Periodontal Host Modulation with Antiproteinase, Anti-Inflammatory, and Bone-Sparing Agents. A Systematic Review

Michael S. Reddy,* Nico C. Geurs,* and John C. Gunsolley†

** University of Alabama at Birmingham School of Dentistry, Department of Periodontology, Birmingham, Alabama.*
† Department of Periodontics, College of Dental Surgery, University of Maryland, Baltimore, Maryland.

Background: The use of modulating agents, including inhibition of matrix metalloproteinases (MMPs) with antiproteinases, blocking production of proinflammatory cytokines and prostaglandins with anti-inflammatory drugs, and inhibiting activation of osteoclasts with bone-sparing agents, has been postulated to be of therapeutic value as an adjunctive therapy to the management of chronic periodontitis.

Rationale: The objective of this systematic review of the literature was to assess the adjunctive efficacy of antiproteinase, anti-inflammatory, and bone-sparing host-modulating agents in the treatment of gingivitis, aggressive periodontitis, and chronic periodontitis.

Focused Questions

1. In patients with periodontal diseases, what is the effect of host-modulation agents, alone or combined with conventional therapy, compared to conventional therapy alone as assessed by clinical, radiographic, adverse, and patient-centered outcomes?
2. In patients with dental implants, what is the effect of host-modulation agents on implant success assessed by clinical, radiographic, adverse, and patient-centered outcomes?

Search Protocol: MEDLINE, Embase, and the Cochrane Library databases were searched without language restrictions through April 1, 2002 for studies that used tetracycline (TET)-related matrix metalloproteinase (MMP) inhibitors, or non-steroidal anti-inflammatory drugs (NSAIDs) and bisphosphonate anti-osteolytic agents. The investigation also included hand searching of journals and contacting authors and industry experts.

Selection Criteria

Inclusion criteria: Only human studies (randomized controlled clinical trials, cohort studies, case-control studies, cross-sectional studies, and case series) were selected. Studies were on subjects with gingivitis, aggressive or chronic periodontitis, or dental implants. Interventions included TET-related MMP inhibitors, NSAIDs, or bisphosphonate anti-osteolytic agents.

Exclusion criteria: Studies that used MMP tissue inhibitors as diagnostic or prognostic indicators of periodontal disease or that evaluated short-term systemic antibodies or locally delivered levels of drugs with antiproteinase activity were excluded.

Data Collection and Analysis: The primary outcomes for assessment were changes in bone or clinical attachment levels (CAL); secondary outcomes included clinical measures of plaque, gingival inflammation, probing depth (PD), and mobility. Summary data appropriate for meta-analysis were pooled using a weighted average and analyzed using a standardized difference; the results were checked with both fixed-effects and random-effects models.

Main Results

1. A meta-analysis done on the studies reporting changes in CAL and PD following administration of sub-antimicrobial doses of doxycycline (SDD) in conjunction with scaling and root planing (SRP) in patients with periodontitis showed a statistically significant beneficial adjunctive effect.
2. There were insufficient data to provide meta-analyses on periodontal patients treated with other host-modulating agents; descriptive tables are included.
3. NSAIDS show promise in their ability to slow periodontal disease.
4. Preliminary data on bisphosphonate agents indicate there is a potential role for these agents in periodontitis management.
5. There are a very limited number of studies on host-modulating agents and dental implants and no analyses were possible.

6. Because the treatment methodologies and clinical variables differed considerably among the studies, it is difficult to summarize the information and identify a reliable total patient population.

Reviewers' Conclusions

1. Large multi-center trials are needed to evaluate the role of host-modulating agents in the treatment of periodontitis.
2. NSAIDS and bisphosphonate drugs may have a potential adjunctive role in periodontal therapy.
3. The adjunctive use of SDD with SRP is statistically more effective than SRP alone in reducing PD and in achieving CAL gain.

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KEY WORDS

Adjunctive therapy; antiproteinase/therapeutic use; anti-inflammatory agents/therapeutic use; host modulation agents/therapeutic use; gingivitis/therapy; periodontitis/therapy; periodontitis, aggressive/therapy; review literature; meta-analysis.

BACKGROUND

The primary etiology of the periodontal diseases and chronic inflammation around dental implants is a bacterial infection.[1] The clinical course of periodontitis in patients can vary greatly despite their harboring similar quantitative and qualitative levels of bacteria.[2] In essence, a Gram-negative infection of the pocket is necessary, but not sufficient to induce the periodontal disease initiation or progression[3] (Fig. 1). Ultimately, it is the host's reaction to the presence of bacteria that mediates tissue destruction. This response can be influenced by environmental (e.g., tobacco use) acquired (e.g., systemic disease), and genetic risk factors.[4] Since destruction of the periodontium is believed to be due to the host response, it is logical to consider therapeutic approaches that modulate the host response in addition to antibacterial approaches in the management of chronic periodontitis and peri-implant disease. Three potential approaches to host modulation have been considered: 1) inhibition of matrix metalloproteinases (MMPs) with antiproteinases, 2) blocking production of proinflammatory cytokines and prostaglandins with anti-inflammatory drugs, and 3) inhibiting activation of osteoclasts with bone-sparing agents.

Antiproteinases

Antiproteinases used in the treatment of periodontitis are tetracyclines. Along with antimicrobial activity, TET agents have the ability to inhibit neutrophils, osteoclasts, and matrix metalloproteinases that appear to

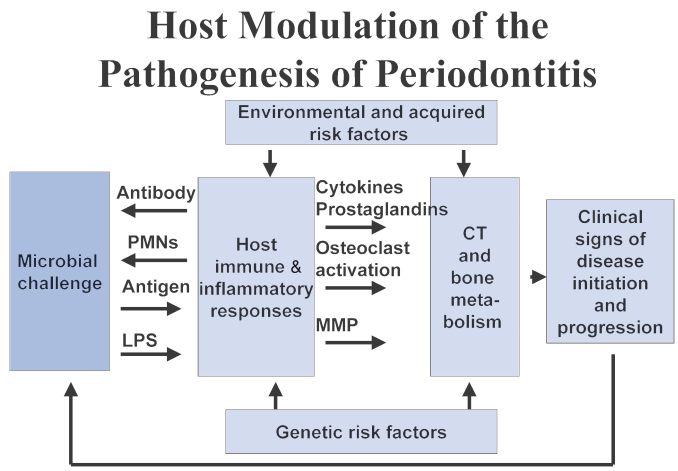

Figure 1.
The potential application of host modulation as a therapeutic intervention in the pathogenesis of periodontitis. PMNs = polymorphonuclear leukocytes; CT = connective tissue; LPS = lipopolysaccharide. Adapted with permission from reference 3.

be involved in the destruction of the periodontium.[5] Tetracyclines have an anti-inflammatory action and may be bone-sparing through inhibition of osteoclasts.[6] Doxycycline is the most studied and strongest collagenase inhibitor of the used tetracyclines.[7]

Anti-Inflammatory Drugs

Arachidonic acid metabolites are proinflammatory mediators that have been implicated in a variety of bone resorptive processes including chronic periodontitis.[8] These mediators can be inhibited by NSAIDs, including some common nonprescription drugs, such as aspirin, ibuprofen, and naproxen, are analgesic, anti-platelet, anti-thrombocytic, and inhibit the enzyme cyclooxygenase, thereby preventing the production of arachidonic acid metabolites. The reduced level of proinflammatory mediators as a result of the use of NSAIDs may limit the host-mediated alveolar bone destruction observed in periodontitis and peri-implant disease.

Bone-Sparing Agents

During the past 10 years, the use of bisphosphonate bone-sparing agents has been incorporated in the management of osteoporosis and other bone-resorptive diseases.[9-12] They are absorbed by the bones and locally released during acidification associated with osteoclastic activity. Bisphosphonates inhibit bone resorption by reducing osteoclast activity.[12] Therefore, they may have a potential role in the inhibition of alveolar bone loss in periodontitis patients and around implants.

RATIONALE

The objective of this systematic review was to assess the adjunctive efficacy of antiproteinase, anti-inflammatory, and bone-sparing host-modulating agents in the treatment of gingivitis, aggressive and chronic periodontitis.

FOCUSED QUESTIONS

We addressed the following focused questions:

1. In patients with periodontal diseases, what is the effect of host-modulating agents (alone or combined with conventional therapy), compared with conventional therapy as assessed by clinical, radiographic, adverse, and patient-centered outcomes?
2. In patients with dental implants, what is the effect of host-modulating agents on implant success assessed by clinical, radiographic, adverse, and patient-centered outcomes?

SEARCH PROTOCOL

Data Sources and Search Strategy

An electronic search of MEDLINE, Embase and the Cochrane Library up to April 1, 2002 without language restrictions was performed. Independent searches were conducted for periodontal diseases and dental implants with respect to the efficacy of antiproteinase, anti-inflammatory, and bone-sparing agents. The antiproteinase strategy was 'protease inhibitors' OR 'antiproteinase' OR 'MMP inhibitor' OR 'matrix metalloproteinases' OR 'tetracycline' OR 'antibiotics, tetracycline' OR 'doxycycline'. The anti-inflammatory strategy was 'anti-inflammatory agents' OR 'NSAIDs' OR 'lipoxins' OR 'hydroxyeicosatetraenoic acids' OR 'cox-2' OR 'cyclooxygenase inhibitors' OR 'interleukin receptors'. The bone-sparing strategy was 'bone density' OR 'osteolysis' OR 'diphosphonates' OR 'serms' OR 'calcium' OR 'estrogens' OR 'calcitonin' OR 'phytoestrogen' OR 'fluorides' OR 'fluorides, topical'.

Hand searching included a perusal of bibliographies of relevant papers and review articles. Major periodontal publications were contacted and any manuscripts relevant to the search known to be "in press" were included. In addition, representatives of industry involved with the manufacture of biopharmaceuticals were contacted to provide missing data and clarity when necessary.

Inclusion criteria: To be eligible for inclusion in the review, manuscripts had to pertain to human studies. Randomized controlled clinical trials, cohort studies, case-control studies, cross-sectional studies, and case series were included. Furthermore, the studies had to be conducted on subjects with gingivitis, aggressive periodontitis, chronic periodontitis, or individuals with dental implants. The types of interventions included were administration of tetracycline-related matrix metalloproteinase inhibitors, NSAIDs, or bisphosphonate anti-osteolytic agents.

Exclusion criteria: Studies that used MMP tissue inhibitors as diagnostic or prognostic indicators of periodontal disease or that evaluated short-term systemic antibiotics or locally delivered levels of drugs with antiproteinase activity were excluded.

Outcomes: The primary outcomes for data assessment were changes in bone or clinical attachment levels (CAL). Secondary outcome data were collected on clinical measures of plaque (plaque indices [PI]), gingival inflammation (gingival index [GI], bleeding on probing [BOP]), probing depth (PD), and mobility. Patient-centered outcomes were tooth survival, function, and comfort.

We also considered the cost/benefit ratio of treatment and adverse outcomes such as drug side effects and adverse events. Summary data were collected on study abstraction forms. When additional information was necessary, whenever possible, study authors were contacted.

Data Collection and Analysis

Screening for appropriate studies was done in duplicate by two independent reviewers, based on pre-selected criteria for study inclusion. Initial screening was from titles and abstracts generated from the search process with an attempt to be inclusive. Investigations were reassessed from full-text papers to arrive at the final group of eligible studies. The number of reviewed articles included and excluded was tabulated along with the reasons for exclusion of some studies. Agreement between independent reviewers was formally assessed mathematically (Cohen's kappa statistic). The reviewers discussed any disagreements and the resolution was recorded.

Studies with sufficient similarities were combined in summary tables with respect to primary and secondary outcomes. Primary and secondary outcome tables were evaluated for potential quantitative analysis. Summary data, which were appropriate for meta-analysis, were pooled using a weighted average in which individual results were assigned weights that were in inverse proportion to their variance. The data were analyzed using a standardized difference as described by Fleiss.[13] The results were checked with both a fixed-effects model and a random-effects model and the results were consistent. To test for heterogeneity, two independent statistical tests were used (Cohen's d unadjusted and Hedges's g adjusted).[14,15] Both heterogeneity tests had to be nonsignificant in order to accept the meta-analysis.

The quality assessment was scored by the quality criteria for the various study types listed below. The studies were scored from 1 to 5, with 1 indicating the highest score based on meeting 5 of 5 of the quality assessment criteria for the various clinical study types. The kappa score for agreement between the 2 reviewers was 0.86, indicating a high level of agreement. For the studies included in the meta-analysis, heterogeneity was nonsignificant. Heterogeneity is a test for consistency among the studies. If the heterogeneity test is nonsignificant, then the studies can be combined in a meta-analysis. If it is significant, then one must explain or find the source of inconsistence between studies.

