J Clin Periodontol 2005; 32: 610–616 doi: 10.1111/j.1600-051X.2005.00728.x

Journal of Clinical Periodontology

Adjunctive subantimicrobial dose doxycycline in smokers and non-smokers with chronic periodontitis

Philip M. Preshaw[1], Arthur F. Hefti[2], Mark H. Bradshaw[3]

[1]School of Dental Sciences, Newcastle University, UK; [2]Philips Oral Healthcare Inc., Snoqualmie, WA, USA; [3]Covance Inc., Princeton, NJ, USA

Preshaw PM, Hefti AF, Bradshaw MH. Adjunctive subantimicrobial dose doxycycline in smokers and non-smokers with chronic periodontitis. J Clin Periodontol 2005; 32: 610–616. doi: 10.1111/j.1600-051X.2005.00728.x. © Blackwell Munksgaard, 2005.

Abstract

Objectives: Previous studies have demonstrated the clinical benefits of subantimicrobial dose doxycycline (SDD) in the treatment of chronic periodontitis (CP). The aim of this study was to retrospectively evaluate the role of SDD as an adjunct to scaling and root planing (SRP) in the treatment of smokers and non-smokers with CP.

Material and Methods: A meta-analysis of two previously reported clinical studies was undertaken. Both were 9-month, double-blind, randomized, placebo-controlled, multi-centre clinical trials that investigated the efficacy of SDD (20 mg doxycycline twice daily) in combination with SRP in subjects with moderate–severe CP. 36.9% of the combined study population were smokers. Three hundred and ninety-two subjects were included in the meta-analysis, which evaluated per-subject mean changes in clinical attachment level (CAL) and probing depth (PD) from baseline and the total number of sites with attachment gains and PD reductions $\geqslant 2$ and $\geqslant 3$ mm from baseline in four subgroups: smokers/SDD; smokers/placebo; non-smokers/SDD; non-smokers/placebo.

Results: A hierarchical treatment response was observed, with non-smokers who received SDD demonstrating the greatest CAL gains and PD reductions. Smokers who received placebo demonstrated the smallest clinical improvements following treatment. Smokers who received SDD demonstrated an intermediate treatment response that was broadly equivalent to that seen in non-smokers who received placebo. In sites with baseline PD 4–6 mm, month 9 CAL gains were 19–45% better in non-smokers who received SDD compared with all other subgroups ($p < 0.05$), and were 21% greater in smokers who received SDD compared with smokers who received placebo ($p < 0.05$). Furthermore, month 9 PD reductions were 21–53% greater in non-smokers who received SDD compared with all other subgroups ($p < 0.01$), and were 26% greater in smokers who received SDD compared with smokers who received placebo ($p < 0.05$).

Conclusion: Adjunctive SDD enhances therapeutic outcomes compared with SRP alone, resulting in clinical benefit in both smokers and non-smokers with CP.

Key words: meta-analysis; scaling and root planing; smoking; subantimicrobial dose doxycycline

Accepted for publication 14 October 2004

Periodontal pathogenesis is mediated by complex interactions between a pathogenic microflora and a susceptible host (Offenbacher 1996). The development of an immune-inflammatory response in the susceptible patient is characterized by release of inflammatory mediators and enzymes, including matrix metalloproteinases (MMPs), by infiltrating and resident cells in the inflamed periodontal tissues (Page et al. 1997). Predominant MMPs in the gingival crevicular fluid (GCF) of patients with periodontitis are MMP-8 and MMP-9, which are derived from PMNs (Golub et al. 1995, 1998), and are particularly effective in degrading type-1 collagen, the predominant collagen type in periodontal ligament (Mariotti 1993). Levels of PMN-type MMPs increase with periodontal disease severity (Golub et al. 1995) and are

secreted in large quantities by infiltrating PMNs in the periodontal tissues, contributing to breakdown of the extracellular matrix in chronic periodontitis (CP). The importance of the host immune-inflammatory response in mediating periodontal destruction is now clearly established (Offenbacher 1996).

