Locally Administered Antimicrobials for the Management of Periodontal Infection

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INTRODUCTION

Periodontal disease (periodontitis) is a common oral infection, and its long-term management generally focuses on reducing bacterial pathogens and the resulting tissue inflammation. Locally administered antimicrobials (LAAs) are a class of chemotherapeutic agents that target the microbial pathogens, and are used adjunctively in managing inflammatory periodontal disease. Evidence from pivotal trials and meta-analyses consistently demonstrate that patients treated adjunctively with LAAs exhibit greater improvements in clinical parameters, including reduction in probing depths. These improvements are argued to be clinically relevant since patients treated with these agents are more likely to respond and shift to “maintenance care” following therapy.\(^1\) Emerging data also suggest that intensive periodontal therapy that includes LAAs may improve surrogate outcome measures for cardiovascular disease (CVD) such as serum C reactive protein (CRP) and endothelial function.\(^2,3\) This review will update the dental clinician on periodontal disease, its causes and associated risk factors, and management with adjunctive LAAs.

PERIODONTAL INFECTION AND INFLAMMATION

Periodontal disease is a common, mixed oral infection affecting the supporting structures around the teeth. Approximately 30% of the adult population exhibits the destructive form of the disease called “chronic periodontitis.”\(^4\) In general, patients with mild or moderate chronic periodontitis are without noticeable symptoms. In contrast, persons with advanced periodontitis may report tissue swelling (abscesses), discomfort, tooth mobility, or migration of the dentition. The diagnostic signs of periodontitis relate to tissue inflammation and destructive changes in the tooth-supporting tissues, and include the formation of periodontal pockets, loss of clinical attachment, and resorption of alveolar bone.\(^5\)

Accordingly, periodontitis begins with a pathogenic shift in the bacterial flora around teeth. Gram-negative organisms, such as Porphyromonas gingivalis, Tannerella forsythia, Treponema denticola, and Aggregatibacter (Actinobacillus) actinomycetemcomitans, infect the subgingival space and organize as a biofilm that is in direct

LEARNING OBJECTIVES:

After reading this article, the individual will learn:

- The causes and associated risk factors of periodontal disease.
- Management of periodontal disease with adjunctive locally administered antimicrobials.

ABOUT THE AUTHORS

**Dr. Paquette** is an associate professor, graduate program director in Periodontology and assistant dean for advanced dental education at the University of North Carolina at Chapel Hill. He received his Doctor of Dental Medicine degree, Master of Public Health, Doctor of Medical Sciences and Certificate in Periodontics from Harvard University. Active in many international and national organizations including the International Association for Dental Research and the American Academy of Periodontology, Dr. Paquette’s major research interests include clinical trials, novel interventions for periodontal disease and the interplay between periodontal disease and systemic conditions, in particular cardiovascular disease and obesity. He is a Diplomate of the American Board of Periodontology and practices Periodontics in Chapel Hill, NC. He can be reached at david_paquette@dentistry.unc.edu

Disclosure: Dr. Paquette has served as a scientific advisor and clinical investigator for OraPharma, Inc. He is also a scientific advisor or consultant for Izun Pharma, The Natural Dentist, Sunstar Americas, GeneEx, Colgate-Palmolive, and The Johnson & Johnson Company.
contact with host tissues along an ulcerated epithelial interface, called a periodontal pocket. Bacteria and their products (e.g., lipopolysaccharide, or endotoxin) penetrate the adjacent periodontal tissues, and this event stimulates host expression of inflammatory mediators such as arachidonic acid metabolites (prostaglandin E2) and cytokines (interleukin(IL)-1 and tumor necrosis factor). These mediators in turn trigger destructive changes in the periodontal tissues. In addition, these local events may be accompanied by systemic changes including transient bacteremia, endotoxemia, and elevation in acute phase reactants, and inflammatory biomarkers such as CRP.

