Chapter 4. Conclusions

Overview

The key question examined in this report was: How does the effectiveness of scaling and root planing therapy (SRP) by itself for the treatment of chronic periodontitis compare to SRP accompanied by adjunctive therapy at varying lengths of time? To focus the evaluation of effectiveness, we relied primarily upon two clinical measures – reduction in probing depth (PD) and gains in clinical attachment level (CAL) – and one specific microbial measure – percentage reduction of spirochetes.

A total of 70 studies (unduplicated) met our inclusion criteria for this evidence report. However, some of these studies had multiple arms involving different adjunctive treatments; therefore, we included some studies more than once in the synthesis (Chapter 3) and evidence tables (Chapter 7). We provide qualitative and descriptive information for all these studies in Chapter 3; in addition, we did a total of nine meta-analyses when we had three or more studies that provided appropriate data for a 6-month follow-up period (plus or minus 3 months).

The adjunctive therapies were all chemical antimicrobials, applied either locally or systemically, which we grouped into 11 separate categories: systemic and local tetracycline, systemic and local minocycline, systemic and local metronidazole, metronidazole in combination with amoxicillin (systemic), chlorhexidine (local), systemic and local other antibiotics, and other local antimicrobials. The populations, severity of periodontitis, types of teeth treated, number of teeth treated, and added supportive therapies used all differed from study to study. In addition, thoroughness of SRP also differed across studies; we accepted studies only when the investigators used the same SRP approach for both the treatment and control groups. Some of the studies performed modified Widman flaps as needed to gain better access for debridement of study teeth. The time periods covered for follow-up of the therapies also varied from only a couple of weeks to 13 years.

The studies demonstrated that, for virtually any length of follow-up period reported, SRP whether or not accompanied by an adjunctive therapy resulted in statistically and clinically significant PD reductions and CAL gains between the baseline and study endpoint measurements. Those data set a context within which to interpret our findings, but effects of SRP are generally well known and so that was not a question that we sought to examine.

Rather, as agreed by the sponsors (the National Institute for Dental and Craniofacial Research [NIDCR], the Agency for Healthcare Research and Quality [AHRQ]), our Technical Expert Advisory Group (see Chapter 1), and our clinical consultants and colleagues from the University of North Carolina and elsewhere, we set out to determine whether the available research findings on using chemical antimicrobial therapy with SRP made an *added* contribution beyond that of the SRP alone. In simple terms, this value is the result of subtracting the baseline-to-follow-up differences for the SRP-only (or SRP with placebo) groups from the baseline-to-follow-up differences for the experimental or treatment groups using SRP and adjunctive therapy, and we characterized this as the net PD reduction or net CAL gain in our discussion.

Summary of Results

Overall Comments

Table 16 summarizes our main findings, focusing on just the two clinical measures (PD and CAL) because those measures were far more commonly reported than changes in microbial environments (even changes in the percentages of spirochetes). We further focus in that table on just the number of "positive" studies – i.e., those that showed a statistically significant net PD reduction or net CAL gain favoring the adjunctive therapy in question. We specify the total number of studies and the number of positive studies (columns 1 and 3) and the range of effect sizes in millimeters for just those positive studies (columns 2 and 4). Finally, we recap the meta-analytic results, showing the overall estimated mean effect size in millimeters and the 95 percent confidence interval (CI) around that estimate (columns 2 and 4).

Across these 11 groupings of adjunctive therapies, we had a total of 84 intervention arms for PD reductions (recalling that some studies examined multiple types of antimicrobials). The two most commonly studied adjunctive therapies were local tetracycline (16) and chlorhexidine (17), followed by local metronidazole (11); least studied were systemic minocycline and the other local antibiotics (two each). Generally, investigators reported less frequently on gains in CAL, so we had only a total of 70 intervention arms; again, the commonly studied therapies were local tetracycline (16) and chlorhexidine (13), followed by local metronidazole and local minocycline (eight each), and the least studied were also systemic minocycline and other local antibiotics (two each).

