yr prior, detectable HCV in serum, plts >100,000, age 19-65 yrs	HIV+, EtOH, IDU, sexually active women refusing contraception, HBV+, decompensated liver disease, pregnancy or breast feeding, depression, other psychiatric illness, cardiovascular comorbidity: CHD, DM, autoimmune disorders, any unstable medical condition	To test two different schedules of high-dose induction therapy w/ IFN in combination w/ RBV, compared w/ a standard IFN/RBV combination therapy

Evidence Table 9: Overall summary of randomized controlled trials of current treatment options for chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Mangia, 2001	Italy	192	Detectable HCV in serum, ALT available for 6 mo, initial liver bx	DM, HBV+, decompensated liver disease: ascites, bleeding varices, and encephalopathy, pregnancy, depression, EtOH, HIV+, plts <100,000, autoimmune disorder, significant medical illness, IFN monotherapy, WBC <3500, Hgb <12 for females and <13 for males, other psychiatric illness	To compare the efficacy of a high dose regimen of IFN alpha2B (5 mu tiw) for 12 mos alone or in combination w/ RBV for the tx of naïve pts w/ CHC. Secondary aims were to evaluate the effects of baseline features on the response to therapy and to determine a reliable point in time during tx to predict non response.
Studies of interferon/amantadine combination therapy, with or without ribavirin					
Caronia, 2001	United Kingdom	179	Age: 18-70, HCV+, detectable HCV in serum, no previous tx, CHC on initial liver bx, ALT 1.3x UL of nl w/i last 6 mos	EtOH >28 units/wk, active IDU, HBV+, liver disease of any other etiology, High ceruplasmin, serum autoantibody titer >1:40	To assess the efficacy of combination therapy w/ IFN alpha and amantadine compared to IFN monotherapy in previously untreated pts w/ CHC

Evidence Table 9: Overall summary of randomized controlled trials of current treatment options for chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Helbling, 2002	Switzerland	246	Tx naïve, HCV proven by bx w/i prior 2 yrs, detectable HCV in serum, Cr <1.5x UL of nl, age 18-65 yrs	Decompensated liver disease, HIV+, depression, other psychiatric illness, pregnancy, refusal to use contraception, presence of fibrosis: 28 Child-Pugh points, HBV+, illicit drug use w/i 1 yr of study, EtOH >20 g/d for females and >40 g/d for males, immune suppression, psychosocial instability, lactation, comorbidity: cardiovascular, neurologic, hematologic, pulmonary, renal, metabolic, rheumatologic, or malignancy, U/S: focal lesion w/i 1 mo of tx, WBC <2000, plts >50,000, TSH el, AFP above nl, IFN	To clarify in a large, double-blind randomized placebo-controlled trial the efficacy, safety and cost-effectiveness of amantadine and IFN alpha for tx of naïve pts w/ CHC
Mangia, 2001a	Italy	200	Detectable HCV in serum, initial liver bx, el ALT for 6 mos	EtOH, current IDU, depresson, other psychiatric illness, HBV+, decompensated liver disease, plts < 100,000, HIV+, DM, significant medical illness, WBC <3,500, immune suppression	To assess the efficacy and safety of IFN+amantadine compared to IFN monotherapy in naïve pts w/ CHC

Evidence Table 9: Overall summary of randomized controlled trials of current treatment options for chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Tabone, 2001	Italy	180	Detectable HCV in serum, HCV+, CHC w/o cirrhosis on initial liver bx, ALT 1.5x UL of nl in 3 lab draws	Chronic EtOH, active IDU, other illicit drug use, depression, other psyciatric illness, HBV+, HIV+, pregnancy, neurologic comorbidity, hematologic comorbidity, cardiovascular comorbidity, autoimmune disease, metabolic disease, renal disase, WBC <2,500, plts <100,00	To assess the efficacy and tolerability of IFN + amantadine in the tx of CHC
Zeuzem, 2000	Germany	120	HCV+, age >18 and <70 y, presence of fibrosis: CHC on liver bx, initial liver bx w/i 1 y, el ALT for >=6 mo before tx, WBC >2500, plts >70,000	EtOH >50 g/d of ethanol, IDU w/i previous year, GI comorbidity, immune suppression: organ transplant or autoimmune disorder, psychiatric illness, HIV+, HBV+, cardiovascular comorbidity, pregnancy, neurologic comorbidity, malignancy comorbidity, anaphylactic allergy to IFN, other comorbidities: liver disease from another cause OR renal disease OR rheumatologic disease, other viral infections: systemic bacterial or fungal infection, lactation, IFN + RBV, IFN monotherapy, amantadine, hematologic comorbidity	To compare the efficacy, safety, and health related quality of life of IFN alpha alone or in combination w/ amantadine for tx of CHC.

Evidence Table 10: Characteristics of patients in randomized controlled trials of current treatment options for chronic hepatitis C

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Studies of current treatment options in naive patients									
Pegylated interferon/ribavirin combination therapy									
Glue, 2000	RCT								
		IFN: peg-IFN2b, .35 ug/kg, qw, 24 wks RBV: 600-800 mg qd, 24 wks	12						
		IFN: peg-IFN2b, .7 ug/kg, qw, 24 wks RBV: 600-1200 mg qd, 24 wks	18						
		IFN: peg-IFN2b, 1.4 ug/kg, qw, 24 wks RBV: 600-1200 mg qd, 24 wks	18						
		IFN: peg-IFN2b, .35 ug/kg, qw, 24 wks	6						
		IFN: peg-IFN2b, .7 ug/kg, qw, 24 wks	9						
		IFN: peg-IFN2b, 1.4 ug/kg, qw, 24 wks	9						

Evidence Table 10: Characteristics of patients in randomized controlled trials of current treatment options for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Manns, 2001	RCT									
		IFN: peg-IFN2b, 1.5 mg/kg, qw, 48 wks	511	43 62.8		Kno	7.9	S3 29		
		RBV: 800 mg qd, 48 wks							1 2, 3 4,5,6	68.10 28.96 3.13
		IFN (initial): peg-IFN2b, 1.5 mg/kg, qw, 4 wks	514	44 66.1		Kno	7.9	S3 30		
		IFN (maintenance): peg-IFN2b, 0.5 mg/kg, qw, 44 wks RBV: 1000-1200 mg qd, 48 wks							1 2, 3 4,5,6	67.90 29.96 2.33
		IFN: alpha-2b, 3 mu tiw, 48 wks RBV: 1000-1200 mg qd, 48 wks	505	43 66.5		Kno	7.8	S3 28		
									1 2, 3 4,5,6	67.92 28.91 3.17

Evidence Table 10: Characteristics of patients in randomized controlled trials of current treatment options for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Pegylated interferon monotherapy										
Heathcote, 2000	RCT									
		IFN: alpha-2a, 3 mu tiw, 48 wks	88	46.9 70.5 C: 87.5, B: 5.68, A: 3.40, O: 3.40	76	HAI	12.8		104.1 1a 1b 2 3 4 not specified	 31.82 21.59 13.64 30.68 0.00 2.27
		IFN: peg-IFN2a, 90 mg, qw, 48 wks	96	47.2 74.0 C: 90.6, B: 1.04, A: 2.08, O: 6.25	79	HAI	12.7		104.1 1a 1b 2 3 4 not specified	 28.13 32.29 7.29 27.08 2.08 3.13
		IFN: peg-IFN2a, 180 mg, qw, 48 wks	87	47.1 72.4 C: 86.2, B: 5.74, A: 2.29, O: 5.74	79	HAI	13.4		123.3 1a 1b 2 3 4 not specified	 37.93 17.24 16.09 22.99 1.15 4.60

Evidence Table 10: Characteristics of patients in randomized controlled trials of current treatment options for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Lindsay, 2001	RCT									
		IFN: peg-IFN2b, 0.5 ng/kg, qw, 48	315	43.1	3	HAI	A 6.8			
		wks		58.7		HAI	S 1.4		18.5	
				C: 90.1					1	67.30
									2	11.11
									3	16.83
									other	4.76
		IFN: peg-IFN2b, 1.0 ng/kg, qw, 48	297	43.7	3	HAI	A 6.9			
		wks		63.3		HAI	S 1.4		20.4	
				C: 90.9					1	67.00
									2	10.10
									3	17.85
									other	5.05
		IFN: peg-IFN2b, 1.5 ng/kg, qw, 48	304	42.9	4	HAI	A 6.7			
		wks		62.5		HAI	S 1.3		19.2	
				C: 94.0					1	73.36
									2	10.53
									3	13.49
									other	2.63
		IFN: alpha-2b, 3 mu tiw, 48 wks	303	42.6	4	HAI	A 7.1			
				68.3		HAI	S 1.4		18.6	
				C: 89.1					1	71.62
									2	9.24
									3	17.49
									other	1.65

Evidence Table 10: Characteristics of patients in randomized controlled trials of current treatment options for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Reddy, 2001	RCT									
		IFN: alpha-2a, 3 mu tiw, 48 wks	33	41.8 78.8 C: 78.7, B; 12.1, A: 3.03, O: 6.06		HAI	10.8		1 non-1 unknown	81.82 15.15 3.03
		IFN: peg-IFN2a, 45 µg, qw, 48 wks	20	41.9 65.0 C: 90, B: 10, A: 0, O: 0		HAI	11.7		1 non-1 unknown	75.00 25.00 0.00
		IFN: peg-IFN2a, 90 µg, qw, 48 wks	20	43.1 70.0 C: 95, B: 0, A: 5, O: 0		HAI	10.6		1 non-1 unknown	70.00 30.00 0.00
		IFN: peg-IFN2a, 180 µg, qw, 48 wks	45	42 82.2 C: 88.8, B: 8.88, A: 0, O: 2.22		HAI	10.7		1 non-1 unknown	77.78 22.22 0.00
		IFN: peg-IFN2a, 270 µg, qw, 48 wks	41	41.6 85.4 C: 87.8, B: 9.75, A: 0, O: 2.43		HAI	10		1 non-1 unknown	63.41 29.27 7.32

Evidence Table 10: Characteristics of patients in randomized controlled trials of current treatment options for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Zeuzem, 2000a	RCT									
		IFN (initial): peg-IFN2a, 180 µg, qw, 48 wks	267	40.5 66.7 C: 86.1, B: 2.24, A: 8.98, O: 2.62		HAI	8.6	A1 65.0 A2 30.0 A3 3.3 S1 88.4 S3 7.1	1a 1b 1b 2 3 4 not specified	29.96 32.96 32.96 9.36 25.47 1.87 0.37
		IFN (initial): alpha-2a, 6 mu tiw, 12 wks IFN (maintenance): alpha-2a, 3 mu, tiw, 36 wks	264	41 66.7 C: 84.8, B; 1.89, A: 9.84, O: 3.40		HAI	3.4	A1 60.0 A2 40.0 A3 0.0 S1 84.8 S1 84.8 S3 4.9	1a 1b 1b 2 3 4 not specified	31.44 29.55 29.55 12.88 23.86 1.14 1.14

Evidence Table 10: Characteristics of patients in randomized controlled trials of current treatment options for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Interferon/ribavirin combination therapy										
Berg, 2000	RCT									
		IFN: alpha-2a, 6 mu tiw, 12 wks	93	42		HAI	S 1.5		70	
		RBV: 7 mg/kg, bid, 12 wks		57.0					15.2	
									1a	24.73
									1a/b	1.08
									1b	47.31
									2a	2.15
									2a/c	1.08
									2b	3.23
									3a	18.28
									4	2.15
		IFN: alpha-2a, 6 mu tiw, 12 wks	92	42		HAI	S 1.5		82	
				55.4					14.7	
									1a	20.65
									1a/b	1.09
									1b	54.35
									2a	2.17
									2a/c	1.09
									2b	1.09
									3a	17.39
									4	2.17
el-Zayadi, 1999										
		IFN: alpha-2b, 3 mu tiw, 24 wks	26	42		HAI	S 5.0		116	
		RBV: 1000 mg qd, 24 wks		100.0		HAI	T 9.4			
		IFN: alpha-2b, 3 mu tiw, 24 wks	26	39		HAI	S 5.0		123	

Evidence Table 10: Characteristics of patients in randomized controlled trials of current treatment options for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
				100.0		HAI	T 9.7			
Ferenci, 2001	RCT									
		IFN (initial 1): alpha-2b, 10 mu, qd, 2 wks	130	39.4 73.8					68	
		IFN (initial 2): alpha-2b, 10 mu, qed, 12 wks IFN (maintenance): alpha-2b, 5 mu, qed, 24 wks RBV: 1000-1200 mg qd, 38 wks							1a 1b 2 3a 4	22.31 50.77 1.54 23.85 1.54
		IFN (initial): alpha-2b, 5 mu, qd, 14 wks	124	42.8 70.2					66	
		IFN (maintenance): alpha-2b, 5 mu, qed, 24 wks RBV: 1000-1200 mg qd, 38 wks							1a 1b 2 3a 4	14.52 53.23 3.23 23.39 5.65
		IFN: alpha-2b, 5 mu, qed, 38 wks RBV: 1000-1200 mg qd, 38 wks	119	39.9 66.4					79	
									1a 1b 2 3a 4	18.49 43.70 4.20 26.89 6.72

Evidence Table 10: Characteristics of patients in randomized controlled trials of current treatment options for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Mangia, 2001	RCT									
		IFN: alpha-2b, 5 mu tiw, 12 mos	96	49		Sch		A>1 19.8		
				71.9		Sch		A0,1 80.2	8	
						Sch		S1,2 93.8	1b	53.13
						Sch		S3 6.2	2a	33.33
									3	9.38
									other	4.17
		IFN: alpha-2b, 5 mu tiw, 12 mos	96	46		Sch		A>1 26.0		
		RBV: 1000-1200 mg qd, 12 mos		61.5		Sch		A0,1 74.0	7	
						Sch		S1,2 89.6	1b	41.67
						Sch		S3 10.4	2a	35.42
									3	17.71
									other	5.21

Evidence Table 10: Characteristics of patients in randomized controlled trials of current treatment options for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Studies of interferon/amantadine combination therapy, with or without ribavirin									
Caronia, 2001	RCT								
		IFN (Pilot study): alpha-2a, 4.5 mu, tiw, 48 wks	18	42	0				1 55.56
		Amantadine (Pilot study): 200 mg, qd, 48 wks IFN (Pilot study): alpha-2a, 4.5 mu, tiw, 48 wks	18	40	0				1 50.00
		IFN (Multicenter): alpha-2a, 4.5 mu, tiw, 48 wks	71	42	10				1 28.17
		Amantadine (Multicenter): 200 mg, qd, 48 wks IFN (Multicenter): alpha-2a, 4.5 mu, tiw, 48 wks	72	43	8				1 26.39
		IFN (Combined): alpha-2a, 4.5 mu tiw, 48 wks		89	42				1 33.71
		Amantadine (Combined): 200 mg, qd, 48 wks IFN (Combined): alpha-2a, 4.5 mu tiw,	90	41	7				1 31.11

Evidence Table 10: Characteristics of patients in randomized controlled trials of current treatment options for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
		48 wks								
Helbling, 2002	RCT									
		Amantadine: 100 mg, bid, 52 wks	125	39				A1 47.2	101	
		IFN (initial): alpha-2a, 6 mu tiw, 20		65.6				A2 34.4		
		wks						A3 14.4	1	52.80
		IFN (maintenance): alpha-2a, 3 mu,						S1-S2 26.4	2	9.60
		tiw, 32 wks						S3 64.8	3	27.20
								S4 4.8	4	4.00
									6	0.80
		Amantadine (initial): Placebo	121	38				A1 52.1	111	
		IFN (initial): alpha-2a, 6 mu tiw, 20		72.7				A2 40.5		
		wks						A3 9.9	1	42.98
		IFN (maintenance): alpha-2a, 3 mu,						S1-S2 24.0	2	9.09
		tiw, 32 wks						S3 75.2	3	41.32
								S4 3.3	4	4.96
Mangia, 2001a	RCT									
		IFN (initial): alpha-2a, 6 mu tiw, 12	101	48		HAI		S0-3 48.5		
		mos		70.3		HAI		S1-3 51.5	7.1	
									1	59.41
									2a	25.74
									3	10.89
									4	3.96
		Amantadine (initial): 100 mg, bid,	99	46		HAI		S0-3 36.4		
		12 mos		61.6		HAI		S1-3 63.6	7.1	
		IFN (initial): alpha-2a, 6 mu tiw, 12							1	52.53
		mos							2a	34.34
									3	7.07

Evidence Table 10: Characteristics of patients in randomized controlled trials of current treatment options for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
									4	6.06
Tabone, 2001	RCT									
		IFN (initial): alpha-2a, 6 mu, qed, 6 mos	90	44 66.7					114	
		IFN (maintenance): alpha-2a, 3 mu, qed, 6 mos							1/4 2/3	58.89 41.11
		Amantadine: 100 mg, bid, 12 mos	90	42 62.2					103	
		IFN (initial): alpha-2a, 6 mu, qed, 6 mos							1/4	52.22
		IFN (maintenance): alpha-2a, 3 mu, qed, 6 mos							2/3	47.78
Zeuzem, 2000	RCT									
		Amantadine: 100 mg, Twice a day, 48 wks	60	42.1 61.7						
		IFN (initial): alpha-2a, 6 mu tiw, 24 wks							1 2	70.00 5.00
		IFN (maintenance): alpha-2a, 3 mu, tiw, 24 wks							3 4	21.67 1.67
		IFN (initial): alpha-2a, 6 mu tiw, 24 wks	60	41.6 60.0						
		IFN (maintenance): alpha-2a, 3 mu, tiw, 24 wks							1 2 3	66.67 5.00 25.00

Evidence Table 10: Characteristics of patients in randomized controlled trials of current treatment options for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
									4 1.67

Evidence Table 11: Methodologic quality of randomized controlled trials of current treatment options for chronic hepatitis C

Author, Year	Representativeness[a]	Bias[b]	Description[c]	Outcomes[d]	Statistics[e]	Conflict[f]	Total[g]
Pegylated interferon/ribavirin combination therapy							
Glue, 2000	63	33	100	85	0	0	56
Manns, 2001	100	83	75	80	88	50	85
Pegylated interferon monotherapy							
Heathcote, 2000	100	67	50	70	83	50	74
Lindsay, 2001	88	83	100	85	100	50	91
Reddy, 2001	63	75	50	70	83	50	68
Zeuzem, 2000a	100	50	75	70	100	100	79
Interferon/ribavirin combination therapy							
Berg, 2000	88	67	75	85	83	0	80
el-Zayadi, 1999	38	50	50	85	33	0	51
Ferenci, 2001	88	33	50	70	75	0	63
Mangia, 2001	75	83	50	60	100	0	74

Evidence Table 11: Methodologic quality of randomized controlled trials of current treatment options for chronic hepatitis C

Author, Year	Representativeness[a]	Bias[b]	Description[c]	Outcomes[d]	Statistics[e]	Conflict[f]	Total[g]
Studies of interferon/amantadine combination therapy, with or without ribavirin							
Caronia, 2001	88	67	50	85	17	50	61
Helbling, 2002	100	100	75	75	100	50	90
Mangia, 2001a	88	67	75	85	100	50	83
Tabone, 2001	88	67	75	85	83	100	80
Zeuzem, 2000	100	100	100	60	100	50	92

Evidence Table 11: Methodologic quality of randomized controlled trials of current treatment options for chronic hepatitis C (continued)

Author, Year	Representativeness[a]	Bias[b]	Description[c]	Outcomes[d]	Statistics[e]	Conflict[f]	Total[g]

[a] ***Representativeness***: The total maximum for this section was 8 points. This included setting and population described and start and end date specified (2 points); detailed description of inclusion and exclusion criteria or statement that all potential trainees enrolled (2 points); information about excluded or not-participating patients (2 points); and description of key patient characteristics at enrollment (2 points).

[b] ***Bias and Confounding***: The total maximum score was 6 points. This included whether assignment of patients to study groups was randomized (2 points); whether groups had any differences in key patient characteristics (2 points); and whether clinicians, patients, and outcome assessors were blinded (2 points).

[c] ***Description of Therapy/Management***: The total maximum score was 4 points. This included sufficiently detailed description of the treatment regimen (2 points); and description of other treatments or tests given to subjects (2 points).

[d] ***Outcomes and Followup:*** The total maximum score was 10 points. This included description of complications, side effects and adverse reactions (2 points); sufficient description of criteria for determining outcomes (2 points); reporting on the numbers and reasons for withdrawals from the study or losses to followup (2 points); proportion of patients who withdrew from the study or were lost to followup (2 points); and sufficiency of the planned length of followup (2 points).