Ranking of Studies

This review was not limited to clinical trials and attempted to be inclusive of all reported human studies.

Therefore, the quality appraisals utilized different criteria based on individual study methodologies, as outlined below.

Clinical trials criteria: Randomization; allocation concealment; multi-centered; masking; and follow-up completeness and accountability.

Cohort studies: Description of the population; masking; control of confounders; completeness of follow-up; and measurement of the exposure.

Case-control studies: Matching criteria; masking; completeness of follow-up; and measurement of the exposure.

Case series: Explicit inclusion criteria; masking; completeness of follow-up; measurement of the exposure; and representative population.

Two reviewers conducted study quality assessments independently and inter-examiner agreement was scored by kappa statistic. Any disagreement was resolved by discussion between the reviewers.

RESULTS

Host Modulation of Periodontal Disease with Antiproteinases

Forty-three studies were initially included. The focused review question for this section was: What is the effect of antiproteinase therapy on periodontal disease alone or in combination with conventional mechanical therapy compared to conventional mechanical therapy alone? Studies that utilized tissue inhibitors of MMPs as diagnostic or prognostic indicators of periodontal diseases were excluded.[16-24] In addition, studies that evaluated short-term systemic antibiotics or locally delivered levels of drugs with antiproteinase activity, such as tetracyclines, in conjunction with mechanical periodontal therapy were excluded.[25-43]

The remaining studies were divided into 3 groups to address the focused question: 1) therapeutic outcomes–long-term administration of tetracycline,[44-46] 2) therapeutic outcomes–subantimicrobial doses of doxycycline,[47-53] and 3) patient-centered and safety outcomes related to long-term antiproteinase therapy.[54-59]

The effect of long-term administration of low-dose tetracycline was reported in 3 case series (Table 1).[44-46] These studies were conducted in the era before TET-related drugs were used as MMPs inhibitors. The clinical impression of the authors was that long-term tetracycline improved periodontal health. The studies used variable doses of tetracycline that resulted in inconsistent blood levels, which may have reached antibacterial levels. They provided a historical basis for the studies that followed.

Characteristics of 7 studies using subantimicrobial doses of doxycycline (SDD) that were included are presented in Table 2. Some of the data were derived by contacting the authors. Table 2 addresses both primary (CAL) and secondary (PD, PI, GI, and BOP) outcomes. Table 3 is a composite summary comparison of the data extracted on CAL, PD, and BOP. Table 3 lists only the data pertaining to 20 mg bid dosing which is commercially available for treatment of chronic periodontitis. The SDD studies usually separated data on the basis of initial PD (e.g., 4 to 6 mm, ≥7 mm).

Overall, the majority of the studies indicated a statistically significant better result with respect to gain in CAL and PD reduction when 20 mg bid doxycycline treatment was used as an adjunct to conventional therapy. No consistent differences were reported between the active and placebo groups for bleeding on probing, gingival inflammation, or plaque. In addition, the

Table 1.

Long-Term Tetracycline

Reference	N Subjects	Study Design	Host Modulations	Periodontal Treatment	Outcome	Location/ Funding	Study Ranking
Fasciano and Fazio[44] 1981	1 chronic periodontitis 1 aggressive periodontitis (LJP)	Case report	250 mg TET bid over 1 year	SRP followed by full-mouth	Bone fill interpreted from radiographs surgery	University/ unfunded	5
Kornman and Karl[45] 1982	20 Chronic periodontitis	Case series; 2-7 year follow-up	250 mg TET per day for 2-7 years vs. 10 subjects off TET for 2 years	Periodontal surgery	Clinical impression of health Decreased Gram-negative flora	University/ government	4
Lindhe et al.[46] 1983	14 Chronic periodontitis	Case series; split-mouth design; uncontrolled	Long-term TET 250 mg qid × 2 weeks and 250 mg qid × 48 weeks; split-mouth SRP (2 quads)	None	Clinical benefit crossed over to untreated side	University/ government	4

Table 2.

Subantimicrobial Dose of Doxycycline (SDD): Primary Therapeutic (gain in CAL) and Secondary Clinical Outcomes

Reference	N Subjects	Study Design	Host Modulations
Ashley[47] 1999	437 adult periodontitis patients with ≥2 sites 5-9 mm CAL & PD	Combined data from 3 randomized placebo-controlled, double-masked trials	10 mg DOXY qid 12 months (n 80) 20 mg DOXY qid 12 months (n 119) 20 mg DOXY bid 12 months (n 119) placebo bid 12 months (n 119)
Caton et al.[48] 2000	190 adult periodontitis (183 intent-to-treat)	Five centers, randomized, double-masked, placebo-controlled parallel arm	20 mg DOXY bid × 9 months and SRP placebo bid × 9 months and SRP
Crout et al.[49] 1996	14 adult periodontitis patients	Non-randomized, masked	20 mg DOXY bid (SDD) 2 on, 2 off, 2 on for 6 months
Golub et al.[50] 2001	51 adults with active periodontitis based on PD and increased collagenase at multiple exams	Treatment (tx) 12 weeks, no tx 12 weeks, tx 12 weeks; placebo-controlled, double-masked, randomized in strata	SSD 5 groups: 1) 20 mg DOXY bid × 12 weeks, 24-36 20 mg qid 2) 20 mg DOXY qid × 12 weeks, 24-36 20 mg qid 3) 20 mg DOXY bid × 4 weeks, 20 mg qid × 8 weeks, 24-36 20 mg qid 4) 20 mg DOXY bid 4 weeks, placebo × 8 weeks, 24-36 placebo 5) placebo (bid), 12 weeks, placebo qid 24-36 weeks
Golub et al.[51] 1997	18 adult periodontitis, 3 groups; different disease levels	Non-masked, non-controlled open label; 2 month duration	20 mg DOXY bid × 2 months
Novak et al.[52] 2002	20 subjects ≤45 years old; severe generalized periodontitis, 20 teeth, >30% of sites ≥5 mm CAL	Double-masked, placebo-controlled parallel arm	20 mg DOXY bid for 24 weeks vs. placebo
Preshaw et al.[53] 2002	208; chronic periodontitis	Multi-center, randomized double-masked placebo-controlled parallel arm	20 mg DOXY bid for 9 months and SRP

Table 2. (continued)

Subantimicrobial Dose of Doxycycline (SDD): Primary Therapeutic (gain in CAL) and Secondary Clinical Outcomes

Periodontal Treatment	Primary Outcome	Secondary Clinical Outcome	Location/Funding	Study Ranking
None; scaling baseline; 12 months	Change in CAL; no significance between placebo, 10 mg or 20 mg qid 20 mg bid CAL PD Placebo 20 mg bid 4-6 +0.44 mm +0.67 mm (P <0.01) ≥7 +0.95 mm +1.27 mm (P <0.05)	Probing depth; no significance between placebo, 10 mg or 20 mg qid 20 mg bid PD PD Placebo 20 mg bid 4-6 –0.46 mm –0.71 mm (P <0.01) ≥7 –0.96 mm –1.39 mm (P <0.05)	Universities/industries	2
SRP	CAL gain (mm) PD Placebo 20 mg bid 0-3 +0.20 +0.25 4-6 +0.86 +1.03 (P <0.05) ≥7 +1.17 +1.55 (P <0.05)	Very high BOP after SRP BOP PD Placebo 20 mg bid 4-6 79% 64% (P <0.05) >7 80% 75% Probing depth PD Placebo 20 mg bid 4-6 –0.69 –0.95 (P <0.001) ≥7 –1.20 –1.68 (P <0.01)	University/industry	1
None, placebo	CAL: 5 sites/pt 6 months (mm) Placebo 20 mg bid –0.2 mm loss +0.05 gain (P <0.05)	5 months–GI – NS PI – NS Probing depth Placebo 20 mg bid No change –2 mm (P <0.05)	University/industry	4
None; scaling baseline, 24 weeks	Gain in CAL 133 sites in 51 subjects: Group 1 – 0.15 mm* Group 2 – 0.9 mm Group 3 – 0.6 mm Group 4 – 0.7 mm Group 5 – 0.8 mm *(P = 0.04)	PD: no significant difference GI: no significant difference BOP: no significant difference	University/industry	2
None; scaling prior to baseline	Change in CAL Control: no change 20 mg severe disease +2 mm 20 mg moderate disease +1.1 mm (P <0.05; from baseline)	Group PD GI PI Control –0.2 +0.1 +0.29 20 mg bid –1.1 –0.43 –0.49 Severe disease 20 mg bid –0.7 –0.36 –0.18 Moderate disease (no significant differences)	University/industry	4
Debridement and oral hygiene instructions for 4 weeks; maintenance at 8, 16, 24, and 36 weeks	Change in CAL CAL Placebo 20 mg/bid 4-6 1.00 mm 0.56 mm >7 1.24 mm 1.78 mm (no significant difference)	Probing depth PD Placebo 20 mg/bid 4-6 mm –0.97 –1.20 >7 mm –1.42 –3.02 (P <0.05) PI, GI, BOP: not significant	University/industry	2
SRP	Change in CAL PD Placebo 20 mg/bid 4-6 0.94 1.27 (P <0.05) >7 1.60 2.09 (P <0.05)	PD Placebo 20 mg/bid 4-6 0.96 1.29 (P <0.05) >7 1.77 2.31 (P <0.05)	University/industry	1

Table 3.

SDD Meta-Analysis Summary Comparison SDD (20 mg bid doxycycline) Versus Placebo (bid)

Reference	Periodontal Treatment	Study Duration	Mean CAL Change (mm/subject + SE)			
			SDD Baseline PD		Placebo Baseline PD	
			4-6 (n)	>7 (n)	4-6 (n)	>7 (n)
Ashley[47] 1999	None, baseline scaling debridement	12 months	0.67 ± 0.08 (119)	1.27 ± 0.12 (119)	0.44 ± 0.09 (119)	0.95 ± 0.11 (119)
Caton et al.[48] 2000	SRP	9 months	1.03 ± 0.05 (90)	1.55 ± 0.13 (79)	0.86 ± 0.05 (93)	1.17 ± 0.13 (78)
Crout et al.[49] 1996	None	6 months cyclic 0-2 bid 4-6 bid	NA	0.5 ± 0.41 (7)	NA	–0.18 ± 0.22 (7)
Golub et al.[50] 2001	None; baseline +24 week scaling	9 months cyclic 0-3 bid 6-9 bid	–0.15 ± 0.16 (13)	NA	–0.80 ± 0.13 (14)	NA
Golub et al.[51] 1997	None; baseline scaling	2 months	1.1 ± 0.40 (7)	2.0 ± 0.57 (5)	0.0 ± 0.60 (6)	NA
Novak et al.[52] 2002	OHI; maintenance	9 months (6 month dosing)	0.56 + 0.48 (10)	1.78 + 0.71 (10)	1.00 + 0.51 (10)	1.24 + 0.68 (10)
Preshaw et al.[53] 2002	SRP	9 months	1.27 ± 0.05 (107)	2.09 ± 0.13 (107)	0.94 ± 0.05 (102)	1.60 ± 0.15 (102)

placebo and conventional therapy groups both tended to show significant improvements from baseline.

SDD Meta-Analysis

Figures 2 through 5 illustrate the forest plots from the meta-analysis regarding SDD. The data are weighted mean differences between SDD and placebo adjunctive therapy that are derived by dividing the difference between the means by the standard deviations of the difference. The forest plots include the sample size for each group (e.g., N_1, N_2). In addition, the normalized effect and 95% confidence interval (horizontal line) for the effect is illustrated by the line plot. An overall effect, confidence interval, and significance level for all studies or a subset of the studies was then calculated. For sites with pretreatment probing depths of 4 to 6 mm and ≥7 mm, a statistically significant adjunctive benefit on clinical attachment levels was found when SDD was used in combination with SRP (Fig. 2 and Fig. 3 combined result[s]).

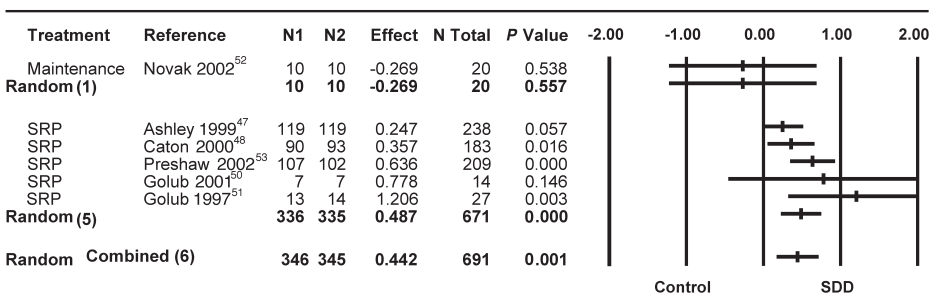

Figure 2.