Recently, interest has focused on the concept of host modulatory therapy (HMT) as a treatment paradigm in the management of periodontitis. Essentially, HMT aims to enhance traditional periodontal therapies by modifying destructive aspects of the immune-inflammatory host response so that periodontal breakdown is reduced and the periodontium is stabilized. One such HMT involves the use of subantimicrobial doxycycline (SDD–20 mg doxycycline twice daily (b.i.d.)) as an adjunct to conventional non-surgical periodontal therapy in the management of CP. Doxycycline downregulates MMP activity and reduces collagenase levels in the GCF of patients with CP (Golub et al. 1990, 1995, 1997). A subantimicrobial dose of 20 mg b.i.d. is not associated with the development of antibiotic resistance or detrimental shifts in the normal periodontal microflora (Crout et al. 1996, Caton et al. 2000, Walker et al. 2000). Long-term, placebo-controlled, double-blind clinical studies have demonstrated the clinical benefit of SDD when used as an adjunct to scaling and root planing (SRP) compared with SRP alone (Caton et al. 2000, 2001, Novak et al. 2002, Preshaw et al. 2004). These studies have reported improvements in clinical attachment level (CAL) and probing depths (PDs) that were significantly greater compared with those observed in patients who received adjunctive placebo. Thus, the adjunctive use of SDD represents a potentially valuable therapeutic modality for managing patients with periodontitis.

Smoking is now clearly established as a major risk factor for periodontitis (Salvi et al. 1997). Indeed, recent epidemiological data have suggested that smoking may be responsible for as many as half the cases of CP seen in the United States (Tomar & Asma 2000). Potential mechanisms for the deleterious effects of smoking in periodontal pathogenesis include effects of noxious components of cigarette smoke on the gingival microvasculature, changes in the subgingival microbial flora such that increasingly pathogenic species predominate, and modification of immune-inflammatory responses in the host tissues (Haber 1994, Persson et al. 2001). Smokers with periodontitis are more likely to have bone/attachment loss than non-smokers (Stoltenberg et al. 1993, Wouters et al. 1993) and the extent of clinical improvements following periodontal treatment is significantly reduced (Preber & Bergstrom 1990, Ah et al. 1994).

Previously reported studies of the adjunctive use of SDD in the treatment of periodontitis did not report treatment outcomes by smoking status. Given the importance of smoking in periodontal pathogenesis and the fact that, in many cases, the most difficult patients to treat are smokers, the aim of this study was to investigate retrospectively the efficacy of SDD as an adjunct to SRP in the treatment of smokers and non-smokers with moderate–severe CP.

Material and Methods

A meta-analysis of the outcomes of two previously reported clinical studies (Caton et al. 2000, Preshaw et al. 2004) was undertaken. These studies had identical study design (reported previously). Briefly, these were 9-month, double-blind, randomized, placebo-controlled, multi-centre, parallel group studies in which the efficacy of SDD as an adjunct to SRP in the treatment of patients with moderate–severe CP was evaluated. All subjects underwent SRP and were randomly allocated to receive either adjunctive SDD (doxycycline hyclate 20 mg b.i.d.) or adjunctive placebo b.i.d. for 9 months, commencing at baseline. Subjects were evaluated 3, 6 and 9 months after baseline, at which time points full-mouth clinical indices were recorded. Subjects were male or female, aged 30–75 years with periodontitis manifested by CAL and PD 5–9 mm with bleeding on probing and radiographic evidence of alveolar bone loss.

Prior to statistical analyses, sites were stratified by the degree of PD at baseline: sites with PD 1–3 mm were considered normal; sites with PD 4–6 mm were considered mild–moderately diseased; and sites with baseline PD $\geqslant$ 7 mm were considered severely diseased (Cobb 2002). Efficacy parameters included the change in CAL from baseline, the change in PD from baseline, and for those sites with a baseline PD $\geqslant$ 4 mm (i.e. those sites with evidence of periodontal disease at baseline), the number of sites that demonstrated attachment gains $\geqslant$2 and $\geqslant$3 mm and PD reductions $\geqslant$2 and $\geqslant$3 mm relative to baseline.