[e] ***Statistical Quality and Interpretation***: The total maximum score was 8 points. This included whether magnitude of difference between groups and an index variability was stated (2 points); whether analyses and statistical tests were clearly identified (2 points); whether adjustment of potential confounders were multi-variate or stratified analyses and coding of confounders (2 points); and appropriate handling of crossovers and/or dropouts in the analysis (2 points).

[f] ***Conflict of Interest***: The total maximum score was 2 points. This included whether the study reported the source of funding and the role played by the funding entity.

[g] ***Total Score*** is the mean of the percentage scores from the categories, Representativeness, Bias and Confounding, Description of Therapy/Management, Outcomes and Followup, and Statistical Quality and Interpretation.

Evidence Table 12: Results of randomized controlled trials of current treatment options for chronic hepatitis C

Author, Year Follow-up	Study Groups	Biochemical Response ETR %	Biochemical Response SR %	Viral Response ETR %	Viral Response SR %	Histological Response %	Adverse Events Disc/Withdr %	Adverse Events Dose Red %
Studies of current treatment options in naïve patients								
Pegylated interferon/ribavirin combination therapy								
Glue, 2000	A IFN: peg-IFN2b, 0.35 ug/kg, qiw, 24 wks			58[a]	17[a]			
6 mos.	RBV: 600-800 mg qd, 24 wks							
	B IFN: peg-IFN2b, 0.7 ug/kg, qiw, 24 wks			69[a]	53[a]			
	RBV: 600-1200 mg qd, 24 wks							
	C IFN: peg-IFN2b, 1.4 ug/kg, qiw, 24 wks			81[a]	60[a]			
	RBV: 600-1200 mg qd, 24 wks							
	D IFN: peg-IFN2b, 0.35 ug/kg, qiw, 24 wks			50[a]	0[a]			
	E IFN: peg-IFN2b, 0.7 ug/kg, qiw, 24 wks			63[a]	44[a]			
	F IFN: peg-IFN2b, 1.4 ug/kg, qiw, 24 wks			50[a]	42[a]			
Manns, 2001	A IFN: peg-IFN2b, 1.5 mg/kg, qiw, 48 wks	65	54	65*	54*	14	2.7	8.3
6 mos.	RBV: 800 mg qd, 48 wks							
	B IFN (initial): peg-IFN2b, 1.5 mg/kg, qiw, 4 wks	63	48	56	47	13	2.5	7.0
	IFN (maintenance): peg-IFN2b, 0.5 mg/kg, qiw, 44 wks							
	RBV: 1000-1200 mg qd, 48 wks							
	C IFN: alpha-2b, 3 mu tiw, 48 wks	69	47	54*	47*	13	2.6	6.7

Evidence Table 12: Results of randomized controlled trials of current treatment options for chronic hepatitis C (continued)

Author, Year Follow-up	Study Groups	Biochemical Response ETR %	Biochemical Response SR %	Viral Response ETR %	Viral Response SR %	Histological Response %	Adverse Events Disc/Withdr %	Adverse Events Dose Red %
	RBV: 1000-1200 mg qd, 48 wks							
	Pegylated interferon monotherapy							
Heathcote, 2000	A IFN: alpha-2a, 3 mu tiw, 48 wks	22*[†]	15*	14*[†]	8.0*	31*[a]	8	14
6 mos.	B IFN: peg-IFN2a, 90 µg, qiw, 48 wks	35*	20	42*	15	44[a]	7	9
	C IFN: peg-IFN2a, 180 µg, qiw, 48 wks	39[†]	34*	44*[†]	30*	54*[a]	13	10
Lindsay, 2001	A IFN: peg-IFN2b, 0.5 ng/kg, qiw, 48 wks	25[c]	17[§c]	33[§]	18[§]	20	2.9	2.9
6 mos.	B IFN: peg-IFN2b, 1.0 ng/kg, qiw, 48 wks	31[c]	24[§c]	41[§]	25[§]	19	3.7	4.7
	C IFN: peg-IFN2b, 1.5 ng/kg, qiw, 48 wks	26[c]	18[§c]	39[§]	23[§]	15	2.3	4.9
	D IFN: alpha-2b, 3 mu tiw, 48 wks	20[c]	12[Rc]	24[R]	12[R]	13	2.0	2.0
Reddy, 2001	A IFN: alpha-2a, 3 mu tiw, 48 wks	15	9.0*[†]	12*[†]	3.0*[†]	57[a]	9	
6 mos.	B IFN: peg-IFN2a, 45 ug, qiw, 48 wks	20	10	30	10	47[a]	10	
	C IFN: peg-IFN2a, 90 ug, qiw, 48 wks	20	25	45	30	59[a]	0	
	D IFN: peg-IFN2a, 180 ug, qiw, 48 wks	38	38*	60	36*	63[a]	22	
	E IFN: peg-IFN2a, 270 ug, qiw, 48 wks	27	27[†]	56[†]	29[†]	66[a]	20	

Evidence Table 12: Results of randomized controlled trials of current treatment options for chronic hepatitis C (continued)

Author, Year Follow-up	Study Groups	Biochemical Response ETR %	Biochemical Response SR %	Viral Response ETR %	Viral Response SR %	Histological Response %	Adverse Events Disc/Withdr %	Adverse Events Dose Red %
Zeuzem, 2000a	A IFN (initial): peg-IFN2a, 180 mcg, qiw, 48 wks	46	45*	69*	39*	63[a]	7	20
6 mos.	B IFN (initial): alpha-2a, 6 mu tiw, 12 wks	39	25	28*	19*	55[a]	10	18
	IFN (maintenance): alpha-2a, 3 mu tiw, 36 wks							
Interferon/ribavirin combination therapy								
Berg, 2000	A IFN: alpha-2a, 6 mu tiw, 12 wks			37*	26		2	24*
6 mos.	RBV: 7 mg/kg, bid, 12 wks							
	B IFN: alpha-2a, 6 mu tiw, 12 wks			29*	17		3	7*
el-Zayadi, 1999	A IFN: alpha-2b, 3 mu tiw, 24 wks	62*	38*	35*	19	56[a]	3.8	35
6 mos.	RBV: 1000 mg qd, 24 wks							
	B IFN: alpha-2b, 3 mu tiw, 24 wks	69*	15*	11*	8	46[a]	3.8	0

Evidence Table 12: Results of randomized controlled trials of current treatment options for chronic hepatitis C (continued)

Author, Year Follow-up	Study Groups	Biochemical Response ETR %	Biochemical Response SR %	Viral Response ETR %	Viral Response SR %	Histological Response %	Adverse Events Disc/Withdr %	Adverse Events Dose Red %
Ferenci, 2001	A IFN (initial 1): alpha-2b, 10 mu, qd, 2 wks	54	50.8	55.3	48.5			7
6 mos.	IFN (initial 2): alpha-2b, 10 mu, every other day, 12 wks							
	IFN (maintenance): alpha-2b, 5 mu, every other day, 24 wks							
	RBV: 1000-1200 mg qd, 38 wks							
	B IFN (initial): alpha-2b, 5 mu, qd, 14 wks	54	41.1	48.4	40.3			10
	IFN (maintenance): alpha-2b, 5 mu, every other day, 24 wks							
	RBV: 1000-1200 mg qd, 38 wks							
	C IFN: alpha-2b, 5 mu, every other day, 38 wks	56	41.1	50.4	40.3			9
	RBV: 1000-1200 mg qd, 38 wks							
Mangia, 2001	A IFN: alpha-2b, 5 mu tiw, 12 mos	40*	23*	34*	21*		8.3	
6 mos.	B IFN: alpha-2b, 5 mu tiw, 12 mos	69*	57*	59*	54*		10.4	
	RBV: 1000-1200 mg qd, 12 mos							

Evidence Table 12: Results of randomized controlled trials of current treatment options for chronic hepatitis C (continued)

Author, Year Follow-up	Study Groups	Biochemical Response ETR %	Biochemical Response SR %	Viral Response ETR %	Viral Response SR %	Histological Response %	Adverse Events Disc/Withdr %	Adverse Events Dose Red %
Studies of interferon combination therapy with amantadine, with or without ribavirin								
	Studies of naïve patients							
Caronia, 2001	A IFN (Pilot study): alpha-2a, 4.5 mu tiw, 48 wks			33[c]	29[c]			
	B Amantadine (Pilot study): 200 mg qd, 48 wks IFN (Pilot study): alpha-2a, 4.5 mu tiw, 48 wks			54[c]	50[c]			
	C IFN (Multicenter): alpha-2a, 4.5 mu tiw, 48 wks			17[c]	15[c]			
	D Amantadine (Multicenter): 200 mg qd, 48 wks IFN (Multicenter): alpha-2a, 4.5 mu tiw, 48 wks			25[c]	18[c]			
	E IFN (Combined): alpha-2a, 4.5 mu tiw, 48 wks			19[c]	17[c]			
	F Amantadine (Combined): 200 mg qd, 48 wks IFN (Combined): alpha-2a, 4.5 mu tiw, 48 wks			31[c]	23[c]			
Helbling, 2002	A Amantadine: 100 mg, bid, 52 weeks	28.9	25.6	30.6	20.7		11.2	24
6 mos.	IFN (initial): alpha-2a, 6 mu tiw, 20 weeks IFN (maintenance): alpha-2a, 3 mu tiw, 32 weeks							
	B IFN (initial): alpha-2a, 6 mu tiw, 20 weeks IFN (maintenance): alpha-2a, 3 mu tiw, 32 weeks	29.6	20.8	28.8	13.6		8.8	18.4

Evidence Table 12: Results of randomized controlled trials of current treatment options for chronic hepatitis C (continued)

Author, Year Follow-up	Study Groups	Biochemical Response ETR %	Biochemical Response SR %	Viral Response ETR %	Viral Response SR %	Histological Response %	Adverse Events Disc/Withdr %	Adverse Events Dose Red %
Mangia, 2001a	A IFN (initial): alpha-2a, 6 mu tiw, 12 mos	34.6	18.8*	28.7*	16.8*		8.0	
	B IFN (initial): alpha-2a, 6 mu tiw, 12 mos	46.5	36.4*	45.5*	29.3*		7.1	
	Amantadine (initial): 100 mg, bid, 12 mos							
Tabone, 2001	A IFN (initial): alpha-2a, 6 mu, qed, 6 mos			37[c]	17[c]			
	IFN (maintenance): alpha-2a, 3 mu, qed, 6 mos							
	B Amantadine: 100 mg, bid, 12 mos			47[c]	24[c]			
	IFN (initial): alpha-2a, 6 mu, qed, 6 mos							
	IFN (maintenance): alpha-2a, 3 mu, qed, 6 mos							
Zeuzem, 2000	A Amantadine: 100 mg, bid, 48 wks	37	20	33	17		7	2
6 mos.	IFN (initial): alpha-2a, 6 mu tiw, 24 wks							
	IFN (maintenance): alpha-2a, 3 mu tiw, 24 wks							
	B IFN (initial): alpha-2a, 6 mu tiw, 24 wks	35	25	33	37		3	8
	IFN (maintenance): alpha-2a, 3 mu tiw, 24 wks							

Evidence Table 12: Results of randomized controlled trials of current treatment options for chronic hepatitis C (continued)

[a] Percentage based on a denominator different from the group N
[c] Complete response, defined as combined virological and biochemical response
* $p < 0.05$ for the pairwise comparison between two groups marked with this symbol
† $p < 0.05$ for the pairwise comparison between two groups marked with this symbol

[§] $p < 0.05$ for the comparison groups marked with this symbol and the group marked [R]
[R] Reference group for comparison

Evidence Table 13: Overall summary of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Studies of current treatment options in nonresponders/relapsers to prior therapy					
Studies of nonresponders					
Barbaro, 1999	Italy	200	IFN monotherapy >3 and/or <6 mo, IFN alpha-2b prior to study (not <3 mo and not >6 mo) and were nonresponders (no biochemical and viral response at end of tx), age <18 y, nonresponse to previous therapy: defined as ALT/HCV response from previous tx, detectable HCV in serum, HCV+, EtOHism	Hepatitis delta infection, decompensated liver disease, HBV+, DM, immune suppression, HIV+, other viral infections: EBV, CMV, and mycobacterial, cardiomyopthies, neurologic comorbidity, malignancy comorbidity, pregnancy, Wilson's disease, PT >5 sec longer than nl, Cr 2x nl, Bili >3x nl, Hgb <10 g/dL, neutrophil <1000, hypertension, use of hepatotoxic drugs in past 6 mo, malnutrition, hemochromatosis, alpha-1-antitrypsin, autoimmune hepatitis, neoplastic disease, metabolic disorder, other comorbidity: malnutrition, WBC <2500	Randomized controlled trial assessing clinical efficacy of IV recombinant IFN-beta compared w/ IFN-alpha-2b + RBV in pts w/ CHC unresponsive to IFN-alpha-2b at standard doses.

Evidence Table 13: Overall summary of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Bresci, 2000	Italy	100	ALT 2x UL of nl, 3 times in last 6 mo, IFN monotherapy: IFN alpha-2b (3 mu tiw, for 4 mo) not w/i 6 mo of the study, detectable HCV in serum	Any antiviral agents w/i 6 mo of study, concomitant liver disease, thyroid dysfunction, pre-existing anemia, metabolic disorders (hemochromatosis, Wilson's disease, alph-1-antitrypsin deficiency), drug-induced liver disease, HIV+, immune suppression, presence of cirrhosis, hepatitis delta infection, HBV+, EtOH >40 g/d	To test the effectiveness of high dose IFN plus RBV vs. high dose IFN alone in previous IFN nonresponders.
Di Bisceglie, 2001	United States	124	Initial liver bx w/i 12 mos of rx, IFN monotherapy >=36 mu, detectable HCV in serum, positive HCV antibodies		To see if nonresponders to IFN alone would respond to a combination of IFN/RBV for either 24 or 48 wks
Ferenci, 2001a	Austria	157	HCV+, detectable HCV in serum, ALT 2x UL of nl, IFN monotherapy 5 mu tiw for 3 mo	Autoimmune thyroiditis, HBV+, depression, HIV+, EtOH >50 g/d, HBV surface antibodies, plts <100,000, uncontrolled DM, other liver diseases, WBC <3000, Hgb <12, cardiovascular or coronary artery disease	To study the efficacy of high-dose IFN alpha w/or w/o RBV in IFN nonresponders.

Evidence Table 13: Overall summary of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Puoti, 2001	Italy	63	Detectable HCV in serum, age 18-60 yrs, ALT 1.5x nl, AFP, U/S, initial liver bx, IFN monotherapy, nonresponse to previous therapy	Depression, other psychiatric illness, pregnancy, adverse reaction to previous therapy, HIV+, HBV+, metabolic disorder, IDU, alcohol abuse, decompensated liver disease, cardiovascular comorbidity, other comorbidities: autoimmune, ascites, encephalopathy, uncontrolled diabetes, uncontrolled diabetes, unable to use OCPS, and neurologic, malignancy comorbidities: hemolytic anemia and thyroid disease, plts <100,000, WBC <3000, Hgb <12 for females and <13 for males	To assess efficacy of varying doses of IFN and RBV in previous nonresponders. Doses of IFN included 3 mu tiw, 5 mu tiw and 5 mu qd.

Evidence Table 13: Overall summary of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Saracco, 2001	Europe	594	HCV+, detectable HCV in serum, initial liver bx w/i prior 2 yrs, nonresponse to previous therapy, IFN monotherapy, age >18 and <65	Concomitant significant medical illness, IDU, HBV+, decompensated liver disease, relapse after previous therapy: >=1 course of IFN, pregnancy, depression, HIV+, cardiovascular comorbidity: ischemic cardiovascular disease, neurologic comorbidity: seizures, hematologic comorbidity: hemolytic anemia or hemophilia, abnl uric acid, obesity-induced liver disease, nonresponse to previous therapy: IFN and ribavirin combination therapy, other comorbidities: Wilson's disease, hemochromatosis, or autoimmune hepatitis, IFN + RBV, WBC <3000, neutrophil <500, Hgb <10 g/dl, plts <70,000, GI comorbidity, alpha-1antitrypsin deficiency	To assess if higher than standard doses of IFN given w/ RBV for prolonged periods of administration improved the rate of sustained response in previous IFN-alone nonresponders. The study compares the efficacy and safety of 3 mu and five mu of IFN plus 1000 mg daily RBV for either 6 or 12 mos
Shiffman, 2000a	United States	140	ALT, IFN monotherapy, pregnancy, nonresponse to previous therapy: IFN monotherapy	IFN monotherapy: max dose 6 mu IFN alpha-2a, OR max dose 9 mg IFN alphacon, OR max dose 3 mu IFN alpha-2b, any other type of liver disease, IDU, EtOH	To determine whether combination IFN/RBV was effective in tx of IFN monotherapy nonresponders. To determine subgroups who did not respond.

Evidence Table 13: Overall summary of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Tripi, 2000	Italy	72	Nonresponse to previous therapy: nonresponse to >= 2 courses of IFN (6 mu tiw, for 4 mo), detectable HCV in serum, ALT 2x UL of nl range, initial liver bx: CHC, IFN monotherapy 6 mo prior to study	HBV+, IDU, other illicit drug use, EtOH >50 g/d, Epstein-Barr virus, cytomegalovirus, immune suppression	To investigate the efficacy of IFN alone or IFN in combination w/ RBV in the retx of HCV+ nonresponders to IFN monotherapy
Studies of relapsers					
Chapman, 2001	New Zealand	32	ALT 1.5x nl, initial liver bx prior to initial tx, IFN monotherapy: 3 mu tiw for 6 mo ; relapsed w/i 6 mo of tx, contraception, detectable HCV in serum	Lactating, cardiovascular comorbidity, pregnancy	To compare the effect of high dose, long-term IFN therapy w/ shorter duration and lower dose IFN and RBV in IFN relapsers.
Di Marco, 2000	Italy	50	HCV+, initial liver bx, relapse after previous therapy, interferon monotherapy, age 18-65 yrs	Hemoglobinopathy, detectable HCV in serum, decompensated liver disease, HCC, immune suppression HIV+, HBV+, autoimmune disease, any antiviral therapy, uncontrolled diabetes, Hgb <12 for females and <13 for males, WBC <3000, plts <100,000, IFN, hematologic comorbidity: anemia, neutropenia, thrombocytopenia	To compare SVR in 6 vs. 12 mos of IFN alpha 2b 6 mu tiw and RBV 1-1.2 g/day in IFN relapsers. To examine the tolerability of higher doses of IFN + RBV. To identify predictors of response. To assess HCV viral dynamics.

