Issue Summary
Blood Products Advisory Committee
October 21-22, 2004

Topic III: FDA's current thinking on Donor Deferral for Potential or Documented Infection with West Nile Virus

Issue:

FDA is considering updating its current guidance on West Nile virus (WNV) based on recent reports that viremia can last for 49 days. FDA seeks the advice of the Blood Products Advisory Committee whether available scientific data support

1) A revised deferral period of 56 days (instead of 28 days) for blood donors who reported symptoms of headache and fever, or had positive screening tests by NAT; and

2) A new recommendation that donors who are deferred either based on a positive test for WNV or suggestive symptoms should be tested and found negative by ID-NAT on a follow-up blood sample prior to reentry after 56 days.

Background (Currently Recommended Donor Deferral Criteria):

A summary of WNV epidemiology and the experience to date with donor screening is provided in an appendix.

Donor deferral based on reactive NAT results
According to the FDA's current guidance (http://www.fda.gov/cber/gdlns/wnvguid.htm), when a donor's sample tests positive on the individual donation, the donor is temporarily deferred, notified of test results and counseled appropriately. FDA recommended a deferral period of 28 days consistent with the longest known duration of the WNV viremic period. However, under the clinical trial INDs, the donor is asked to enroll in follow-up studies to document IgM seroconversion with a suitable serologic test, and, additionally, a negative NAT result after 28 days is required for donor reentry. Alternatively, the donor may be re-tested prior to 28 days to confirm results obtained on the index donation. If negative NAT results are obtained, the donor may be reinstated after the 28-day period. If NAT results are positive, the donor should be deferred for an additional 28 days, whether or not the IgM test is positive. Note that one IND recently has been modified to permit donor reentry after 56 days in the absence of ID NAT testing.

Data collected in these clinical trials have shown that, in rare instances, an extended viremic period may occur in blood donors for up to 49 days. FDA is in the process of modifying the guidance to address these new data. FDA's current thinking is to recommend extension of the deferral period from 28 days to 56 days following a positive

WNV NAT result or implication of the donor in a possible WNV transfusion-transmission. In addition, FDA's current thinking is to recommend a negative ID-NAT result as a precondition for re-entry in these situations. However, it has been suggested that FDA should consider recommending "automatic" donor re-entry after 56 days in the absence of follow-up testing by IgM or NAT.

Donor deferral based on WNV symptoms

Based on information from previous studies where the longest known period of viremia was 28 days, the current guidance recommends that potential donors with a medical diagnosis of WNV infection (including diagnosis based on symptoms and laboratory results) should be deferred for 28 days from the onset of illness or 14 days after the condition is considered to be resolved, whichever is the later date. In well-documented instances of WNV transmission by blood transfusion, the blood donor later reported symptoms immediately before or after the donation that was found to be negative using a MP-NAT method. Questions regarding previous symptoms are included as part of current donor selection criteria. The current guidance recommends that donors should be questioned about fever and headache in the past week, and those who report these symptoms should be deferred for 28 days from the date of the interview. There are no data on the predictive value of the donor questions, since donors that report fever and headache in the previous week are not tested for WNV. Likewise, the duration of viremia in donors who may be deferred for these symptoms has not been studied. FDA's current thinking is to recommend extension of the deferral period to 56 days for a donor reporting headache with fever in the past week, and to allow automatic re-entry after 56 days. Current thinking also includes re-entry of such donors after 28 days when a WNV ID-NAT or WNV IgM test is negative.

Discussion:

Risk of blood infectivity at different stages of WNV infection

Blood units identified as WNV NAT positive can be classified into different stages of infection: (1) The early phase with very low viral load only detected sporadically by ID NAT and with no IgM; (2) low viral load consistently detected by ID NAT but still negative by MP-NAT and IgM negative; (3) higher viral load detectable by MPNAT and IgM negative; (4) decreased viral load only detectable by ID NAT and IgM positive; (5) convalescent phase with low viral load sporadically detected by ID NAT and IgM/IgG positive. Although WNV has been transmitted by donations from donors with negative MP NAT, but positive ID NAT, the infectivity of such units, particularly those containing IgM, needs to be further investigated. Infectivity studies in non-human primates using low-level viremic donor units in the presence and absence of coexisting IgM antibodies are essential to determine the role of antibodies in WNV transmission by blood transfusion. Currently, such studies are under development.

Current knowledge about the viremic period in human WNV infection

The dynamics of WNV infection and replication in human are poorly understood. Based on follow up data of blood donor screening collected as part of clinical trials for WNV NAT INDs, the period of viremia after WNV infection can in some cases be as long as 49 days. A low level of viremia in the presence of IgM and/or IgG antibodies was found to occur for days or weeks in some cases. Data on the duration of WNV viremia that were obtained from the clinical trials will be presented. In addition, the committee will be updated on the outcome of ID-NAT testing which was performed in high WNV incidence areas in 2004.

Questions for the Committee:

1. Do the available scientific data support extending the currently recommended deferral period of 28 days to 56 days
    a. for blood donors with positive WNV NAT screening tests; and
    b. for blood donors who report symptoms of headache with fever in the week before donation?