Forest plot of changes in CAL for initial PD of 4 to 6 mm in randomized clinical trials that utilized SDD (20 mg doxycycline bid). N1 represents the number of subjects in the active group. N2 represents the number of subjects in the control group. The vertical bar indicates the weighted mean difference (mm) for adjunctive SDD and the horizontal line is the extent of the lower and upper 95% confidence interval for the study or combined data for a group of studies. For combined data, the number of studies pooled for the meta-analysis is indicated. A vertical bar to the right of zero indicates a beneficial effect for SDD over placebo.

Table 3. (continued)

SDD Meta-Analysis Summary Comparison SDD (20 mg bid doxycycline) Versus Placebo (bid)

Mean PD Change (mm/subject + SE)				BOP % sites/person (n)				
SDD Baseline PD		Placebo Baseline PD		SDD		Placebo		Study Ranking
4-6 (n)	>7 (n)	4-6 (n)	>7 (n)	4-6 (n)	>7 (n)	4-6 (n)	>7 (n)	
0.71 ± 0.06 (119)	1.39 ± 0.10 (119)	0.46 ± 0.09 (119)	0.96 ± 0.11 (119)	52% (119)	69% (119)	61% (119)	80% (119)	2
0.95 ± 0.05 (90)	1.68 ± 0.12 (79)	0.69 ± 0.05 (93)	1.2 ± 0.12 (78)	64% (93)	75% (79)	70% (93)	80% (78)	1
NA	2.05 ± 0.4 (7)	NA	0.3 ± 0.3 (7)	NA	NA	NA	NA	4
0.11 ± 0.14 (13)	NA	0.01 ± 0.18 (14)	NA	NA	NA	NA	NA	2
0.7 ± 0.20 (7)	1.1 ± 0.38 (5)	0.2 ± 0.46 (6)	NA	NA	NA	NA	NA	4
1.20 ± 0.26 (10)	3.02 ± 0.66 (10)	0.97 ± 0.26 (10)	1.42 ± 0.66 (10)	53% (10)	60% (10)	44% (10)	50% (10)	2
1.29 ± 0.05 (107)	2.31 + 0.12 (107)	0.96 ± 0.06 (102)	1.77 ± 0.13 (102)	NA	NA	NA	NA	1

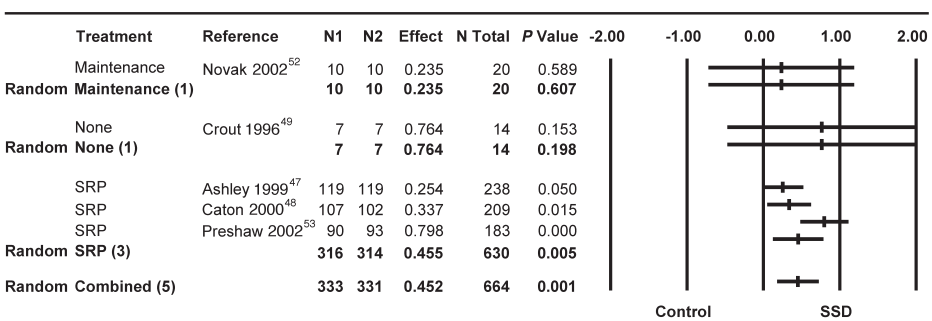

Figure 3.
Forest plot of changes in CAL for initial PD of ≥7 mm in randomized clinical trials that utilized SDD (20 mg doxycycline bid). See explanation of forest plot in Figure 2.

For PD changes, a significant adjunctive benefit was noted after the combination of scaling and root planing and SDD for pre-treatment probing depths of 4 to 6 mm and ≥7 mm (Figs. 4 and 5).

Six studies addressed patient safety and adverse outcomes of tetracycline and SDD (Table 4). The majority of the literature addressed the long-term (6- to 12-month) administration of SDD. Overall, no qualitative or quantitative changes in the oral and subgingival flora were observed.[54-58] Caton et al. reported no post-treatment disease progression or rebound for a 3-month follow-up after 9 months of treatment with SDD and scaling and root planing.[57] Throughout the SDD studies the reported adverse events and side effects were not significantly different from placebo and/or conventional therapy. One case report of tetracycline used in combination with SRP reported a significant and rare adverse event of pseudotumor cerebri.[59]

Antiproteinase Agents and Dental Implants

None of the 11 studies initially evaluated addressed the focused question. Two studies assessed the effect of local delivery of tetracycline;[60,61] 7 investigations used tetracyclines to treat peri-implantitis as an antibiotic, detoxifying agent or addition to a bone graft;[62-68]

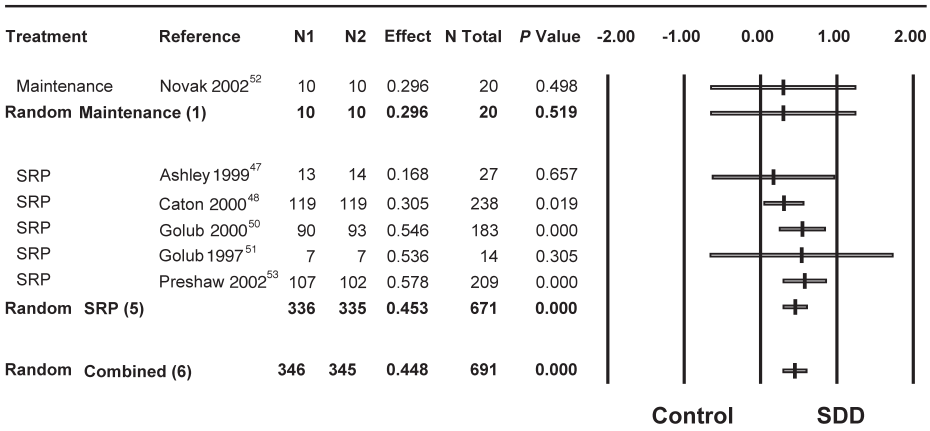

Figure 4.
Forest plot of changes in PD for initial PD of 4 to 6 mm in randomized clinical trials that utilized SDD (20 mg doxycycline bid). See explanation of forest plot in Figure 2.

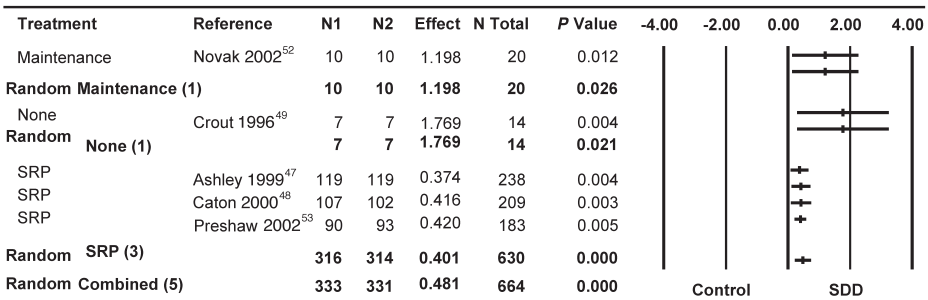

Figure 5.
Forest plot of changes in PD for initial PD of ≥7 mm in randomized clinical trials that utilized SDD (20 mg doxycycline bid). See explanation of forest plot in Figure 2.

another used tetracycline as a histologic marker;[69] and 1 study reported implant placement in a patient receiving an antiproteinase inhibitor as an antiretroviral therapy for HIV infection.[70] None of these studies addressed the focused review question.

Periodontal Disease Host Modulation with Anti-Inflammatory Agents

Twenty-nine studies were initially evaluated. The focused review question for this section was, "What is the effect of anti-inflammatory therapy on periodontal disease alone or in combination with conventional treatment compared to conventional therapy alone?" Investigations that utilized gingival crevicular fluid analysis as diagnostic or prognostic indicators of periodontal diseases were excluded.[71-74] In addition, studies that evaluated anti-inflammatory agents not for the treatment of periodontitis, or where the primary outcome was not related to periodontal diseases or periodontal therapy were excluded.[75-81]

The remaining clinical trials were considered in 2 groups and addressed 1) therapeutic outcome expressed in CAL measurements or bone change measurement,[8,27,32,82-88] and 2) therapeutic outcome expressed in PD measurements and assessment of plaque and gingival inflammation.[27,32,82-87,89-93]

Ten studies addressed primary outcomes[8,27,32,82-88] of the focused review questions and 13 studies addressed secondary clinical outcomes.[27,32,82-84,88-93] The majority of these studies were double-masked placebo-controlled clinical trials.[8,27,83-88] All were single-center studies with small to moderate size subject groups. A range of NSAIDs was used which represent mild (e.g., aspirin) to potent (e.g., flurbiprofen, ketorolac) anti-inflammatory activity. The most commonly evaluated drug was flurbiprofen.[8,83-85,87] The mode of administration varied from systemic administration to topical application in an oral rinse or dentifrice. The concomitant conventional treatment also varied from scaling and oral hygiene to guided tissue regeneration procedures. Most studies included chronic periodontitis subjects and one specifically addressed aggressive periodontitis subjects. In general, the heterogeneity of the studies limited quantitative summary analyses.

Six studies used a measure of alveolar bone support as the primary outcome to assess nonsurgical treatment or scaling and oral hygiene instructions.[8,82-86] These investigations tended to consistently show a statistically significant benefit favoring use of adjunctive non-steroidal anti-inflammatories when compared to a placebo group (Table 5). This was noted despite the small sample sizes and methodology variability. Nine studies addressed clinical attachment levels as one primary outcome.[27,32,82-88] In general, in the anti-inflammatory studies (Table 5), no statistically significant differences were reported with respect to less attachment loss.

Ten anti-inflammatory investigations reported changes in probing depth measurements (Table 6).[27,32,82-89,93] The vast majority reported no significant difference between test and control groups concerning PD reductions when SRP plus NSAIDs were compared to SRP alone. Two studies demonstrated a benefit when a non-steroidal anti-inflammatory was used.[86,88] Eight studies presented abstractable data regarding gingival inflammation.[32,84,85,89-93] Seven of these reported no statisti-

Table 4.

Tetracycline and Subantimicrobial Dose of Doxycycline (SDD): Safety and Adverse Outcomes

Reference	N Subjects	Study Design	Host Modulations	Periodontal Treatment	Patient Outcome	Location/ Funding	Study Ranking
Thomas et al.[54] 1998	38		20 mg DOXY bid or placebo bid	SRP 2 quads split-mouth	No change in subgingival flora	University/ industry	1
Walker et al.[55] 2000	76	Randomized to receive 20 mg bid or placebo	20 mg DOXY bid or placebo bid	Split-mouth; SRP	No quantitative change in flora; SRP decreased quantity	University/ industry	1
Ciancio and Ashley[56] 1998	Unreported	Combined summary data of 2 SSD studies	20 mg DOXY bid	Varied	No qualitative or quantitative shifts in flora, similar adverse event profile	University/ industry	2
Caton et al.[57] 2001	151 of 190 initially enrolled in RCT	3 month masked posttreatment follow up of RCT	20 mg DOXY bid or placebo bid (previous 9 months)	None	Attachment level: no progressive attachment loss after treatment stopped	University/ industry	2
Thomas et al.[58] 2000	251	Antibiotic susceptibility after SDD	10 mg DOXY qid, 20 mg DOXY qid, 20 mg DOXY bid, or placebo bid	Post-treatment	No change in antibiotic susceptibility or increased resistant species	University/ industry	3
Minutello et al.[59] 1988	1	Case report	TET therapy	SRP	Pseudotumor cerebri	University/ unfunded	5

cally significant differences in the gingival index between groups, while one noted a reduction in gingival inflammation in the NSAID group.[92]

Dental Implants and Host Modulation with Anti-Inflammatory Agents

Four studies were initially evaluated. The focused review question for this section was: In patients with dental implants, what is the effect of host-modulating agents on implant success assessed by clinical, radiographic, adverse, and patient-centered outcomes? Two studies were excluded because the primary outcome did not evaluate the role of anti-inflammatory treatment for bone maintenance around dental implants.[94,95] One paper was a case report that described the potential benefits of anti-inflammatory therapy for the healing of dental implants. Beneficial effects of flurbiprofen in the healing around dental implants were reported using subtraction radiography as the method of outcome assessment.[96]

The other report was a double-masked randomized controlled clinical trial.[97] The intervention was a 3-month regimen of 50 mg flurbiprofen, 100 mg flurbiprofen, or placebo during the healing after placement of dental implants. Twenty-nine patients with mandibular implants were evaluated using digital subtraction radiography. A decrease in bone loss was noted after 6 months in implants in the high-dose flurbiprofen group ($P<0.001$).