Evidence Table 13: Overall summary of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Enriquez, 2000	Spain	120	HCV+, detectable HCV in serum, 6-mo duration of HCV+, el ALT for 6 mo, initial liver bx, relapse after previous therapy, nonresponse to previous therapy, 18-55 yrs	Cardiovascular comorbidity, IDU w/i the last year, presence of cirrhosis, decompensated liver disease, immune suppression, depression, HIV+, PT <50%, neurologic or GI comorbidity, renal insufficiency, poorly controlled DM, WBC <3000, neutrophil <1500, Hgb <12 for females and <13 for males, plts <100,000, other psychiatric illness	To see whether retx w/ IFN plus RBV for 24 or 48 wks would be beneficial in pts who relapsed or did not respond to previous IFN monotherapy
Studies of nonresponders and relapsers					
Bonkovsky, 2001	United States		Age >17, HCV+, detectable HCV in serum, prior tx w/ IFN w/ nonresponse or relapse, ALT 1.2x UL of nl, WBC >2,500, neutrophils >1,500, Hgb >12, plts >75,000	Decompensated liver disease, pregnancy, breastfeeding, or women of childbearing age refusing to use contraception, Immune suppression, depression or other psychiatric illness, cardiovascular comorbidity, alpha-1-antitrypsin deficiency, EtOH/non-EtOH steatohepatosis, hemochromatosis, Wilson's disease, severe renal disease, pulmonary disease, creatinine >2.0, transplant recipient, steroids/immunosuppression	To determine whether 600 mg RBV/day would prove as efficacious as 1000-1200 mg/day when combined w/ IFN (3 mu, tiw) for therapy of pts who relapsed or failed to respond to standard IFN

Evidence Table 13: Overall summary of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Cavalletto, 2000	Italy	100	Nonresponse to previous therapy, HCV+, detectable HCV in serum, presence of fibrosis: CHC, presence of cirrhosis: CHC, age 18-60 yrs, relapse after previous therapy, peg-IFN alpha monotherapy >= 6 mo, initial liver bx w/i 12 mo of enrollment, initiation of therapy 12-24 mo after last tx w/alpha-IFN	Adverse reaction to previous therapy, allergy to IFN: intolerant to 1st course, pregnancy or "rejects contraception," HIV+, hematologic comorbidity: hemolytic disorder, HBV+, "recent" history of IDU, "recent" history of EtOH, decompensated liver disease: bx <1 yrs	To assess the effect of adding RBV to alpha-IFN for the retx of alpha-IFN relapsers and of previous alpha-IFN nonresponders.
Min, 2001	United States	154	IFN monotherapy for >3 mos, abnl ALT, initial liver bx showing CHC and/or cirrhosis, detectable HCV in serum	Women unwilling or unable to use contraceptives, IFN w/i 3 mos, IFN + RBV w/i 3 mos, immunomodulating or antiviral drugs w/i 3 mos, seizure disorder, other liver disease, cardiovascular comorbidity, severe psychiatric disorder, immune suppression, decompensated liver disease	To evaluate the efficacy of high dose IFN in combination w/ RBV in treating pts w/ CHC resistant to IFN monotherapy

Evidence Table 13: Overall summary of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Studies of interferon/amantadine combination therapy, with or without ribavirin					
Studies of nonresponders					
Brillanti, 2000	Italy		Nonresponse to previous therapy: defined as no HCV-RNA clearance and no ALT normalization; IFN alpha 3-6 mu, HCV+, absence of circulating anti-IFN antibodies, IFN monotherapy, 3-6 mu Ly or r IFN alpha for >=4 mo, initial liver bx: before first tx,el ALT for 6 mo, detectable HCV in serum	Comorbidities: GI, "other causes of chronic liver disease," pulmonary, renal, neurologic, seizure, diabetes, and cardiovascular, HBV+, immune suppression, depression, other psychiatric illness, HIV+, decompensated liver disease, plts <100,000 autoimmune hepatitis, alcoholic liver disease, WBC <3000, Hgb <12 in women and <13 in men	
Gaeta, 2001	Italy	40	Initial liver bx w/i prior 12 mo, ALT 1.5x UL of nl, nonresponsive to previous IFN alpha therapy, detectable HCV in serum, HCV+, HCV genotype 1b, age <60 yrs	Antihistamine, contraindication to IFN, renal disease, psychiatric illness, HIV+, decompensated liver disease, HBV+	To evaluate the efficacy and tolerability of high dose IFN plus amantadine for CHC pts who were nonresponders to a previous course of IFN

Evidence Table 13: Overall summary of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Teuber, 2001	Germany	55	Age: 18-70, HCV+, detectable HCV in serum, ALT, initial liver bx, nonresponse to previous IFN, WBC >2,500, Plts >70,000	EtOH >50g, IDU or other illicit drug use w/i past year, HBV+, HIV+, decompensated liver disease, pregnancy and lactation, immune suppression, depression, other psychiatric illness, cardiovascular comorbidity, neurologic comorbidity, bleeding disorders, malignancy, autoimmune disorders, metabolic disease, renal disease, rheumatologic	To evaluate the efficacy, tolerability, and health-related quality of live of IFN alpha 2a plus amantadine in omparison w/ IFN alpha 2a plus placebo in previous nonresponders
Younossi, 2001	United States	118	Nonresponse to previous IFN monotherapy, initial liver bx, IFN monotherapy tiw for >=12 wk, HCV+	Other liver diseases, decompensated liver disease, immune suppression, severe depression, other severe psychiatric illness, HIV+, seizure disorders, DM, renal insufficiency, uncontrolled thyroid disease, plts <100,000, WBC <3000, Hgb <13 for males and <12 for females, active cardiovascular disease	To compare a 24 wk regimen of IFN alpha-2b plus RBV to IFN alpha-2b plus amantadine in nonresponders to previous IFN monotherapy

Evidence Table 13: Overall summary of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Studies of treatment outcomes in other subgroups					
Subgroup: Renal					
Campistol, 1999	Spain	36	Detectable HCV in serum, HCV+	HIV+, HBV+	Multicenter randomized trial assessing the efficacy and tolerance of IFN alpha-2b in tx of HCV induced chronic hepatitis in pts undergoing hemodialysis, w/ evaluation following renal transplant.
Subgroup: Race/ethnicity					
McHutchison, 2000	United States	1712			To evaluate racial differences in response to therapy in pts w/ CHC, and potential contributing factors that might account for such differences
Reddy, 1999	United States Canada	470			To retrospectively analyze data from the consensus IFN trial looking at outcomes in the specific tx arms (IFN-alpha-2b 3 mu tiw and alphacon IFN 9 mg) based on race.

Evidence Table 13: Overall summary of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Subgroup: Hemophiliacs					
Rumi, 1997	Italy	95	HCV+, detectable HCV in serum, ALT >= 2x nl on 3 occasions over 6 mo, HIV+	Peg-IFN monotherapy, HBV+, decompensated liver disease, HCC, EtOH >80 g/d, Peg-IFN + RBV, IFN, IFN + RBV, IFN monotherapy, steroid, WBC <3000, plts < 100,000, non-organ-specific autoantibodies, thyroid dysfunction	To evaluate the efficacy of long term (6 mo) IFN tx in hemophiliac pts
Subgroup: HBV/HCV coinfection					
Villa, 2001	Italy	30	Consecutively seen in clinic, ALT 2x nl for 6 mos, HBV+, HCV+	IFN tx, peg-IFN + RBV tx	To determine the outcome of medium to high doses of IFN therapy in pts w/ HBV-HCV.

Evidence Table 13: Overall summary of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Studies of interferon in nonresponders/relapsers					
Bresci, 1996	Italy	150	ALT 2x UL of nl 3 times w/i 6 mo, 3 mu of rIFN, tiw, for 6 mo, nonresponse to previous therapy: detectable HCV in serum	Alpha-1-antitrypsin deficiency, Wilson's disease, hemochromatosis, drug-induced liver disease, immune suppression: autoimmune factors (+ANA, ASMA), presence of cirrhosis, hepatitis delta infection, HBV+, EtOH >40 g/d	To investigate the efficacy of different types of IFN and dosages in previous nonresponders to IFN tx (3 mu, tiw, for 6 mos)
Chemello, 1997	Italy	88	ALT 2.5x UL of nl, IFN monotherapy, detectable HCV in serum, relapse after previous therapy: 3 mu IFN alpha tiw for 6 mo or 3-6 mu IFN alpha tiw for 12 mo, nonresponse to previous therapy: 3 mu IFN alpha tiw for 6 mo or 3-6 mu IFN alpha tiw for 12 mo, age >18 and <55 yrs	Autoimmune disease, EtOH, HBV+, decompensated liver disease, HIV+, plts <100,000, metabolic disorders, ascites, varices, encephalopathy, WBC <3000, adverse reaction to previous therapy	Efficacy of retx w/ IFN in previous nonresponders and relapsers. The endpoints addressed were 1) predictors of virological and biochemical response and 2) influence of initial tx schedule on retx.
Gaeta, 1997	Italy	69	ALT 2x UL on 3 consecutive monthly samples, initial liver bx to test for HCV, LyIFN alpha for >= 4 mo, r IFN alpha for >=4 mo, nonresponse to previous therapy for >=4 mos w/ either r or LyIFN alpha, detectable HCV in serum	Abnl thyroid function, HIV+: tested for antibodies, decompensated liver disease, HBV+: screened for surface antigen HBsAg, immune suppression	To evaluate the efficacy and safety of leukocyte IFN-alpha in the retx of pts w/ chronic HCV who have failed to respond to therapy w/ either recombinant IFN-alpha or LyIFN-alpha.

Evidence Table 13: Overall summary of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Heathcote, 1998	United States Canada	337	Plts 75 x 10^9, neutrophil >1.5 x 10^6, Hgb >10, ALT >48 x 2 consecutive values, consensus IFN 9 μγ tiw for 24/52 mo, consensus IFN 3 μγ tiw for 24/52 mo, IFN monotherapy 3 mu tiw for 24/52 mo	Seizure disorder and currently taking medication, thyroid disease in which nl thyroid function was not attainable, neurologic comorbidity, HIV+, depression, decompensated liver disease, IDU, EtOH	To determine the safety and efficacy of retx of CHC w/ consensus IFN for 24 wks vs. 48 wks at higher doses (15 μg) in nonresponders and relapsed pts.
Kagawa, 1998	Japan	62	ALT el persistently for >= 6 mo, initial liver bx: active CHC, detectable HCV in serum	HCC, hepatitis delta infection, HBV+	To evaluate the effect of higher doses of IFN in initial nonresponders. To evaluate early virologic response as a predictor of sustained response.
Payen, 1998	France	247	Abnl ALT for 6 mo, initial liver bx IFN monotherapy: 3 mu IFN, tiw for 6 mo, HCV+, detectable HCV in serum	Adverse reaction to previous therapy: grade 3 or 4 by WHO classification, HBV+, presence of cirrhosis, age <18 yrs, HIV+, Fe deposition in liver, women of childbearing age not using contraceptives, severe associated disease, pregnancy	To compare the efficacy of IFN alpha2b regimens in pts w/ CHC who relapsed after an initial 6 mo IFN tx

Evidence Table 13: Overall summary of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Poynard, 1999	France	58	ALT 1.5x nl in last 6 mo, IFN monotherapy: >= 3 mu tiw, for 24-48 wk, detectable HCV in serum, relapse after previous therapy, liver bx with CHC w/o cirrhosis, age 18-70 yrs	Neurologic comorbidity, EtOH 50 g/d, IDU, other illicit drug use, HBV+, hepatitis delta infection, immune suppression, depression, other psychiatric illness, cardiovascular comorbidity, plts <70,000, hematologic comorbidity, renal disease, pulmonary disease, thyroid disease, severe medical disorder, MRI HCC, AFP >100, neutrophil <2, HIV+	To compare the effect of high-dose, short duration (14 wks) IFN regimen in relapsers w/ standard 6 mo IFN regimen of 3 mu tiw.
Shiffman, 1999	United States	53	Nl alpha-antitrypsin, HCV+, detectable HCV in serum, nonresponse to previous therapy: IFN alfa-2b, histologic response to prior IFN tx, nl ceruloplasmin, nl antinuclear antibody, nl anti-smooth-muscle antibody, initial liver bx, ALT el 6 mo, WBC, IFN monotherapy, nl hepatic Fe levels, plts >90,000	HIV+, active IDU, abnl Alb, abnl Bili, HBV+, immune suppression, chronic EtOH, abnl prothrombin, abnl AFT, pregnancy	To assess if continued maintenance of IFN prevents HCV progression in virologic nonresponders who achieved a histological response after an initial 6 mo IFN tx.

Evidence Table 14: Characteristics of patients in randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Studies of current treatment options in nonresponders/relapsers to prior therapy										
Studies of nonresponders										
Barbaro, 1999	RCT									
		IFN: beta IFN, 6 mu, 6 days/week,	100	33		HAI	S 2.3		178	
		12 wks		67.0		HAI	T 11.7			
									1b	45.00
									2a/c	43.00
									3a	12.00
		IFN: alpha-2b, 6 mu tiw, 12 wks	100	32		HAI	S 2.2		175	
		RBV: 1000-1200 mg qd, 12 wks		65.0		HAI	T 11.5			
									1b	43.00
									2a/c	44.00
									3a	13.00
Bresci, 2000	RCT									
		IFN: 6 mu tiw, 6 mos	50	52		HAI	S 2.0		149	
		RBV: 1000-1200 mg qd, 6 mos		56.0		Kno	A 10.3		7	
									1	78.00
		IFN: 6 mu, bid, 6 mos	50	48		HAI	S 2.2		150	
				52.0		Kno	A 9.7		8	

Evidence Table 14: Characteristics of patients in randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
									1	74.00
Di Bisceglie, 2001	RCT									
		IFN: alpha-2b, 3 mu tiw, 24 wks	63	43		Sch		A0 20.6	90	
		RBV: 1000-1200 mg qd, 24 wks		69.8		Sch		A1 30.2		
				C: 96.8		Sch		A2 25.4	1	74.60
						Sch		A3 23.8	2	19.05
									3	6.35
		IFN: alpha-2b, 3 mu tiw, 48 wks	61	46		Sch		A0 18.0	100	
		RBV: 1000-1200 mg qd, 48 wks		57.4		Sch		A1 21.3		
				C: 98.3		Sch		A2 41.0	1	86.89
						Sch		A3 19.7	2	9.84
									3	3.28

Evidence Table 14: Characteristics of patients in randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Ferenci, 2001a	RCT									
		IFN (initial): alpha-2b, 5 mu tiw, 3 mos	76	71.1				S3, A2 55.3 S4, A3 21.1	65.4	
		IFN (maintenance): alpha-2b, 10 mu, tiw, 3 mos							1a	15.79
									1a/b	2.63
									1b	68.42
									3	6.58
									4	6.58
		IFN (initial): alpha-2b, 5 mu tiw, 3 mos	81	70.4				S3, A2 63.0 S4, A3 17.3	69.8	
		IFN (maintenance): alpha-2b, 10 mu, tiw, 3 mos							1a	22.22
									1a/b	2.47
		RBV: 1000-2000 mg qd, 6 mos							1b	62.96
									3	6.17
									4	6.17

Evidence Table 14: Characteristics of patients in randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Puoti, 2001										
		IFN: alpha-2b, 3 mu tiw, 24 wks	21							
		RBV: 1000-1200 mg qd, 24 wks		85.7					12	
									1	71.43
									2	19.05
									3	4.76
									4	4.76
		IFN: alpha-2b, 5 mu tiw, 24 wks	21							
		RBV: 1000-1200 mg qd, 24 wks		81.0					10	
									1	71.43
									2	23.81
									3	4.76
									4	4.76
		IFN: alpha-2b, 5 mu, qd, 24 wks	21							
		RBV: 1000-1200 mg qd, 24 wks		81.0					15	
									1	61.90
									2	9.52
									3	14.29
									4	14.29

Evidence Table 14: Characteristics of patients in randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Saracco, 2001	RCT									
		IFN: alpha-2b, 3 mu tiw, 12 mos	139	46	12	ISH	A 2.6			
		RBV: 1000 mg qd, 12 mos		66.2		ISH	S 6.2			
									1	66.91
									2	16.55
									3	9.35
									4	7.19
		IFN: alpha-2b, 5 mu tiw, 12 mos	162	44	9	ISH	A 2.5			
		RBV: 1000 mg qd, 12 mos		74.7		ISH	S 6.4			
									1	60.49
									2	19.14
									3	13.58
									4	6.79
		IFN: alpha-2b, 3 mu tiw, 6 mos	142	46	15	ISH	A 2.8			
		RBV: 1000 mg qd, 6 mos		76.8		ISH	S 6.2			
									1	67.61
									2	14.79
									3	14.08
									4	3.52
		IFN: alpha-2b, 5 mu tiw, 6 mos	151	45	7	ISH	A 2.6			
		RBV: 1000 mg qd, 6 mos		78.1		ISH	S 6.0			
									1	68.87
									2	13.25
									3	11.26
									4	6.62

Evidence Table 14: Characteristics of patients in randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
.										
Shiffman, 2000a	RCT									
		IFN (initial): alpha-2b, 5 mu tiw, 3 mos IFN (maintenance): alpha-2b, 5 mu, tiw, 3 mos	48	44.5 60.4 C: 50, B: 50	21	Kno	7.3		1	89.58
		IFN (initial): alpha-2b, 3 mu tiw, 3 mos IFN (maintenance): alpha-2b, 5 mu, tiw, 3 mos RBV: 1000-1200 mg, Divided dose, twice daily, 9 mos	42	43.6 69.0 C: 69.0, B: 30.9	19	Kno	7		1	88.10
		IFN: alpha-2b, 5 mu tiw, 6 mos RBV: 1000-1200 mg, Divided dose, twice daily, 9 mos	50	42.9 66.0 C: 64, B: 36	14	Kno	6.4		1	90.00

Evidence Table 14: Characteristics of patients in randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Tripi, 2000	RCT									
		IFN: Leukocyte IFN alpha, 6	24	46.2		HAI	A 1.3		184.5	
		mu tiw, 6 mos		50.0		HAI	S 3.4			
									1a	12.50
									1b	66.67
									2a	12.50
									2a and b	4.17
									2b	4.17
		IFN: Leukocyte IFN alpha, 6	48	49.4		HAI	A 2.1		168.8	
		mu tiw, 6 mos		75.0		HAI	S 4.8			
		RBV: 1200 mg qd, 6 mos							1a	4.17
									1b	70.83
									2a	10.42
									2a and b	2.08
									2b	12.50
Studies of relapsers										
Chapman, 2001	RCT									
		IFN (initial): alpha-2a, 6 mu tiw, 6 mos		16	37					
				56.3						
		IFN (maintenance): alpha-2a, 3 mu, tiw, 6 mos							1	75.00
									2	25.00
		IFN: alpha-2a, 3 mu tiw, 6 mos	16	38						
		RBV: 1000 mg qd, 3 mos		62.5						
									1	37.50

Evidence Table 14: Characteristics of patients in randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
									2	62.50
Di Marco, 2000	RCT									
		IFN: alpha-2b, 6 mu tiw, 6 mos	25	46.1	12	Met		A1, A2 64.0		
		RBV: 1000-1200 mg, bid, 6 mos		68.0		Met		A3 36.0		
						Met		S1-S3 88.0	1b	76.00
						Met		S4 12.0	other	24.00
		IFN: alpha-2b, 6 mu tiw, 12 mos	25	45.6	16	Met		A1-A2 72.0		
		RBV: 1000-1200 mg, bid, 12 mos		84.0		Met		A3 28.0		
						Met		S1-S3 84.0	1b	40.00
						Met		S4 16.0	other	28.00
Enriquez, 2000	RCT									
		IFN: alpha-2b, 3 mu tiw, 24 wks	58	40.22						
		RBV: 1000-1200 mg qd, 24 wks		79.3						
									1	82.76
									non-1	15.52
		IFN: alpha-2b, 3 mu tiw, 48 wks	62	39.87						
		RBV: 1000-1200 mg qd, 48 wks		77.4						
									1	80.65
									non-1	17.74

Evidence Table 14: Characteristics of patients in randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Studies of nonresponders and relapsers										
Bonkovsky, 2001	RCT									
		IFN: alpha-2b, 3 mu tiw, 24 wks	35	44						
		RBV: 600 mg, 400 mg A.M./200 mg		68.6						
		P.M., 24 wks		C: 91.4,					1	68.57
				B: 0, A: 0,					non-1	28.57
				O: 8.57					not specified	2.86
		IFN: alpha-2b, 3 mu tiw, 24 wks	34	44						
		RBV: 1000-1200 mg qd, 24 wks		61.8						
				C: 97.0,					1	70.59
				B: 2.94, A: 0,					non-1	26.47
				O: 0					not specified	2.94
Cavalletto, 2000	RCT									
		IFN (initial): natural IFN, 6 mu tiw,	50	38		ISH	A 3.0			
		2 mos		60.0		ISH	S 8.9			
		IFN (maintenance): natural IFN, 3				ISH		3-4 22.0	1	56.00
		mu tiw, 6 mos				ISH		6 12.0	2	20.00
									3	24.00
		IFN (initial): natural IFN, 6 mu tiw,	50	40		ISH	A 3.1			
		2 mos		94.0		ISH	S 9.6			
		IFN (maintenance): natural IFN, 3				ISH		3-4 28.0	1	68.00
		mu tiw, 6 mos				ISH		6 12.0	2	20.00
		RBV: 1000-1200 mg qd, 6 mos							3	12.00

Evidence Table 14: Characteristics of patients in randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Min, 2001	RCT									
		IFN: alpha-2b, 3 mu tiw, 12 mos	81	47						
		RBV: 1000-1200 mg, bid, 12 mos		69.1						
				C: 77.7, B: 6.17, O: 16.0					1 non-1	87.65 12.35
		IFN: alpha-2b, 5 mu tiw, 12 mos	73	47.2						
		RBV: 1000-1200 mg, bid, 12 mos		74.0						
				C: 80.8, B: 8.21, O: 10.9					1 non-1	83.56 17.81

Evidence Table 14: Characteristics of patients in randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Studies of interferon/amantadine combination therapy, with or without ribavirin										
Studies of nonresponders										
Brillanti, 2000	RCT									
		Amantidine:	20	47						
		IFN: alpha-2b, 5 mu tiw, 12 mos		65.0						
		RBV: 800 - 1000 mg qd, 12 mos							1	55.00
									2	30.00
									3	10.00
									4	5.00
		Amantidine: 200 mg qd, 12 mos	40	49						
		IFN: alpha-2b, 5 mu tiw, 12 mos		67.5						
		RBV: 800 - 1000 mg qd, 12 mos							1	57.50
									2	27.50
									3	7.50
									4	7.50