We found it interesting to compare aggregate results (numbers of positive studies and percentages of total studies) for systemic and local therapies. Of the five categories of systemic therapies, we included 25 studies that measured PD reductions; of these, 7 (28 percent) reported a statistically significant net result favoring the adjunctive therapy (in this case metronidazole, metronidazole with amoxycillin, and various other systemic antibiotics). By contrast, of the six categories of local therapies, we included 60 studies with PD data; of these 16 (27 percent) reported a significant net result for the adjunctive therapy (mainly tetracycline and metronidazole).

For systemic therapies with CAL data, we included 19 studies; of these 6 (32 percent) reported net CAL gains favoring the adjunctive agent (tetracycline, metronidazole, and other systemic antibiotics). For the local treatments, we included 50 studies; of these, 11 (22 percent) had significant net gains (spread across all categories except the group of other antimicrobials).

In short, taking systemic and local applications together, tetracycline, metronidazole, and chlorhexidine were the most frequently studied therapies. PD reductions were measured slightly more often than CAL gains, but both were far more commonly reported than microbial changes. Some, but by no means all, investigators reported data by subgroups defined largely by baseline PD levels, but across those trials, the categories differed somewhat. For neither the systemic therapy studies nor the local therapy studies, taken as two groups, were more than about one-quarter to one-third reflective of statistically significant PD reductions or CAL gains.

Therapy-Specific Findings

Again referring mainly to Table 16, we summarize below the results from positive studies (as defined above) and our meta-analyses (i.e., the overall estimate of mean effect size and the 95 percent CI, with the number of studies in the meta-analyses noted in the text). Chapter 3 provides more details on both the qualitative and quantitative results.

Tetracycline

Systemic Tetracycline. Of the five studies of systemic tetracycline, all pointed in the direction of greater net improvement in PD, but none showed a significant difference. The mean effect size (three studies) was a nonsignificant 0.15 mm. Four of these studies reported on CAL gains, of which one had a significant 0.31 mm result favoring the adjunctive therapy. We did no meta-analysis on the CAL studies because one provided no quantitative data and two did not run the appropriate study period.

Local Tetracycline. For the locally delivered tetracycline (fibers, irrigation, gel, strips, ointment), the 16 studies included four with significant PD results ranging from 0.41 mm to 0.93 mm. The mean effect size (six studies) was 0.47 mm (95 percent CI, 0.22 to 0.72). Of these same 16 studies, two yielded significant CAL gains ranging from 0.15 mm to 0.48 mm. The mean effect size (nine studies) was 0.24 mm (95 percent CI, 0.07 to 0.42).

Taking a nearly half-millimeter of PD reduction as one that the practicing and academic dental community would likely regard as clinically meaningful, we would highlight this result for local tetracycline as providing consistent evidence supportive of the use of this particular therapy and modality. We are less certain that a CAL gain of 0.24 mm would be regarded as notable in clinical terms, but it does lend additional support to the conclusion that adjunctive local tetracycline confers some clinical benefit.

Minocycline

Systemic Minocycline. Only two studies involved systemic minocycline. Neither provided statistically significant results for either PD reduction or CAL gain. We did no meta-analyses on these trials.

Local Minocycline. Locally applied minocycline stands in some contrast to systemic minocycline. Eight studies tested minocycline in this modality (as ointment, gel, or microencapsulated powder). Overall, four of these studies had statistically significant net PD reductions ranging from 0.30 mm to 1.10 mm (the latter for patients with baseline PD of 7 mm or greater). The mean effect size (six studies) was 0.49 mm (95 percent CI of 0.40 to 0.58). The gain in CAL for the three studies reporting significant net gains ranged from 0.39 mm to 0.8 mm. The mean effect size (five studies) was 0.46 mm (95 percent CI, 0.32 – 0.60). Thus, as with local tetracycline, these nearly half-millimeter net improvements on the clinical measures might well be regarded as clinically meaningful.