Periodontal Disease Host Modulation with Bone-Sparing Agents

Twenty-one studies were initially evaluated. The focused review question for this section was, "What is the effect of bone-sparing host modulation as a therapy for periodontal diseases?" Epidemiological studies that related systemic bone density loss or osteoporosis to oral bone loss or tooth loss were excluded.[98-104] In addition, investigations not directed at a form of periodontal disease (e.g., hormone replacement therapy) or compared to conventional therapy were excluded.[79,105-116]

Table 5.

Anti-Inflammatory Drugs: Primary Bone Changes and Attachment Levels

Reference	N Subjects	Study Design	Host Modulation	Periodontal Treatment
Williams et al.[8] 1989	44; radiographic evidence of alveolar bone loss	Double-masked; randomized; placebo-controlled	Flurbiprofen 50 mg bid for 6 months	Scaling and oral hygiene instructions
Reddy et al.[82] 1993	22; rapidly progressive periodontitis stratified into 3 groups N not reported for the different groups	Double-masked; randomized; placebo-controlled	Meclofenamate 50 mg or 100 mg bid for 6 months	SRP
Ng and Bissada[32] 1998	32; generalized moderate adult periodontitis; 2 teeth >5 mm PD	Split-mouth; randomized	Ibuprofen 800 mg/day for 6 weeks; placebo	Half mouth SRP; half mouth no therapy
Jeffcoat, et al.[83] 1995 and Cavanaugh et al.[84] 1998	55; untreated adult periodontitis	Double-masked, RCT	Twice daily rinse with ketorolac tromethamine or 50 mg flurbiprofen bid	Untreated
Heasman et al.[85] 1993	49 moderate to advanced chronic periodontitis, AAP type III or IV	Double-masked; RCT; placebo-controlled	25 = 1% flurbiprofen toothpaste bid for 12 months; 24 = placebo	Non-surgical
Haffajee et al.[27] 1995	17 with evidence of prior attachment loss; 20 teeth with >4 mm PD 4 sites with AL >3 mm		Ibuprofen (n = 6) or placebo (n = 11) 400 mg tid for 30 days	MWF or SRP
Bichara et al.[86] 1999	12 test, 12 control; adult periodontitis with vertical osseous defects ≥4 mm, 2 wall or combination	Randomized controlled masked clinical study, 9 months	Bid 500 mg naproxen sodium postsurgery	GTR with bioabsorbable membranes

Table 5. (continued)

Anti-Inflammatory Drugs: Primary Bone Changes and Attachment Levels

Outcome Bone Changes		Outcome CAL		Location/ Funding	Study Ranking
Placebo	Active	Placebo	Active		
	Decrease in rate of bone loss at 12 ($P = 0.01$) and 18 months ($P = 0.07$) 4 times more bone preserved	No CAL data reported		University/ industry	2
BL to 6 months –0.42 ± 0.06 mm	50 mg: BL to 6 months; 0.07 ± 0.05 mm; 50 mg–placebo: 0.47 mm 100 mg: BL to 6 months; 0.20 ± 0.07; 100 mg–placebo: 0.62 mm (P <0.001)	BL: 5.28 ± 0.33 6 months: 4.61 ± 0.33	50 mg BL: 4.95 ± 0.34 6 months: 4.61 ±0 .34 100 mg; BL 5.47 ± 0.38 6 months: 4.61 ± 0.43 CAL: NS	University/ industry	2
		Measurements from stent BL (±SD) SRP: 9.0 ± 1.9 NSRP: 9.5 ± 2.3; 24 weeks SRP: 9.9 ± 0.8 NSRP: 10.4 ± 0.5	BL (±SD) SRP: 8.8 ± 0.9 NSRP: 8.6 ± 1.4; 24 weeks SRP: 9.0 ± 0.1 NSRP: 9.2 ± 0.5; CAL: NS	University	3
Bone loss linear BL to 6 months –0.63 ± 0.11 mm Bone mass –16.21 ± 3.52 mg	Bone loss linear Ketorolac: BL to 6 months; 0.21 ± 0.11 mm (P <0.001) Flurbirofen; BL to 6 months –0.10 ± 0.12 mm (P <0.002) Bone Mass Ketorolac: BL to 6 months; 3.67 ± 3.42 mg (P <0.001) Flurbiprofen; BL to 6 months –6.44 ± 3.76 mg ($P = 0.065$)	BL (±SD) 5.11 ± 0.53 mm; follow-up data only reported in graphs with error bars: 3 months: 4.5 mm Change BL to 6 months: 55 mm	Ketorolac: BL 5.06 ± 0.5 mm 3 months: 4.7 mm 6 months: 4.9 mm Change from BL to 6 months: 16 mm Flurbiprofen; BL: 4.75 ± 0.39 mm 3 months: 4.6 mm 6 months: 4.28 mm Change from BL to 6 months: 0.47 mm NS	University/ industry	3
Radiographic measurements of bone change % of sites: Gain: 3.3%; Loss: 12% No change: 84.7%	Radiographic measurements of bone change % of sites: Gain: 8%; Loss: 14% No change: 78%	CAL data from splint extracted from graphs: BL: 10.14 mm 12 months: 9.60 mm	CAL data from splint extracted from graphs: BL: 10.16 mm 12 months: 9.75 mm	University/ industry	2
		CAL; BL (±SD): 3.5 ± 1.2 Change 10 months: Data extracted from graph: 0.02	CAL; BL (±SD): 3.7 ± 1.1 Change 10 months: Data extracted from graph: 0.02 Difference NS	University/ government	3
Direct measurement Defect depth BL (±SD): 4.58 ± 0.60 9 months: 1.13 ± 1.13 Crestal resportion –1.42 ± 0.85 Bone fill: 2.04 ± 1.71	Direct measurement Defect depth BL (±SD): 4.75 ± 0.87; 9 months: 1.29 ± 1.50 Crestal resorption –1.50 ± 1.15 Bone fill: 1.96 ± 1.27	CAL; BL (±SD): 6.75 ± 1.44; 9 months: CAL; 5.75 ± 1.12 Change: 1.00 ± 1.72	CAL; BL (±SD): 8.67 ± 2.02 9 months: 6.42 ± 1.51 Change: 2.25 ± 1.41	University/ industry	2

(continued)

Table 5. (continued)

Anti-Inflammatory Drugs: Primary Bone Changes and Attachment Levels

Reference	N Subjects	Study Design	Host Modulation	Periodontal Treatment
Bragger et al.[87] 1997	19; moderate to severe adult periodontitis	Placebo-controlled 3 and 6 months	10 = 50 mg flurbiprofen tid for 30 days; 9 = placebo	Initial therapy and MWF or no surgical treatment
Flemmig et al.[88] 1996	30; untreated moderate to severe periodontitis	Placebo-controlled; double-masked; randomized	Aspirin 500 mg qid for 6 weeks	SRP or no treatment

Abbreviations: BL = baseline; MWF = modified Widman flap.

Table 6.

Anti-Inflammatory Drugs: Secondary Clinical Outcomes of Probing Depth and Inflammation Changes

Reference	N Subjects	Study Design	Host Modulation	Periodontal Treatment
Reddy et al.[82] 1993	22; rapidly progressive periodontitis; stratified into 3 groups No N reported for the different groups	Double-masked; randomized; placebo-controlled	Meclofenamate 50 mg or 100 mg bid for 6 months	SRP
Ng and Bissada[32] 1998	32; general moderate adult periodontitis; 2 teeth >5 mm PD	Split-mouth; randomized	Ibuprofen 800 mg/day for 6 weeks; placebo	SRP or no therapy
Jeffcoat et al.[83] 1995 and Cavanaugh et al.[84] 1998	55; untreated adult periodontitis	Double-masked; RCT	Twice daily rinse with ketorolac tromethamine or 50 mg flurbiprofen bid	Untreated

Table 5. (continued)

Anti-Inflammatory Drugs: Primary Bone Changes and Attachment Levels

Outcome Bone Changes		Outcome CAL		Location/ Funding	Study Ranking
Placebo	Active	Placebo	Active		
No linear data reported; density ranges reported; not extractable		Non-surgery; BL (±SD): 6.33 ± 0.97; 3 months: 5.28 ± 1.23; 6 months: 1.13 ± 1.41 Surgery; BL (±SD): 7.00 ± 1.33; 3 months: 6.06 ± 1.30; 6 months: 5.78 ± 1.48	Non-surgery; BL (±SD): 5.50 ± 1.82; 3 months: 5.10 ± 2.10; 6 months: 5.00 ± 2.11 Surgery; BL (±SD): 7.10 ± 1.83; 3 months: 5.95 ± 1.93; 6 months: 620 ± 1.85; NS	University/ government	3
		No treatment; BL (±SD): 3.60 ± 0.87 Change 6 weeks from graph: 0.05 SRP; BL (±SD): 3.57 ± 1.17 Change 6 weeks from graph: 0.20	No treatment; BL (±SD): 3.35 ± 0.79 Change 6 weeks from graph: 0.07 SRP; BL (±SD): 3.48 ± 0.68 Change 6 weeks from graph: 0.27; NS	University/ government	2

Table 6. (continued)

Anti-Inflammatory Drugs: Secondary Clinical Outcomes of Probing Depth and Inflammation Changes

Outcome Probing Depth		Outcome Inflammation		Location/ Funding	Study Ranking
Placebo	Active	Placebo	Active		
BL (±SD): 5.87 ± 0.5 6 months: 4.46 ± 0.53	50 mg BL: 5.52 ± 0.55 6 months: 4.69 ± 0.55 100 mg BL: 6.02 ± 0.62 6 months: 4.23 ± 0.71; NS	No data reported		University/ industry	2
BL (±SD): SRP: 4.3 ± 0.9; NSRP: 4.5 ± 1.4; 24 weeks SRP: 4.6 ± 0.4; NSRP: 5.0 ± 0.4	BL (±SD): SRP: 4.0 ± 0.5; NSRP: 4.0 ± 0.5; 24 weeks SRP: 4.0 ± 0.5; NSRP: 4.0 ± 0.4; NS	GI (±SD) SRP: 0.6 ± 0.3; NSRP: 0.6 ± 0.4; 24 weeks SRP 01.6 ± 0.2; NSRP: 0.6 ± 0.1	GI (±SD) SRP: 1.0 ± 0.6; NSRP: 1.0 ± 0.6; 24 weeks SRP: 0.7 ± 0.8 NSRP: 0.9 ± 0.7; NS	University	3
BL (±SD): 5.4 ± 0.7 mm follow-up data only reported in graphs with SE bars: 6 months: 4.33 mm Change from BL 6 months: 0.86 mm	Ketorolac; BL: 5.7 ± 0.6 mm 6 months: 4.84 mm Change from BL: 6 months: 0.86 mm Flurbiprofen; BL: 5.2 ± 0.3 mm 6 months: 4.1 mm Change from BL: 6 months: 1.10 mm; NS	GI: NS		University/ industry	2

(continued)

Table 6. (continued)

Anti-Inflammatory Drugs: Secondary Clinical Outcomes of Probing Depth and Inflammation Changes

Reference	N Subjects	Study Design	Host Modulation	Periodontal Treatment
Haffajee et al.[27] 1995	17 with evidence of prior attachment loss; 20 teeth with >4 mm 4 sites with AL >3 mm		Ibuprofen (n = 6) or placebo (n = 11) 400 mg tid for 30 days	MWF or SRP
Bichara et al.[86] 1999	12 test, 12 control; adult periodontitis with vertical osseous defects ≥4 mm, 2 wall or combo	Randomized controlled masked clinical study; 9 months	Bid 500 mg naproxen sodium postsurgery	GTR with bioabsorbable membranes
Bragger et al.[87] 1997	19; moderate to severe adult periodontitis	Placebo-controlled 3 and 6 months	10 = 50 mg flurbiprofen tid for 30 days; 9 = placebo	Initial therapy and modified Widman flap or no surgical treatment
Flemmig et al.[88] 1996	30; untreated moderate to severe periodontitis	Placebo-controlled; double-masked; randomized	Aspirin 500 mg qid for 6 weeks	SRP or no treatment
Heasman et al.[89] 1989	24 healthy individuals	Randomized; double-masked placebo-controlled clinical trial	100 ml flurbiprofen irrigation	Abstinence from oral hygiene
Heasman et al.[90] 1994	47 ≥18 years old; ≥20 permanent teeth	Double-masked; parallel	23 = 50 mg flurbiprofen bid and tooth brushing 24 = placebo and tooth brushing	Scaling, polishing, and oral hygiene instructions; abstained from OH for 21 days
Jones et al.[91] 1999	9	Double-masked, placebo-controlled; RCT	5 topical flurbiprofen, 4 placebo for 7 nights	Abstinence of oral hygiene in area protected from brushing by splint
Flemmig et al.[92] 1995	60 maintenance patients with periodontitis	Placebo-controlled; double-masked; randomized	Home irrigation with aspirin 0.3%	Periodontal maintenance therapy
Vogel et al.[93] 1984	18 dental students	Placebo-controlled; double-masked; randomized	Topical steroidal gel (T), systemic NSAID (S), or placebo (P)	

Abbreviations: BL = baseline; GI = gingival index; OH = oral hygiene; PI = plaque index; MWF = modified Widman flap.