In the meta-analysis, patient data from both studies were combined in a single analysis, while retaining identifiers for investigational sites. Because the two studies were virtually identical in design, including investigational site in the model was more relevant than including a test for inter-study differences. Comparisons between groups were made using ANCOVA. One ANCOVA model was used for all four subgroups (i.e. smokers/SDD; smokers/placebo; non-smokers/SDD; non-smokers/placebo) to test the main effect of treatment (SDD *versus* placebo), the main effect of smoking, and the treatment by smoking interaction, along with differences between investigational sites. Subject-level mean changes from baseline were analysed in the ANCOVA model, which included factors for treatment group, smoking status and their interaction, and included the actual baseline value of the parameter for each subject as a covariate. Pairwise multiple comparisons among the four subgroups of interest were conducted within the primary analysis of variance model using Fisher's LSD test. Three separate meta-analyses were conducted, each analysis restricted to tooth sites falling into one of the three baseline pocket depth strata discussed above. All tests of significance were two sided; differences were considered statistically significant when $p < 0.05$. The numbers of periodontal sites that displayed CAL gains of $\geqslant$2 and $\geqslant$3 mm or PD reductions of $\geqslant$2 and $\geqslant$3 mm from baseline were also determined, and compared between treatment groups using a GEE model with adjustment for within-subject correlations among sites.

Results

Baseline demographic data are shown in Table 1, and are based on 398 subjects; those subjects who had a baseline visit and provided demographic data. There were no statistically significant differences between the treatment groups (placebo *versus* adjunctive SDD) for mean age, gender or racial distribution (Table 1). The total number of smokers in the population was 147 (36.9%), and the total number of ex-smokers was 118 (29.6%). There were significantly more

smokers in the adjunctive SDD group (42.0%) than the adjunctive placebo group (31.8%) ($p < 0.05$). Given the difficulty in obtaining reliable information from patients relating to past smoking status (Scott et al. 2001), it was not possible to gather definitive data regarding the length of elapsed time since ex-smokers quit smoking. Hence for meta-analysis purposes, it was decided to create only two smoking strata rather than three or more. Thus, for the purpose of this article, ex-smokers and non-smokers were considered together and described as non-smokers.

The treatment groups were similar with regard to other baseline characteristics: medical history, medication history, oral hygiene practices, and concomitant medications. Three hundred and twenty-eight subjects completed the studies. The reasons for premature withdrawal of study subjects have been reported previously (Caton et al. 2000, Preshaw et al. 2004). Data from those subjects who prematurely withdrew were included in the final analyses using a last observation carried forward algorithm.

The meta-analysis was based on the intent-to-treat populations from two studies; 183 subjects from Caton et al. (2000) and 209 subjects from Preshaw et al. (2004) for a total of 392 subjects.

The mean per-subject changes in CAL from baseline to month 9 are shown in Figs 1 and 2. In all four subgroups (i.e. smokers/SDD; smokers/placebo; non-smokers/SDD; non-smokers/placebo), improvements in CAL from baseline were demonstrated, as would be expected following a course of SRP. A hierarchical treatment response was identified with the best treatment outcomes (CAL gains) being observed in non-smokers who received adjunctive SDD and the poorest treatment outcomes being observed in smokers who received adjunctive placebo. Smokers who received adjunctive SDD and non-smokers who received placebo had an intermediate treatment response, with broadly equivalent outcomes. In sites with baseline PD 4–6 mm, month 9 mean CAL gains were significantly greater (range 19–45% better) in non-smokers who received SDD than in all other subgroups (1.23 *versus* 0.85–1.03 mm, $p < 0.05$). Month 9 CAL gains from baseline in smokers who received SDD were 21% greater than smokers who received placebo (1.03 *versus* 0.85 mm, respectively, $p < 0.05$). In sites with baseline PD $\geqslant$ 7 mm, month 9 CAL gains were significantly greater (range 20–32% greater) in non-smokers who received SDD than in either of the placebo groups (smokers or non-smokers) (1.89 *versus* 1.43–1.58 mm, $p < 0.01$).