Metronidazole

Systemic Metronidazole. Of the seven studies of systemically delivered metronidazole, most showed a pattern of greater net reduction in PD for at least some of their patient subgroups, but only two studies provided statistically significant results, with PD reductions ranging from 0.47 mm (for patients with baseline PD of 4 mm to 6 mm) to 1.64 mm (for patients with baseline PD of more than 6 mm). With respect to CAL gains, two of five studies reported significant net improvements for the adjunctive therapy, ranging from 0.47 mm to 1.19 mm (in both cases only for patients with relatively deep PD at baseline). We did not do meta-analytic estimates of the mean effect size for either of these measures because of lack of data or the length of the study.

Local Metronidazole. Four of the 11 studies of locally delivered metronidazole (irrigant, gel, strips) yielded significant net PD reductions ranging from 0.18 mm to 0.80 mm (one study did not report specific data). The mean effect size (seven studies) was 0.32 mm (95 percent CI, 0.20 to 0.44). The statistically significant CAL gains in two of the eight studies ranged between 0.40 mm and 0.66 mm; the mean effect size (seven studies) was only 0.12 mm (95 percent CI, 0.01 to 0.24). Thus, although both clinical measures appear to reflect statistically significant impacts of local metronidazole, the clinical importance of the CAL gains might be debated.

Metronidazole and Amoxicillin Combination

Of the four studies of this systemically given combination of drugs, one reported a statistically significant net PD reduction of 0.7 mm; none reported any data for significant CAL gains favoring the drug therapy. We did no meta-analyses of these studies because no more than two reported any specific data.

Chlorhexidine

Our review included 17 studies of locally administered chlorhexidine (irrigant, rinse, gel, chip). Many of the studies had small numbers of subjects but larger numbers of sites or pockets as the unit of analysis. Even so, only two of these trials (both using chlorhexidine chips) produced statistically significant PD reductions for the experimental groups, ranging from 0.26 mm to 0.33 mm. Moreover, one large trial with more than 400 pockets (each) in the treatment and control groups as the units of analysis showed a statistically significant net PD reduction of 0.46 mm favoring the control group (Table 12 in Chapter 3). The mean effect size (eight studies) was 0.24 mm (95 percent CI, 0.13 mm to 0.35 mm).

CAL gains were generally lower: three studies with significant results ranging from 0.16 mm to 0.28 mm. The mean effect size (seven studies) was 0.16 mm (95 percent CI, 0.04 mm to 0.28 mm), practically speaking the same as for the reduction in PD.

The chlorhexidine results seem to point to about a one-fifth to a one-quarter millimeter of improvement in these clinical measures. These are statistically significant results, but we remain uncertain as to whether they should be considered clinically meaningful.

Other Systemic 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 rinse) were quite heterogeneous in size, duration, and other variables, and we were not able to combine any into a meta-analysis. Of these, three had reported statistically significant results for PD reductions, which ranged from 0.47 mm (for spiramycin capsules) to 0.87 mm (for azithromycin among patients with initial PD levels of 6 mm or greater). Two claimed significant results for CAL gains; only one gave specific data (a gain with doxycycline of 1.3 mm). Given the diversity of these therapies, modalities, and overall study designs, we believe caution is warranted in interpreting them as convincing evidence of effectiveness, especially in the light of the generally negative results for other, more commonly studied systemic antibiotics.

Other Local 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. These results are perhaps promising, as they come from a trial examining 108 treatment and 108 control sites, but they should also be interpreted in the more conservative context of multiple studies of more commonly used local adjunctive therapies.

Other Antimicrobials

Neither is it possible to say much about the collection of five studies (one with two experimental arms) grouped together as other antimicrobials (amine flouride 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 trial reported an 0.8 mm net reduction at 52 weeks for hydrogen peroxide; for CAL gains, no study had significant improvements favoring the treatment group. Given the appreciable heterogeneity across these studies, we did no meta-analyses on other antimicrobials. In the light of the level of improvements from adjunctive use of some local antibiotics, the PD findings for hydrogen peroxide may seem promising, but they are from only a single small study.