Evidence Table 14: Characteristics of patients in randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Gaeta, 2001	RCT									
		Amanitidine (initial): 100 mg, bid, 4 wks	21	44.7 66.7	5	Kno Sch	S 5.0 A 1.5			
		Amanitidine (maintenance): 100 mg, bid, 5 mos							1b	100.00
		IFN (initial): alpha-2a, 4.5 mu, qd, 4 wks IFN (maintenance): alpha-2a, 6 mu, tiw, 5 mos								
		IFN (initial): alpha-2a, 4.5 mu, qd, 4 wks IFN (maintenance): alpha-2a, 6 mu, tiw, 5 mos	19	48.4 63.2	11	Kno Sch	S 5.5 A 1.5		1b	100.00
Teuber, 2001	RCT									
		Amantidine: 100 mg, bid, 48 wks	26	47.7					73	
		IFN (initial): alpha-2a, 6 mu tiw, 24 wks IFN (maintenance): alpha-2a, 6 mu, tiw, 24 wks		73.1					10.9 1 non-1	 84.62 15.38
		Amantidine: Placebo	29	45.7					64	
		IFN (initial): alpha-2a, 6 mu tiw, 24 wks IFN (maintenance): alpha-2a, 6 mu,		41.4					14.9 1 non-1	 93.10 6.90

Evidence Table 14: Characteristics of patients in randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
		tiw, 24 wks								
Younossi, 2001	RCT									
		IFN: alpha-2b, 3 mu tiw, 24 wks	59	46.1	17	HAI	8.1			
		RBV: 800 mg qd, 24 wks		62.7 C: 79.6, B: 18.6, O: 1.69					1a/b other	83.05 13.56
		Amantidine: 200 mg qd, 24 wks	59	45.6	17	HAI	7.1			
		IFN: alpha-2b, 3 mu tiw, 24 wks		61.0 C: 72.8, B: 10.1, O: 10.1					1a/b other	71.19 25.42

Studies of treatment outcomes in other subgroups

Subgroup: Renal

Campistol, 1999	RCT									
		IFN: alpha-2b, 3 mu tiw, 6 mos	19	42 47.4						
		IFN: None	17	48 58.8						

Evidence Table 14: Characteristics of patients in randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Subgroup: Race/ethnicity									
McHutchison, 2000	RCT								
		IFN (210 pts): alpha-2b, 3 mu tiw, 24 wks	1600	43 65.1		HAI Kno	7.1 S 1.5		17
		IFN (461 pts): alpha-2b, 3 mu tiw, 24 wks				Kno Kno		S3 1.1 S4 0.2	1 non- 1 65.06 34.94
		IFN (464 pts): alpha-2b, 3 mu tiw, 48 wks							
		IFN (465 pts): alpha-2b, 3 mu tiw, 48 wks							
		RBV (461 pts): 1000/1200 mg qd, 24 wks							
		RBV (464 pts): 1000/1200 mg qd, 48 wks							

Evidence Table 14: Characteristics of patients in randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
		IFN (12 pts): alpha-2b, 3 mu tiw, 24 wks IFN (13 pts): alpha-2b, 3 mu tiw, 48 wks IFN (13 pts): alpha-2b, 3 mu tiw, 48 wks IFN (15 pts): alpha-2b, 3 mu tiw, 24 wks RBV (13 pts): 1000/1200 mg qd, 48 wks RBV (15 pts): 1000/1200 mg qd, 24 wks	53	46 67.9		HAI Kno Kno Kno	7.8 S 1.7	S3 47.2 S4 11.3	18 1 non-1	96.23 3.77
		IFN (1 pts): alpha-2b, 3 mu tiw, 24 wks IFN (13 pts): alpha-2b, 3 mu tiw, 24 wks IFN (6 pts): alpha-2b, 3 mu tiw, 48 wks IFN (7 pts): alpha-2b, 3 mu tiw, 48 wks RBV (13 pts): 1000/1200 mg qd, 24 wks RBV (7 pts): 1000/1200 mg qd, 48 wks	27	45 81.5		Kno Kno	S 1.5	S4 40.7	21 1 non-1	59.26 40.74

Evidence Table 14: Characteristics of patients in randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
		IFN (12 pts): alpha-2b, 3 mu tiw, 48	32	45		HAI	7.9			
		wks		75.0		HAI		40.6	21	
		IFN (5 pts): alpha-2b, 3 mu tiw, 48				Kno			1	78.13
		wks				Kno	S3	6.2	non- 1	21.88
		IFN (7 pts): alpha-2b, 3 mu tiw, 24				Kno	S4	88		
		wks								
		IFN (8 pts): alpha-2b, 3 mu tiw, 24								
		wks								
		RBV (12 pts): 1000/1200 mg qd, 48								
		wks								
		RBV (8 pts): 1000/1200 mg qd, 24								
		wks								
Reddy, 1999	RCT									
		IFN (Caucasians): alpha-2a, 3 mu	380	42				S4 3.16	132	
		or alphacon1, 9 mu tiw, 24 wks		73.9		HAI	7			
									1	2.11
									1a	37.89
									1b	26.05
									2a	3.95
									2b	12.11
									3	3.95
									other/mixed	2.89

Evidence Table 14: Characteristics of patients in randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
		IFN (African Americans): alpha-2a,	40	43				S4 12.5	116	
		3 mu or alphacon1, 9 mu tiw, 24 wks		62.5		HAI	6			
									1	2.50
									1a	52.50
									1b	32.50
									2a	10.00
									2b	2.50
									3	0.00
									other/mixed	0.00

Evidence Table 14: Characteristics of patients in randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
		IFN (Hispanics): alpha-2a, 3 mu or alphacon1, 9 mu tiw, 24 wks	40	45 70.0		HAI	8	S4 50.0	118	
									1	2.50
									1a	40.00
									1b	25.00
									2a	2.50
									2b	12.50
									3	10.00
									other/mixed	7.50
		IFN (Asians): alpha-2a, 3 mu or alphacon1, 9 mu tiw, 24 wks	10	50 70.0		HAI	8	S4 80.0	117	
									1	0.00
									1a	20.00
									1b	20.00
									2a	20.00
									2b	30.00
									3	0.00
									other/mixed	10.00

Evidence Table 14: Characteristics of patients in randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Subgroup: Hemophiliacs										
Rumi, 1997	RCT									
		IFN: alpha-2b, 3 mu tiw, 6 mos	45	33						
									1a	57.78
									1b	22.22
									2	6.67
									3	24.44
		IFN: None	50	34						
									1a	38.00
									1b	18.00
									2	18.00
									3	28.00

Evidence Table 14: Characteristics of patients in randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Subgroup: HBV/HCV coinfection										
Villa, 2001	RTnc									
		IFN: 6 mu tiw, 6 mos	14	34		HAI	A 1.9			
				71.4		HAI	S 11.6			
									1a	7.14
									1b	78.57
									2a	14.29
		IFN: 9 mu tiw, 6 mos	16	33		HAI	A 1.7			
				75.0		HAI	S 11.9			
									1a	31.25
									1b	43.75
									2a	25.00

Evidence Table 14: Characteristics of patients in randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Studies of interferon in nonresponders/relapsers									
Bresci, 1996	RCT								
		IFN: alpha-2b, 3 mu tiw, 6 mos	30	46 56.7				S3, A2 70.7	120 8
		IFN: alpha-2b, 6 mu tiw, 6 mos	30	50 66.7				S3, A2 76.7	140 9
		IFN: alphacon1, 3 mu tiw, 6 mos	30	49 53.3				S3, A2 80.0	138 7
		IFN: natural IFN, 3 mu tiw, 6 mos	30	47 60.0				S3, A2 73.3	136 9
		IFN: None	30	48 56.7				S3, A2 76.7	146 8

Evidence Table 14: Characteristics of patients in randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Chemello, 1997	RCT									
		IFN: 3-6 mu tiw, 6-12 mos	26	26						
				88.5						
									1	88.46
									2	88.46
									3	0.00
		IFN: 3-6 mu tiw, 6-12 mos	66	46						
				72.7						
									1	57.58
									2	34.85
									3	7.58
Gaeta, 1997	RCT									
		IFN (initial): Leukocyte IFN, 3 - 6 mu tiw, 6 mos	44	51.02		HAI		11.4		
				61.4						
		IFN (maintenance): Leukocyte IFN, 3 - 6 mu tiw, 6 mos							1a	13.64
									1b	34.09
									2a	11.36
									3 or 4	4.55
		IFN (initial): Recombinant or lymphoblastoid IFN alpha, 3 - 6 mu, tiw, 12 mos	25	47.2		HAI		24		
				64.0						
									1a	8.00
									1b	64.00
									2a	4.00
									3 or 4	4.00

Evidence Table 14: Characteristics of patients in randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Heathcote, 1998	RCT									
		IFN (Relapsers): alphacon1, 15 µg, tiw, 24 wks	167	44.7 74.3					1	70.06
		IFN (Nonresponders): alphacon1, 15 µg, tiw, 24 wks	167	44.7 74.3					1	70.06
		IFN (Relapsers): alphacon1, 15 µg, tiw, 48 wks	170	44.3 75.9					1	74.12
		IFN (Nonresponders): alphacon1, 15 µg, tiw, 48 wks	170	44.3 75.9					1	74.12

Evidence Table 14: Characteristics of patients in randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Kagawa, 1998	RCT								
		Early responders IFN (initial): alphacon1, 6 mu, qd, 4 wks Early responders IFN (maintenance): alphacon1, 6 mu tiw, 22 wks	30						
		IFN (initial): alphacon1, 6 mu, qd, 4 wks IFN (maintenance): alphacon1, 6 mu, tiw, 22 wks	16						
		IFN (initial): alphacon1, 6 mu, qd, 4 wks IFN (maintenance): alphacon1, 6 mu, tiw, 18 wks	16						

Evidence Table 14: Characteristics of patients in randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Payen, 1998	RCT									
		IFN: alpha-2b, 3 mu tiw, 6 mos	75	45.6		HAI	7.2			
				92.0					8.83	
				C: 98.6					1	5.33
									1a	10.67
									1b	28.00
									2	13.33
									3	16.00
									other	8.00
		IFN: alpha-2b, 3 mu tiw, 12 mos	91	44.1		HAI	7.6			
				71.4					9.47	
				C: 100					1	3.30
									1a	3.30
									1b	29.67
									2	15.38
									3	23.08
									other	5.49
		IFN: alpha-2b, 10 mu tiw, 6 mos	81	42.1		HAI	8			
				70.4					9.08	
				C: 100					1	2.47
									1a	3.70
									1b	33.33
									2	9.88
									3	28.40
									other	6.17

Evidence Table 14: Characteristics of patients in randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Poynard, 1999									
		IFN: alpha-2b, 3 mu tiw, 24 wks	29	38 62.1					2.6 2.92 1 48.28 2/3 37.93 4 13.79
		IFN (initial): alpha-2b, 10 mu, 6 days a week, 2 wks IFN (maintenance): alpha-2b, 10 mu, tiw, 12 wks		29 39 62.1					3.17 1 51.72 2/3 37.93 4 6.90
Shiffman, 1999	RCT								
		IFN: None	27	48.8 51.9 C: 85.1, O: 14.8	22	Kno Kno	A 14.8 S 3.4		
		IFN: alpha-2b, 5 mu tiw, 24 mos	26	47.8 57.7 C: 88.4, O: 11.5	27	Kno Kno	A 7.7 S 1.8		

Evidence Table 15: Methodologic quality of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C

Author, Year	Representativeness[a]	Bias[b]	Description[c]	Outcomes[d]	Statistics[e]	Conflict[f]	Total[g]
Studies of current treatment options in nonresponders/relapsers to prior therapy							
Studies of nonresponders							
Barbaro, 1999	100	83	50	80	100	0	83
Bresci, 2000	50	67	50	75	50	0	58
Di Bisceglie, 2001	75	67	50	85	67	50	69
Ferenci, 2001a	63	17	50	70	38	0	47
Puoti, 2001	75	50	50	85	100	50	72
Saracco, 2001	88	83	100	70	88	0	86
Shiffman, 2000a	100	100	100	60	83	50	89
Tripi, 2000	63	58	50	85	38	50	59
Studies of relapsers							
Chapman, 2001	38	50	50	65	17	50	44
Di Marco, 2000	88	67	50	80	100	0	77
Enriquez, 2000	75	33	50	80	100	0	68
Studies of nonresponders and relapsers							
Bonkovsky, 2001	88	83	100	80	50	100	80
Cavalletto, 2000	100	67	50	90	100	50	81

Evidence Table 15: Methodologic quality of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Representativeness[a]	Bias[b]	Description[c]	Outcomes[d]	Statistics[e]	Conflict[f]	Total[g]
Min, 2001	100	50	75	80	83	50	78
Studies of interferon/amantadine combination therapy, with or without ribavirin							
Studies of nonresponders							
Brillanti, 2000	100	67	100	75	100	50	88
Gaeta, 2001	50	67	100	70	0	0	57
Teuber, 2001	75	92	75	85	83	0	82
Younossi, 2001	63	100	100	80	100	100	89
Studies of treatment outcomes in other subgroups							
Subgroup: Renal							
Campistol, 1999	33	67	75	65	100	0	68
Subgroup: Race/ethnicity							
McHutchison, 2000	25	33	50	40	88	50	47
Reddy, 1999	38	75	75	80	63	50	66
Subgroup: Hemophiliacs							
Rumi, 1997	75	58	100	90	75	0	80
Subgroup: HBV/HCV coinfection							
Villa, 2001	88	83	75	35	67	100	70

Evidence Table 15: Methodologic quality of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Representativeness[a]	Bias[b]	Description[c]	Outcomes[d]	Statistics[e]	Conflict[f]	Total[g]
Studies of interferon in nonresponders/relapsers							
Bresci, 1996	88	50	50	70	67	0	65
Chemello, 1997	88	58	75	30	63	50	63
Gaeta, 1997	50	50	100	80	50	50	66
Heathcote, 1998	50	67	100	80	67	0	73
Kagawa, 1998	50	17	100	75	67	50	62
Payen, 1998	75	83	50	85	83	50	75
Poynard, 1999	63	83	75	65	83	50	74
Shiffman, 1999	63	67	50	75	83	50	68

Evidence Table 15: Methodologic quality of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Representativeness[a]	Bias[b]	Description[c]	Outcomes[d]	Statistics[e]	Conflict[f]	Total[g]

[a] ***Representativeness***: The total maximum for this section was 8 points. This included setting and population described and start and end date specified (2 points); detailed description of inclusion and exclusion criteria or statement that all potential trainees enrolled (2 points); information about excluded or not-participating patients (2 points); and description of key patient characteristics at enrollment (2 points).

[b] ***Bias and Confounding***: The total maximum score was 6 points. This included whether assignment of patients to study groups was randomized (2 points); whether groups had any differences in key patient characteristics (2 points); and whether clinicians, patients, and outcome assessors were blinded (2 points).

[c] ***Description of Therapy/Management***: The total maximum score was 4 points. This included sufficiently detailed description of the treatment regimen (2 points); and description of other treatments or tests given to subjects (2 points).

[d] ***Outcomes and Followup:*** The total maximum score was 10 points. This included description of complications, side effects and adverse reactions (2 points); sufficient description of criteria for determining outcomes (2 points); reporting on the numbers and reasons for withdrawals from the study or losses to followup (2 points); proportion of patients who withdrew from the study or were lost to followup (2 points); and sufficiency of the planned length of followup (2 points).

[e] ***Statistical Quality and Interpretation***: The total maximum score was 8 points. This included whether magnitude of difference between groups and an index variability was stated (2 points); whether analyses and statistical tests were clearly identified (2 points); whether adjustment of potential confounders were multi-variate or stratified analyses and coding of confounders (2 points); and appropriate handling of crossovers and/or dropouts in the analysis (2 points).

[f] ***Conflict of Interest***: The total maximum score was 2 points. This included whether the study reported the source of funding and the role played by the funding entity.

[g] ***Total Score*** is the mean of the percentage scores from the categories, Representativeness, Bias and Confounding, Description of Therapy/Management, Outcomes and Followup, and Statistical Quality and Interpretation.

Evidence Table 16: Results of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C

Author, Year Follow-up	Study Groups	Biochemical Response ETR %	Biochemical Response SR %	Viral Response ETR %	Viral Response SR %	Histological Response %	Adverse Events Disc/Withdr %	Adverse Events Dose Red %
Studies of current treatment options in nonresponders/relapsers to prior therapy								
Studies of nonresponders								
Barbaro, 1999	A IFN: beta IFN, 6 mu, 6 days/wk, 12 wks			17		65*[a]	2	24
10 mos.	B IFN: alpha-2b, 6 mu tiw, 12 wks			12		35*[a]	3	7
	RBV: 1000-1200 mg qd, 12 wks							
Bresci, 2000	A IFN: 6 mu tiw, 6 mos	20	14	38*[c]	8[c]		24	
12 mos.	RBV: 1000-1200 mg qd, 6 mos							
	B IFN: 6 mu, bid, 6 mos	16	15	12*[c]	6[c]			
Di Bisceglie, 2001	A IFN: alpha-2b, 3 mu tiw, 2 mos	69	38	49	41		17	17
6 mos.	RBV: 1000-1200 mg qd, 2 mos							
	B IFN: alpha-2b, 3 mu tiw, 4 mos	64	47	36	36		26	23
	RBV: 1000-1200 mg qd, 4 mos							
Ferenci, 2001a	A IFN (initial): alpha-2b, 5 mu tiw, 3 mos	26*	1.3	11*	1.3		22	
6 mos.	IFN (maintenance): alpha-2b, 10 mu tiw, 3 mos							
	B IFN (initial): alpha-2b, 5 mu tiw, 3 mos	43*	8.6	31*	8.6		21	
	IFN (maintenance): alpha-2b, 10 mu tiw, 3 mos							
	RBV: 1000-2000 ml, qd, 6 mos							

Evidence Table 16: Results of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year Follow-up	Study Groups	Biochemical Response ETR %	Biochemical Response SR %	Viral Response ETR %	Viral Response SR %	Histological Response %	Adverse Events Disc/Withdr %	Adverse Events Dose Red %
Puoti, 2001 6 mos.	A IFN: alpha-2b, 3 mu tiw, 24 wks RBV: 1000-1200 mg qd, 24 wks	52	5	52	5*†			38
	B IFN: alpha-2b, 5 mu tiw, 24 wks RBV: 1000-1200 mg qd, 24 wks	52	10	52	10*			38
	C IFN: alpha-2b, 5 mu, qd, 24 wks RBV: 1000-1200 mg qd, 24 wks	70	38	70	38			43
Saracco, 2001 6 mos.	A IFN: alpha-2b, 3 mu tiw, 12 mos RBV: 1000 mg qd, 12 mos	47	16 §	25 §	15		12	
	B IFN: alpha-2b, 5 mu tiw, 12 mos RBV: 1000 mg qd, 12 mos	55*	30 R	42 R	23*		14	
	C IFN: alpha-2b, 3 mu tiw, 6 mos RBV: 1000 mg qd, 6 mos	37*	14 §	22 §	11*		12	
	D IFN: alpha-2b, 5 mu tiw, 6 mos RBV: 1000 mg qd, 6 mos	49*	17	26 §	16		13	

Evidence Table 16: Results of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

		Biochemical Response		Viral Response		Histological Response	Adverse Events	
		ETR	SR	ETR	SR		Disc/Withdr	Dose Red
Author, Year Follow-up	**Study Groups**	%	%	%	%	%	%	%
Shiffman, 2000a	A IFN (initial): alpha-2b, 5 mu tiw, 3 mos	6.3	0	0	0		21	
6 mos.	IFN (maintenance): alpha-2b, 5 mu tiw, 3 mos							
	B IFN (initial): alpha-2b, 3 mu tiw, 3 mos	74	38	26	14		16.7	
	IFN (maintenance): alpha-2b, 5 mu tiw, 3 mos							
	RBV: 1000-1200 mg, divided dose, bid, 9 mos							
	C IFN: alpha-2b, 5 mu tiw, 6 mos	72	30	30	12		20	
	RBV: 1000-1200 mg, divided dose, bid, 9 mos							
Tripi, 2000	A IFN: alpha, 6 mu tiw, 6 mos	25	0	4.2*	0			
6 mos.	B IFN: alpha, 6 mu tiw, 6 mos	38	8.3	25*	6.3		6	
	RBV: 1200 mg qd, 6 mos							
Studies of relapsers								
Chapman, 2001	A IFN (initial): alpha-2a, 6 mu tiw, 6 mos		44	63	50			25
6 mos.	IFN (maintenance): alpha-2a, 3 mu tiw, 6 mos							19
	B IFN: alpha-2a, 3 mu tiw, 6 mos		50	69	50			
	RBV: 1000 mg qd, 3 mos							

