Evidence-Based Considerations for the Clinical Use of Locally Delivered, Controlled-Release Antimicrobials in Periodontal Therapy

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Abstract

Purpose: Locally delivered, controlled-release antimicrobials have long been available in dentistry. Their utilization in routine clinical practice, however, has been slow, perhaps because of concerns about clinical benefits or costs or possibly due to a lack of understanding of their efficacy or proper use. In this paper the evidence regarding locally delivered, controlled-released antimicrobials is considered, and some of the controversies surrounding these agents are discussed. Evidence-based considerations regarding their use are also summarized. Scaling and root planing (SRP) procedures are the backbone of non-surgical periodontal therapy. Since a number of well designed clinical trials have demonstrated that adjunctive, locally delivered, controlled-release antimicrobials make SRP significantly more effective to reduce clinical signs of chronic periodontitis with a known safety profile, and since SRP procedures have previously been considered the standard of care for non-surgical periodontal therapy, a case is made that SRP in combination with adjunctive therapy, administered in a manner consistent with the approved full prescribing information, could be considered a new standard.

Keywords: antimicrobials, clinical trials, controlled-release, local delivery, periodontitis

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Introduction

The technologies for the clinical use in dentistry of locally delivered, controlled-release antimicrobials, both antibiotic and antiseptic formulations, have been available for more than a decade, but their routine incorporation in clinical practice for patient treatment has been slow despite the recognition of the bacterial initiation of periodontal disease, that the efficacy of scaling and root planing (SRP) or other mechanical therapy generally is a consequence of either a reduction of the bacterial load or an alteration of the composition of the bacterial flora at the gingival or periodontal site, and that the antibacterial effect of mechanical treatment alone is less than complete. It would therefore seem intuitive that the clinician should desire to augment chemically the antibacterial effect of mechanical therapy.

Four locally delivered, controlled-release antimicrobial products have been developed for use in dentistry in the U.S. based on 4 different antimicrobials: tetracycline (TET) fiber, chlorhexidine (CHX) chip, doxycycline (DOX) gel, and minocycline (MIN) microspheres.[1-4] The TET fiber was the first product introduced to the U.S. market and was the prototypic system. Although the TET fiber is no longer available in the U.S., it is included in this discussion because the data generated from studies of the TET fiber are pertinent for a discussion of the general effects of locally delivered, controlled-release antimicrobials. The effects of locally delivered, controlled-release antimicrobials are considered as a drug class rather than individually. Since appropriate comparative trials have not been performed, there are insufficient data on which to base any comparison of agents or to consider differential indications for use. The indications for use for each product can only be based on the indications as noted in the respective full prescribing information.

The appropriate clinical use of locally delivered, controlled-release antimicrobials has been the subject of some controversy, perhaps at least partly fostered by comments and recommendations in position papers that were published shortly after the introduction of these agents into the U.S. market, recommendations published even though a number of them seemed to be based on clinical opinions and not well supported by research data.[5,6] The positions were subsequently supported by other reports,[7-9] although concerns regarding these positions have also been published.[10,11]

It has been well accepted that optimal patient

care should be evidence-based.[12,13] Thus, it is appropriate in this review to revisit the clinical evidence regarding locally delivered, controlled-release antimicrobials. A discussion of perceived controversies and previously published concerns is also needed. This review has been limited mainly to studies with Phase III designs, since these represent the strongest clinical evidence available for the purpose of clinical decision making and are typically the studies on which regulatory decisions are based. Other studies (e.g., Phase I, Phase II) are usually more exploratory in nature to give initial information regarding drug compounds, including preliminary safety or efficacy or to explore doses, but are not sufficiently adequate or well-controlled to provide conclusive data regarding either efficacy or safety. Other studies, although perhaps of high quality to give preliminary information, cannot provide data on which to base clinical decisions. The U.S. Food and Drug Administration (FDA) website notes the common characteristics of study designs that are considered adequate and well-controlled (Table I).[14] Comments regarding less robust studies are included as appropriate, although this discussion was not intended to be a systematic review of the literature. The purpose of this paper is to consider existing clinical evidence for the use of these agents and follow with an evidence-based consideration of the appropriate use of locally delivered, controlled-release antimicrobials for patient treatment. Included is a discussion of treatment outcomes, clinical significance and the value of these agents versus other available local therapies, including irrigation.