The mean per-subject changes in PD from baseline to month 9 are shown in Figs 3 and 4. Again, as would be expected following SRP, improvements in PD from baseline were observed in all subgroups. Again, a hierarchical treatment response was identified with the best treatment outcomes (PD reductions) being observed in non-smokers who received adjunctive SDD and the poorest treatment outcomes being observed in smokers who received adjunctive placebo. Smokers who received adjunctive SDD and non-smokers who received placebo had similar, and intermediate, treatment responses. In sites with baseline PD 4–6 mm, month 9 mean PD reductions were significantly greater (range 21–53% greater) in non-smokers who received SDD than in all other subgroups (1.22 *versus* 0.80–

Table 1. Demographic characteristics of combined intent-to-treat populations

Characteristic	SRP+placebo, $n = 198$	SRP+SDD, $n = 200$	p
Age (years)			
Mean (SD)	48.1 (10.9)	47.6 (9.6)	0.67*
Range	31–75	30–75	
Gender, *n* (%)			
Male	109 (55.1)	112 (56.0)	0.81†
Female	89 (44.9)	88 (44.0)	
Race/ethnicity, *n* (%)			
White Caucasian	136 (68.7)	150 (75.0)	0.38†
Black	43 (21.7)	33 (16.5)	
Asian	8 (4.0)	8 (4.0)	
Hispanic	11 (5.6)	9 (4.5)	
Tobacco use, *n* (%)			
Smoker	63 (31.8)	84 (42.0)	0.03†
Ex-smoker	66 (33.3)	52 (26.0)	0.13†

*Determined using analysis of variance.
†Determined using the Cochran–Mantel–Haenszel test.
SRP, scaling and root planing; SDD, subantimicrobial dose doxycycline.

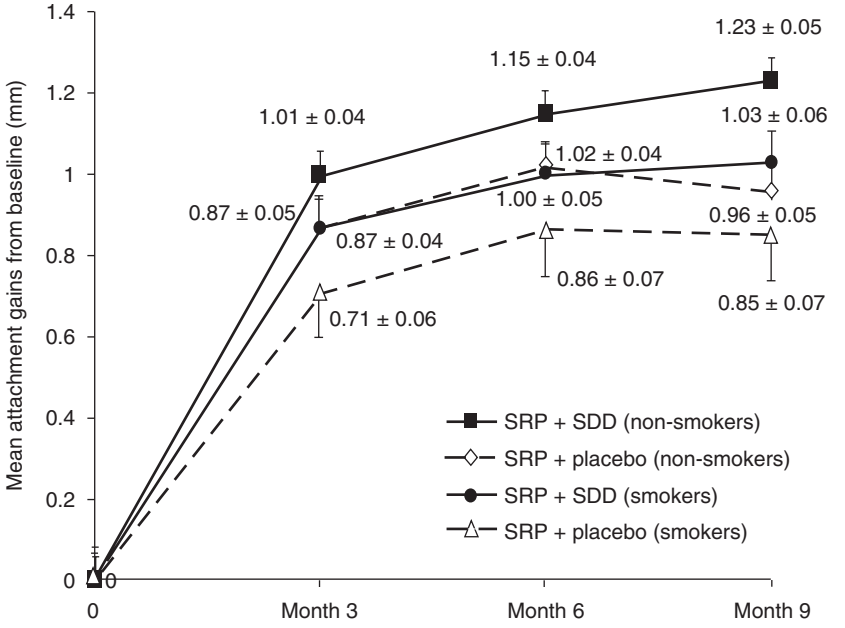

Fig. 1. Mean attachment gains in sites with baseline probing depths 4–6 mm. Subjects received scaling and root planing (SRP) at baseline, and then received either subantimicrobial dose doxycycline (SDD) 20 mg twice daily (b.i.d.) or placebo b.i.d. for 9 months. The mean per-subject changes from baseline and standard errors are presented, stratified by smoking status and study product allocation.