Evidence Table 16: Results of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

		Biochemical Response		Viral Response		Histological Response	Adverse Events	
		ETR	SR	ETR	SR		Disc/Withdr	Dose Red
Author, Year Follow-up	Study Groups	%	%	%	%	%	%	%
Di Marco, 2000 6 mos.	A IFN: alpha-2b, 6 mu tiw, 6 mos RBV: 1000-1200 mg, bid, 6 mos				36*		12	
	B IFN: alpha-2b, 6 mu tiw, 12 mos RBV: 1000-1200 mg, bid, 12 mos				72*		16	
Enriquez, 2000 6 mos.	A IFN: alpha-2b, 3 mu tiw, 24 wks RBV: 1000-1200 mg qd, 24 wks			45	16*			5
	B IFN: alpha-2b, 3 mu tiw, 48 wks RBV: 1000-1200 mg qd, 48 wks			47	37*			3

Evidence Table 16: Results of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year Follow-up	Study Groups	Biochemical Response ETR %	Biochemical Response SR %	Viral Response ETR %	Viral Response SR %	Histological Response %	Adverse Events Disc/Withdr %	Adverse Events Dose Red %
Studies of both nonresponders and relapsers								
Bonkovsky, 2001	A IFN: alpha-2b, 3mu tiw, 24 wks RBV: 600 mg qd, 24 wks	57	31	46	34		11	
	B IFN: alpha-2b, 3 mu tiw, 24 wks RBV: 1000-1200 mg qd, 24 wks	53	26.5	53	35		9	
Cavalletto, 2000 6 mos.	A IFN (initial): natural IFN, 6 mu tiw, 2 mos IFN (maintenance): natural IFN, 3 mu tiw, 6 mos				10			
	B IFN (initial): natural IFN, 6 mu tiw, 2 mos IFN (maintenance): natural IFN, 3 mu tiw, 6 mos RBV: 1000-1200 mg qd, 6 mos				24			
Min, 2001 6 mos.	A IFN: alpha-2b, 2 mu tiw, 12 mos RBV: 1000-1200 mg, bid, 12 mos			28	14		12.3	
	B IFN: alpha-2b, 5 mu tiw, 12 mos RBV: 1000-1200 mg, bid, 12 mos			29	22		21.9	

Evidence Table 16: Results of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year Follow-up	Study Groups	Biochemical Response ETR %	Biochemical Response SR %	Viral Response ETR %	Viral Response SR %	Histological Response %	Adverse Events Disc/Withdr %	Adverse Events Dose Red %
Studies of interferon combination therapy with amantadine, with or without ribavirin								
Studies of nonresponders								
Brillanti, 2000	A IFN: alpha-2b, 5 mu tiw, 12 mos	20*	10*	10*	5*		0	
6 mos.	RBV: 800 - 1000 mg qd, 12 mos							
	B Amantidine: 200 mg qd, 12 mos	78*	58*	68*	48*		0	
	IFN: alpha-2b, 5 mu tiw, 12 mos							
	RBV: 800 - 1000 mg qd, 12 mos							
Gaeta, 2001	A Amanitidine (initial): 100 mg, bid, 4 wks	29		0			4.8	
6 mos.	Amanitidine (maintenance): 100 mg, bid, 5 mos							
	IFN (initial): alpha-2a, 4.5 mu, qd, 4 wks							
	IFN (maintenance): alpha-2a, 6 mu tiw, 5 mos							
	B IFN (initial): alpha-2a, 4.5 mu, qd, 4 wks	16		0			16	
	IFN (maintenance): alpha-2a, 6 mu tiw, 5 mos							

Evidence Table 16: Results of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

		Biochemical Response		Viral Response		Histological Response	Adverse Events	
		ETR	SR	ETR	SR		Disc/Withdr	Dose Red
Author, Year Follow-up	**Study Groups**	%	%	%	%	%	%	%
Teuber, 2001	A Amantadine: 100 mg, bid, 48 wks	19	4	4	0			
	IFN (initial): alpha-2a, 6 mu tiw, 24 wks							
	IFN (maintenance): alpha-2a, 6 mu tiw, 24 wks							
	B Amantadine: Placebo	28	14	14	7			
	IFN (initial): alpha-2a, 6 mu tiw, 24 wks							
	IFN (maintenance): alpha-2a, 6 mu tiw, 24 wks							
Younossi, 2001	A IFN: alpha-2b, 3 mu tiw, 24 wks	56.7	12.1	34.8	3.9		20	
6 mos.	RBV: 800 mg qd, 24 wks							
	B Amantidine: 200 mg qd, 24 wks	47.1	7.8	19.6	0		17	
	IFN: alpha-2b, 3 mu tiw, 24 wks							
Subgroup: Renal								
Campistol, 1999	A IFN: alpha-2b, 3 mu tiw, 6 mos			58	26		53	
24 mos.	B IFN: None			6				

Evidence Table 16: Results of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year Follow-up	Study Groups	Biochemical Response ETR %	Biochemical Response SR %	Viral Response ETR %	Viral Response SR %	Histological Response %	Adverse Events Disc/Withdr %	Adverse Events Dose Red %
Subgroup: Race/ethnicity								
McHutchison,2000	A IFN (210 pts): alpha-2b, 3 mu tiw, 24 wks				27*			
6 mos.	IFN (461 pts): alpha-2b, 3 mu tiw, 24 wks							
	IFN (464 pts): alpha-2b, 3 mu tiw, 48 wks							
	IFN (465 pts): alpha-2b, 3 mu tiw, 48 wks							
	RBV (461 pts): 1000-1200 mg qd, 24 wks							
	RBV (464 pts): 1000-1200 mg qd, 48 wks							
	B IFN (12 pts): alpha-2b, 3 mu tiw, 24 wks				11*			
	IFN (15 pts): alpha-2b, 3 mu tiw, 24 wks							
	IFN (13 pts): alpha-2b, 3 mu tiw, 48 wks							
	IFN (13 pts): alpha-2b, 3 mu tiw, 48 wks							
	RBV (13 pts): 1000-1200 mg qd, 24 wks							
	RBV (7 pts): 1000-1200 mg qd, 48 wks							
	C IFN (1 pt): alpha-2b, 3 mu tiw, 24 wks				44			
	IFN (13 pts): alpha-2b, 3 mu tiw, 24 wks							
	IFN (6 pts): alpha-2b, 3 mu tiw, 48 wks							
	IFN (7 pts): alpha-2b, 3 mu tiw, 48 wks							
	RBV (13 pts): 1000-1200 mg qd, 24 wks							
	RBV (7 pts): 1000-1200 mg qd, 48 wks							
	D IFN (7 pts): alpha-2b, 3 mu tiw, 24 wks				16			
	IFN (8 pts): alpha-2b, 3 mu tiw, 24 wks							
	IFN (12 pts): alpha-2b, 3 mu tiw, 48 wks							
	IFN (5 pts): alpha-2b, 3 mu tiw, 48 wks							
	RBV (8 pts): 1000-1200 mg qd, 24 wks							
	RBV (12 pts): 1000-1200 mg qd, 48 wks							

Evidence Table 16: Results of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

		Biochemical Response		Viral Response		Histological Response	Adverse Events	
		ETR	SR	ETR	SR		Disc/Withdr	Dose Red
Author, Year Follow-up	**Study Groups**	%	%	%	%	%	%	%
Reddy, 1999	A IFN (Caucasians): alpha, tiw, 24 wks	44*	22*	33*	12		4	16
6 mos.	B IFN (African Americans): alpha, tiw, 24 wks	12.5*	8*	5*	2.5		12	18
	C IFN (Hispanics): alpha, tiw, 24 wks	25	10	28	10		8	18
	D IFN (Asians): alpha, tiw, 24 wks	40	30	40	30		10	20
Subgroup: Hemophiliacs								
Rumi, 1997	A IFN: alpha-2b, 3 mu tiw, 6 mos		26[c]		13[c]			
12 mos.	B IFN: None		0[c]		0[c]			
Subgroup: HBV/HCV coinfection								
Villa, 2001	A IFN: 6 mu tiw, 6 mos	64		86				
	B IFN: 9 mu tiw, 6 mos	81		75				
Studies of interferon in nonresponders/relapsers								
Bresci, 1996	A IFN: alpha-2b, 3 mu tiw, 6 mos	16.7	7.7	7.7[c]	3.3[c]			
6 mos.	B IFN: alpha-2b, 6 mu tiw, 6 mos	30	10	16.7[c]	7.7[c]			
	C IFN: alphacon1, 3 mu tiw, 6 mos	20	7.7	10[c]	3.3[c]			
	D IFN: natural IFN, 3 mu tiw, 6 mos	23	7.7	10[c]	3.3[c]			
	E IFN: None	10	10	0[c]	0[c]			

Evidence Table 16: Results of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

		Biochemical Response		Viral Response		Histological Response	Adverse Events	
		ETR	SR	ETR	SR		Disc/Withdr	Dose Red
Author, Year Follow-up	**Study Groups**	%	%	%	%	%	%	%
Chemello, 1997	A IFN: 3-6 mu tiw, 6-12 mos	8	0	0	0			
	B IFN: 3-6 mu tiw, 6-12 mos	42	20	23	20			
Gaeta, 1997	A IFN (initial): alpha, 3 - 6 mu tiw, 6 mos	30*	23*	14	6.8			
12 mos.	IFN (maintenance): alpha, 3 - 6 mu tiw, 6 mos							
	B IFN: alpha, 3 - 6 mu tiw, 12 mos	0*	0*	0	0			
Heathcote, 1998	A IFN (Relapsers): alphacon1, 15 ug, tiw, 24 wks	88	39	72	28			
6 mos.	B IFN (Nonresponders): alphacon1, 15 ug, tiw, 24 wks	26	12	19	5			
	C IFN (Relapsers): alphacon1, 15 ug, tiw, 48 wks	76	52	76	58			
	D IFN (Nonresponders): alphacon1, 15 ug, tiw, 48 wks	25	17	17	13			

Evidence Table 16: Results of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

		Biochemical Response		Viral Response		Histological Response	Adverse Events	
		ETR	SR	ETR	SR		Disc/Withdr	Dose Red
Author, Year Follow-up	**Study Groups**	%	%	%	%	%	%	%
Kagawa, 1998	A Early responders IFN (initial): alphacon1, 6 mu, qd, 4 wks		67	80	63 [R]			
6 mos.	Early responders IFN (maintenance): alphacon1, 6 mu tiw, 22 wks							
	B IFN (initial): alphacon1, 6 mu, qd, 4 wks		13	25	6 [§]		12.5	
	IFN (maintenance): alphacon1, 6 mu tiw, 22 wks							
	C IFN (initial): alphacon1, 6 mu, qd, 4 wks		6	44	0 [§]		6.25	
	IFN (maintenance): alphacon1, 6 mu tiw, 18 wks							
Payen, 1998	A IFN: alpha-2b, 3 mu tiw, 6 mos	71	12 [§]	44 [§]	11 [§]	46[a]		14
6 mos.	B IFN: alpha-2b, 3 mu tiw, 12 mos	69	36 [R]	43 [§]	24 [R]	57[a]		38.5
	C IFN: alpha-2b, 10 mu tiw, 6 mos	84	19 [§]	60 [R]	14 [§]	38[a]		30.8
Poynard, 1999	A IFN: alpha-2b, 3 mu tiw, 24 wks	86	17	38	14	28*	21	
11 mos.	B IFN (initial): alpha-2b, 10 mu, 6 days a wk, 2 wks	79	6.9	28	0	6.9*	14	
	IFN (maintenance): alpha-2b, 10 mu tiw, 12 wks							
Shiffman, 1999	A IFN: Placebo	41		3.7		37*		
36 mos.	B IFN: alpha-2b, 5 mu tiw, 24 mos	62		23		62*		

Evidence Table 16: Results of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

[a] Percentage based on a denominator different from the group N
[c] Complete response, defined as combined virological and biochemical response
* $p < 0.05$ for the pairwise comparison between two groups marked with this symbol
† $p < 0.05$ for the pairwise comparison between two groups marked with this symbol

[§] $p < 0.05$ for the comparison groups marked with this symbol and the group marked [R]
[R] Reference group for comparison

Evidence Table 17: Overall summary of long-term outcomes of chronic hepatitis C

Author, Year	Location	N	Cohort Source	Inclusion Criteria	Exclusion Criteria	Study Aims
Randomized controlled trials						
Bernardinello, 1999	Italy	61	Tertiary care	IFN monotherapy, presence of cirrhosis: >= 2 regenerative nodules on bx, presence of fibrosis: >= 2 regenerative nodules on bx, age 18-65 yrs	Plts <50,000, WBC <2000, Child's C, portal hypertension, renal dysfunction, thyroid disease, immune suppression, decompensated liver disease, EtOH >80 g/d	To find the short- and long-term effects of IFN tx in pts w/ CHC w/ a long-term follow-up of 5 yrs.
Chemello, 1999	Italy	157	Unclear	ALT 2x UL nl for 6 mo prior to randomization, initial liver bx showing chronic liver disease, detectable HCV in serum, age 18-60 yrs	Thyroid disease, active EtOH, IDU, pregnancy, immune suppression, other causes of liver disease, plts <100,000, portal hypertension, ascites, varices, IFN monotherapy, WBC <3000, hematologic comorbidity: cytopenia	A 5 yr followup of a RCT comparing daily and tiw human leukocyte IFN alpha induction in CHC, followed by 3 mu IFN alpha tiw for 3 mos
Nishiguchi, 2001	Japan	90	Tertiary care	Abnl ALT for >1 yr, presence of cirrhosis, detectable HCV in serum	Plts <50,000, liver disease of any other etiology, HIV+, immune suppression: excluded for autoimmune hepatitis, HCC, HBV+, EtOH	To assess Child-Pugh progression, mortality, and HCC at long-term followup of 8 yrs after IFN tx alpha in HCV infected cirrhotic pts.
Long-term outcomes of treatment						
Aizawa, 2000	Japan	153	Tertiary care	ALT 2xUL nl, initial liver bx, HCV+	HBV+	Long-term observation of pts w/ CHC to elucidate the incidence of HCC and the factors that predict HCC.

Evidence Table 17: Overall summary of long-term outcomes of chronic hepatitis C (continued)

Author, Year	Location	N	Cohort Source	Inclusion Criteria	Exclusion Criteria	Study Aims
Benvegnu, 1997	Italy	429	Tertiary care	Presence of cirrhosis, detectable HCV in serum, HCV+	Autoimmune or metabolic liver disease, HCC, HBV+, excessive EtOH	To investigate the relationship between HCV genotype and the natural course of HCV, its complications, and development of HCC in cirrhotic pts
Bruno, 1997	Milan, Italy	163	Tertiary care	Presence of cirrhosis, HCV+, presence of fibrosis	IFN, HCC, Child's C, hemochromatosis, autoimmune hepatitis, sclerosing cholangitis, age >70 yrs, ALT >400	To prospectively follow a cohort of HCV pts w/ cirrhosis and evaluate if the HCV genotype impacts the development of HCC. In addition, the aim was to elicit other independent risk factors for HCC.
Fattovich, 1997	Italy, France, United Kingdom	329	Tertiary care	ALT 1.5x UL of nl for 6 mo, compensated cirrhosis, presence of cirrhosis, HCV+	Ascites, varices, encephalopathy, jaundice, any other potential cause of chronic liver disease, HCC, HBV+	To evaluate the role of IFN alpha in preventing the development of HCC or decompensation in a cohort of Caucasian pts w/ compensated cirrhosis.
Horiike, 1998	Japan	88	Unclear			To elucidate the effect of IFN therapy on the subsequent development of HCC in pts

Evidence Table 17: Overall summary of long-term outcomes of chronic hepatitis C (continued)

Author, Year	Location	N	Cohort Source	Inclusion Criteria	Exclusion Criteria	Study Aims
						w/ CHC.
Ikeda, 2001	Japan	694	Tertiary care	Presence of cirrhosis, detectable HCV in serum, HCV+	Aggressive CHC, subacute hepatitis, HIV+	To elucidate whether IFN suppresses the rate of carcinogenesis in pts w/ HCV cirrhosis; To show the role of IFN in cancer presentation in liver cirrhosis type C. 1) To what extent could IFN decrease the carcinogenesis rate from HCV-related cirrhosis. 2) To explore the effective tx by using IFN therapy in prevention.
Inoue, 2000	Japan	923	Tertiary care	Positive HCV antibodies	Presence of cirrhosis, HBV+	To evaluate whether IFN reduces the incidence of HCC
Shibata, 1998	Japan	242	Tertiary care	AFP <2x nl, HCV+	Inadequate liver samples for histological assessment, presence of cirrhosis, presence of fibrosis, HCC, hepatitis A or HBV+	To determine if irregular regeneration of hepatocytes is a risk factor for HCC in pts w/ chronic hepatitis or cirrhosis of the liver caused by the HCV.

Evidence Table 17: Overall summary of long-term outcomes of chronic hepatitis C (continued)

Author, Year	Location	N	Cohort Source	Inclusion Criteria	Exclusion Criteria	Study Aims
Shindo, 2001	Japan	250	Community based	ALT 1.5x UL of nl for 6 mo, CHC on initial liver bx, detectable HCV in serum, HCV+	Refusal to take IFN, other forms of liver disease, presence of cirrhosis, HBV+, EtOH	To study the impact of long-term biochemical response to IFN in pts who did not have serum viral response, and to determine their clinical characteristics and long-term outcomes of cirrhosis and HCC.
Tanaka, 2000	Japan	726	Tertiary care	HCV+: 1st or 2nd generation ELISA, reside in Osaka Prefecture at time of dx of HCV	HBV+ at initial dx of HCV	To study the effects of IFN on long-term outcome of pts w/ CHC namely on incidence of HCC.
Toyoda, 2001	Japan	291	Community based	All Pts treated w/varied doses but only nonresponders were included, relapse after previous therapy, detectable HCV in serum, HCV+	Presence of cirrhosis, presence of fibrosis, HBV+	To evaluate the effects of dose and duration of IFN tx on rates of HCC in pts w/ non-sustained response to tx. The pts are non-cirrhotics.
Yabuuchi, 2000	Japan	419	Tertiary care	Initial liver bx	Serious illness, immune suppression, pregnancy, HBV+	To determine the characteristics of pts w/ CHC showing long-term normal-ization in ALT levels but not viral eradication. Also, the study investigated the incidence of HCC in these pts

Evidence Table 17: Overall summary of long-term outcomes of chronic hepatitis C (continued)

Author, Year	Location	N	Cohort Source	Inclusion Criteria	Exclusion Criteria	Study Aims
Yatsuhashi, 2000	Japan	186	Tertiary care	ALT el for 6 mos, initial liver bx showing CHC, detectable HCV in serum, positive HCV	AFP >400, U/S if evidence of HCC, HCC, presence of cirrhosis, presence of fibrosis, HBV+, daily EtOH >80 g/d for 5 yrs	To measure the natural history outcome in incidence of HCC of HCV in 186 individuals.
Long-term studies of natural history						
Barrett, 2001	Ireland	155	Community based	Detectable HCV in serum, HCV+	Mode of transmission: anti-D immunoglobulin in 1997, HCV genotype 1b, female	To study the natural history of HCV in a cohort of women w/ either chronic infection or spontaneous self-limited infection. Histology, symptomatology, psychosocial impact, and extrahepatic manifestations of HCV, and HLA class II associations evaluated.
Benhamou, 2001	France		Tertiary care	HCV+, detectable HCV in serum, presence of fibrosis/cirrhosis, HIV+, antiretroviral therapy for HIV	HBV+, immune suppression, doubtful compliance with antiretroviral therapy	To analyze the impact of different retroviral agents, including protease inhibitor therapy on HCV related liver fibrosis in HIV/HCV coinfected pts

Evidence Table 17: Overall summary of long-term outcomes of chronic hepatitis C (continued)