Table I: Characteristics of Adequate and Well-Controlled (Phase III) Clinical Trial Designs*

1. Type I error rate control
2. Clear statement of the objectives, proposed and actual
3. Methods of analysis in the protocol, statistical analysis plan and reports
4. Methods of adequate assurance of patient selections
5. Patient assignments that minimize bias, group comparability
6. Methods to minimize bias for all parties: patients, investigators, and data analysts
7. Endpoints well-defined and address the primary hypothesis
8. Analysis of results allows for the interpretability of the effects of the study drug

*Adapted from US Food and Drug Administration 21CFR314.126[14]

Previously Published Positions

The position papers[5,6] and review[7] cited above suggested that the best place to use locally delivered, controlled-release antimicrobials may be at the periodontal site that has not responded to other treatment, essentially recommending that these agents need not be used until other therapy has failed. Supportive evidence for this view is lacking, however, since adequate comparative data from responding versus non-responding sites are not available. Thus, the recommendation seems to be based on opinion rather than evidence, a conclusion also reached at a symposium sponsored by the Oral Health Research Group, co-sponsored by the Periodontal Research Group, at the 2001 Annual Meeting of the American Association for Dental Research (AADR) to consider the clinical significance of non-surgical periodontal therapy.[15] Other reports, however, do support the efficacy of locally delivered, controlled-release antimicrobials in persistent pockets or in non-responding sites as an alternative to further SRP or perhaps to surgical treatment, although a lack of additional benefit in non-responding sites has also been reported.[16-18]

The Research, Science and Therapy Committee of the American Academy of Periodontology has published that they "strongly feel that mechanical instrumentation can usually achieve the same result as local delivery when administered as a monotherapy or when it is used as an adjunct to treatment."[19] However, no supportive data were referenced, especially regarding the adjunctive use of local delivery. The literature suggests otherwise, that locally delivered, controlled-release antimicrobials significantly augment the efficacy of SRP. Multiple clinical trials have consistently shown, in at least 6 multi-centered, randomized, Phase III-style trials, that SRP plus adjunctive treatment resulted in significantly greater efficacy, as measured by probing depth reduction, compared with SRP alone.[2,4,20-22] Probing depth is thought to be a clinically meaningful endpoint for periodontitis trials, an appropriate outcome measure of inflammation and predictive of further disease progression, although the progression of periodontitis may be most meaningfully measured by loss of attachment or alveolar bone.[23-31]

The efficacy of local adjuncts was subsequently supported in 2003 by an international workshop, which also concluded that the clinical result obtained following SRP that includes the adjunctive use of a locally delivered, controlled-release anti-

microbial is significantly enhanced in comparison with that following SRP alone.[32] The conclusion was based on data derived from multiple randomized clinical trials, long recognized as the strongest and most compelling evidence on which to base clinical treatment.[12,13,33]

Clinical Significance

The mean differences in clinical trials between the probing depth reduction from baseline between treated groups (SRP plus adjunctive agent) and control (SRP plus placebo or SRP alone) were reported in terms of tenths of a millimeter (approximately 0.2 to 0.7 mm).[2,4,20-22] The changes numerically seem small and of little clinical significance, but they need to be viewed from a number of perspectives. For example, it is commonly believed that only a low percentage of periodontal sites are "active," i.e., actively evidencing tissue breakdown, and that most sites are relatively stable and "inactive."[27,34-36] Since most sites may be stable at most times, it might be anticipated that, in a clinical trial of all patients and all periodontal sites, unless it is a trial which is specifically enriched for "active" sites, there may not be much difference between treated and control in most patients. In other words, many of the data points used to define a mean difference may be small or near zero (i.e., no difference versus the control group, SRP alone). In addition, clinical trials for FDA registration are typically performed using an intent-to-treat analysis. All entered patients are included in the analysis whether they finish the trial or not, therefore, the expected small mean changes may be even further diluted by data recorded prior to the planned endpoint. The trials that have been cited included data from subjects who did not complete the trials per protocol and for whom treatment was incomplete. It would have thus been expected that the outcome as mean changes would be small, further highlighting the importance of the statistical analyses of the changes. Adjunctive locally delivered, controlled-release antimicrobials have consistently shown this statistical benefit in multiple, well designed clinical trials, for example, improving mean probing depth reduction across all tested sites entered, including those patients with incomplete treatment, in a number of trials approximately from 22% to 68% compared with control (Table II), a change that certainly seems clinically significant. A significant mean percentage change versus control implies that the response curve is significantly shifted toward increased benefit for the population under study.