Table 6. (continued)

Anti-Inflammatory Drugs: Secondary Clinical Outcomes of Probing Depth and Inflammation Changes

Outcome Probing Depth		Outcome Inflammation		Location/ Funding	Study Ranking
Placebo	Active	Placebo	Active		
BL (± SD): 3.6 ± 0.5 Change 10 months: Data extracted from graph: 0.42	BL (± SD): 3.6 ± 0.4 Change 10 months: Data extracted from graph: 0.42 NS			University/ government	3
BL (± SD): 5.92 ± 0.95 9 months: CAL 3.25 ± 0.94 Change: 2.67 ± 1.30	BL: (± SD): 7.00 ± 1.55 9 months: 3.58 ± 0.82 Change: 3.42 ± 1.93			University/ industry	2
Non-surgery BL (± SD): 5.22 ± 0.55 3 months: 3.83 ± 0.79; 6 months: 3.61 ± 0.98 Surgery BL (± SD): 5.56 ± 0.78 3 months: 3.39 ± 0.61 6 months: 3.39 ± 0.70	Non-surgery BL (± SD): 5.30 ± 1.26 3 months: 4.90 ± 1.59 6 months: 4.78 ± 1.66 Surgery BL (± SD): 6.15 ± 1.18; 3 months: 3.65 ± 0.99; 6 months: 4.10 ± 1.02; NS			University/ government	3
No treatment BL (± SD): 3.14 ± 0.59 Change: 6 weeks from graph: 0.05 SRP; BL (± SD): 3.21 ± 0.98 Change: 6 weeks from graph: 0.42	No treatment BL (± SD): 2.90 ± 0.61 Change: 6 weeks from graph: 0.12 SRP; BL (± SD): 3.12 ± 0.61 Change: 6 weeks from graph: 0.61 Difference between groups significant for both (P <0.001)			University/ government	2
Median BL: 0.95 17 days: 0.98	Median BL: 0.98; 17 days: 1.14 Change: NS	GI and PI: NS		University/ industry	2
No PD data			PI, GCF flow: NS GI: greater reduction in flurbiprofen (P = 0.04)	University/ industry	2
			GI reduced in flurbiprofen	University/ industry	3
			PD, GI: NS; PI reduction of a median of 0.24, P <0.01	University/ government	3
		GI PI GCF (µl/200) T 0.9 NS 2.6 S 1.7 NS 3.3 P 1.8 NS 4.3			3

Three studies addressed the clinical and radiographic effects of bisphosphonates on periodontitis (Table 7).[115-117] Two were randomized controlled double-masked clinical trials of 40 subjects each[115,116] and one was a report of 4 cases.[117] All reports had a 6- or 9-month follow-up and included conventional therapy in addition to adjunctive administration of a bisphosphonate drug. The controlled trials utilized scaling and root planing in addition to a bisphosphonate (i.e., alendronate; 10 mg/day for 6 months). The case reports used SRP and/or surgical therapy in conjunction with the bisphosphonate etidronate 200 mg daily for 2 weeks.

Jeffcoat and Reddy demonstrated a statistically significant decrease in the proportion of teeth demonstrating alveolar bone loss at 9 months after use of alendronate.[115] Rocha et al. also demonstrated a statistically significant difference in bone height favoring the alendronate group.[116] In addition, in this study of type II diabetic subjects, a decrease of glycated hemoglobin (HBA_{1c}) levels was noted for both groups. Similarly, the urine N-telopeptide/creatine ratio, a marker for bone resorption, was statistically significantly improved in the alendronate group at the end of the study. The case series by Takaishi et al. indicated that there was a clinical and radiographic improvement when a bisphosphonate was combined with conventional periodontal treatment.[117]

Overall, the small number of subjects and different populations and outcome measures used in these studies prevent further statistical analysis of the data. Additional data are needed before a definitive benefit of bisphosphonates as a host-modulating factor for periodontitis can be addressed.

Bone-Sparing Agents and Dental Implants

Seven studies were initially included. Two studies discussed the implications of decreased bone mineral density and osteoporosis as a risk factor in implant success.[118,119] Two studies discussed the potential utilization of bisphosphonates in implant therapy; however, no patient data were presented or could be extracted.[120,121] Another case report suggested that bisphosphonate therapy induced implant failure.[122] Two other papers were reviews of therapeutic management of oral and systemic osteoporosis and osteolytic disease without patient-derived data.[123,124] At this time, the majority of the data relating to bone-sparing agents and dental implants are from tissue culture and animal models.

DISCUSSION

The complex group of bacteria that cause periodontal infections induce a series of host responses. The preliminary response is the release of proinflammatory mediators by the monocyte/macrophage axis of the host. These proinflammatory mediators induce other host cells, such as fibroblasts and epithelial cells, to pro-

Table 7.

Bisphosphonates and Periodontal Disease Study Outcomes

Reference	N Subjects	Study Design	Host Modulations	Periodontal Treatment	Outcome	Location/ Funding	Study Ranking
Jeffcoat and Reddy[115] 1996	40 chronic periodontitis	Parallel arm, randomized, placebo-controlled	Alendronate 10 mg/day for first 6 months versus placebo	SRP	Placebo: 40% of sites lost bone height Treatment: 20% of sites lost bone height (9 months $P = 0.04$)	University/ industry	2
Rocha et al.[116] 2001	40 chronic periodontitis with type 2 diabetes	Parallel arm, randomized, placebo-controlled	Alendronate 10 mg/day for 6 months versus placebo	SRP	1.3 ± 1.33 mm difference in bone height ($P = 0.003$) 0.52 ± 0.85 mm gain in attachment level ($P = 0.013$)	University/ industry	2
Takaishi et al.[117] 2001	4 acute or chronic periodontitis	Case report	Etidronate 200 mg/day for 2 weeks	Varied	Improved clinical and radiograph impressions	University	5

duce prostaglandins and matrix metalloproteinases. In addition, the proinflammatory cytokines and prostaglandins activate osteoclasts. The net result is alveolar bone loss and connective tissue destruction. Recognition that host response is a component of the etiology of the periodontal diseases has provided a rationale for adjunctively treating the host with medicaments in addition to conventional treatment aimed at suppression of the bacterial infection. Adjunctive drugs that suppress or inhibit matrix metalloproteinases, prostaglandin production, and osteoclast activation could have a beneficial effect on slowing periodontal disease progression when combined with conventional therapy.

The data available to date indicate that inhibition of MMP by subantimicrobial doses of DOXY may be helpful in the management of chronic periodontitis.[47-53] One multicenter study in the U.S. and one in the United Kingdom indicated that there was a statistically significant gain of clinical attachment level and probing depth reduction with the adjunctive use of SDD. When the data were pooled from several studies and subjected to meta-analysis an adjunctive effect in clinical attachment levels and probing depths was found at sites 4 to 6 mm deep and ≥7 mm deep (Table 3).

Furthermore, studies that addressed adverse events and "rebound" after treatment indicated that no adverse effects on the oral flora were observed and gains achieved by SDD were not lost in the subsequent 3 months.

There were no major clinical differences between the number of sites that bled on probing between the groups that were and were not administered adjunctive SDD.[47,48,52] In fact, throughout these studies both groups demonstrated high levels of BOP. The high level of bleeding on probing may indicate a lack of maintenance or inadequate therapy. The data suggest that in the presence of inflammation, as noted by bleeding on probing, SDD still had a beneficial effect.

The PD reduction and CAL gain for each probing depth category in the multi-center studies were very similar. This indicates that nearly all the probing depth reduction was due to clinical attachment gain.[48,53] Usually some of the probing depth reduction is due to recession. Thus, the similarity between PD reduction and gain of CAL could be attributed to measurement error. However, the measurement error would be equally applicable to both the test and control groups and therefore would probably be accounted for in the statistical analysis. Therefore, it can be concluded that there was a trend for better results when SDD was used as an adjunct to scaling and root planing; however, the quantitative results may have been affected by measurement error. Limited alveolar bone loss measurement data were reported in the studies that addressed SDD use. Overall, use of SDD appears to be a promising adjunctive approach in the management of periodontal disease.

Studies ranging from animal models to human clinical trials support the hypothesis that inhibition of local arachidonic acid metabolites with non-steroidal anti-inflammatory drugs slow periodontal disease progression by preventing or limiting alveolar bone loss.[128] Several non-steroidal anti-inflammatory drugs were examined in proof-of-principle clinical trials. The primary outcome for the NSAID studies was usually alveolar bone loss. However, alveolar bone loss was presented as rates or percentages and only 3 studies utilized bone loss measurements (mm) as a primary outcome.[82-84] In addition, the study populations, treatments, and study duration tended to vary, which precluded performing a meta-analysis. A descriptive summary of data indicates that there is a potential role for anti-inflammatory drugs in the treatment of chronic and aggressive periodontitis via their effect on alveolar bone loss.

No clear effects on secondary outcomes were observable (e.g., reduction of probing depth and gingival inflammation). Since non-steroidal anti-inflammatory drugs may be associated with increased bleeding time and gastric ulcers, the drugs should be prescribed with caution. Large-scale multi-center studies are needed to evaluate NSAIDs before a clear indication could be made for their utilization in the management of periodontal disease.

Preliminary studies that used bisphosphonates as bone-sparing agents in the treatment of periodontitis have been published.[115-117] While the use of bisphosphonates for other bone-resorptive diseases such as osteoporosis and osteopenia has dramatically increased in the past decade, there are still limited data available concerning their use in the management of periodontal diseases. The use of bone-sparing agents appears promising, however multicenter clinical trials will be necessary to fully evaluate the potential benefits in periodontology.

Focused review questions utilized to examine host-modulation therapies for periodontitis patients were also used to assess their application in patients with dental implants. While it is logical that benefits in periodontal disease management with antiproteinases, anti-inflammatory drugs, and bone-sparing agents would apply to dental implants, at present there are insufficient data to evaluate their efficacy as a treatment.

REVIEWERS' CONCLUSIONS

1. The reviewed studies indicate that there may be a role for the use of host-modulating agents in the treatment of periodontitis in conjunction with conventional therapy. Most of the discussed data represent initial investigations with these agents. Furthermore, it should be noted that there may be a publication bias and a tendency for significant or beneficial findings to be published over nonsignificant results for novel therapies.

2. Based on a meta-analysis from the preliminary data available regarding the adjunctive use of subantimicrobial doses of doxycycline with definitive scaling and root planing, it was demonstrated that it provided a statistically significant improvement with respect to probing depth reductions and gains of clinical attachment when compared to scaling and root planing alone. The use of SDD appears safe and may be an adjunctive aid in the management of chronic periodontitis.

3. Clinical trials concerning non-steroidal anti-inflammatory drugs support the basic hypothesis that inhibition of arachidonic acid metabolites slow alveolar bone loss and this approach may be an adjunct to conventional mechanical treatment. Large multicentered studies with comparable outcomes are necessary to fully evaluate this therapy.

4. Bisphosphonate bone-sparing agents have promise in limiting alveolar bone loss. However, additional studies are needed to evaluate their potential as an adjunctive therapy.

5. At present too little data are available to reach any conclusions regarding the use of host modulation and the treatment of peri-implant disease.

FUTURE DIRECTIONS FOR RESEARCH

A systematic review of the literature helps present evidence in an unbiased manner. Its objective is to synthesize data from studies that provide different levels of evidence regarding the efficacy of different treatment methods. In addition, these data also need to be interpreted regarding their clinical meaningfulness.