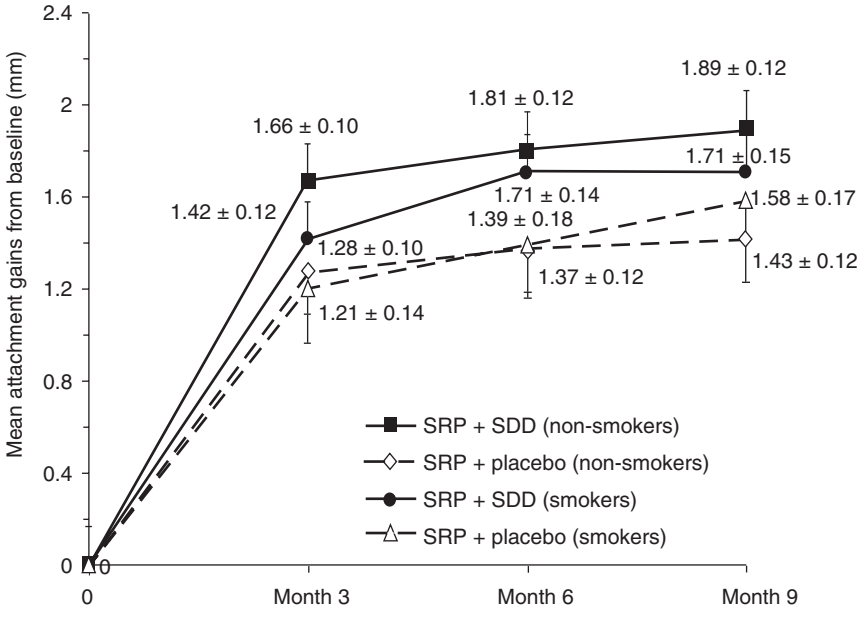

Fig. 2. Mean attachment gains in sites with baseline probing depths ⩾7 mm. Subjects received scaling and root planing (SRP) at baseline, and then received either sub-antimicrobial dose doxycycline (SDD) 20 mg twice daily (b.i.d.) or placebo b.i.d. for 9 months. The mean per-subject changes from baseline and standard errors are presented, stratified by smoking status and study product allocation.

