Summary

Objectives

Periodontal diseases are bacterial infections that occur at or below the gum line. In contrast to gingivitis, which affects only the gums, periodontitis (severe periodontal disease) may involve the soft tissue and bone supporting the teeth. An estimated 70 percent of the adult U.S. population is affected by these infections. This includes 20–30 percent who have periodontitis that threatens the loss of teeth. Approximately $5 billion is spent on treatment of periodontal diseases each year. This report deals with the treatment of chronic periodontitis in adults.

The key question is whether scaling and root planing (SRP) accompanied by an antimicrobial agent, as a supplemental or adjunct treatment, results in improved outcomes that persist over time in adults with chronic periodontitis when compared with SRP alone (or SRP and placebo) . The primary outcomes of interest in this report are reductions in probing depth (PD) and gains in clinical attachment level (CAL). Of secondary interest are reductions in selected disease-causing bacteria, particularly reduction in the percentage of spirochetes present in dental plaque or in fluid from the gingival crevice.

Methodology

Search Strategy

The research team performed automated searches of MEDLINE™ and EMBASE™ to identify published primary research that contained evidence related to the key question. The authors tailored the searches to the key question. They did not seek out unpublished research, but hand-searched the last 12 months of the three most relevant journals, to be sure to include recent articles that might not have been indexed in time for the searches. Using key words, the authors limited the MEDLINE searches by dental condition (periodontitis), treatments (scaling, root planing, use of specific antimicrobial drugs), and study designs (controlled clinical trials) of interest. EMBASE was searched by condition and study design.

Selection Criteria

Only research articles published in English involving human subjects, and whose study design was a controlled clinical trial, were included in the review. The trials all had to test one or more chemical antimicrobial agents as an adjunct to SRP. To be included, the study needed to have a concurrent control group that received the same type of SRP as did the treatment group. Generally, if multiple antimicrobials were being tested, the study had to report outcomes for each agent separately. An exception was made for one commonly used drug combination (metronidazole and amoxicillin). Outcomes had to be reported for specified, fixed time periods.

The authors included only studies in which their samples were described as persons with chronic (or adult) periodontitis; thus, studies of forms of the disease described as aggressive, early onset, juvenile, and refractory were excluded. Also excluded were studies of people with diabetes, smokers, and those infected with HIV/AIDS, because of behavioral or comorbid factors

that can complicate treatment. Despite the authors' effort to standardize the type of disease studied, the samples of subjects remained diverse, including persons never before treated for periodontitis, those on maintenance regimens, and subjects with active disease. In addition, the patient samples typically were described as covering a range of disease severity, such as moderate to severe periodontitis.

Data Collection and Analysis

The researchers performed independent, dual reviews of titles or abstracts on a total of 599 articles that were found using automated searches of MEDLINE and EMBASE and through hand-searches of reviews and recent journals. These searches were used to identify potentially useful articles that were obtained and abstracted. Data from these abstracted articles was included in evidence tables separately by the type of antimicrobial agent used and whether the agent was delivered systemically or locally.

A single reviewer read the relevant portions of each article to establish its eligibility for inclusion in the report. Another reviewer independently assessed the excluded articles to assure that they were properly removed from full review and abstraction. Individual abstractors extracted data from the tables and text of included articles, and the report's authors independently confirmed the abstracted data as they prepared the evidence and text tables, and analyzed the results. Articles excluded after the start of data abstraction were reviewed by a second reviewer, as described above, for confirmation of the exclusion decision.

This process reduced the total number of included articles to 67. Suggestions made during peer review of the draft report led to the inclusion of an additional three studies, for a total of 70 articles. Several studies had multiple intervention arms, so that a single study could contribute to the evidence on more than one adjunct therapy. Analysis of these studies consisted of a descriptive synthesis—primarily of changes in PD, CAL, and microbiological composition. When necessary data was available from at least three studies, the authors also conducted a meta-analysis to provide a quantitative synthesis and overall estimates of the adjunct's effectiveness.