Perhaps the most compelling evidence to support clinical significance comes from the consideration of large changes. A probing depth reduction of 2 mm or greater from baseline is commonly considered evidence of clinical significance.[2,4,37] The adjunctive use of locally delivered, controlled-release antimicrobials resulted in a significantly greater proportion of patients or sites with a probing depth reduction from baseline of 2 mm or more in comparison with SRP alone (Table II). This level of reduction may ultimately translate into a clinical outcome of fewer lost teeth, but this hypothesis remains to be tested in clinical trials with tooth mortality as the primary objective rather than surrogate endpoints.[38] Thus, the data support that adjunctive therapy is not only statistically significant but clinically significant as well. The clinical significance of the adjunctive benefit was also acknowledged at a symposium to consider locally delivered chemotherapeutic agents in periodontal therapy sponsored by the Periodontal Research Group at the 1998 Annual Meeting of the AADR.[39]

To consider the results from another perspective, surgery is a common treatment for patients with periodontal pockets, but the mean differences in probing depth reduction between sites treated surgically versus sites treated with SRP alone is also in the neighborhood of several tenths of a millimeter.[40,41] If a mean change of tenths of a millimeter is not clinically significant, then it could be questioned whether any patient prospectively ever really needs any periodontal treatment beyond SRP. This conclusion has been supported by the published suggestion that continued nonsurgical therapy usually provides a mean probing depth reduction of 2 mm or greater.[19] With respect to periodontal surgery, the 1996 World Workshop in Periodontics concluded that "[o]utcomes [following both surgical and non-surgical therapy] after several years are generally similar."[42]

Further, with respect to a potential comparison with surgical outcomes, it has been suggested verbally, starting as early as 1993 (Killoy WJ, personal communication, 2002), and in print in 1998, that adjunctive locally delivered, controlled-release antimicrobials may improve outcomes following regenerative periodontal surgery.[43,44] In a pilot clinical trial, the adjunctive use of CHX chip with regenerative surgery resulted in more than a 100% greater mean improvement from baseline in bone height and mass 9 months after surgical treatment compared with SRP alone and surgery.[45] Interestingly, both groups had also received prophylactic systemic antimicrobial treatment as well prior to surgery (mostly cephalexin).

Table II: Summary of locally delivered, controlled-release antimicrobials with SRP