Author, Year	Location	N	Cohort Source	Inclusion Criteria	Exclusion Criteria	Study Aims
Chiaramonte, 1999	Italy	259	Tertiary care	Presence of cirrhosis, HBV+, HCV+	Wilson's disease, hemochromatosis, alcoholic liver disease, <12-mo f/u, immune suppression, HCC, decompensated liver disease	To prospectively assess the incidence of HCC in pts w/ HBV, HCV, or both w/ Child's Grade A viral cirrhosis
Cottone, 1994	Italy	147	Unclear	Age > 40 yrs, Child's A cirrhosis		To determine the risk of HCC in Child's A cirrhosis, whether 6 mos screening interval is adequate, and determine the role of AFP in screening
Forns, 2001	Spain	116	Unclear	ALT el for 6 mos, histopathologic dx of HCV	Negative anti-HCV during f/u, Wilson's disease, autoimmune hepatitis, anti-smooth muscle antibody 1:100, antinuclear antibody 1:100, decompensated liver disease, HBV+, EtOH >40 g/d	To analyze the long-term outcome of a large cohort of Spanish pts w/ CHC followed for more than 20 yrs to identify risk factors associated w/ progression of the disease
Furusyo, 2000	Japan		Community based	ALT, plt count, AST, GGT, Serum HA, serum type IV collagen	Current IFN, anti-retroviral therapy for HIV, lamivudine for HBV	To evaluate the liver damage of hemodialysis pts w/ HCV viremia through ALT and markers of hepatic fibrogenesis

Evidence Table 17: Overall summary of long-term outcomes of chronic hepatitis C (continued)

Author, Year	Location	N	Cohort Source	Inclusion Criteria	Exclusion Criteria	Study Aims
Gentilini, 1997	Italy	405	Unclear	Abdominal U/S, presence of cirrhosis, initial liver bx, prothrombin, upper Cl endoscopy, ALT, plts, Bili, Alb, GGT	EtOH, pulmonary or metabolic disorder, HBV+, decompensated liver disease: portal hypertension, renal insufficiency	To examine the natural history of HBV and HCV in cirrhotics w/o portal hypertension
Harris, 2002	United Kingdom	1400	Community based		Dates of counseling not clear, transfused after blood tested for HCV, not flagged in NHS central register, any other exposure to blood products, IDU	To determine the clinical course of HCV infection in the first decade of infection in a group of pts who acquired their infections on a known date
Hayashi, 2000	Japan	274	Community based	ALT nl, AFP yearly 1994-1998, U/S yearly 1994-1998, HCV+, HCV genotype	HBV+	To clarify the mechanism of liver damage induced by HCV and whether it is related to HCC
Ikeda, 1993	Japan	795	Unclear	Presence of fibrosis/cirrhosis	HCC, idiopathic portal hypertension, Budd-Chiari syndrome, subacute hepatitis, chronic aggressive hepatitis w/ severe bridging necrosis, types of cirrhosis other than viral or alcoholic	To examine the incidence of HCC and explore risk factors for HCC in pts w/ cirrhosis, focusing on the difference between HCV and HBV

Evidence Table 17: Overall summary of long-term outcomes of chronic hepatitis C (continued)

Author, Year	Location	N	Cohort Source	Inclusion Criteria	Exclusion Criteria	Study Aims
Kliem, 1996	Germany	162	Tertiary care	Seen on 4-12 occasions/y, immune suppression: kidney transplant, HCV+	HCC, HBV+	To determine the impact of CHC on morbidity and mortality after kidney transplantation.
Kobayashi, 1996	Japan	136	Tertiary care	Histological assessment: examination >= 5 yrs after initial examination, abnl ALT 3 times in 6 mos prior to tx, age 18-60 yrs	Therapy: antiviral or immunosuppressive agents during f/u, complications that would affect prognosis, HIV+ HBV+, EtOH >80 g/d	To assess if the long-term histological outcome differs between HCV genotypes 1 and 2
Kobayashi, 2000	Japan	61	Unclear	Initial liver bx, IFN monotherapy for 6 mos, positive HCV antibodies		To assess the correlation between serial changes in ALT levels and histological outcome 5 yrs after tx of pts w/ CHC w/ IFN for 6 mos.
Lesens, 1999	Canada		Tertiary care	Detectable HCV in serum		To determine if HCV behaves like an opportunistic infection in which progressive liver failure is the primary manifestation in HCV/HIV coinfected pts
Matsumura, 2000	Japan	527	Tertiary care	Detectable HCV in serum, positive HCV antibodies	Nl ALT, immune suppression, HBV+	To study the progression of HCV in 527 pts as compared by genotypes

Evidence Table 17: Overall summary of long-term outcomes of chronic hepatitis C (continued)

Author, Year	Location	N	Cohort Source	Inclusion Criteria	Exclusion Criteria	Study Aims
Meijer, 1999	Netherlands	45	Tertiary care	Detectable HCV in serum	Other liver disease, HIV+, HBV+	To elucidate the natural history of HCV in HIV negative pts w/ coagulation disorders.
Murakami, 1999	Japan	357	Tertiary care	Transfusion, ALT abnl >6 mos, no history of antiviral therapy, HCV+, detectable HCV in serum	Autoimmune hepatitis, multiple transfusion, HBV+, tattoo, GI comorbidity: primary biliary cirrhosis, IDU, metabolic liver disease, drug-induced hepatitis, IFN monotherapy, no history of EtOH >= 80 g/d for >= 3 yrs	To identify factors related to the development of cirrhosis and HCC in pts w/ HCV and w/ a history of transfusion.
Persico, 2000	Italy	37	Tertiary care	ALT persistently nl >=3 times during the year, initial liver bx, no signs or symptoms of chronic liver disease, HCV+	Decompensated liver disease, presence of fibrosis, HBV+, IDU	Prospectively evaluate progression of disease in a group of HCV+ pts w/ persistently nl ALT levels.
Punyagupta, 1999	Thailand	63	Tertiary care			To assess long-term outcomes (5-15 yrs) of HCV pts in Thailand
Rodger, 1999	Australia	105	Tertiary care		No obtainable medical record, <16 yrs	To evaluate rates of HCC, cirrhosis and death in a cohort of HCV+ pts after 25

Evidence Table 17: Overall summary of long-term outcomes of chronic hepatitis C (continued)

Author, Year	Location	N	Cohort Source	Inclusion Criteria	Exclusion Criteria	Study Aims
						yrs.
Rostaing, 1996	France	31	Tertiary care	Azathioprine, CSA, renal transplant, duration of HCV+ <10 yrs, HCV+		To determine whether immune suppression for renal transplant affects liver histology in pts w/ CHC
Takano, 1995	Japan	351	Tertiary care	Histological dx of CPH or CAH, initial liver bx, AFP w/in nl range, reside w/in 1 hr commute for > 5 yrs and had already been followed >= 5 years	Presence of fibrosis/cirrhosis, decompensated liver disease, HCC at time of initial bx, concurrent HCV & HBV	To compare the incidence of HCC in pts w/ CHC vs. chronic HBV
Thomas, 2000	United States	1667	Community based	HCV+, IDU, age >17 yrs	HIV+	To assess the natural history and frequency of end stage liver disease and viral clearance in a cohort of persons infected w/ HCV secondary to intravenous drugs.
Yano, 1996	Japan	70	Unclear	Initial liver bx, HCV+	Any previous therapy, immune suppression, presence of cirrhosis, HBV+, habitual heavy EtOH	To study the pathological evolution of chronic HCV hepatitis over time

Evidence Table 18: Characteristics of patients in studies evaluating long-term outcomes of chronic hepatitis C

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Randomized controlled trials										
Bernardinello, 1999	RCT									
		IFN (initial): beta IFN, 6 mu tiw, 6 mos	38	56 50						
		IFN (maintenance): beta IFN, 3 mu, tiw, 6 mos							1 2 3	76.32 23.68 0.00
		IFN (initial): None	23	58						
		IFN (maintenance):		61					1 2 3	69.57 26.09 4.35

Evidence Table 18: Characteristics of patients in studies evaluating long-term outcomes of chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Chemello, 1999	RCT									
		IFN (maintenance): 3 mu tiw, 6	108	48				S1-S2 25.9	242	
		mos		58				S3 49.1	9.92	
								S4 17.6	1	48.15
									2	24.07
									3	13.89
									undetermined	6.48
		IFN (initial): 3 mu, qd, 3 mos	49	19				S1-S2 20.4	204	
		IFN (maintenance): 3 mu tiw, 3		73				S3 67.3	9.83	
		mos						S4 12.2	1	59.18
									2	20.41
									3	10.20
									undetermined	10.20
Nishiguchi, 2001	RCT									
		IFN (maintenance): Usual care	45	57.3		HAI	T 11.8		100	
				51						
									1	0.00
									2	73.33
									3	17.78
									4	8.89
		IFN (maintenance): 6 mu tiw, 24	45	54.7		HAI	T11.7		117	
		wks		62						
									1	2.22
									2	77.78
									3	13.33
									4	6.67

Evidence Table 18: Characteristics of patients in studies evaluating long-term outcomes of chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Long-term outcomes of treatment									
Aizawa, 2000	CohR								
			153	48.3 75		Des Des Des Des Des Des Des Des		A1 42.5 A1-A2 86.3 A2-A3 57.5 A3 13.7 S1 22.9 S2 29.4 S3 24.8 S4 22.9	
Benvegnu, 1997	Coh?								
			62	57.3 29				S4, A3 14.5	
			194	57 15				S4, A3 45.2	
			133	60.2 11				S4, A3 31.0	
			34	1 3				S4, A3 7.9	
			6	55 50				S4, A3 1.4	

Evidence Table 18: Characteristics of patients in studies evaluating long-term outcomes of chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Bruno, 1997	CohP									
		IFN (initial): IFN-alpha; Only	163	57.8						
		82/163 patients elected to go through treatment, 6 mu tiw, 6 mos		50						
		IFN (maintenance): IFN-alpha; Only patients who responded to the initial 6 mo regimen went through the maintenance phase, 3 mu tiw, 6 mos							1a	0.61
									1b	61.96
									2a/c	29.45
									3a	1.23
									mixed	1.84
									not specified	4.91
Fattovich, 1997	CohR									
		IFN (maintenance):	193	57						
			136	53						

Evidence Table 18: Characteristics of patients in studies evaluating long-term outcomes of chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Horiike, 1998	CohR									
			33	48.3		HAI		S1 81.8		
				64		HAI		S2 9.1		
						HAI		S3 9.1	1	33.33
									1/2	9.09
									2	57.58
			55	48.7		HAI		S1 54.5		
				73		HAI		S2 16.4		
						HAI		S3 29.1	1	72.73
									1/2	3.64
									2	23.64
			61	45.7		HAI		S1 47.5		
				70		HAI		S2 29.5		
						HAI		S3 23.0	1	45.90
									1/2	0.00
									2	16.39

Evidence Table 18: Characteristics of patients in studies evaluating long-term outcomes of chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Ikeda, 2001	CohR									
		IFN (maintenance): None	581	58					53	
				62						
									1	57.31
									2	14.29
									other	3.61
		IFN (maintenance): Usual care, 3-6 mu, <12 mos	88	51 75					71	
									1	46.59
									2	48.86
									other	0.00
		IFN (maintenance): Usual care, 3-6 mu, >/= 12 mos	25	25 72					62	
									1	76.00
									2	20.00
									other	4.00
Inoue, 2000	CohR									
		IFN (maintenance): Not specified	224							
				70						
		IFN (maintenance): No treatment	699							
				56						

Evidence Table 18: Characteristics of patients in studies evaluating long-term outcomes of chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Shibata, 1998	CohP								
			179	52.6 61					
			63	54.1 60 A: 100					

Evidence Table 18: Characteristics of patients in studies evaluating long-term outcomes of chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Shindo, 2001	CohR									
			67	48		HAI	A 1.5		137	
				46		HAI	S 8.4			
									1b	56.72
									non-1b	43.28
			26	55		HAI	S 8.3		106	
				77						
									1b	73.08
									non-1b	26.92
			70	46		HAI	A 1.5		127	
				76		HAI	S 7.5			
									1b	91.43
									non-1b	8.57
			87	54		HAI	A 1.5		166	
				54		HAI	S 10.0			
									1b	91.95
									non-1b	8.05
			89	51		HAI	A 1.6		97	
						HAI	A 2.3			
						HAI	S 7.5		1b	
									non-1b	

Evidence Table 18: Characteristics of patients in studies evaluating long-term outcomes of chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Tanaka, 2000	CohR									
		IFN tx groups	134	52.2						
				70						
									1	58.96
									2	8.21
									not available	40.30
		Control	594	51.7						
				69						
									1	70.03
									2	23.74
									not available	6.23
Toyoda, 2001	CohR									
		IFN (initial): natural IFN, >500 mu,	183	49.9		HAI/Des		S0-S1 61.2		
				63		HAI/Des		S2 27.9		
						HAI/Des		S3 10.9	1b	68.31
									2a	23.50
									2b	7.10
									mixed	1.09
		IFN (initial): natural IFN, <500 mu,	108	51.6		HAI/Des		S0-S1 56.5		
				61		HAI/Des		S2 29.6		
						HAI/Des		S3 13.9	1b	74.07
									2a	20.37
									2b	5.56
									mixed	0.00

Evidence Table 18: Characteristics of patients in studies evaluating long-term outcomes of chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Yabuuchi, 2000	CohR								
			126	50.8		HAI		S1 38.1	
				71		HAI		S2 33.3	
						HAI		S3/S4 28.6	
			49	52.6		HAI		S1 51.0	
				59		HAI		S2 30.6	
						HAI		S3/S4 18.4	
			244	53.8		HAI		S1 24.6	
				66		HAI		S2 32.0	
						HAI		S3/S4 43.4	
Yatsuhashi, 2000	CohP								
			186	46		HAI		A1 28.0	
				75		HAI		A2 47.8	
						HAI		A3 24.2	
						HAI		S0 29.0	
						HAI		S1 38.2	
						HAI		S2 19.9	
						HAI		S3 18.3	

Evidence Table 18: Characteristics of patients in studies evaluating long-term outcomes of chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Long-term studies of natural history									
Barrett, 2001	CohP								
			87	45.7		HAI	A 4.1		
				0		HAI	S 1.1		23
				O: 100					1b 100.00
			68	45.8		HAI	A 2.1		
				0		HAI	S 0.2		23
				O: 100					1b 100.00
Benhamou, 2001	CohR								
			63	37.7					
				60					16.62
									1 23.81
			77	36.3					
				100					14.05
									1 33.77
Chiaramonte, 1999	CohP								
			66	44.8					
				76					
			166	55.5					
				52					
			27	48.8					

Evidence Table 18: Characteristics of patients in studies evaluating long-term outcomes of chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
				81						
Cottone, 1994	CohP									
			147	58						
				55						
Forns, 2001	CohR									
			116	42.9					161	
				59						
Furusyo, 2000	CohP									
			80							
									7.7	
									1b	81.25
									2a	13.75
									2b	2.50
									undetermined	2.50
			153							
									3.4	
			228							
									1b	88.60
									2a	9.65
									2b	1.75
Gentilini, 1997	CohP									
			405	54	100					

Evidence Table 18: Characteristics of patients in studies evaluating long-term outcomes of chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
				58						
Harris, 2002	CohR									
			925	43.6 48 C: 84.6, O: 14.5	4					
			475	41.5 47 C: 68.4, O: 31.5						
Hayashi, 2000	CohP									
			102							
				37						
									1a	91.18
									2a	8.82
									2b	0.00
			92							
				58						
									1a	89.13
									2a	9.78
									2b	1.09
			80							
				71						
									1a	87.50
									2a	11.25
									2b	1.25

Evidence Table 18: Characteristics of patients in studies evaluating long-term outcomes of chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Ikeda, 1993	CohP									
		IFN (initial):	795	53						
				71						
				A: 100						
Kliem, 1996	CohR									
			162	44.5						
				59						
Kobayashi, 1996	CohR									
			100	45.8		HAI	A 2.2		89	
				68		HAI	S 8.0			
									1b	96.00
									other 1	4.00
			36	42.7		HAI	A 2.1		114	
				78		HAI	S 8.1			
									2a	55.56
									2b	16.67
									other 2	27.78
Kobayashi, 2000	CohR									
		IFN (initial): 6-10 mu, qd, 4-8 wks	61						96	
		IFN (maintenance): 6-10 mu tiw, 16-22 wks		77						
									1b	86.89
									other	13.11

Evidence Table 18: Characteristics of patients in studies evaluating long-term outcomes of chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Lesens, 1999	CS								
			81						
			53						
Matsumura, 2000	CohR								
			245	45.9 64					
			143	51.6 58					
			45	55.1 49					
			39	55.6 59					
			55	62.1 67					

Evidence Table 18: Characteristics of patients in studies evaluating long-term outcomes of chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Meijer, 1999	CohR									
			26	38						
									19	
									1a	42.31
									1b	30.77
									2a	3.85
									2b	11.54
									3a	7.69
									unclassified	3.85
			12	35						
									19	
									1a	33.33
									1b	33.33
									2a	16.67
									2b	8.33
									3a	8.33
									unclassified	0.00
			7	46						
									19	
									1a	42.86
									1b	14.29
									2a	0.00
									2b	28.57
									3a	14.29
									unclassified	0.00

Evidence Table 18: Characteristics of patients in studies evaluating long-term outcomes of chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Murakami, 1999	CohP									
			161	55.9						
				43						
									1b	68.94
									2a	24.22
									2b	6.83
			196	56.9						
				44						
									1b	69.39
									2a	25.00
									2b	5.61
Persico, 2000	CohP									
			37	40.8		ISH	S 8.0			
				54						
									1a	5.41
									1b	37.84
									2a	51.35
Punyagupta, 1999	CohR									
			63					S1 47.6		
				54				S2 31.7		
				A: 100				S3 11.1		
								S4 9.5		

Evidence Table 18: Characteristics of patients in studies evaluating long-term outcomes of chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Rodger, 1999	CC									
			35	44 71						
			70	52 57						
Rostaing, 1996	CohR									
			31	48 68					13.3	
Takano, 1995	CohR									
			124	49.6 67						
			127	33.2 80						
Thomas, 2000	CohP									
			40							
									1a	65.00
									1b	32.50
			1627							
									1a	61.95
									1b	26.00
									other	11.99

Evidence Table 18: Characteristics of patients in studies evaluating long-term outcomes of chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Yano, 1996	CohR		70	44.6 86 A: 100					

Evidence Table 19: Methodologic quality of studies evaluating long-term outcomes of chronic hepatitis C

Author, Year	Representativeness[a]	Bias[b]	Description[c]	Outcomes[d]	Statistics[e]	Conflict[f]	Total[g]
Randomized controlled trials							
Bernardinello, 1999	75	67	100	35	67	50	69
Chemello, 1999	75	83	75	95	83	50	82
Nishiguchi, 2001	100	83	100	80	88	50	90
Long-term outcomes of treatment							
Aizawa, 2000	63	0	50	50	88	0	50
Benvegnu, 1997	75	75	75	40	50	50	63
Bruno, 1997	100	38	100	88	63	50	78
Fattovich, 1997	63	50	0	95	50	50	52
Horiike, 1998	38	50	0	60	50	0	40
Ikeda, 2001	38	38	75	85	88	0	65
Inoue, 2000	75	25	0	88	63	50	50
Shibata, 1998	88	25	50	88	100	50	70
Shindo, 2001	83	--	100	80	63	0	81
Tanaka, 2000	88	25	100	75	100	100	78
Toyoda, 2001	75	100	75	80	100	50	86

Evidence Table 19: Methodologic quality of studies evaluating long-term outcomes of chronic hepatitis C (continued)

Author, Year	Representativeness[a]	Bias[b]	Description[c]	Outcomes[d]	Statistics[e]	Conflict[f]	Total[g]
Yabuuchi, 2000	38	33	0	40	67	0	36
Yatsuhashi, 2000	50	50	50	50	67	0	53
Long-term studies of natural history							
Barrett, 2001	100	75	0	44	63	0	56
Benhamou, 2001	100	50	0	67	83	0	60
Chiaramonte, 1999	63	--	0	70	75	50	52
Cottone, 1994	50	0	0	30	100	0	36
Forns, 2001	88	--	--	94	100	50	94
Furusyo, 2000	63	0	100	50	50	0	53
Gentilini, 1997	75	0	0	80	50	50	41
Harris, 2002	100	50	0	100	100	100	70
Hayashi, 2000	100	75	--	44	67	0	71
Ikeda, 1993	88	0	25	55	100	0	54
Kliem, 1996	63	0	100	81	83	0	65
Kobayashi, 1996	88	100	--	100	83	100	93
Kobayashi, 2000	67	75	0	67	100	0	62
Lesens, 1999	38	17	0	94	63	50	42

Evidence Table 19: Methodologic quality of studies evaluating long-term outcomes of chronic hepatitis C (continued)

Author, Year	Representativeness[a]	Bias[b]	Description[c]	Outcomes[d]	Statistics[e]	Conflict[f]	Total[g]
Matsumura, 2000	75	--	--	50	100	0	75
Meijer, 1999	88	50	--	63	75	0	69
Murakami, 1999	88	--	50	100	100	0	84
Persico, 2000	88	--	--	70	83	0	80
Punyagupta, 1999	25	--	0	67	0	0	23
Rodger, 1999	25	25	50	38	25	0	33
Rostaing, 1996	38	0	0	67	13	0	23
Takano, 1995	100	0	0	70	38	0	42
Thomas, 2000	75	--	0	85	67	50	57
Yano, 1996	88	--	--	100	100	0	96

Evidence Table 19: Methodologic quality of studies evaluating long-term outcomes of chronic hepatitis C (continued)

Author, Year	Representativeness[a]	Bias[b]	Description[c]	Outcomes[d]	Statistics[e]	Conflict[f]	Total[g]

[a] ***Representativeness***: The total maximum for this section was 8 points. This included setting and population described and start and end date specified (2 points); detailed description of inclusion and exclusion criteria or statement that all potential trainees enrolled (2 points); information about excluded or not-participating patients (2 points); and description of key patient characteristics at enrollment (2 points).