2. Do the scientific data support a recommendation to obtain a negative result by ID NAT prior to reentry of blood donors who are deferred
    a. on the basis of reactive NAT; and
    b. on the basis of symptoms?

3. Are there other alternatives that should FDA consider regarding criteria to reenter donors who are deferred for WNV based either on NAT or symptoms?

Appendix

History of West Nile Virus Outbreaks

West Nile virus (WNV) is an arbovirus in the *Flaviviridae* family, for which most (80%) infections are asymptomatic. WNV symptomatic infections range from mild febrile illness, meningitis, encephalitis, and death. Primarily a wild bird infection transmitted by mosquito-bites, WNV also infects mammals including humans. WNV was first recognized in the Western Hemisphere during an outbreak in New York in 1999, followed by rapid dissemination across North America, and its geographic range now encompasses 47 of the 48 contiguous United States and Puerto Rico, 7 Canadian provinces and several Mexican states.

While sporadic outbreaks have been documented around the world including, Israel (1951-54, 1957 and 2000), France (1962 and 2000), South Africa (1974), Romania (1996), Italy (1997), Russia (1999), the sixth consecutive outbreak is now occurring in the US (1999 – 2004). Since the first outbreak, the virus has caused 14,163 known human cases (62 in 1999, 21 in 2000, 66 in 2001, 4,156 in 2002 and 9,858 in 2003) and at least 565 human deaths (6 in 1999, 2 in 2000, 9 in 2001, 284 in 2002 and 264 in 2003). CDC has reported the spread of infection among mosquito species to include C. tarsalis which is known to bite equally both birds and mammals.

The epidemics of WNV in the US in 2002 and in 2003 represent the largest outbreaks of WNV ever reported, with highest number of cases of neuroinvasive illnesses (including: meningitis, encephalitis and meningoencephalitis) in the western hemisphere, with 2,942 cases in 2002 and 2,863 in 2003. Neurological illness occurs in 1:150 infected people. Based on the number of cases of neurological illness reported to the CDC, it is calculated that there were over 400,000 cases of WNV infection in each of 2002 and 2003 epidemics.

CDC first report of human infection in 2004 epidemic was in early May. As of August 31, 2004 there are 1053 human cases, mostly in the West of the country (Arizona and California) and 28 fatalities reported

Human-to-human transmission of WNV – In 2002 CDC reported that WNV could be transmitted from human to human through organ transplantation, breast-feeding, transplacental from mother-to child and by blood transfusion. Retrospective studies in 2002 led to the identification of 23 cases of WNV transmission by blood transfusion. From June to December 2003 approximately 6 million donations were tested for WNV as part of nationwide clinical trial under IND for NAT assays, resulting in the identification of over 818 viremic donations, which were removed from the blood supply. Clearly screening assays improved blood safety. Nevertheless, six cases of transmission by transfusion of blood components containing low level of virus were identified by investigational studies of WNV reported cases to the CDC or as result of retrospective studies of MP-NAT non-reactive units re-tested individually (ID-NAT) to determine the sensitivity and adequacy of MP-NAT testing algorithms.

WNV and blood screening – In 2003, two newly developed nucleic acid tests (NAT) for blood donation screening were approved by the FDA and implemented under the approved Investigational New Drug (IND) mechanism in a nationwide clinical trial. Initial screening protocols included NAT performed on mini-pools (MP NAT) of samples from six or 16 donations, depending on the test-kit manufacturer. Individual donation tests (ID-NAT) are performed in all samples composing a reactive mini-pool to identify and retrieve the infected unit(s) from the blood supply. In addition, selected blood banks in areas with high epidemic activity discontinued use of the MP NAT screening algorithm and implemented ID-NAT screening during limited periods of the epidemic season. Donations that were ID NAT-reactive were not released for transfusion, and these donors were deferred from donation. As a result of the widespread use of these tests, it is estimated that at least 818 (I thought there were >1000 cases) presumptively viremic donations were removed from the blood supply in 2003.

The 2004 epidemic started in early May (MMWR June 11,2004: 484). By August 26, there were 329 IR blood donations. Of these 123 were confirmed by alternate NAT and/or IgM/G; 95 were negative; the remaining results are pending.

Unit management - FDA considers the test result on the individual donation to indicate the infectious status of the donation. According to current testing algorithms if one or more reactive donations were identified upon individual donation testing, all non-reactive units are released (if donations are deemed otherwise suitable for release). Reactive results obtained with the investigational test are confirmed by testing a follow-up sample. The sample is tested using an investigational NAT, and validated IgM and alternate NAT assay. A positive IgM test result confirms a reactive NAT result obtained on the index donation. This additional testing helps to validate the investigational test and establish its performance characteristics with regard to sensitivity and specificity.
If a master pool is reactive and all individual donations are non-reactive, a fresh specimen from each of the index donations is tested using the original NAT and the alternate NAT method. If reactive results are obtained on further testing, the donor is notified of deferral.

Selected References

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(2) Pealer LN, Marfin, AA, Petersen LR, et al. Transmission of West Nile Virus Through Blood Transfusion in the United States in 2002. N Engl J Med 2003; 349:1236-1245
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(4) MMWR Intrauterine West Nile Virus Infection – New York 2002. Vol 51, No 50; 1135 12/20/2002
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