Agent	Use	Study Duration	Mean PD Outcome	Numbers or Proportions of Sites or Sites Per Patient Evidencing a PD Reduction ≥2 mm from Baseline	Reference
Minocycline microspheres	Adjunctive	9 months	• 22% greater reduction vs SRP alone • 32% greater reduction vs SRP + vehicle (both p<0.001)	• 23% increase vs SRP alone • 40% increase vs SRP + vehicle (both p<0.001)	4
Doxycycline gel	Monotherapy	9 months	Study 1 • 22% greater reduction vs SRP alone (p=0.05) • 37% greater reduction vs vehicle (p=0.001) • 120% greater reduction vs OH alone (p<0.001) Study 2 • No difference vs SRP alone (p=0.765) • 30% greater reduction vs vehicle (p=0.001) • 40% greater reduction vs OH alone (p<0.001)	Study 1 • 3% increase vs SRP alone • 45% increase vs vehicle • 113% increase vs OH alone Study 2 • 4.7% decrease vs SRP alone • 52% increase vs vehicle • 78% increase vs OH alone (statistical analysis of PD reduction ≥2 mm not reported)	3
Chlorhexidine chip*	Adjunctive	9 months	• 46% greater reduction vs SRP alone (p=0.00001) • 38% greater reduction vs SRP + vehicle (p=0.00056)	• 139% increase vs SRP alone (p<0.0001) • 48% increase vs SRP + vehicle (p=0.039)	2
Chorhexidine chip	Adjunctive	6 months	• 66% greater reduction vs SRP alone (p≤0.0001)	• 66% increase vs SRP alone (p≤0.0001)	22
Chorhexidine chip	Adjunctive	6 months	• Approximately 50% greater reduction vs SRP alone (p<0.001)	• 113% increase vs SRP alone (p<0.01)	21
Tetracycline fiber	Adjunctive	6 months	• 68% greater reduction vs SRP alone (p<0.01)	• Not reported	20
Tetracycline fiber	Monotherapy	60 days	• 42% greater reduction vs SRP alone (p=0.0002) • 67% greater reduction vs control fiber (p=0.0001) • 133% greater reduction vs no treatment (p=0.0001)	• Not reported	1

SRP, scaling and root planing; PD, probing depth; OH, oral hygiene. *Pooled data from 2 studies

Other reports support the lack of efficacy of systemic antimicrobials and the benefit of locally delivered antimicrobials as adjunctive treatments in the regenerative setting.[46,47] If confirmed by subsequent trials, the collective data could support the use of this intervention to enhance outcomes of regenerative periodontal procedures. Additionally, Aichelmann-Reidy and coworkers have suggested that regenerative surgical procedures should include an adjunctive locally de-

livered, controlled-release antimicrobial agent in order to provide a more consistent clinical benefit (e.g., improved regeneration).[48] However, this hypothesis remains to be tested in prospective trials.

Potentially even more important for a greater number of patients, in a subset of patients from the CHX chip clinical trials, some patients treated with SRP alone lost bone over 9 months as measured by subtraction radiography, but no patient treated adjunctively showed any radiographic evidence of bone loss.[49] Adequate and well-controlled clinical trials are needed to test the hypothesis that adjunctive, locally delivered controlled-release antimicrobials may reduce radiographic bone loss.

Adjunctive Therapy and Cigarette Smoking

Smoking has long been identified as a strong risk factor for the development or progression of periodontitis and may limit the effectiveness of periodontal therapy.[50-53] The adjunctive use of a locally delivered, controlled-release antimicrobial may enhance the efficacy of SRP in smokers. In a 3 month trial SRP plus adjunctive DOX gel resulted in significantly greater probing depth reduction and clinical attachment gain versus SRP alone approximately equally in both smokers and non-smokers.[54] This result was consistent with subset analyses of current smokers, former smokers and non-smokers from 2 multi-center trials (DOX gel)[55] and smokers versus non-smokers (MIN microspheres).[4] These findings were replicated and extended by a later clinical trial (MIN microspheres).[56] Additional periodontal microbiological alterations suggested as beneficial changes in adjunctively treated sites compared with SRP alone have also been reported (DOX gel and MIN microspheres).[56-58] A 2 year trial with a small number of patients provided further supportive evidence of clinical efficacy (DOX gel).[59] Thus, adjunctive therapy may lessen the adverse impact of smoking on the periodontium and improve treatment outcomes in patients who smoke. A recent systematic review regarding DOX gel and MIN microspheres has suggested that the available evidence for an additional clinical benefit of adjunctive therapy is insufficient to support any definitive conclusions regarding smokers, noting that new randomized clinical trials are necessary to assess outcomes.[60]