Human cohort studies demonstrate that periodontal destructive changes (disease progression) are not continuous in patients over time but appear restricted to “random bursts” of activity confined to short intervals of 6 months or less. Risk factors associated with progressive periodontitis include smoking, diabetes mellitus, obesity, poor plaque control, and certain genetic polymorphisms. In addition, the presence of inflamed pockets is associated with higher odds for long-term destructive changes. Paulander and coworkers recently found that subjects with moderate (4 to 5 mm) and deep (≥ 6 mm) pocket depths were 2 to 3 times more likely to exhibit alveolar bone loss over a 10-year period. For nonsmoking subjects with deep pocket depths, the odds ratio for progressive bone loss rose to 8.0 (95% confidence interval [CI], 3.0 to 21.5). When a similar analysis was conducted for tooth loss as the dependent variable, the odds ratio for moderate and deep pockets were 2.9 (95% CI, 1.9 to 4.2) and 4.2 (95% CI, 2.4 to 7.3), respectively. These data indicate that pocket depth reduction remains a clinically important treatment goal.

**TREATMENT MODELS AND LOCALLY ADMINISTERED ANTIMICROBIALS**

Strategies for treating periodontitis principally focus on addressing the etiologic microbial biofilm. Conventional treatment follows a mechanical model whereby the bacterial biofilm is disrupted and removed via scaling and root planing (SRP) procedures. These debridement procedures can be accomplished nonsurgically or surgically, and both approaches result in predictable pocket depth reductions in patients. Several chemotherapeutic approaches have also been developed and tested to enhance the clinical benefits of scaling and root planing. For example, peroral (systemic) antibiotics (used alone or as adjuncts) consistently and significantly improve probing parameters in periodontitis patients versus control therapies. Because of the risk of systemic reactions, peroral use of antibiotics is usually reserved for generalized, severe, or aggressive cases of periodontitis or those with symptomatic periodontal abscesses. A number of LAAs have been developed as site-specific therapies to minimize systemic exposures and risks in patients. These LAAs follow a complementary medical-mechanical model, and typically feature an antibiotic within a polymer system to prolong drug release within the periodontal pocket (controlled-release delivery). Examples include tetracycline in an ethylene vinyl acetate fiber, chlorhexidine gluconate in a gelatin chip, doxycycline hyclate in a poly(DL-lactide) copolymer gel, and minocycline in polyglycolideco-DL-lactide (PGLA) microspheres.

A recent systematic review and meta-analysis demonstrated that adjunctive LAAs improved pocket depth over SRP alone in chronic periodontitis patients. The investigators identified clinical studies fitting inclusion criteria for the meta-analysis (28 randomized controlled clinical trials, 2 cohort and 2 case control studies). These studies involved a variety of LAAs including minocycline, doxycycline, tetracycline, metronidazole, and chlorhexidine formulations. The resulting meta-analysis and forest plot indicated an overall significant reduction in pocket depth with adjunctive local antimicrobials versus SRP alone. These consistent findings support the use of LAAs in combination with SRP in patients with chronic periodontitis, especially for those patients who are hard to manage or those at risk for disease progression.

**EVIDENCE ON MINOCYCLINE MICROSPHERES AND CLINICAL RELEVANCE**

Minocycline microspheres (Arestin, OraPharma) comprise a locally administered antimicrobial formulation approved for the adjunctive treatment of chronic periodontitis. The PGLA copolymer (3 mg per unit dose)
resorbs to water and carbon dioxide over a 21-day period during which minocycline hydrochloride (1 mg per unit dose) is maintained at concentrations effective against periodontal pathogens. Two recent reports confirm that adjunctive treatment with minocycline microspheres significantly reduces “red-complex” periodontal pathogens like P gingivalis when compared to SRP alone.\(^{26,27}\) Minocycline microsphere treatment may also block host collagenases that are implicated in periodontal tissue breakdown.\(^{28}\) The delivery system (cartridge and syringe) is designed for quick and easy administration of one unit dose of minocycline microspheres subgingivally per periodontal pocket measuring 5 mm or more in depth (Figures 1 and 2).