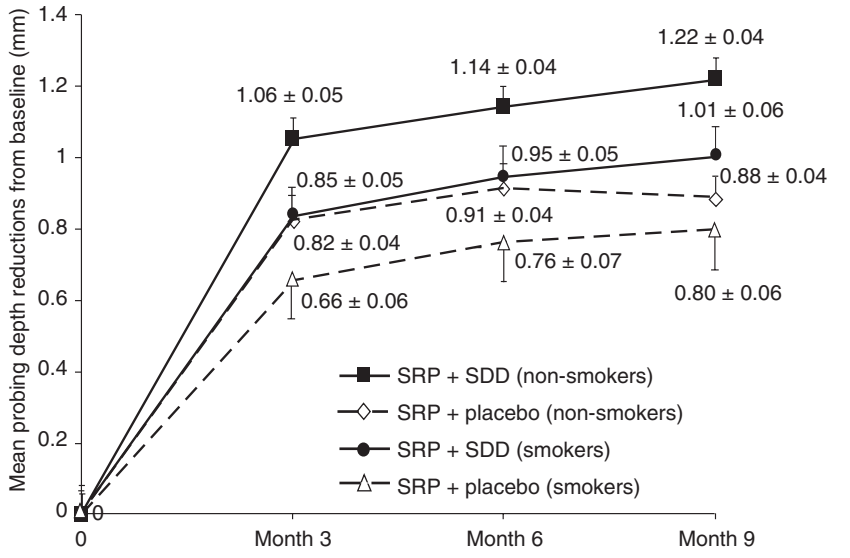

Fig. 3. Mean probing depth (PD) reductions in sites with baseline PD 4–6 mm. Subjects received scaling and root planing (SRP) at baseline, and then received either sub-antimicrobial dose doxycycline (SDD) 20 mg twice daily (b.i.d.) or placebo b.i.d. for 9 months. The mean per-subject changes from baseline and standard errors are presented, stratified by smoking status and study product allocation.

1.01 mm, $p<0.01$). Month 9 PD reductions from baseline in smokers who received SDD were 26% greater than smokers who received placebo (1.01 *versus* 0.80 mm, respectively, $p<0.05$). In sites with baseline PD⩾7 mm, month 9 PD reductions were significantly greater (range 20–41% greater) in non-smokers who received SDD than in all other subgroups (2.16 *versus* 1.53–1.80 mm, $p<0.05$).

The percentages of periodontal sites (baseline PD⩾4 mm) achieving thresholds of clinical improvement (CAL gains ⩾2 and ⩾3 mm, and PD reductions ⩾2 and ⩾3 mm) at 9 months are shown in Table 2. It is clear from Table 2 that in all subgroups, these thresholds of clinical improvement were achieved for a considerable number of sites. However, a hierarchical treatment response was observed such that non-smokers who received SDD demonstrated the greatest number of sites achieving these thresholds of change. The smallest number of sites achieving these thresholds was observed in the smokers who received placebo. Smokers who received adjunctive SDD and non-smokers who received placebo demonstrated a similar, and intermediate, number of sites achieving these thresholds of change.

An identical threshold analysis was performed for those sites that demonstrated baseline PDs of 6 mm or greater (Table 3). Again, thresholds of change (CAL gains ⩾2 and ⩾3 mm, and PD reductions ⩾2 and ⩾3 mm) at 9 months were observed for a considerable number of sites. A hierarchical treatment response was observed such that non-smokers who received SDD demonstrated the greatest number of sites achieving these thresholds of change and smokers who received placebo demonstrated the least. Smokers who received adjunctive SDD and non-smokers who received placebo demonstrated a similar, and intermediate, number of sites achieving these thresholds of change.

Discussion

Smoking is clearly a risk factor for periodontitis. A multitude of cross-sectional, longitudinal, and case–control studies have established associations between smoking and periodontal disease (Bergstrom & Eliasson 1987, Haber et al. 1993, Grossi et al. 1994, Machtei et al. 1997, Tomar & Asma 2000), with smokers experiencing a greater incidence of tooth loss and edentulism, and a less favourable response to periodontal treatment than ex-smokers or non-smokers (Preber & Bergstrom 1985, Ah et al. 1994, McGuire & Nunn 1996). In support of the contention that smokers tend to respond less favourably to periodontal therapy is the finding that the majority of patients with refractory disease are indeed smokers (MacFarlane et al. 1992). The level of addiction to nicotine, as assessed by the number of cigarettes smoked per day and the number of years of exposure to