Magnitude of Mean Probing Depth Reduction

The 1996 World Workshop reported that the mean probing depth reduction to be expected following SRP in sites with initial probing depth of 4 to 6 mm is 1.29 mm.[61] However, the data from randomized, multi-centered, blinded (mostly double-blinded) clinical trials that have been performed largely for FDA registration have consistently shown a mean reduction of about 1 mm in sites that were either 4 to 6 mm or 5 mm or greater (largely 5 to 6 mm) at baseline.[2-4,20-22,37,62,63] Whether the SRP procedures were performed within a pre-specified time limit or performed to the clinical endpoint of smooth roots with no time limit did not impact the extent of the result. The observed mean probing depth reduction has consistently been about 1 mm in at least 11 randomized trials, even when SRP procedures were performed with no time limitation.[2-4,20-22,37,62,63] In reported trials there was a variety of SRP methods used, along with a range of the number of included teeth with probing depth greater than 4 or 5 mm (generally 2 to 4 teeth).[2-4,20-22,37,62,63] One cannot assess the number of teeth that actually required SRP or the amount of time actually necessary to complete the instrumentation. Thus, comparisons of these reported trials with other reports in the literature are not appropriate, and the concerns do not detract from the findings of statistically significant changes within these internally controlled trials. Indeed, the largest numerical difference between treated and control arms was observed in a trial in which no time limitation for SRP procedures was noted, although this trial was conducted in a private practice setting.[20]

Trial Design

The randomized clinical trials that confirmed the efficacy of locally delivered, controlled-release antimicrobials and supported FDA registration were well designed to give unequivocal outcomes. Concerns may always be raised regarding trial designs, but multi-centered clinical trials are enormously expensive and are difficult to perform. Trials must be designed appropriately to address the hypotheses of interest. The efficacy of locally delivered, controlled-release antimicrobials for the indication of periodontal disease to reduce probing depth or improve attachment level has been established in multiple trials, otherwise treated groups would not have separated from control (or would not have been equivalent to control).[1-4,20-22] These results have included trial designs both of adjunctive use with SRP or of monotherapy (Table II).

It has been speculated that trial results might have been different had control groups also received repeated treatment (i.e., repeated SRP).[19]

However, if the control group had received repeated SRP, the adjunctively treated group also would have had to receive repeated instrumentation to maintain design balance. Results for both groups may have been different, not just control. Additionally, locally delivered, controlled-release antimicrobials may be effective in the presence of calculus or with reduced amounts of instrumentation.[64,65] Additional instrumentation also would have made data interpretation more difficult; multiple treatments at multiple times make it more difficult to separate treatment effects meaningfully. Further, in support of the lack of an impact of additional instrumentation on the outcome, a similarly significant difference was reported when both treatment arms received SRP at baseline and a supragingival prophylaxis at 3 months.[21]

In summary, in the registration trials of local adjunctive therapy for 2 products (MIN microspheres, CHX chip),[2,4] all sites received SRP at baseline ± adjunctive drug as per the randomization. At 3 and 6 months, sites randomized to drug received additional drug only if probing depth remained ≥5 mm (i.e., only a fraction of those sites). If the adjunctive therapy had no effect, probing depth at these sites would have trended back toward baseline as in the SRP alone sites; the observation that probing depth remained reduced clearly demonstrated that the drug was efficacious. The FDA agreed that the designs were adequate and well-controlled. An alternative design might have been to have all sites treated with mechanical instrumentation at 3 and 6 months with drug added per the randomization in sites with probing depth ≥5 mm. With this design, in order to have demonstrated significant changes, most likely a much greater number of patients would have had to have been studied for a greater length of time, a design that may not have practically been feasible.

Clinical trials need to be conducted in a reasonable time frame and with a reasonable number of subjects. Current designs are generally limited to the evaluation of surrogate endpoints (e.g., probing depth) rather than direct endpoints, such as tooth survival. Surrogate variables, however, are considered reasonable endpoints in periodontal clinical trials and relevant to tooth retention, although the inherent weaknesses of surrogate outcome variables have been noted.[38,66,67]

Clinical Use and Costs

It has been noted that locally delivered, controlled-release antimicrobials are associated with greater acquisition costs in comparison with readily available antiseptics such as povidone (PVP)-iodine or sodium hypochlorite.[68] These agents are discussed in more depth later in this paper. However, since these agents have not been adequately tested in clinical trials, and neither their safety nor their effectiveness have been established, these antiseptics must be considered investigational for the treatment of periodontitis and therefore not appropriate for inclusion in cost-effectiveness analyses.