The pivotal trials of minocycline microspheres involved approximately 750 subjects with generalized moderate to advanced chronic periodontitis recruited at 18 centers.\(^{24}\) Subjects meeting inclusion criteria at baseline were randomized to one of 3 treatments: (1) SRP alone (positive control), (2) SRP plus placebo microspheres (vehicle control), or (3) SRP plus minocycline microspheres. Minocycline versus placebo microspheres were applied at baseline following SRP and at 3 and 6 months per the randomization in all pockets (≥ 5 mm) identified at baseline. Full mouth probing examinations were performed at baseline (prior to treatment) and at 1, 3, 6, and 9 months. Overall, an analysis of co-variance (ANCOVA) adjusting for the different centers indicated significant inter-group differences in pocket depth reductions at all time points following baseline (\(P < .001\)). In particular, subjects treated with adjunctive minocycline microspheres exhibited significantly greater pocket depth reductions after a single administration (at 1 and 3 months) and with re-administration (at 6 and 9 months) compared to subjects treated with SRP alone. When subjects who exhibited advanced periodontitis (mean baseline PD > 6 mm, Figure 3) or subjects who smoked (Figure 4) were considered, ANCOVA indicated significant pocket depth reductions with adjunctive minocycline microspheres over control treatments.\(^{24,29}\) Indeed, inter-group differences in PD reduction were greater among advanced periodontitis subjects versus the overall population.

The incidence of pocket resolution (post-treatment pocket depth < 5 mm) was also designated as a meaningful outcome. A significantly and consistently higher percent of pockets “resolved” with adjunctive mino-cycline microspheres versus SRP alone both for all subjects and for smokers (Table).\(^{30}\) For this trial, a shift in subject mean pocket depth < 5 mm with treatment was considered a clinically important response. When regression analyses were performed comparing response odds of adjunctive minocycline microsphere treatment versus SRP alone, the odds ratios for subjects with advanced periodontitis or who smoked were 2.06 (95% CI, 1.10 to 3.85) and 2.86 (95% CI, 1.45 to 5.66), respectively.\(^{1}\) These data indicate that patients with advanced periodontitis or smokers are 2 to 3 times more likely to respond when adjunctive

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**Figure 1.** Clinical set-up for administration of minocycline microspheres with syringe and loaded cartridge system.

**Figure 2.** Insertion of cartridge tip into periodontal pocket and clinical administration of minocycline microspheres.
minocycline was used. No serious side effects were observed among patients treated with adjunctive minocycline microspheres. Thus, treatment with adjunctive minocycline microspheres is safe and significantly increases the odds of shifting patients to more stable or maintainable case definition.

A large post-marketing trial has been conducted to evaluate the use of minocycline microspheres in private practices throughout the United States. There were 895 dentists, and 2,805 patients were recruited. According to the study protocol, patients were treated with SRP at baseline with one application of minocycline microspheres in all pockets (≥ 5 mm). Minocycline microsphere treatment was repeated at 3 months, and probing assessments were made at 3 and 6 months. There were 1,095 patients who were treated with 2 applications of minocycline microspheres per protocol, and 1,710 patients received only one application but returned for subsequent evaluations. Mean pocket depth reduction from baseline in the 1,710 patients was 1.82 mm (P < .0001), and for the 1,095 patients at 6 months it was 1.94 mm (P < .0001). Similar results were obtained in smokers, patients with diabetes, and patients with a history of CVD. After one minocycline microsphere treatment, 62% of sites had decreased to less than 5 mm, and after 2 treatments 67% of the sites demonstrated this outcome. There were no serious adverse events in the study. This practice-based study demonstrated that minocycline microspheres and SRP were effective in reducing pocket depth and that efficacy increased with retreatment.