This review was comprehensive. However, there is little information available on many host-modulating therapies related to periodontitis and scarce data on the application of host-modulation therapy to dental implants. The lack of data represents the timeliness of this review. For example, only 2 clinical trials of 40 patients were available on the drug alendronate for this review.[115,116] However, while alendronate is a common therapy for osteoporotic diseases today, approximately 10 years ago there were few data and the drug was not approved for treatment of osteoporosis. In essence, this review of host-modulation therapy may be a harbinger of therapies that may alter the management of periodontal patients.

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REFERENCES

1. Socransky SS, Haffajee AD. Evidence of bacterial etiology: A historical perspective. *Periodontol 2000* 1994;5: 7-25.
2. Kornman KS, Page RC, Tonetti MS. The host response to the microbial challenge in periodontitis: Assembling the players. *Periodontol 2000* 1997;14:33-53.
3. Page RC, Kornman KS. The pathogenesis of human periodontitis: An introduction. *Periodontol 2000* 1997;14: 9-11.
4. Salvi GE, Lawrence HP, Offenbacher S, Beck JD. Influence of risk factors on the pathogenesis of periodontitis. *Periodontol 2000* 1997;14:173-201.
5. Ingman T, Sorsa T, Suomalainen K, et al. Tetracycline inhibition and cellular source of collagenase in gingival crevicular fluid in different periodontal diseases. A review article. *J Periodontol* 1993;64:82-88.
6. Vernillo AT, Ramamurthy NS, Golub LM, Rifkin BR. The nonantimicrobial properties of tetracycline for the treatment of periodontal disease. *Curr Opin Periodontol* 1994; 111-118.
7. Golub LM, Sorsa T, Lee H-M, et al. Doxycycline inhibits neutrophil (PMN)-type matrix metalloproteinases in human adult periodontitis gingiva. *J Clin Periodontol* 1995; 22:100-109.
8. Williams RC, Jeffcoat MK, Howell TH, et al. Altering the progression of human alveolar bone loss with the nonsteriodal anti-inflammatory drug flurbiprofen. *J Periodontol* 1989;60:485-490.
9. Watts NB, Harris ST, Genant HK, et al. Intermittent cyclical etidronate treatment of postmenopausal osteoporosis. *N Engl J Med* 1990;323:73-79.
10. Jung A, Van Ouwenaller C, Chantraine A, Courvoisier B. Parental diphosphonates for treating malignant hypercalcemia. *Cancer* 1981;48:1922-1925.
11. O'Doherty DP, Gertz BJ, Tindale W, Sciberras DG, Survill TT, Kanis JA. Effects of five daily 1 h infusions of alendronate in Paget's disease of bone. *J Bone Miner Res* 1992; 7:81-87.
12. Sato M, Grasser W, Endo N, et al. Bisphosphonate action. Alendronate localization in rat bone and effects on osteoclast ultrastructure. *J Clin Invest* 1991;88:2095-2105.
13. Fleiss JL. The statistical basis of meta-analysis. *Stat Methods Med Res* 1993;2:121-145.
14. Katerndahl DA, Cohen PA. Quantitatively reviewing the literature: The application of meta-analysis. *Fam Pract Res J* 1987;6(3):123-129.
15. Heges L, Olkin I. *Statistical Methods of Meta-Analysis.* Orlando: Academic Press; 1985.

16. Alpagot T, Bell C, Lundergan W, Chambers DW, Rudin R. Longitudinal evaluation of GCF MMP-3 and TIMP-1 levels as prognostic factors for progression of periodontitis. *J Clin Periodontol* 2001;28:353-359.
17. Atici K, Yamalik N, Eratalay K, Etikan I. Analysis of gingival crevicular fluid intracytoplasmic enzyme activity in patients with adult periodontitis and rapidly progressive periodontitis. A longitudinal study model with periodontal treatment. *J Periodontol* 1998;69:1155-1163.
18. Bader HI, Boyd RL. Neutral proteases in crevicular fluid as an indicator for periodontal treatment intervention. *Am J Dent* 2001;14:314-318.
19. Giannopoulou C, Andersen E, Demeurisse C, Cimasoni G. Neutrophil elastase and its inhibitors in human gingival crevicular fluid during experimental gingivitis. *J Dent Res* 1992;71:359-363.
20. Haerian A, Adonogianaki E, Mooney J, Docherty JP, Kinane DF. Gingival crevicular stromelysin, collagenase and tissue inhibitor of metalloproteinase levels in healthy and diseased sites. *J Clin Periodontol* 1995;22: 505-509.
21. Haerian A, Adonogianaki E, Mooney J, Manos A, Kinane DF. Effects of treatment on gingival crevicular collagenase, stromelysin and tissue inhibitor of metalloproteinases and their ability to predict response to treatment. *J Clin Periodontol* 1996;23:83-91.
22. Korostoff JM, Wang JF, Sarment DP, Stewart JCB, Feldman RS, Billings PC. Analysis of in situ protease activity in chronic adult periodontitis patients: Expression of activated MMP-2 and a 40 kDa serine protease. *J Periodontol* 2000;71:353-360.
23. Said S, Mohd H, Sander L, Rönkä H, Sorsa T, Kinane DF. GCF levels of MMP-3 and MMP-8 following placement of bioresorbable membranes. *J Clin Periodontol* 1999; 26:757-763.
24. Xiao Y, Bunn CL, Bartold PM. Detection of tissue plasminogen activator (t-PA) and plasminogen activator inhibitor 2(PAI-2) in gingival crevicular fluid from healthy, gingivitis and periodontitis patients. *J Clin Periodontol* 2000;27:149-156.
25. Atilla G, Balcan M, Biçakçi N, Kazandi A. The effect of non-surgical periodontal and adjunctive minocycline-HCL treatments on the activity of salivary proteases. *J Periodontol* 1996;67:1-6.
26. Freeman E, Ellen RP, Thompson G, Weinberg SE, Song M, Lazarus RH. Gingival crevicular fluid concentration and side effects of minocycline: A comparison of two dose regimens. *J Periodontol* 1992;63:13-18.
27. Haffajee AD, Dibart S, Kent RL Jr, Socransky SS. Clinical and microbiological changes associated with the use of 4 adjunctive systemically administered agents in the treatment of periodontal infections. *J Clin Periodontol* 1995;22: 618-627.
28. Hoerman KC, Lang RL, Klapper L, Beery J. Local tetracycline therapy of the periodontium during orthodontic treatment. *Quintessence Int* 1985;16:161-166.
29. Lee W, Aitken S, Kulkarni G, et al. A. Collagenase activity in recurrent periodontitis: Relationship to disease progression and doxycycline therapy. *J Periodont Res* 1991; 26:479-485.
30. McCulloch CAG, Birek P, Overall C, Aitken S, Lee W, Kulkarni G. Randomized controlled trial of doxycycline in prevention of recurrent periodontitis in high-risk patients: Antimicrobial activity and collagenase inhibition. *J Clin Periodontol* 1990;17:616-622.
31. Moskow BS, Tannenbaum P. Enhanced repair and regeneration of periodontal lesions in tetracycline-treated patients. Case reports. *J Periodontol* 1991;62: 341-350.
32. Ng VW-K, Bissada NF. Clinical evaluation of systemic doxycycline and ibuprofen administration as an adjunctive treatment for adult periodontitis. *J Periodontol* 1998; 69:772-776.
33. Österberg SK-Å, Williams BL, Jorgensen J. Long-term effects of tetracycline on the subgingival microflora. *J Clin Periodontol* 1979;6:133-140.
34. Pourtaghi N, Radvar M, Mooney J, Kinane DF. The effect of subgingival antimicrobial therapy on the levels of stromelysin and tissue inhibitor of metalloproteinases in gingival crevicular fluid. *J Periodontol* 1996; 67:866-870.
35. Preus H, Gjermo P. Clinical management of prepubertal periodontitis in 2 siblings with Papillon-Lefèvre syndrome. *J Clin Periodontol* 1987;14:156-160.
36. Preus HR. Treatment of rapidly destructive periodontitis in Papillon-Lefèvre syndrome. Laboratory and clinical observations. *J Clin Periodontol* 1988;15:639-643.
37. Ramberg P, Rosling B, Serino G, Hellström M-K, Socransky SS, Lindhe J. The long-term effect of systemic tetracycline used as an adjunct to non-surgical treatment of advanced periodontitis. *J Clin Periodontol* 2001;28:446-452.
38. Saxén L, Asikainen S, Kanervo A, Kari K, Jousimies-Somer H. The long-term efficacy of systemic doxycycline medication in the treatment of localized juvenile periodontitis. *Arch Oral Biol* 1990;35(Suppl.):227S-229S.
39. Timmerman MF, van der Weijden GA, van Steenbergen TJM, Mantel MS, de Graaff J, van der Velden U. Evaluation of the long-term efficacy and safety of locally-applied minocycline in adult periodontitis patients. *J Clin Periodontol* 1996;23:707-716.
40. van Steenberghe D, Bercy P, Kohl J, et al. Subgingival minocycline hydrochloride ointment in moderate to severe chronic adult periodontitis: A randomized, double-blind, vehicle-controlled, multi-center study. *J Periodontol* 1993;64:637-644.
41. van Steenberghe D, Rosling B, Söder P-Ö, et al. A 15-month evaluation of the effects of repeated subgingival minocycline in chronic adult periodontitis. *J Periodontol* 1999;70:657-667.
42. Yoshinari N, Tohya T, Kawase H, et al. Effect of repeated local minocycline administration on periodontal healing following guided tissue regeneration. *J Periodontol* 2001; 72:284-295.
43. Zarkesh N, Nowzari H, Morrison JL, Slots J. Tetracycline-coated polytetrafluoroethylene barrier membranes in the treatment of intraosseous periodontal lesions. *J Periodontol* 1999;70:1008-1016.
44. Fasciano RW, Fazio RC. Periodontal regeneration with long term tetracycline therapy. *Quintessence Int* 1981; 12:1081-1088.