In a clinical trial of more than 450 patients to study costs associated with the CHX chip, adjunctive therapy increased total treatment costs by approximately 50%, but reduced the likelihood for surgical treatment during the length of the trial by about 50% in comparison with patients treated conventionally.[69] Other dental treatment was sufficiently reduced to offset about half of the acquisition costs of the adjunctive antimicrobial. This result was consistent with a previously published modeled assessment regarding the CHX chip.[70] After 12 months, the examining periodontists recommended similar further amounts of surgery for both groups.[69] No information was available, however, regarding any further disease progression or tooth mortality or whether patients received any further surgical care. Additionally, no information was available for these patients regarding any differential outcomes with either follow-up surgical care or continued non-surgical maintenance with SRP and adjunctive therapy. Heasman et al have recently reviewed the cost-effectiveness of adjunctive antimicrobials in the treatment of periodontitis, and noted the continued need for long-term studies to assess effects on tooth mortality or other patient-reported outcomes.[71]

It has been suggested that the adjunctive benefits of locally delivered, controlled-release antimicrobials may only be short-term (i.e., clinical trials extended for only 6 or 9 months, however, these products can routinely be re-administered as needed.[2,4,9,20-22] A number of clinical trials, including studies of MIN microspheres, DOX gel and CHX chip, have provided evidence for the safety and efficacy of locally delivered, controlled-release antimicrobials for periodontal maintenance.[17,72-80] The same could be suggested regarding SRP, that the benefits of SRP may only be short-term. The clinical benefits of SRP seem to result from continued maintenance treatment for life. Similarly, the true benefits of locally delivered, controlled-release antimicrobials most likely will result from their routine use as adjuncts with SRP as well as in a periodontal maintenance program as indicated.

Finally, it has been suggested that other therapies (e.g., systemic antimicrobials) should be considered when there are multiple pockets.[5,8,9] It seems likely that locally delivered, controlled-release antimicrobials are effective because of the high concentration of active drug achieved and maintained in the gingival crevicular fluid (GCF),[81-83] perhaps especially needed because of the protective biofilm structure in the periodontal ecosystem[84,85] (for reviews, see Palmer[86] or Kuboniwa and Lamont[87]). Drug concentrations within the GCF with systemic antimicrobials are orders of magnitude less than those achievable with local agents and cannot provide an equivalent, alternative therapy.[83,88] Bacterial biofilms may be highly resistant to penetration by fluids,[89] providing further evidence for the critical need for high GCF concentrations of active antimicrobial, concentrations only achievable with suitable locally delivered controlled-release agents and not possible via systemic routes. Additionally, Drisko has suggested that the high concentrations of antimicrobial in the GCF as a result of local delivery may help to reach infected sites within the root or the pocket.[90] Other potential benefits include decreased systemic, off-target effects or a decreased risk for promoting microbial resistance.

Informed Consent and Legal Considerations

Clinicians must treat all patients under the principles of informed consent, and all patients must provide their consent for all treatment. The FDA (adapted from 21CFR 50.25(a)[91]) describes 8 elements of informed consent that include:

1. A description of the planned treatment
2. A description of reasonably foreseeable risks or discomforts
3. A description of any reasonably expected benefits
4. Disclosure of appropriate alternative treatment
5. A description of procedures to maintain confidentiality
6. Disclosure of associated costs
7. Answering all questions
8. Disclosure that all treatment is voluntary

Appropriate treatment that satisfies the principles of informed consent includes treatment that is evidence-based, i.e., supported by appropriate research data. Since locally delivered, controlled-release antimicrobials as adjuncts have been consistently shown in clinical trials to enhance the efficacy of SRP within the timeframe of treatment, performing SRP, but not at least offering an adjunctive agent, seems to violate the principles of informed consent. Clinicians have a responsibility to offer all appropriate treatment options, including adjunctive therapy.