Emerging data from other intervention trials suggest that intensive periodontal therapy that includes local minocycline microspheres may potentially improve systemic surrogate outcomes for CVD. In a preliminary trial, D’Aiuto, et al2 randomized 65 systemically healthy subjects with severe generalized periodontitis to one of 3 groups: (1) no treatment (negative control), (2) SRP alone (positive control), or (3) SRP plus minocycline microspheres.
The investigators assessed periodontal parameters and serum markers including CRP, IL-6, total cholesterol, and low-density lipoprotein (LDL) cholesterol. After 2 months, serum CRP levels remained unchanged for the negative control subjects. In contrast, subjects treated with either SRP alone or SRP plus minocycline microspheres exhibited significant reductions in serum CRP (0.5 ± 0.2 mg/L and 0.8 ± 0.2 mg/L respectively). Similar improvements in serum IL-6, total and LDL cholesterol were also observed, and they were greatest on average for subjects treated with SRP plus minocycline microspheres.

In a larger trial, Tonetti, et al. randomly assigned 120 patients with severe periodontitis to community-based periodontal care (control therapy) versus intensive periodontal treatment, which they defined as SRP plus minocycline microspheres, and extraction of hopeless teeth. These investigators evaluated endothelial function by measuring flow-mediated dilatation of the brachial artery in addition to serum inflammatory biomarkers over a 6 month post-treatment period. Flow-mediated dilatation was significantly lower, and serum inflammatory markers were significantly elevated one day following intensive treatment. This was likely due to transient bacteremia secondary to mechanical instrumentation and extraction procedures. However at 2 and 6 months, flow-mediated dilatation was significantly improved in the intensive-treatment group as compared to the control groups. The observed improvement in endothelial function was associated with improvement in measures of periodontal disease.

The early evidence from these 2 trials suggests that intensive periodontal treatment including LAAs may reduce the local as well as the systemic inflammatory burden and may improve endothelial dysfunction. These improvements may be associated with reduced risk for CVD. Further research is needed to confirm this finding.

**SUMMARY AND CONCLUSIONS**

Residual or persistent periodontal inflammation is associated with periodontal disease progression and tooth loss. Hence, resolving periodontal inflammation remains an important goal of periodontal treatment. Clinical trials consistently demonstrate that LAAs combined with SRP effectively reduce tissue inflammation in patients with chronic periodontitis. These changes are clinically relevant, and preliminary data suggest that this approach to periodontal treatment may be associated with improvements in systemic outcomes.
REFERENCES


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POST EXAMINATION QUESTIONS

1. Evidence demonstrates that patients treated adjunctively with LAAs exhibit greater improvements in clinical parameters. However, these improvements are not clinically relevant.
   a. First statement is false, second is true.
   b. First statement is true, second is false.
   c. Both statements are false.
   d. Both statements are true.

2. In general, patients with mild or moderate periodontitis are without noticeable symptoms. Persons with advanced periodontitis may report tissue swelling, tooth mobility, and migration of the dentition.
   a. First statement is false, second is true.
   b. First statement is true, second is false.
   c. Both statements are false.
   d. Both statements are true.

3. Risk factors associated with progressive periodontitis include:
   a. diabetes mellitus.
   b. obesity.
   c. certain genetic polymorphisms.
   d. all of the above.

4. Which of the following is a Gram-positive organism?
   a. Porphyromonas gingivalis
   b. Treponema denticola
   c. Tannerella forsythia
   d. None of the above

5. Periodontal destructive changes (disease progression) are not continuous in patients over time. They appear to involve cycles of activity taking place over long intervals that are often years apart.
   a. First statement is false, second is true.
   b. First statement is true, second is false.
   c. Both statements are false.
   d. Both statements are true.

6. The following is/are a locally administered antimicrobial (LAA):
   a. minocycline.
   b. doxycycline.
   c. metronidazole.
   d. all of the above.

7. Data indicate that patients with advanced periodontitis or smokers are _____ times more likely to respond when adjunctive minocycline was used versus scaling and root planing alone.
   a. 1.5  b. 2 to 3  c. 3 to 4  d. 4 to 5

8. LAA formulations typically feature an antibiotic within a polymer system. This formulation prolongs drug release within the periodontal pocket.
   a. First statement is false, second is true.
   b. First statement is true, second is false.
   c. Both statements are false.
   d. Both statements are true.
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