Concluding Comments

Several themes emerge from these findings. First, PD reductions seemed to be more frequently measured (and statistically significant) than CAL gains although the two are clearly related; whether this has any practical or clinical ramifications is debatable, however. Second, adjunctive local antibiotics appeared to have more impact than adunctive systemic antibiotics, measured in terms of net PD reductions or CAL gains relative to SRP alone. Third, judging from trials with statistically significant results based on either our qualitative synthesis or our meta-analyses, the major PD reductions were in the range of about one-quarter to one-half millimeter, and the major CAL gains in the range of about one-tenth to one-half millimeter. As noted earlier, we take no stand on what might be considered a clinically meaningful change, but note that if the dental community were to consider improvements in the neighborhood of 0.50 mm as clinically important, then some of the therapies studied here do fall into that domain.

Fourth, combining PD and CAL results suggests that local minocycline might be the most promising adjunctive therapy (meta-analysis estimates of 0.49 mm for PD reduction and 0.46 mm for CAL gain), followed by local tetracycline (estimates of 0.47 mm for PD reduction and 0.24 mm for CAL gain). Local metronidazole and chlorhexidine results are well below these levels.

Fifth, in the absence of statistical significance, or when the evidence base is very small in terms of overall numbers of studies, the question of whether the evidence for adjunctive treatment is meaningful in a clinical sense does not need to be addressed, except to say the available evidence does not support its use. On the basis of the literature reviewed in this report, some experts might reach this conclusion for systemic tetracycline, systemic minocycline, systemic metronidazole, metronidazole with amoxicillin, and the various other systemic or local antibiotics and antimicrobials; others might disagree.

Sixth, by and large, harms from these adjunctive therapies are relatively minor. We take note, however, of concerns about bacterial resistance from overuse of systemic antibiotics, and we would urge that the positive findings reported here be interpreted in terms of whether the PD or CAL improvements justify that risk (for the individual patient but, perhaps more importantly, over the population).

Seventh, other important factors – supportive and follow-up care as well as self-care – may well affect the long-term periodontal status of patients as much if not more than use of these adjuncts to SRP, perhaps especially for patients with relatively early or moderate periodontitis. We did not review any body of literature directly on this point, but some results of trials that we did review suggested that added effectiveness of adjunctive treatment was greater in circumstances of more severe periodontitis where supportive or self-care may be less well executed. These situations may include patients with refractory periodontitis or who have deep pockets, defects or furcation involvement, or circumstances in which modified Widman flap surgery is not done (which would enable proper debridement of otherwise hard-to-reach areas). Routine use of appropriate (i.e., efficacious) adjunctive therapies might arguably be reserved for patients such as these.

Eighth, we cannot say from the trials reviewed here now how long the added effects of adjunctive treatment last (regardless of whether we would conclude they are either statistically or clinically significant). The endpoints for these studies varied tremendously, and even trying to narrow the field for the meta-analysis to trials lasting 6 months required us to allow in results from trials lasting 3 months to 9 months. What seems to occur in these studies is that if the adjunctive treatment is to have a more positive clinical effect (e.g., reduce PD or increase CAL) than SRP alone, then that effect seems to appear within a few weeks (1 to 2 months). However, with time, the difference in effect between SRP alone and SRP with adjunctive therapy narrows. Nonetheless, at all time periods, the SRP with adjunctive therapy seems to be more effective than SRP only, even if the net differences are quite small and not statistically significant.

Finally, putting all these results into the context of the results of SRP alone is imperative. SRP alone seems to produce significant improvements in mean PD reductions or CAL gains in the range of 1.5 mm to 2 mm or more, clearly making it the standard for nonsurgical (and nonpharmacologic) treatment of chronic periodontitis. The improvements produced by adjunctive antimicrobials beyond those levels – i.e., approximately one-quarter to one-third of the impact of SRP alone – pose a difficult "value" question for clinicians and patients alike that goes quite beyond the question of what adjunctive antibiotics to use. For example, one can

question whether these improvements justify the added effort on the part of periodontists and dentists (and their staffs) or of patients or the likely added costs (either to dental insurance plans or to patients facing out-of-pocket payments). Moreover, as discussed in the next chapter, this literature on adjunctive therapies has enough drawbacks and gaps that a substantial research agenda remains before many of these issues can be resolved.