With respect to the issue of malpractice, undiagnosed or under-treated periodontitis are major sources of dental malpractice litigation.[92] Since SRP procedures are commonly considered the standard of care for non-surgical periodontal therapy, and available data support that adjunctive locally delivered, controlled-release antimicrobials enhance the efficacy of SRP, at least over the time frame of the clinical trials, then SRP plus adjunctive therapy could potentially be considered a new standard.[7,9,32] Other authors have noted the clinical relevance of locally delivered, controlled-release antimicrobials.[15,17,39,43,44,73,90,93-109] Would it be plausible to consider a possible defense in a malpractice litigation of alleged improperly managed periodontitis if it were claimed that the patient had not been offered maximally effective therapy (i.e., SRP with an adjunctive agent)?

Combination Adjunctive Therapy

Locally delivered, controlled-release antimicrobials have been clearly shown to enhance the clinical efficacy of SRP. Adjunctive systemic therapy with low-dose (20 mg) doxycycline, given orally twice daily as a host-modulating agent (subsequently reported as a once daily, modified release formulation[110]), has also been shown to enhance the clinical efficacy of SRP.[37,62,63] For a review of matrix metalloproteinase modulation as a treatment strategy for periodontitis, see Reddy et al[111] or Ryan and Golub.[112] An obvious question is whether a combination of antimicrobial and host modulating adjunctive therapies will result in a greater clinical benefit compared with either adjunctive agent used alone.

In a 6 month clinical trial, combination adjunctive therapies resulted in significantly greater improvements in probing depth and clinical attachment as compared with SRP alone.[113] More sites showed a probing depth reduction ≥2 mm, and fewer sites had residual probing depth ≥5 mm.[113] Since the appropriate control groups (SRP plus single adjunctive therapy) were not included in the trial, definitive conclusions regarding any increased benefit from combination versus single adjunctive therapy cannot be made. The potential for combined adjunctive therapy to enhance clinical benefit is promising and warrants additional research.

Locally Delivered Antimicrobials or Other Chemotherapeutics, not Controlled-Release

Many chemotherapeutic agents have been studied subgingivally as adjuncts to SRP as well, mainly via irrigation. None of these studies, however, satisfied the requirements necessary to make treatment recommendations (i.e., level 3 evidence based on adequate and well-controlled trials). A brief commentary regarding some of the most well published of these agents is in order, although a complete review of all tested adjunctive agents is out of scope for this paper.

Povidone-iodine: PVP-iodine is a broad spectrum antimicrobial reported to be effective against a broad range of periodontal pathogens and suggested as a beneficial adjunct to SRP as a subgingival irrigant.[68,114-116] Its use has recently been reviewed by Sahrmann et al.[117] The authors concluded that the adjunctive use of PVP-iodine with SRP may result in an additional clinical benefit but also noted that most of the reviewed studies were small and of low quality, with discordant results - 7 studies were ultimately considered, of which 3 supported a benefit for adjunctive PVP-iodine, but the other four concluded that there was no evidence to support any additional adjunctive benefit.[115,118-123] The above studies and review considered a range of PVP-iodine administrations including, for example, irrigation, rinsing and single visit instrumentation. These were included in order to consider available data regarding PVP-iodine and periodontal treatment. Since the authors are not aware of any adequate and well-controlled trials comparing SRP plus adjunctive therapy with subgingivally irrigated PVP-iodine with SRP alone, no further comments can be made regarding the adjunctive efficacy of PVP-iodine.

Chlorhexidine: Chlorhexidine is a broad spectrum antimicrobial with a long history in dentistry, primarily as a supragingival mouth rinse.[124] The use of chlorhexidine as an adjunct to SRP administered via subgingival irrigation has been studied by many investigators. Although some trials suggest a clinical benefit,[125-128] the current consensus is that there is little evidence that subgingivally irrigated chlorhexidine, as an adjunct to SRP, offers any clinical benefit in comparison with SRP alone, that no additional probing depth reduction can be achieved with adjunctive irrigation.[129-136]

Bleach/Peroxide: Dilute bleach solutions or peroxides, alone or in combination, have been suggested to provide an additional clinical benefit as an adjunct to SRP. For example, activity has been reported against periodontal pathogens in vitro and against Actinobacillus (now Aggregatibacter) actinomycetemcomitans clinically.[137-139] Sodium hypochlorite has also been suggested as an adjunct to curettage.[140] Other investigators, however, have reported no additional clinical benefit of salt and/or peroxide as an adjunct to SRP.[136,141] Minimal microbiological differences were noted as well.[135,142] Since appropriately designed randomized clinical trials have not been performed, there are insufficient data to support any conclusions regarding the use of these agents in periodontal therapy.