[b] ***Bias and Confounding***: The total maximum score was 6 points. This included whether assignment of patients to study groups was randomized (2 points); whether groups had any differences in key patient characteristics (2 points); and whether clinicians, patients, and outcome assessors were blinded (2 points).

[c] ***Description of Therapy/Management***: The total maximum score was 4 points. This included sufficiently detailed description of the treatment regimen (2 points); and description of other treatments or tests given to subjects (2 points).

[d] ***Outcomes and Followup:*** The total maximum score was 10 points. This included description of complications, side effects and adverse reactions (2 points); sufficient description of criteria for determining outcomes (2 points); reporting on the numbers and reasons for withdrawals from the study or losses to followup (2 points); proportion of patients who withdrew from the study or were lost to followup (2 points); and sufficiency of the planned length of followup (2 points).

[e] ***Statistical Quality and Interpretation***: The total maximum score was 8 points. This included whether magnitude of difference between groups and an index variability was stated (2 points); whether analyses and statistical tests were clearly identified (2 points); whether adjustment of potential confounders were multi-variate or stratified analyses and coding of confounders (2 points); and appropriate handling of crossovers and/or dropouts in the analysis (2 points).

[f] ***Conflict of Interest***: The total maximum score was 2 points. This included whether the study reported the source of funding and the role played by the funding entity.

[g] ***Total Score*** is the mean of the percentage scores from the categories, Representativeness, Bias and Confounding, Description of Therapy/Management, Outcomes and Followup, and Statistical Quality and Interpretation.

Evidence Table 20: Results of studies evaluating long-term outcomes of patients with chronic hepatitis C

Author, Year	Group Description	Avg Length of f/u (Yr)	HCC 5 yr Incidence %	Overall Incidence %	Cirrhosis 5 yr Incidence %	Overall Incidence %	HCV Overall Mortality %	All Cause Related Mortality %	Annual Fibrosis Progression %	Overall Rate of Decompensation %	Comments
Randomized controlled trials											
Bernardinello, 1999	A: 6 mu B IFN/tiw for 6 mos - 3 mu for 6 mos	5.0		5.3				9		24*	Probable death includes OTL
	B: No tx	5.0		4.3				4.4		35*	
Chemello, 1999	A: 3 mu IFN alpha tiw x 6 mos	6									SVR: @ 6 mos., 9% @ 72 mos., 9%
	B: 3 mu IFN alpha qd x 3 mos, then tiw for 3 mos	6									SVR: @ 6 mos., 12% @ 72 mos., 12%
Nishiguchi, 2001	A: Pts w/ HCV given symptomatic tx	8.2	38	73*		56*		58*			
	B: Pts w/ HCV given 6 mu IFN alpha, tiw for 24 wks	9.2	4	27*		29*		11*			

Author, Year	Group Description	Avg Length of f/u (Yr)	HCC 5 yr Incidence %	Overall Incidence %	Cirrhosis 5 yr Incidence %	Overall Incidence %	HCV Overall Mortality %	All Cause Related Mortality %	Annual Fibrosis Progression %	Overall Rate of Decompensation %	Comments
Long-term outcomes of treatment											
Aizawa, 2000	A: IFN therapy	8.25	0	26	-		-				HCC predictors: increased age, heavy drinking, histologic staging
	B: No IFN therapy	8.25	12	45	-		-		-		
Benvegnu, 1997	A: IFN therapy	5.6		5.5							
	B: No IFN therapy	5.6		30.2							
Bruno, 1997	A: IFN therapy	5.7		0							Risk factors included genotype 1b age >60, males
	B: No IFN therapy	5.7		28							
Fattovich, 1997	A: Pts w/ HCV, treated w/ IFN alpha	4.8	4	4					8*		
	B: Untreated controls	5.3	11	12					29*		
Horiike, 1998	A: Complete responders to IFN	7.6	0	0*							Groups A v C and B v C are significant
	B: Nonresponders to IFN	7.6	1.5	2*							
	C: No IFN received	7.6	5	15*							

Author, Year	Group Description	Avg Length of f/u (Yr)	HCC 5 yr Inci-dence %	Over all Inci-dence %	Cirrhosis 5 yr Incidence %	Over all Inci-dence %	HCV Over all Mor-tality %	All Cause Related Mor-tality %	Annual Fibrosis Pro-gression %	Over all Rate of Decomp-ensation %	Comments
Ikeda, 2001	A: No IFN	7.6	28.4	52.5			21	45.8			10 year rate for HCC
	B: Short-term IFN <12 mos	7.6	24.7	64.9			11	19.3			
	C: Long-term IFN >/= 12 mos	7.6	16.0	21.2			8	12			
Inoue, 2000	A: Pts treated w/ IFN	4.6	2.2*	2.2			0	2			Cox 69% decrease in HCC in patients receiving IFN
	B: Pts not treated w/ IFN	5.9	9.5*	14.4			15	12			
Shibata, 1998	A: Chronic hepatitis	3.5		7							Untreated cirrhotics 52% HCC treated noncirrhotics 6.29%
	B: Cirrhosis	3.5		52							

Author, Year	Group Description	Avg Length of f/u (Yr)	HCC 5 yr Inci-dence %	Over all Inci-dence %	Cirrhosis 5 yr Incidence %	Over all Inci-dence %	HCV Over all Mor-tality %	All Cause Related Mor-tality %	Annual Fibrosis Pro-gression %	Over all Rate of Decomp-ensation %	Comments
Shindo M, 2001	A: Complete responders to tx (serum viral response and serum biochemical response)	8-11	3	0	8	8					
	B: Biochemical responders (nl ALT but no loss of virus)		3.9	0	8	8					
	C: Short-term responders (relapse of ALT)				8	8					
	D: Nonresponders				52	65.5					
	E: Control group				35	39					
Tanaka, 2000	A: Pts in IFN tx group w/ sustained response.	5.0	1.2	2			1				Risk of HCC in SR or TR vs controls=.16
	B: Pts in IFN tx group w/ transient response.	4.7	3.7	3			6				
	C: Pts who were nonresponders to IFN.	4.6	10	10			6				
	D: Control group - no IFN	5.6	14	13.1			7				
	E: Groups A, B, C			5.5			7				

Author, Year	Group Description	Avg Length of f/u (Yr)	HCC 5 yr Inci-dence %	Over all Inci-dence %	Cirrhosis 5 yr Incidence %	Over all Inci-dence %	HCV Over all Mor-tality %	All Cause Related Mor-tality %	Annual Fibrosis Pro-gression %	Over all Rate of Decomp-ensation %	Comments
Toyoda, 2001	A: Pts who received >500 mu of IFN.	5		0							Results reported for both groups combined, no difference in HCC by duration, but significant by total dose.
	B: Pts who received <500 mu of IFN.	5		15							
Yabuuchi, 2000	A: Complete responders	4.9	2.3								Group A vs C and group B vs C are significant.
	B: HCV virus+ biochemical responders	5.2	2.0								
	C: Nonresponders	4.9	14.3								
Yatsuhashi, 2000	O: Natural history of HCV in 186 individuals		3.9	45		37					
Long-term studies of natural history											
Barrett, 2001	A: Polymerase chain reaction+ women w/ CHC	22.0		0.0		0.0					
	B: Polymerase chain reaction negative women w/ CHC			0.0		0.0					

Author, Year	Group Description	Avg Length of f/u (Yr)	HCC 5 yr Inci-dence %	Over all Inci-dence %	Cirrhosis 5 yr Incidence %	Over all Inci-dence %	HCV Over all Mor-tality %	All Cause Related Mor-tality %	Annual Fibrosis Pro-gression %	Over all Rate of Decomp-ensation %	Comments
Benhamou, 2001	A: HIV/HCV coinfected pts treated w/ protease inhibitor				2	9			1.36*		
	B: HIV/HCV coinfected pts not treated w/ protease inhibitor				5	27			2.1*		
Chiaramonte, 1999	A: Pts+ for HBsAg	5.5	9	10							Risk factors: age >50, dual infection, male
	B: HCV+ Pts		20	21							
	C: Pts+ for both HBsAg and HCV		40	23							
Cottone, 1994	O: Overall		19								
Forns, 2001	O: Pts w/ noncirrhotic non-A, non-B hepatitis diagnosed at a tertiary hospital between 1971 and 1977	39	6	22	11						

Author, Year	Group Description	Avg Length of f/u (Yr)	HCC 5 yr Inci-dence %	Over all Inci-dence %	Cirrhosis 5 yr Incidence %	Over all Inci-dence %	HCV Over all Mor-tality %	All Cause Related Mor-tality %	Annual Fibrosis Pro-gression %	Over all Rate of Decomp-ensation %	Comments
Furusyo, 2000	A: Hemodialysis pts w/ HCV+ RNA in serum	10	4								
	B: Hemodialysis pts w/ HCV- RNA in serum										
	C: Village residents with HCV viremia										
Gentilini, 1997	O: Pts w/ viral induced cirrhosis		8.6	9		19					
Harris, 2002	A: Transfusion recipients infected w/ HCV	11				1	13				Age, gender, alcohol increase mortality. HCV-RNA level, age >40, duration associated with liver disease.
	B: Transfusion recipients negative for HCV					2	9				
Hayashi, 2000	A: nl ALT levels	5		0*							
	B: Itermittenlty abnl ALT			4*							
	C: Aways abnl ALT			31							
Ikeda, 1993	O: Pts w/ cirrhosis	5.8		28		29					

Author, Year	Group Description	Avg Length of f/u (Yr)	HCC 5 yr Incidence %	Overall Incidence %	Cirrhosis 5 yr Incidence %	Overall Incidence %	HCV Overall Mortality %	All Cause Related Mortality %	Annual Fibrosis Progression %	Overall Rate of Decompensation %	Comments
Kliem, 1996	O: Anit-HCV+ Pts	7.4						9			HBV increases risk of progressive deterioration.
Kobayashi, 1996	A: Pts infected w/ HCV genotype 1	9.4		29							More severe progression in patients w/ genotype 1 than genotype 2
	B: Pts infected w/ HCV genotype 2			6							
Kobayashi, 2000	O: Consecutive pts w/ CHC	5									
Lesens, 1999	A: HIV and HCV+ hemophiliacs	5					9	60			Rate of progressive liver disease: 27% Group A, 6% Group B
	B: HCV+ and HIV- hemophiliacs						0	21			
Matsumura, 2000	A: Pts w/ mild fibrosis	5							12		Overall rate for f1, f2, f3
	B: Pts w/ moderate fibrosis										
	C: Pts w/ severe fibrosis										

Author, Year	Group Description	Avg Length of f/u (Yr)	HCC 5 yr Inci-dence %	Over all Inci-dence %	Cirrhosis 5 yr Incidence %	Over all Inci-dence %	HCV Over all Mor-tality %	All Cause Related Mor-tality %	Annual Fibrosis Pro-gression %	Over all Rate of Decomp-ensation %	Comments
	D: Pts w/ cirrhosis E: Pts w/ HCC										
Meijer, 1999	A: Nl liver/spleen by U/S B: Nl liver, enlarged spleen w/ patent portal splenic veins C: Abnl liver w/ patent portal/splenic veins	19									
Murakami, 1999	A: Pts analyzed for progression to cirrhosis. B: Pts analyzed for progression to HCC.	5.0		12	21						As age at original transfusion inc., cumulative % HCC dec.
Persico, 2000	O: Asymptomatic HCV w/ persistently nl ALT levels	7.0				14					Cirrhosis in patients who did not have persistent nl ALT
Punyagupta, 1999	O: HCV positive patients	5-15		16	3						60% deceased at 10 years and 85% at 15 years.

Author, Year	Group Description	Avg Length of f/u (Yr)	HCC 5 yr Inci-dence %	Over all Inci-dence %	Cirrhosis 5 yr Incidence %	Over all Inci-dence %	HCV Over all Mor-tality %	All Cause Related Mor-tality %	Annual Fibrosis Pro-gression %	Over all Rate of Decomp-ensation %	Comments
Rodger, 1999	A: 35 anti-HCV+ individuals (followed up from a cohort of 238)			0	2						
	B: 70 anti-HCV- controls (followed up from a cohort of 1182)			0	1						
Rostaing, 1996	O: Renal transplant Pts given liver bx										
Takano, 1995	A: CHC pts				10.5						Patients with CHC more histologically advanced
	B: Chronic HBV pts			3.9							
Thomas, 2000	A: IDUs who are HCV w/ ESLD	8.8			7	2	25		2	98	Reported for all groups combined
	B: IDUs who are HCV w/o ESLD										
Yano, 1996	O: HCV+ Pts w/ chronic liver disease	8.8			50						

* denotes statistical significance for a comparison between groups ($p<0.05$)

Evidence Table 21: Overall summary of study addressing efficacy of screening tests for hepatocellular carcinoma to improve outcomes in patients with chronic hepatitis C

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Solmi, 1996	Italy	2530	AFP, U/S, initial liver bx, chronic liver disease regardless of etiology (cirrhotics and noncirrhotics)	HCC	To evaluate the possibilities of diagnosis of HCC at an early stage through the use of serial U/S and AFP on a population at risk for HCC

Evidence Table 22: Characteristics of patients in study addressing efficacy of screening tests for hepatocellular carcinoma to improve outcomes in patients with chronic hepatitis C

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Solmi, 1996	CohP								
		A: Chronic liver disease Pts w/o	360	52	71			S3, A2	29.4
		cancer followed in study center		76					
		B: Pts w/ liver cirrhosis or chronic	2170	56	70			S3, A2	29.9
		hepatitis followed in US clinics		65					

Evidence Table 23: Methodologic quality of study containing efficacy of screening tests for hepatocellular carcinoma to improve outcomes in patients with chronic hepatitis C

Author, Year	Representativeness[a]	Bias[b]	Description[c]	Outcomes[d]	Statistics[e]	Conflict[f]	Total[g]
Solmi, 1996	100	50	100	65	33	0	70

[a] ***Representativeness***: The total maximum for this section was 8 points. This included setting and population described and start and end date specified (2 points); detailed description of inclusion and exclusion criteria or statement that all potential trainees enrolled (2 points); information about excluded or not-participating patients (2 points); and description of key patient characteristics at enrollment (2 points).

[b] ***Bias and Confounding***: The total maximum score was 6 points. This included whether assignment of patients to study groups was randomized (2 points); whether groups had any differences in key patient characteristics (2 points); and whether clinicians, patients, and outcome assessors were blinded (2 points).

[c] ***Description of Therapy/Management***: The total maximum score was 4 points. This included sufficiently detailed description of the screening tests (2 points); and description of other treatments or tests given to subjects (2 points).

[d] ***Outcomes and Followup:*** The total maximum score was 10 points. This included description of complications, side effects and adverse reactions (2 points); sufficient description of criteria for determining outcomes (2 points); reporting on the numbers and reasons for withdrawals from the study or losses to followup (2 points); proportion of patients who withdrew from the study or were lost to followup (2 points); and sufficiency of the planned length of followup (2 points).

[e] ***Statistical Quality and Interpretation***: The total maximum score was 8 points. This included whether magnitude of difference between groups and an index variability was stated (2 points); whether analyses and statistical tests were clearly identified (2 points); whether adjustment of potential confounders were multi-variate or stratified analyses and coding of confounders (2 points); and appropriate handling of crossovers and/or dropouts in the analysis (2 points).

[f] ***Conflict of Interest***: The total maximum score was 2 points. This included whether the study reported the source of funding and the role played by the funding entity.

[g] ***Total Score*** is the mean of the percentage scores from the categories, Representativeness, Bias and Confounding, Description of Therapy/Management, Outcomes and Followup, and Statistical Quality and Interpretation.

Evidence Table 24: Results of study evaluating efficacy of screening tests for hepatocellular carcinoma to improve outcomes in patients with chronic hepatitis C

Article ID	Author, Year	Screening Groups		N	Mean Followup (months)	# Cases HCC	Unifocal at Diagnosis	Resectable at Diagnosis (≤3.0 cm)
2818	Solmi, 1996	A	Chronic liver disease pts w/o cancer followed in study center	360	56	24	18	18
		B	Pts w/ liver cirrhosis or chronic hepatitis followed in US clinics	2170	56	129	20	20

Evidence Table 25: Overall summary of studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Studies of AFP (with or without other tests)					
Studies of HCV patients					
Prospective cohort studies					
Bruno, 1997	Italy	163	Presence of cirrhosis, HCV+, presence of fibrosis	IFN, HCC, Child's C, hemochromatosis, autoimmune hepatitis, sclerosing cholangitis, age >70 yrs, ALT >400	To prospectively follow a cohort of HCV pts w/ cirrhosis and evaluate if the HCV genotype impacts the development of HCC. In addition, the aim was to elicit other independent risk factors for HCC.
Tradati, 1998	Italy	385	Large pool clotting factor concentrates >= 10 yrs before start of study, ALT 1.5x UL of nl 3-6 mos apart		To assess the natural history of HCC in Italian hemophiliacs w/ el ALT To assess whether HCC screening (U/S and AFP) leads to early detection and improved chance of curative tx
Diagnostic Test Design					
Raedle, 1995	Germany	147	Detectable HCV in serum, ALT el	HIV+, other causes of cirrhosis or HCC	To determine the sensitivity and specificity of anti-p53 in screening for HCC in pts w/ CHC

Evidence Table 25: Overall summary of studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Studies of patients with HCV or HBV					
Prospective cohort studies					
Cottone, 1994	Italy	147	Age > 40 yrs, Child's A cirrhosis		To determine the risk of HCC in Child's A cirrhosis, whether 6 mos screening interval is adequate, and determine the role of AFP in screening
Ishii, 2000	Japan	734	HCC at time of entry or w/i 1 yr, presence of fibrosis: histological dx in Pts w/ CHC, agreed to >= 1-y f/u and had >= 6-mo f/u before entry, PIVKA-II, AFP, U/S if HCC was not detected		To determine if AFP and protein induced by vitamin K absence (PIVKA-II) measurements can improve detection of HCC in pts w/ chronic hepatitis.
Izzo, 1998	Italy	1125	Positive sera for HBV surface antigen in 3 separate measures at 3-mo intervals or positive sera for anti-HCV in 3 separate measures at 3-mo intervals, chronic HBV or CHC or both for >5 yrs	Positive previous dx of any type of malignancy, decompensated liver disease: Child's B or C cirrhosis, encephalopathy, bleeding GI varices, ascites	To determine the incidence of HCC (resectable HCC and survival rate) in pts w/ chronic HBV and HCV
Izzo, 1999	Italy	1520	HBsAg in 3 samples at 3-mo intervals or serum positive for anti-HCV virus in 3 samples at 3-mo intervals, chronic HBV or CHC infection or both for >= 5 yrs	Gastroesophageal varices, ascites, hepatic encephalopathy, bleeding, Child's B or C disease, positive history of any type of malignancy	To compare soluble IL-2 receptor to AFP as methods of screening for HCC in pts w/ chronic HBV or HCV. Also, to assess the usefulness of soluble IL-2 receptor as a marker of successful HCC tx and recurrence of disease.