45. Kornman KS, Karl EH. The effect of long-term low-dose tetracycline therapy on the subgingival microflora in refractory adult periodontitis. *J Periodontol* 1982;53:604-610.
46. Lindhe J, Liljenberg B, Adielsson B. Effect of long-term tetracycline therapy on human periodontal disease. *J Clin Periodontol* 1983;10:590-601.
47. Ashley RA. Clinical trials of a matrix metalloproteinase inhibitor in human periodontal disease. *Ann N Y Acad Sci* 1999;878:335-346.
48. Caton JG, Ciancio SB, Blieden TM, et al. Treatment with subantimicrobial dose doxycycline improves the efficacy of scaling and root planing in patients with adult periodontitis. *J Periodontol* 2000;71:521-532.
49. Crout RJ, Lee HM, Schroeder K, et al. The "cyclic" regimen of low-dose doxycycline for adult periodontitis: A preliminary study. *J Periodontol* 1996;67:506-514.
50. Golub LM, McNamara TF, Ryan ME, et al. Adjunctive treatment with subantimicrobial doses of doxycycline: Effects on gingival fluid collagenase activity and attachment loss in adult periodontitis. *J Clin Periodontol* 2001; 28:146-156.
51. Golub LM, Lee HM, Greenwald RA, et al. A matrix metalloproteinase inhibitor reduces bone-type collagen degradation fragments and specific collagenases in gingival crevicular fluid during adult periodontitis. *Inflamm Res* 1997;46:310-319.
52. Novak MJ, Johns LP, Miller RC, Bradshaw MH. Adjunctive benefits of subantimicrobial dose doxycycline in the management of severe, generalized, chronic periodontitis. *J Periodontol* 2002;73:762-769.
53. Preshaw PM, Hefti AF, Novak MJ, et al. Subantimicrobial dose doxycycline enhances scaling and root planing. *J Dent Res* 2002;81(Spec. Issue A):A-127 (Abstr. 0841).
54. Thomas JG, Metheny RJ, Karakiozis JM, Wetzel JM, Crout RJ. Long-term subantimicrobial doxycycline (Periostat®) as adjunctive management in adult periodontitis: Effects on subgingival bacterial population dynamics. *Adv Dent Res* 1998;12:32-39.
55. Walker C, Thomas J, Nangó S, Lennon J, Wetzel J, Powala C. Long-term treatment with subantimicrobial dose doxycycline exerts no antibacterial effect on the subgingival microflora associated with adult periodontitis. *J Periodontol* 2000;71:1465-1471.
56. Ciancio S, Ashley R. Safety and efficacy of subantimicrobial-dose doxycycline therapy in patients with adult periodontitis. *Adv Dent Res* 1998;12:27-31.
57. Caton JG, Ciancio SB, Blieden TM, et al. Subantimicrobial dose doxycycline as an adjunct to scaling and root planing: Post-treatment effects. *J Clin Periodontol* 2001;28:782-789.
58. Thomas J, Walker C, Bradshaw M. Long-term use of subantimicrobial dose doxycycline does not lead to changes in antimicrobial susceptibility. *J Periodontol* 2000;71:1472-1483.
59. Minutello JS, Dimayuga RG, Carter J. Pseudotumor cerebri, a rare adverse reaction to tetracycline therapy. A case report. *J Periodontol* 1988;59:848-851.
60. Flemmig TF, Weinacht S, Rüdiger S, Rumetsch M, Jung A, Klaiber B. Adjunctive controlled topical application of tetracycline HCl in the treatment of localized persistent or recurrent periodontitis. Effects on clinical parameters and elastase-α_1-proteinase inhibitor in gingival crevicular fluid. *J Clin Periodontol* 1996;23:914-921.
61. Schenk G, Flemmig TF, Betz T, Reuther J, Klaiber B. Controlled local delivery of tetracycline HCl in the treatment of periimplant mucosal hyperplasia and mucositis. A controlled case series. *Clin Oral Impl Res* 1997;8: 427-433.
62. Ayangco L, Sheridan PJ. Development and treatment of retrograde peri-implantitis involving a site with a history of failed endodontic and apicoectomy procedures: A series of reports. *Int J Oral Maxillofac Implants* 2001; 16:412-417.
63. Ibbott CG, Kovach RJ, Carlson-Mann LD. Acute periodontal abscess associated with an immediate implant site in the maintenance phase: A case report. *Int J Oral Maxillofac Implants* 1993;8:699-702.
64. McAllister BS, Masters D, Meffert RM. Treatment of implants demonstrating periapical radiolucencies. *Pract Periodontics Aesthet Dent* 1992;4:37-41.
65. Mellonig JT, Griffiths G, Mathys E, Spitznagel J Jr. Treatment of the failing implant: Case reports. *Int J Periodont Rest Dent* 1995;15:385-395.
66. Pepelassi EM, Bissada NF, Greenwell H, Farah CF. Doxycycline-tricalcium phosphate composite graft facilitates osseous healing in advanced periodontal furcation defects. *J Periodontol* 1991;62:106-115.
67. Tinti C, Parma-Benfenati S. Treatment of peri-implant defects with the vertical ridge augmentation procedure: A patient report. *Int J Oral Maxillofac Implants* 2001;16: 572-577.
68. van Winkelhoff AJ, Wolf JWA. *Actinobacillus actinomycetemcomitans*-associated peri-implantitis in an edentulous patient. A case report. *J Clin Periodontol* 2000;27: 531-535.
69. Tadjoedin ES, de Lange GL, Holzmann PJ, Kuiper L, Burger EH. Histological observations on biopsies harvested following sinus floor elevation using a bioactive glass material of narrow size range. *Clin Oral Impl Res* 2000;11:334-344.
70. Rajnay ZW, Hochstetter RL. Immediate placement of an endosseous root-form implant in an HIV-positive patient: Report of a case. *J Periodontol* 1998;69:1167-1171.
71. Abramson MM, Wolff LF, Offenbacher S, Aeppli DM, Hardie ND, Friedman HM. Flurbiprofen effect on gingival crevicular fluid prostaglandin and thromboxane levels in humans. *J Periodont Res* 1992;27: 539-543.
72. Paquette DW, Lawrence HP, McCombs GB, et al. Pharmacodynamic effects of ketoprofen on crevicular fluid prostanoids in adult periodontitis. *J Clin Periodontol* 2000; 27:558-566.
73. Preshaw PM, Lauffart B, Brown P, Zak E, Heasman PA. Effects of ketorolac tromethamine mouthrinse (0.1%) on crevicular fluid prostaglandin E_2 concentrations in untreated chronic periodontitis. *J Periodontol* 1998;69: 777-783.
74. Been V, Engel D. The effects of immunosuppressive drugs on periodontal inflammation in human renal allograft patients. *J Periodontol* 1982;53:245-248.
75. Lawrence HP, Paquette DW, Smith PC, et al. Pharmaco-

kinetic and safety evaluations of ketoprofen gels in subjects with adult periodontitis. *J Dent Res* 1998;77: 1904-1912.
76. Pais JM, Rosteiro FM. Nimesulide in the short-term treatment of inflammatory process of dental tissues: A double-blind controlled trial against oxyphenbutazone. *J Int Med Res* 1983;11:149-154.
77. O'Brien TP, Roszkowski MT, Wolff LF, Hinrichs JE, Hargreaves KM. Effect of a non-steroidal anti-inflammatory drug on tissue levels of immunoreactive prostaglandin E_2, immunoreactive leukotriene, and pain after periodontal surgery. *J Periodontol* 1996;67:1307-1316.
78. Goldman HM, Ruben MP. Desquamative gingivitis and its response to topical triamcinolone therapy. *Oral Surg Oral Med Oral Pathol* 1966;21:579-593.
79. von Wowern N, Klausen B, Ølgaard K. Steroid-induced mandibular bone loss in relation to marginal periodontal changes. *J Clin Periodontol* 1992;19:182-186.
80. Williams RC. Non-steroidal anti-inflammatory drugs for altering periodontal bone loss. *J Dent Res* 1999;78: 638-642.
81. Campan P, Planchand P-O, Duran D. Pilot study on n-3 polyunsaturated fatty acids in the treatment of human experimental gingivitis. *J Clin Periodontol* 1997;24: 907-913.
82. Reddy MS, Palcanis KG, Barnett ML, Haigh S, Charles CH, Jeffcoat MK. Efficacy of meclofenamate sodium (Meclomen®) in the treatment of rapidly progressive periodontitis. *J Clin Periodontol* 1993;20:635-640.
83. Jeffcoat MK, Reddy MS, Haigh S, et al. A comparison of topical ketorolac, systemic flurbiprofen, and placebo for the inhibition of bone loss in adult periodontitis. *J Periodontol* 1995;66:329-338.
84. Cavanaugh PF Jr, Meredith MP, Buchanan W, Doyle MJ, Reddy MS, Jeffcoat MK. Coordinate production of PGE_2 and IL-1β in the gingival crevicular fluid of adults with periodontitis: Its relationship to alveolar bone loss and disruption by twice daily treatment with ketorolac tromethamine oral rinse. *J Periodont Res* 1998;33: 75-82.
85. Heasman PA, Offenbacher S, Collins JG, Edwards G, Seymour RA. Flurbiprofen in the prevention and treatment of experimental gingivitis. *J Clin Periodontol* 1993; 20:732-738.
86. Bichara J, Greenwell H, Drisko C, et al. The effect of postsurgical naproxen and a bioabsorbable membrane on osseous healing in intrabony defects. *J Periodontol* 1999;70:869-877.
87. Brägger U, Mühle T, Fourmousis I, Lang NP, Mombelli A. Effect of the NSAID flurbiprofen on remodeling after periodontal surgery. *J Periodont Res* 1997;32: 575-582.
88. Flemmig TF, Rumetsch M, Klaiber B. Efficacy of systemically administered acetylsalicylic acid plus scaling on periodontal health and elastase-α_1-proteinase inhibitor in gingival crevicular fluid. *J Clin Periodontol* 1996;23:153-159.
89. Heasman PA, Seymour RA, Boston PF. The effect of a topical non-steroidal anti-inflammatory drug on the development of experimental gingivitis in man. *J Clin Periodontol* 1989;16:353-358.
90. Heasman PA, Seymour RA, Kelly PJ. The effect of systemically-administered flurbiprofen as an adjunct to toothbrushing on the resolution of experimental gingivitis. *J Clin Periodontol* 1994;21:166-170.
91. Jones DS, Irwin CR, Woolfson AD, Djokic J, Adams V. Physicochemical characterization and preliminary in vivo efficacy of bioadhesive, semisolid formulations containing flurbiprofen for the treatment of gingivitis. *J Pharm Sci* 1999;88:592-598.
92. Flemmig TF, Epp B, Funkenhauser Z, et al. Adjunctive supragingival irrigation with acetylsalicylic acid in periodontal supportive therapy. *J Clin Periodontol* 1995;22: 427-433.
93. Vogel RI, Copper SA, Schneider LG, Goteiner D. The effects of topical steroidal and systemic non-steroidal anti-inflammatory drugs on experimental gingivitis in man. *J Periodontol* 1984;55:247-251.
94. Eder A, Watzek G. Treatment of a patient with severe osteoporosis and chronic polyarthritis with fixed implant-supported prosthesis: A case report. *Int J Oral Maxillofac Implants* 1999;14:587-590.
95. Gregg JM, Ann R. Neuropathic complications of mandibular implant surgery: Review and case presentations. *Australas Coll Dent Surg* 2000;15:176-180.
96. Reddy MS, Jeffcoat MK, Richardson RC. Assessment of adjunctive flurbiprofen therapy in root-form implant healing with digital subtraction radiography. *J Oral Implantol* 1990;16:272-276.
97. Jeffcoat MK, Reddy MS, Wang IC, Meuninghoff LA, Farmer JB, Koth DL. The effect of systemic flurbiprofen on bone supporting dental implants. *J Am Dent Assoc* 1995;126:305-311.
98. Earnshaw SA, Keating N, Hosking DJ, et al. Tooth counts do not predict bone mineral density in early postmenopausal Caucasian women. *Int J Epidemiol* 1998;27: 479-483.
99. Lundstrom A, Jendle J, Stenstrom B, Toss G, Ravald N. Periodontal conditions in 70-year-old women with osteoporosis. *Swed Dent J* 2001;25:89-96.
100. May H, Reader R, Murphy S, Khaw K-T. Self-reported tooth loss and bone mineral density in older men and women. *Age Ageing* 1995;24:217-221.
101. Mohammad AR, Bauer RL, Yeh CK. Spinal bone density and tooth loss in a cohort of postmenopausal women. *Int J Prosthodont* 1997;10:381-385.
102. Mohammad AR, Brunsvold M, Bauer R. The strength of association between systemic postmenopausal osteoporosis and periodontal disease. *Int J Prosthodont* 1996;9:479-483.
103. von Wowern N, Gotfredsen K. Implant-supported overdentures, a prevention of bone loss in edentulous mandibles? A 5-year follow-up study. *Clin Oral Impl Res* 2001;12:19-25.
104. Weyant RJ, Pearlstein ME, Churak AP, Forrest K, Famili P, Cauley JA. The association between osteopenia and periodontal attachment loss in older women. *J Periodontol* 1999;70:982-991.
105. Flaggert JJ, Heldt LV, Gareis FJ. Recurrent giant cell granuloma occurring in the mandible of a patient on high dose estrogen therapy for the treatment