Antibiotics and Other Agents: Various antibiotics or other chemotherapeutics in non-controlled release formulations have been studied as subgingivally administered adjuncts to SRP. Topically delivered antimicrobial adjuncts may be useful for periodontitis, but definitive evidence is lacking.[68,116,143-145] For example, long term non-surgical periodontal therapy (15 months) that included SRP and subgingival minocycline ointment was reported as clinically and microbiologically superior to SRP alone.[146] Others have also reported additional clinical or microbiological benefit with adjunctive subgingival antibiotics (metronidazole or tetracycline),[125,147] but the absence of any further benefit has also been reported (tetracycline, minocycline).[133,148,149]

Substantial data from adequate and well-controlled, randomized clinical trials exist to support a clinical recommendation for the routine, adjunctive use of locally delivered, controlled-release antimicrobials in the treatment of periodontitis. With regard to locally delivered antimicrobials not in controlled-release formulations, there are some preliminary data that support the need for additional research of these agents for adjunctive clinical use. Until adequate and well-controlled clinical trials are conducted to establish safety and efficacy that could support regulatory registration, however, these agents should still be considered investigational in the U.S. as subgingivally administered adjuncts to SRP for the indication of periodontitis.

Conclusion

There is strong evidence that locally delivered, controlled-release antimicrobials make SRP significantly more effective when used adjunctively, therefore, SRP without adjunctive treatment in appropriately eligible sites (i.e., probing depth ≥5 mm) may be less than maximally effective. As was stated at a symposium to consider the clinical significance of locally delivered antimicrobials at the

2001 AADR Meeting, "[t]he case is stronger for local delivery than for surgery."[15]

It is no longer appropriate to determine therapy based solely on clinical judgment. The best an individual practitioner can do is to evaluate the evidence and suggest a treatment that the current data predict has the greatest probability for success. All available treatment options should be presented to the patient. Spielman and Wolff have commented on the unfortunate tendency for many dentists to base treatment on personal experience and not on reported evidence; they highlight that optimal care is evidence-based.[150] As an example of the sub-optimal care that can result from the lack of incorporation of the best available evidence into clinical practice, O'Donnell and colleagues recently reported on the underutilization of pit-and-fissure sealants in the dental office despite published ADA recommendations.[151,152]

There is strong evidence to support the routine, adjunctive use of locally delivered, controlled-release antimicrobials, and that these agents provide a significant additional clinical benefit. Many adjuncts are available for clinical use with SRP, including devices for subgingival cleaning and plaque removal and antiseptics or antibiotics for subgingival irrigation. The most robust data available, however, to support an adjunctive benefit to enhance the efficacy of SRP to reduce probing depth may be the data from clinical trials of locally delivered, controlled-release antimicrobials.

The appropriate clinical use of locally delivered, controlled-release antimicrobials therefore seems clear. SRP have previously been considered the non-surgical standard of care.[7,9] The evidence supports that adjunctive locally delivered, controlled-release antimicrobials make SRP more effective[32] with a known safety profile. In conclusion, based on the currently available data, when these agents are used routinely as adjuncts to SRP when indicated either as part of initial periodontal treatment or maintenance therapy, clinicians can expect an enhanced result as measured by a significantly greater mean reduction in probing depth as a result of treatment in comparison with SRP alone. Thus, SRP plus adjunctive therapy, used in a manner that is consistent with the approved label, could potentially be considered a new standard for non-surgical periodontal therapy.

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Disclosure

Dr. Finkelman is a full time employee of AstraZeneca LP and owns stock in AstraZeneca. Dr. Polson reports no conflicts of interest.

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