Evidence Table 25: Overall summary of studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Larcos, 1998	Australia	232			To determine the incidence of HCC in pts w/ cirrhosis or chronic hepatitis and to assess cost and potential benefit of sonographic screening
Tong, 2001	United States	602	1 yr-f/u in clinic prior to study, presence of cirrhosis, HBV+ or HCV+	HCC	To determine whether AFP or U/S was more accurate in detecting HCC, and to elucidate problems encountered using these two modalities. Clinical outcomes of pts in whom HCC was detected are also evaluated.
Trevisani, 1995	Italy	475			To determine the prevalence of etiologic factors and clinical manifestations of HCC in pts w/ and w/o cirrhosis
Diagnostic Test Design					
Nomura, 1996	Japan	128		Obstructive jaundice	To assess the diagnostic values of new enzyme immunoassays for des-gamma-carboxy prothrombin (DCP) compared to AFP in small sized HCC

Evidence Table 25: Overall summary of studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Case control studies					
Sassa, 1999	Japan	195	Des-gamma-carboxy prothrombin, AFP		To investigate the effectiveness of high sensitivity des-gamma-carboxy prothrombin and Lens culinaris agglutinin A-reactive AFP screening tests in diagnosing small HCC.
Sato, 1993	Japan	361	Presence of cirrhosis, AFP >= 30 ng/mL		To determine the lectin reactivity of AFP in pts w/ cirrhosis who did and did not develop HCC
Tsai, 1994	China	404			To determine the frequency of raised AFP level among Chinese pts w/ HCC related to HBV and HCV
Tsai, 1995	Tiawan	256	Presence of cirrhosis, no previous therapy, serum samples collected		To evaluate the diagnostic efficacy of AFP and 4% PEG-CICs, and C1 q-CICs in detecting HCC in cirrhotic patients
Tsai, 1997	China	238	HCC group A, presence of cirrhosis: groups A and B	Previous treatment for cirrhosis or HCC, EtOH for HCC pts but not clear for control group	To evaluate the diagnostic efficacy of urinary transforming factor B-1 (TGF-B1) and AFP levels for detection of HCC in cirrhotic pts.

Evidence Table 25: Overall summary of studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Van Roey, 2000	Belgium	140	Initial liver bx, HCC	Non-HCC primary lesion of liver at dx or f/u	To study the characteristics of HCC pts w/ emphasis on the difference between cirrhotic HCC and noncirrhotic HCC pts
Cross-sectional studies					
Cedrone, 2000	Italy	350	ALT >2 x UL of nl	Pregnancy, autoimmune disorders, chronic alcohol abuse	To verify (in Western pts) w/ post-viral chronic liver disease, the utility of AFP for the detection of HCC, and the influence of HCV and HBV viral etiology on AFP levels in HCC.
Studies of other serological tests (without AFP)					
Studies of HCV patients					
Prospective cohort studies					
Kakumu, 1997	Japan	82			To understand the roles of sTNF-alpha, IL-10, and IL-15 in the pathogenesis of type C chronic liver disease using ELISA.
Studies of patients with HCV or HBV					
Cross-sectional studies					
Tsuzurahara, 1997	Japan	170	HBV+, detectable HCV in serum, HCV+		To determine whether MAGE-4 protein is detectable in sera of pts w/ HCC and other liver diseases

Evidence Table 25: Overall summary of studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Case control studies					
Nagai, 2001	Japan	129	ALT, AFP, initial liver bx, HCC (not an inclusion criteria in the controls), presence of cirrhosis, presence of fibrosis, HCV+		To assess if cytokeratin 19 fragment (CK19) will be increased in serum from pts w/ hepatoma.
Studies of imaging (without AFP)					
Studies of HCV patients					
Prospective cohort studies					
Kasahara, 1998	Japan	1022	ALT >= 2x UL of nl for >=6 mos, initial liver bx, positive HCV antibodies	<200 mu IFN, duration of f/u <12 mos, encephalopathy, ascites, varices, autoimmune liver disease, alcoholic liver disease, HCC w/i 1 yr of IFN therapy, HBV+	To evaluate the effect of IFN on HCC by assessing risk factors for carcinogenesis and incidence of HCC in pts w/ CHC treated w/ IFN.
Studies of patients with HCV or HBV					
Prospective cohort studies					
Colombo, 1991	Japan	447	Age > 36 yrs, Presence of fibrosis/cirrhosis, Childs A or B, willing to participate in follow-up visits	HCC	To assess the magnitude of risk, the natural history of disease, and the possibilities of detecting potentially resectable tumors.

Evidence Table 26: Characteristics of patients in studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Studies of AFP (with or without other tests)										
Studies of HCV patients										
Prospective cohort studies										
Bruno, 1997	CohP									
		O: All HCV+ cirrhotic pts attending an outpt clinic	163	57.8 50						
									1a	0.61
									1b	61.96
									2a/c	29.45
									3a	1.23
									mixed	1.84
									not specified	4.91
Tradati, 1998	CohP									
		O: Hemophiliacs treated w/ blood or plasma products w/ el aminotransferases	385	31 [m] 98	10				20	
Diagnostic Test Design										
Raedle, 1995	DTD									
		O: Pts w/ CHC	147	47.1 60						

Evidence Table 26: Characteristics of patients in studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Studies of patients with HCV or HBV									
Prospective cohort studies									
Cottone, 1994	CohP	O: Child's A cirrhosis pts receiving periodic screening by AFP and U/S of the liver	147	58 55					
Ishii, 2000	CohP	A: HBsAg+ Pts w/ cirrhosis	27						
		B: HCV+ Pts w/ chronic hepatitis	295						
		C: HCV+ Pts w/ cirrhosis	268						
		D: HBsAg+ Pts w/ cirrhosis, who were+ for HCV	4						
Izzo, 1998	CohP	O: 1125 Pts w/ HBV or HCV or HBV and C infection of >5 yrs	1125	56.1				S3, A2 28.9 S3, A2 71.1	 10.2
Izzo, 1999	CohP	O: 1520 Pts w/ HBV, HCV or HBV and HCV for >5 yrs	1520	56 61				S3, A2 69.9 S4, A3 30.1	 10.6

Evidence Table 26: Characteristics of patients in studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Larcos, 1998	CohP								
		O: Pts w/ chronic hepatitis and/or cirrhosis	232	51 66 A: 20.6				S3 A2 51.3	
Tong, 2001	CohP								
		A: Pts w/ HBV infection	160	46 71 C: 13.7, B: 4.37, A: 78.7, O: 3.12					
		B: Pts w/ HCV infection	429	53 54 C: 55.9, B: 6.29, A: 17.7, O: 20.0					
		C: Pts w/ both HBV and HCV infections	13	49 77 C: 46.1, A: 46.1, O: 7.69					

Evidence Table 26: Characteristics of patients in studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Trevisani, 1995	CohR								
		A: HCC pts w/ cirrhosis	373	61.5 79					
		B: HCC pts w/o cirrhosis	102	58 61					
Diagnostic Test Design									
Nomura, 1996	DTD								
		A: HCC	27	74					
		B: Cirrhosis	69						
		C: Minimal or mild chronic hepatitis with no or mild fibrosis	17						
		D: Moderate or severe chronic hepatitis with moderate or severe fibrosis	15						

Evidence Table 26: Characteristics of patients in studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Case control studies									
Sassa, 1999	CC								
		A: Cases: HCC <2 cm maximum diameter in Pts w/ CHC and cirrhosis	61	62 A: 100					
		B: Controls: Pts w/ chronic hepatitis or cirrhosis	134	A: 100					
Sato, 1993	CC								
		A: Cirrhosis caused by HCV or HBV w/ baseline AFP >/= 30 ng/mL and subsequent HCC	33	54 73					
		B: Cirrhosis caused by HCV or HBV w/ baseline AFP >/= 30 ng/mL w/o subsequent HCC	32	50 81					
Tsai, 1994	CC								
		A: HCC pts	177	59 85					
		B: Health community controls	177	85					

Evidence Table 26: Characteristics of patients in studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Tsai, 1995	CC								
		A: Cirrhotics w/ HCC	101	57 91					
		B: Sex-age matched controls w/ cirrhosis	101						
		C: Healthy volunteers	54	55 85					
Tsai, 1997	CC								
		A: Non-alcoholic cirrhotic HCC	94	58 [m] 81					
		B: Cirrhosis alone	94						
		C: Healthly controls: anti-HCV and anti-HBV negative	50	55 [m] 78					
Van Roey, 2000	CC								
		A: Noncirrhotics w/ HCC	56	50 61					36
		B: Cirrhotics w/ HCC	84	62 82					64

Evidence Table 26: Characteristics of patients in studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Cross sectional studies									
Cedrone, 2000	XS								
		A: Pts w/ HCC and cirrhosis	74	65.5					
		B: Pts w/ cirrhosis	72	61.3					
		C: Pts w/ chronic hepatitis	197	53.7					
		D: Pts w/ nl liver at bx	7	54.5					

Evidence Table 26: Characteristics of patients in studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Studies of other serological tests (without AFP)									
Studies of HCV patients									
Prospective cohort studies									
Kakumu, 1997	CohP								
		A: Asymptomatic HCV carriers w/ nl ALT for at least 1 yr	10	49 50					32
		B: Pts w/ chronic hepatitis and el ALT for at least 1 yr	28	54 71					111
		C: Pts+ for HCV-RNA w/ el ALT for at least 1 yr and cirrhosis	22	61 73					85
		D: Pts w/ HCC	11	66 82					78
		E: Healthy, HCV- controls, w/o a history of hepatitis and w/o liver disease	11	45 64					

Evidence Table 26: Characteristics of patients in studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Studies of HCV or HBV patients									
Cross sectional studies									
Tsuzurahara, 1997	XS								
		A: Chronic HCV	70	51.2 49 A: 100					
		B: Chronic HCV w/ cirrhosis	55	61.5 44 A: 100					
		C: Chronic HCV w/ HCC	45	63.4 82 A: 100					
		D: Others							

Evidence Table 26: Characteristics of patients in studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Studies of patients with HCV or HBV									
Case control studies									
Nagai, 2001	CC								
		A: Pts w/ HCC	70	60 76 A: 100					
		B: Pts w/ CAH	14	53 64 A: 100					
		C: Pts w/ liver cirrhosis	45	58 67 A: 100					

Evidence Table 26: Characteristics of patients in studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Studies of imaging (without AFP)										
Studies of HCV patients										
Prospective cohort studies										
Kasahara, 1998	CohP									
		A: Sustained responders (6 mos following tx)	313	52.4 67		HAI	9			
									1	35.46
									2	34.82
									mixed	2.56
									unclassified	0.96
									untested	26.20
		B: Transient response	304	52.6 66		HAI	8.9			
									1	68.42
									2	10.53
									mixed	0.99
									unclassified	0.00
									untested	20.07
		C: Nonresponders	405	53.5 68		HAI	9.6			
									1	67.90
									2	9.63
									mixed	0.00
									unclassified	0.25
									untested	22.22

Evidence Table 26: Characteristics of patients in studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Studies of patients with HCV or HBV									
Prospective cohort studies									
Colombo, 1991	CohP								
		A: (Overall) Italian pts with cirrhosis	447	55 69					
		B: detectable with HCC at enrollment	30	59 80					
		C: detectable with HCC over follow-up	29	58 79					

[m] Value given is a median

Evidence Table 27: Methodologic quality of studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C

Author, Year	Representativeness[a]	Bias[b]	Description[c]	Outcomes[d]	Statistics[e]	Conflict[f]	Total[g]
Studies of AFP (with or without other tests)							
Studies of HCV patients							
Prospective cohort studies							
Bruno, 1997	100	50	50	83	67	50	70
Tradati, 1998	63	100	100	33	50	50	69
Diagnostic Test Design							
Raedle, 1995	75	50	100	0	100	0	65
Studies of patients with HCV or HBV							
Prospective cohort studies							
Cottone, 1994	50	50	100	13	100	0	63
Ishii, 2000	75	--	100	83	67	0	81
Izzo, 1998	75	0	100	25	50	50	50
Izzo, 1999	83	50	100	25	75	0	67
Larcos, 1998	25	50	100	100	25	0	60
Tong, 2001	63	0	100	50	67	0	56

Evidence Table 27: Methodologic quality of studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C (continued)

Author, Year	Representativeness[a]	Bias[b]	Description[c]	Outcomes[d]	Statistics[e]	Conflict[f]	Total[g]
Trevisani, 1995	88	50	50	0	100	50	58
Diagnostic Test Design							
Nomura, 1996	25	50	100	0	0	0	35
Case control studies							
Sassa, 1999	13	0	50	50	50	0	33
Sato, 1993	50	50	100	0	67	0	53
Tsai, 1994	88	50	50	67	100	50	71
Tsai, 1995	50	50	100	100	100	0	80
Tsai, 1997	63	50	50	50	100	0	63
Van Roey, 2000	38	50	50	100	75	0	63
Cross sectional studies							
Cedrone, 2000	88	50	100	50	100	0	78
Studies of other serological tests (without AFP)							
Studies of HCV patients							
Prospective cohort studies							
Kakumu, 1997	50	--	100	17	100	50	67

Evidence Table 27: Methodologic quality of studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C (continued)

Author, Year	Representativeness[a]	Bias[b]	Description[c]	Outcomes[d]	Statistics[e]	Conflict[f]	Total[g]
Studies of patients with HCV or HBV							
Cross sectional studies							
Tsuzurahara, 1997	25	50	50	100	100	50	65
Case control studies							
Nagai, 2001	38	0	50	100	67	0	51
Studies of imaging (without AFP)							
Studies of HCV patients							
Prospective cohort studies							
Kasahara, 1998	100	100	100	69	67	0	87
Studies of patients with HCV or HBV							
Prospective cohort studies							
Colombo, 1991	88	0	100	83	75	0	69

Evidence Table 27: Methodologic quality of studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C (continued)

Author, Year	Representativeness[a]	Bias[b]	Description[c]	Outcomes[d]	Statistics[e]	Conflict[f]	Total[g]

[a] ***Representativeness***: The total maximum for this section was 8 points. This included setting and population described and start and end date specified (2 points); detailed description of inclusion and exclusion criteria or statement that all potential trainees enrolled (2 points); information about excluded or not-participating patients (2 points); and description of key patient characteristics at enrollment (2 points).

[b] ***Bias and Confounding***: The total maximum score was 2 points. This included whether there was an independent, blind comparison with a reference standard.

[c] ***Description of Therapy/Management***: The total maximum score was 2 points. This included sufficiently detailed description of the screening tests

[d] ***Outcomes and Followup:*** The total maximum score was 8 points. This included description of complications, side effects and adverse reactions (2 points); sufficient description of criteria for determining outcomes (2 points); reporting on the numbers and reasons for withdrawals from the study or losses to followup (2 points); and proportion of patients who withdrew from the study or were lost to followup (2 points).

[e] ***Statistical Quality and Interpretation***: The total maximum score was 6 points. This included whether magnitude of difference between groups and an index variability was stated (2 points); whether analyses and statistical tests were clearly identified (2 points); and appropriate handling of crossovers and/or dropouts in the analysis (2 points).

[f] ***Conflict of Interest***: The total maximum score was 2 points. This included whether the study reported the source of funding and the role played by the funding entity.

[g] ***Total Score*** is the mean of the percentage scores from the categories, Representativeness, Bias and Confounding, Description of Therapy/Management, Outcomes and Followup, and Statistical Quality and Interpretation.

Evidence Table 28: Results of studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C

Author, year	N	Study Design	Test (cutoff)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Studies of AFP (with or without other tests)							
Studies of HCV patients							
Cohort studies							
Bruno, 1997	163	CohP	AFP >20 ng/mL	27			
			AFP >400 ng/mL	4.5			
Tradati, 1992	385	CohP	AFP >11mg/mL	100			
			AFP >400 mg/mL	17			
Diagnostic Test Design							
Raedle, 1995	174	DTD	AFP >20 ng/mL	86	86		
			AFP >100 ng/mL	43	99		
			AFP >400 ng/mL	14			
			+anti-p53	43	100		
			AFP >20 ng/mL & +anti-p53	86	86		
			AFP >100 ng/mL & +anti-p53	71	99		

Evidence Table 28: Results of studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C (continued)

Author, year	N	Study Design	Test (cutoff)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Studies of patients with HCV or HBV							
Prospective cohort studies							
Cottone, 1994	147	CohP	AFP >50 ng/mL	36			
			AFP >400 ng/mL	0			
Ishii, 2000	734	CohP	AFP >= 20 ng/mL	61	78	6.5	98
			AFP >= 40 ng/mL	45			
			PIVKA-II >60 mA U/mL	41	91	16	97
			AFP >= 40ng/mL and PIVKA II >80 mAU/mL	66	85	15	98
Izzo, 1998	1125	CohP	AFP >10 ng/mL	75			
			U/S	87			
			U/S or AFP >10 ng/mL	100			

Evidence Table 28: Results of studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C (continued)

Author, year	N	Study Design	Test (cutoff)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Izzo, 1999	1520	CohP	AFP >10 ng/mL	80	95	81	94
			S-IL2R >850 U/mL	99	96	86	100
			U/S	66			
			CT/MRI	100			
Larcos, 1998	232	CohP	AFP >81 ng/mL	17		3%	
			U/S			24	
Tong, 2001	1204	CohP	AFP >13 ng/mL	59	91	11	99
			AFP >19 ng/mL	45	94	11	99
			AFP >21 ng/mL	41	94	11	99
			AFP >24 ng/mL	41	95	12	99
			U/S	100	98	78	100

Evidence Table 28: Results of studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C (continued)

Author, year	N	Study Design	Test (cutoff)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Trevisani, 1995	475	CohR	AFP>20 Solitary HCC	50			
			AFP>20 Massive HCC	50			
			AFP>20 Diffuse	70			
			AFP>20 Multimodular	70			
			AFP>40 Solitary	14			
			AFP>40 Massive	38			
			AFP>40 Diffuse	38			
			AFP>40 Multimodular	27			
Diagnostic Test Design							
Nomura, 1996	128	DTD	AFP >20	63			
			Conventional DCP	17			
			Overnight DCP	29			
			Avidin biotin complex DCP	33			

Evidence Table 28: Results of studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C (continued)

Author, year	N	Study Design	Test (cutoff)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Case control studies							
Sassa, 1999	195	CC	AFP >200 mg/mL	8	100		
			AFP >200 ng/mL and AFP L3 >10%	25	99	94	74
			AFP L3 >10%	23	99	93	74
			H-DCP >40 mAU/mL	45	99	93	80
			H-DCP > and AFP >200 ng/mL	47.5	99	94	81
			H-DCP > and AFP L3 >10%	54	98	92	83
Sato, 1993	361	CC	AFP >=30 ng/mL	68			
			AFP <30 ng/mL	86			
Tsai, 1994	404	CC	AFP >20 ng/mL	74	100		
			AFP >400 ng/mL	54			

Evidence Table 28: Results of studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C (continued)

Author, year	N	Study Design	Test (cutoff)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Tsai, 1995	256	CC	AFP >20 ng/mL	77			
			AFP >120 ng/mL	67			
			AFP >400 ng/mL	64			
			3% PEG circulating immune complexes	65			
			AFP >120 ng/mL + 3% PEG CIC	84	100		
			AFP >400 ng/mL + 3% PEG CIC	83	100		
Tsai, 1997			AFP >100 ng/mL	55	99	98	69
			AFP >400 ng/mL	48	100	100	66
			TGF B1>=50 mg/gCr	53	99	98	68
			TGF B1 >=50 or AFP >100 ng/mL	84	98	98	86
			TGF B1>=50 mg/gCr or AFP >400 ng/mL	80	99	99	83

Evidence Table 28: Results of studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C (continued)

Author, year	N	Study Design	Test (cutoff)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Van Roey, 2000	140	CC	AFP>20 ng/mL	62			
			AFP>50 ng/mL	55			
			AFP>400 ng/mL	43			
			U/S	51			
Cross sectional studies							
Cedrone, 2000			AFP >13 ng/mL	70	83	53	
			AFP >13 ng/mL in cirrhotic pts.	70	71	71	
			AFP >20 ng/mL	55	88	55	
			AFP >20 ng/mL in cirrhotic pts.	55	79	73	
			AFP >50 ng/mL	35	94	70	
			AFP >50 ng/mL in cirrhotic pts.	35	94	87	
Studies of other serological tests (without AFP)							
Studies of HCV Patients							
Prospective cohort studies							
Kakumu, 1997	80	CohP	IL10>5 pg/ml	63			
			IL15 >70 pg/ml	45			

Evidence Table 28: Results of studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C (continued)

Author, year	N	Study Design	Test (cutoff)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Studies of HCV or HBV patients							
Cross sectional studies							
Tsuzurahara, 1997	170	XS	MAGE 4 >1.04 ng/mL	47	77	43	80
Case control studies							
Nagai, 2001	129	CC	CK >2.5 ng/mL	47	95	92	61
Studies of imaging (without AFP)							
Studies of HCV patients							
Prospective cohort studies							
Kasahara, 1998	1022	CohP	U/S and CT		96		
Studies of HCV or HBV patients							
Prospective cohort studies							
Colombo, 1991	447	CohP	U/S	49			
			U/S + CT	93			