of Sotos' syndrome. *J Oral Maxillofac Surg* 1987;45: 1074-1076.
106. Grodstein F, Colditz GA, Stampfer MJ. Post-menopausal hormone use and tooth loss: A prospective study. *J Am Dent Assoc* 1996;127:370-377.
107. Harris M. Central giant cell granulomas of the jaws regress with calcitonin therapy. *Br J Oral Maxillofac Surg* 1993;31:89-94.
108. Krall EA, Garcia RI, Dawson-Hughes B. Increased risk of tooth loss is related to bone loss at the whole body, hip, and spine. *Calcif Tissue Int* 1996;59:433-437.
109. Krall EA, Wehler C, Garcia RI, Harris SS, Dawson-Hughes B. Calcium and vitamin D supplements reduce tooth loss in the elderly. *Am J Med* 2001;111: 452-456.
110. Payne JB, Reinhardt RA, Nummikoski PV, Patil KD. Longitudinal alveolar bone loss in postmenopausal osteoporotic/osteopenic women. *Osteoporos Int* 1999; 10:34-40.
111. Payne JB, Zachs NR, Reinhardt RA, Nummikoski PV, Patil K. The association between estrogen status and alveolar bone density changes in postmenopausal women with a history of periodontitis. *J Periodontol* 1997;68: 24-31.
112. Reinhardt RA, Payne JB, Maze C, Babbitt M, Nummikoski PV, Dunning D. Gingival fluid IL-1β in postmenopausal females on supportive periodontal therapy. A longitudinal 2-year study. *J Clin Periodontol* 1998;25:1029-1035.
113. Reinhardt RA, Payne JB, Maze CA, Patil KD, Gallagher SJ, Mattson JS. Influence of estrogen and osteopenia/osteoporosis on clinical periodontitis in postmenopausal women. *J Periodontol* 1999;70: 823-828.
114. Ronderos M, Jacobs DR, Himes JH, Pihlstrom BL. Associations of periodontal disease with femoral bone mineral density and estrogen replacement therapy: Cross-sectional evaluation of US adults from NHANES III. *J Clin Periodontol* 2000;27:778-786.
115. Jeffcoat MK, Reddy MS. Alveolar bone loss and osteoporosis: Evidence for a common mode of therapy using the bisphosphonate alendronate. In: Davidovitch Z, Norton LA, eds. *Biological Mechanisms of Tooth Movement and Craniofacial Adaptation*, vol 1. Boston: Harvard Society for the Advancement of Orthodontics; 1996:365-373.
116. Rocha M, Nava LE, Vazquez de la Torre C, Sánchez-Marín F, Garay-Sevilla ME, Malacara JM. Clinical and radiological improvement of periodontal disease in patients with type 2 diabetes mellitus treated with alendronate: A randomized, placebo-controlled trial. *J Periodontol* 2001;72:204-209.
117. Takaishi Y, Miki T, Nishizawa Y, Morii H. Clinical effect of etidronate on alveolar pyorrhoea associated with chronic marginal periodontitis: Report of four cases. *J Int Med Res* 2001;29:355-365.
118. Weber RL, Wiesen MJ, Iacono VJ, Baer PN. Osteoporosis: A risk factor for dental implants and in the prognosis of periodontal therapy. *Periodontal Clin Investig* 1997; 19:5-8.
119. von Wowern N. General and oral aspects of osteoporosis: A review. *Clin Oral Invest* 2001;5:71-82.
120. Rodan GA, Martin TJ. Therapeutic approaches to bone diseases. *Science* 2000;289:1508-1514.
121. Friberg B, Ekestubbe A, Mellstrom D, Sennerby L. Brånemark implants and osteoporosis: A clinical exploratory study. *Clin Implant Dent Related Res* 2001;3: 50-56.
122. Starck WJ, Epker BN. Failure of osseointegrated dental implants after diphosphonate therapy for osteoporosis: A case report. *Int J Oral Maxillofac Implants* 1995;10: 74-78.
123. Yoshinari M, Oda Y, Ueki H, Yokose S. Immobilization of bisphosphonates on surface modified titanium. *Biomaterials* 2001;22:709-715.
124. Nakaya H, Osawa G, Iwasaki N, Cochran DL, Kamoi K, Oates TW. Effects of bisphosphonate on matrix metalloproteinase enzymes in human periodontal ligament cells. *J Periodontol* 2000;71:1158-1166.
125. Paquette DW, Williams RC. Modulation of host inflammatory mediators as a treatment strategy for periodontal diseases. *Periodontol 2000* 2000;24:239-252.

Correspondence: Dr. Michael S. Reddy, UAB School of Dentistry, Department of Periodontology, 1530 3rd Avenue South, SDB 412, Birmingham, AL 35294-0007. Fax: 205-934-7901.

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APPENDIX A

CONSENSUS REPORT

Members of the Section read and studied the review titled "Periodontal Host Modulation with Antiproteinase, Anti-Inflammatory, and Bone-Sparing Agents. A Systematic Review" by Michael S. Reddy, Nico C. Geurs, and John C. Gunsolley. The focused PICO question addressed by this evidence-based systematic review is: "In patients with chronic periodontitis, what is the effect of host-modulation agents, alone or in combination with conventional therapy, as assessed by clinical, radiographic, adverse and patient-centered outcomes?"

Introduction

MEDLINE, Embase, and the Cochrane Library databases were searched without language restrictions through April 1, 2002 for studies that used tetracycline (TET)-related matrix metalloproteinase (MMP) inhibitors, or non-steroidal anti-inflammatory drugs (NSAIDs), or bisphosphonates. The investigation also included hand searching of journals and contacting authors and industry experts.

Hand searching included a perusal of bibliographies of relevant papers and review articles. Major peri-

odontal publications were contacted and any manuscripts relevant to the search known to be "in press" were included. In addition, representatives of industry involved with the manufacture of biopharmaceuticals were contacted to provide missing data and clarity when necessary.

To be eligible for inclusion in the review, manuscripts had to pertain to human studies. Randomized controlled clinical trials, cohort studies, cross-sectional studies, and case series were included. Furthermore, the studies had to be conducted on subjects with gingivitis, aggressive periodontitis, chronic periodontitis, or dental implants. The types of interventions included were administration of tetracycline-related matrix metalloproteinase inhibitors, non-steroidal anti-inflammatory drugs, or bisphosphonates.

Section members evaluated the manuscript that summarized all screened information and, in open forum, evaluated the evidence and conclusions brought forth from this review. Section members noted that conventional therapy included 3 types of mechanical intervention: scaling and root planing, scaling alone, and ultrasonic debridement. Throughout this report the term conventional therapy will be used.

1. Does the section agree that the evidence-based systematic review is complete and accurate?

The Section accepted the systematic review paper and noted that the authors had ably compiled data and answered the focused questions. The charge to the reviewers was to determine, in patients with chronic periodontitis, what is the effect of host-modulation agents, alone or in combination with conventional therapy on periodontal disease as assessed by clinical, radiographic, adverse, and patient-centered outcomes. The focused review questions were further divided into specific host-modulation therapies.

First, what is the effect of matrix metalloproteinase (MMP) inhibitor therapy on chronic periodontitis alone or in combination with conventional therapy compared to conventional therapy alone?

1. Well-conducted research has examined the effect of MMP inhibitors in conjunction with conventional therapy for the treatment of chronic periodontitis.

2. Forty-three studies were screened. After elimination of those studies that did not directly address the focused question, 7 studies were evaluated. These studies were used to conduct a meta-analysis of the effectiveness of subantimicrobial dose doxycycline (SDD). Three were randomized, multi-centered clinical trials with substantial numbers of subjects. The other 4 were single-center studies with fewer subjects.

3. There are insufficient data to evaluate the effect of the use of MMP inhibitors administered without-conventional therapy for the treatment of chronic periodontitis.

4. There were no studies available to answer the question of whether MMP inhibitors are efficacious in treating peri-implantitis.

The second focused review question was "What is the effect of NSAID therapy on chronic periodontitis alone or in combination with conventional therapy compared to conventional therapy alone?"

1. Twenty-nine studies were initially screened.

2. Ten studies evaluated the effect of NSAIDs on clinical attachment level changes and/or changes in alveolar bone levels. Thirteen studies addressed secondary clinical outcomes. The majority of these studies were double-masked placebo-controlled clinical trials. All were single-center studies with fewer than 60 subjects.

3. There were insufficient data to evaluate the use of NSAIDs in the absence of conventional therapy in the treatment of chronic periodontitis.

Data suggesting a beneficial role for NSAIDs in slowing peri-implant bone loss were insufficient to allow critical evaluation.

The third focused review question was "What is the effect of bisphosphonates as a therapy for chronic periodontitis?"

1. Twenty-one studies were initially screened.

2. Three studies addressed the clinical and radiographic effects of bisphosphonates in the treatment of chronic periodontitis and were evaluated. Two were randomized, controlled, double-masked clinical trials of 40 subjects each, and one was a report of 4 cases.

3. There are insufficient data to evaluate the use of bisphosphonates in the absence of conventional therapy in the treatment of chronic periodontitis.

4. There are insufficient data to evaluate the effect of bisphosphonates on the bone loss around dental implants.

2. Has any new information been generated or discovered since the evidence-based search cut-off date?

1. Twenty abstracts and 2 recent publications were reviewed.

2. Five abstracts provided information on the focused review questions regarding MMP inhibitors. Of the 5, one abstract, a sub-analysis of a randomized controlled clinical trial (RCT) included in the meta-analysis, examined the use of SDD in the treatment of chronic periodontitis in smokers. Two evaluated the use of MMP inhibitors in diabetics; one focused on subjects 65 years and older; and one reported findings of the effect of MMP inhibitors

in conjunction with access flap surgery. These abstracts did not change the conclusions in the systematic review.

3. Two publications provided additional information on the effect of NSAIDs in the treatment of chronic periodontitis. These papers did not change the conclusions in the systematic review.

4. The Section members noted that a multi-center RCT evaluating the effect of the bisphosphonate alendronate has been completed but has not yet been reported.

3. Does the Section agree with the interpretations and conclusions of the reviewers?

The Section members were in agreement that the interpretation of the data, and the conclusions drawn by the reviewers, accurately reflected the evidence for a role of host modulation in the management of chronic periodontitis.

These conclusions were as follows:

1. The reviewed studies indicate that there is a role for the use of host modulation agents as an adjunct to conventional therapy in the treatment of chronic periodontitis.

2. A meta-analysis of randomized clinical trials conducted to study the use of SDD as an MMP inhibitor in conjunction with conventional therapy demonstrated a statistically significant benefit, compared with conventional therapy alone, in the treatment of chronic periodontitis.

3. The use of SDD is safe for a 12-month treatment period consistent with the approved labeling.

4. Multi-centered RCTs are not available to evaluate the use of NSAIDs in the treatment of chronic periodontitis. Single-center human clinical trials of NSAIDs, used in conjunction with conventional therapy, suggest that NSAIDs can provide a statistically significant inhibition of bone loss associated with chronic periodontitis. However, these studies were not suitable for meta-analysis.

5. Limited data suggest that bisphosphonates can limit the alveolar bone loss associated with chronic periodontitis.

4. What further research needs to be done relative to the focused questions of the evidence-based review?

Host modulation therapy is inherently different from conventional anti-infective therapy. While anti-infective therapy is generally short-term, successful host modulation therapy may require long-term administration to patients with chronic periodontitis in order to achieve an optimum effect. While the benefits of relatively short-term (up to 12 months) therapy with host modulating agents has been established, the longer-term use of these drugs in the management of chronic periodontitis needs further evaluation, particularly with regard to disease progression over time. In addition, there are a variety of inflammatory mediators known to play a role in the periodontal disease process, the inhibition of which is yet to be addressed in periodontal research.

1. At least 2 multi-center RCTs are needed to evaluate the effects of NSAIDs or bisphosphonates as adjuncts to conventional therapy in the management of chronic periodontitis.

2. Multi-center RCTs are needed to evaluate the effects of MMP inhibitors, NSAIDs, and bisphosphonates in the prevention or treatment of bone loss around dental implants.

3. Additional studies are needed to evaluate the effects of host-modulation therapy in high-risk patient populations.

4. Studies should evaluate the potential synergistic effect of combining host-modulation therapies with each other and with anti-infective agents.

5. The section members recommend that patients being treated systemically with various host-modulating agents for other systemic disease (e.g., rheumatoid arthritis, osteoporosis, cardiovascular disease) should be evaluated for the effect of these drugs on progression of chronic periodontitis.

6. Host-modulation therapy should be studied in conjunction with surgical periodontal procedures including regenerative procedures.

7. Topical administration of host-modulating agents should be evaluated.

8. Further research is required to identify those patients and specific periodontal conditions that may be most responsive to host-modulation therapy.

5. How can the information from the evidence-based review be applied to patient management?

A. There is evidence supporting the use of SDD as an adjunct to conventional therapy in the management of chronic periodontitis. The clinician's decision to use adjunctive SDD therapy remains a matter of individual clinical judgment, based on the phase of treatment and the patient's status and preferences.

The evidence indicates that in patients with chronic periodontitis, the adjunctive use of SDD combined with conventional therapy does not result in significant adverse events.

Level of Evidence:[1] Strong.

Rationale: Meta-analysis of 7 RCTs, 3 of which are multi-center studies and 4 of which are single-center studies. There were 5 clinical studies that addressed safety and adverse outcomes.

B. The evidence indicates that the use of NSAIDs as an adjunct to conventional therapy can slow the bone loss of chronic periodontitis. However, the safety profile does not support long-term ingestion of NSAIDs due to potentially significant side effects.

Level of Evidence: Moderate.

Rationale: This level of evidence is based on 10 single-center RCTs.

C. There is some evidence to suggest that topical application of NSAIDs may be effective in inhibiting the bone loss of chronic periodontitis.

Level of Evidence: Limited.

Rationale: This level of evidence is based on 3 single-center RCTs with small study populations.

D. There is insufficient evidence supporting the use of bisphosphonates as an adjunct to conventional treatment in the management of chronic periodontitis.

Level of Evidence: Insufficient.

Rationale: This level of evidence is based on 2 single-center RCTs and one case series.

E. There is insufficient evidence supporting the use of host modulating agents for the treatment of bone loss around dental implants.

Level of Evidence: Insufficient.

Rationale: Inadequate data. There are no well-designed studies on this topic.

REFERENCE

1. Newman MG, Caton J, Gunsolley JC. The use of the evidence-based approach in a periodontal therapy contemporary science workshop. *Ann Periodontol* 2003;8:1-11.

SECTION MEMBERS