Findings

The authors conducted separate analyses of the following agents as adjuncts to SRP: tetracycline, minocycline, metronidazole, the combination of metronidazole and amoxicillin, and chlorhexidine. For tetracycline, minocycline, and metronidazole, they did separate analyses for systemically and locally delivered adjunct treatments. Local treatment delivery methods included irrigants, gels, ointments, microcapsules, and impregnated strips, chips, and fibers.

The authors also analyzed agents that appeared in the literature as part of only one or two identified eligible studies. These were grouped together, either as other antibiotics (doxycycline, azithromycin, spiramycin, and ofloxacin), or as other antimicrobials (fluorides, hydrogen peroxide, povidone iodine, triclosan, and tetrapotassium peroxydiphosphate).

Tetracycline. For systemic tetracycline (five studies), there was a greater reduction in PD with adjunct treatment than using SRP alone, but no individual difference reached statistical

significance. The meta-analysis produced an estimated overall difference of 0.15 mm in PD reductions, favoring the use of SRP with systemic tetracycline over SRP alone, but this difference also did not reach statistical significance. One of the four studies that measured CAL gain produced a statistically significant reduction of 0.31 mm, favoring the use of the adjunct with SRP over SRP alone.

The weight of the available evidence supports the effectiveness of locally applied tetracycline as an adjunctive therapy. Of the 16 studies of locally applied tetracycline preparations, four demonstrated statistically significant PD reductions ranging from 0.41 mm to 0.93 mm, favoring the experimental group. The overall estimated PD reduction—0.47 mm—was statistically significant, favoring the adjunct treatment. Only two studies in this group showed a statistically significant gain in CAL, 0.15 mm and 0.48 mm, respectively; the overall effect size from the meta-analysis was a statistically significant 0.24 mm CAL gain.

Minocycline. Neither of the two studies of systemic minocycline used as an adjunct to SRP provided any statistically significant evidence for its use in reducing PD or increasing gains in CAL.

The eight studies of locally applied minocycline are more supportive of its use as an adjunct to SRP. Four studies reported statistically significant reductions in PD. These ranged from 0.30 mm to 1.10 mm, with this latter amount reported for persons whose initial probing depth was 7 mm or greater. The mean effect size from the meta-analysis was a statistically significant 0.49 mm reduction in PD, favoring use of local minocycline. A very similar result was reported for CAL gain, with three studies showing statistically significant gains in CAL of 0.39 mm to 0.80 mm. The mean effect size from the meta-analysis was a statistically significant 0.46 mm gain in CAL and favored the use of the adjunct.

Metronidazole. Only two of the seven studies of systemic metronidazole used as an adjunct to SRP reported statistically significant reductions in PD over SRP alone. They ranged from 0.47 mm to 1.64 mm and represented subpopulations with initial probing depths of 4 mm to 6 mm and more than 6 mm, respectively. Two studies also reported statistically significant gains in CAL with the adjunctive use of systemic metronidazole, ranging from 0.47 mm to 1.19 mm, again in persons with relatively deep initial PD.

Four of the 11 studies of SRP plus locally delivered metronidazole yielded statistically significant reductions in PD ranging from 0.18 mm to 0.80 mm. The overall effect size estimated from the meta-analysis was 0.32 mm favoring local metronidazole as an adjunct to SRP; this effect was found to be statistically significant. Two studies reported statistically significant CAL gains of 0.40 mm and 0.66 mm, again favoring the adjunctive use of local metronidazole. The mean effect size estimated from the meta-analysis was only 0.12 mm, favoring adjunctive local metronidazole, but it is statistically significant.

Metronidazole and Amoxicillin Combination. Only one of the four studies of this systemically administered drug combination plus SRP reported a statistically significant greater PD reduction than SRP alone (0.7 mm). One of the four studies of CAL gain reported a

statistically significant improvement over SRP alone, but the exact amount of the difference was not reported.

Chlorhexidine. Of the 17 studies of locally administered chlorhexidine included in the review, most had small numbers of subjects but larger numbers of sites or pockets as the unit of analysis. Despite this, only two of these trials (both using chlorhexidine chips) produced statistically significant PD reductions. The reductions favoring the use of chlorhexidine as an adjunct to SRP ranged from 0.26 mm to 0.33 mm. Conversely, one large trial showed a statistically significant net PD reduction of 0.46 mm favoring the control group. The statistically significant overall effect size from the meta-analysis was 0.24 mm, reflecting the moderating effect of the contrary results from the larger trial reporting greater PD reduction with SRP alone.

Gains in CAL with the use of chlorhexidine as an adjunct were generally lower than were the reductions in PD. Three studies had statistically significant results ranging from 0.16 mm to 0.28 mm, favoring chlorhexidine use. The statistically significant mean effect size estimated from the meta-analysis was 0.16 mm.

Other Antibiotics. The seven trials in the group of other systemic antibiotics (doxycycline, spiramycin, the combination of spiramycin and metronidazole, azithromycin, amoxicillin and clavulanic acid, and amoxicillin plus chlorhexidine) were quite varied in size, duration, and other variables. The authors were not able to combine these trials into a meta-analysis. Three of the studies reported statistically significant results for PD reduction, ranging from 0.47 mm (for spiramycin) to 0.87 mm (for azithromycin, among patients with initial PD levels of 6 mm or greater). Two studies reported statistically significant results for CAL gains; only one gave specific data, a gain of 1.3 mm with doxycycline. Given the diversity of these therapeutic agents, means of therapy, and overall study designs, the authors believe that caution is warranted in interpreting these studies as convincing evidence of effectiveness, especially in the light of the generally negative results for other, more commonly studied systemic antibiotics.

Only two trials dealt with other local antibiotics (doxycycline gel and ofloxacin inserts), and only the one with doxycycline provided data showing a 0.44 mm PD reduction and a 0.37 mm CAL gain, both statistically significant. These results are promising, as they come from a relatively large trial, but the strength of the evidence should be interpreted conservatively when compared to that represented by the multiple studies of the more commonly used local adjunct therapies.

Other Antimicrobials. It is not possible to say much about the group of five studies (one with two experimental arms) grouped together as other antimicrobials (amine fluoride gel, stannous fluoride gel, triclosan gel and dentifrice, hydrogen peroxide, povidone–iodine, and tetrapotassium perioxydiphosophate), all of which are locally delivered. As regards PD reduction, one of the six trials reported a statistically significant 0.8 mm net reduction at 52 weeks, favoring hydrogen peroxide used as an adjunct to SRP; however, for CAL gains, no study had statistically significant improvements favoring the treatment group. In light of the level of improvements from adjunct use of some locally administered antibiotics, the PD findings for hydrogen peroxide may seem promising, but they are from only a single, small study.

Conclusions

Although the findings differ for each antimicrobial and mode of delivery, the authors make some important overall observations relating to the key question. First, relative to the PD reductions achieved from the baseline measurement to the study end-point measurement, the difference in measurements between the treatment and control groups typically favored the treatment group, but was relatively modest. With respect to CAL gains, the picture was similar, but the effects are smaller and statistical significance was less common.

Of the antimicrobials investigated, studies of locally applied tetracycline and minocycline—and locally delivered chlorhexidine—have fairly consistent results in moderately large studies that often reach statistical significance; improvements observed in these studies typically average in the neighborhood of 0.3 mm to 0.6 mm. The other agents and delivery modes produced less consistent outcomes and fewer outcomes that reached statistical significance; the majority of studies showed small, statistically nonsignificant PD improvements. CAL outcomes were not as positive as those for PD. The question remains, the authors note, whether such improvements are clinically meaningful.