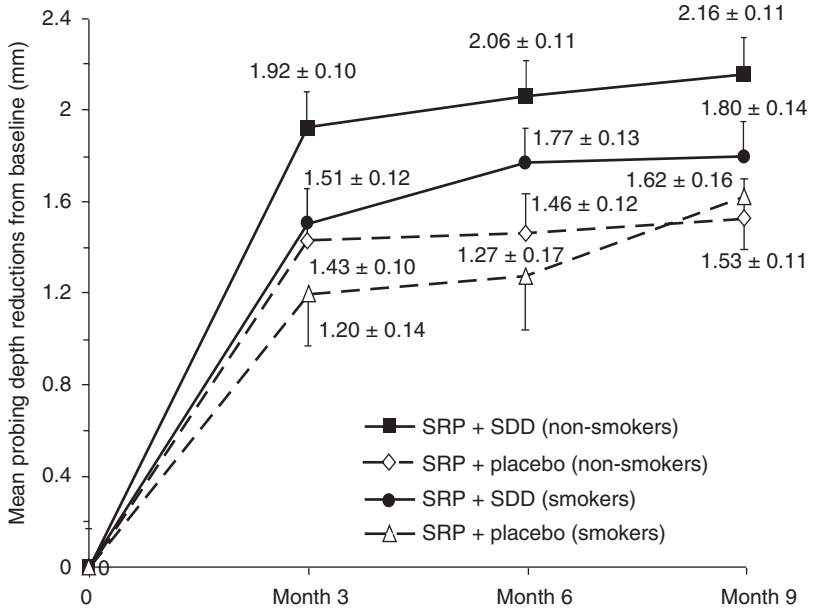

Fig. 4. Mean probing depth (PD) reductions in sites with baseline PD $\geqslant$ 7 mm. Subjects received scaling and root planing (SRP) at baseline, and then received either sub-antimicrobial dose doxycycline (SDD) 20 mg twice daily (b.i.d.) or placebo b.i.d. for 9 months. The mean per-subject changes from baseline and standard errors are presented, stratified by smoking status and study product allocation.

Table 2. Effect of SDD on clinical attachment gains and PD reductions at month 9 in all sites (baseline PD $\geqslant$ 4 mm) by smoking status and randomization

Threshold change from baseline	Non-smokers		Smokers	
	SRP+placebo (n = 4100), % (n)	SRP+SDD (n = 3891), % (n)	SRP+placebo (n = 2193), % (n)	SRP+SDD (n = 3042), % (n)
CAL gain $\geqslant$ 2 mm	32.1 (1316)	43.1*** (1675)	29.4 (645)	32.3 (984)
CAL gain $\geqslant$ 3 mm	10.9 (448)	15.9* (619)	9.0 (198)	11.5 (349)
PD reduction $\geqslant$ 2 mm	29.5 (1208)	42.8*** (1666)	20.8 (456)	28.4* (863)
PD reduction $\geqslant$ 3 mm	7.8 (319)	15.0*** (583)	5.1 (112)	7.5 (228)

*$p < 0.05$ and ***$p < 0.001$ compared with placebo within smoking category (determined using GEE model with adjustment for within-subject correlations among sites).
PD, probing depth; SRP, scaling and root planing; SDD, subantimicrobial dose doxycycline; CAL, clinical attachment level.

Table 3. Effect of SDD on clinical attachment gains and PD reductions at month 9 in sites with baseline PD $\geqslant$ 6 mm by smoking status and randomization

Threshold change from baseline	Non-smokers		Smokers	
	SRP+placebo (n = 1330), % (n)	SRP+SDD (n = 1250), % (n)	SRP+placebo (n = 733), % (n)	SRP+SDD (n = 925), % (n)
CAL gain $\geqslant$ 2 mm	43.3 (576)	59.1** (739)	36.8 (270)	44.1 (408)
CAL gain $\geqslant$ 3 mm	19.2 (256)	32.6** (407)	15.0 (110)	21.3 (197)
PD reduction $\geqslant$ 2 mm	44.4 (591)	62.8*** (785)	31.4 (230)	45.2** (418)
PD reduction $\geqslant$ 3 mm	18.5 (246)	36.9*** (461)	13.4 (98)	20.0 (185)

**$p < 0.01$, and ***$p < 0.001$ compared with placebo within smoking category (determined using GEE model with adjustment for within-subject correlations among sites).
PD, probing depth; SRP, scaling and root planing; SDD, subantimicrobial dose doxycycline; CAL, clinical attachment level.

tobacco products, has been linked to periodontal disease severity in a dose–response relationship (Jette et al. 1993, Grossi et al. 1994, Alpagot et al. 1996).

Mechanisms for the influence of the constituents of tobacco smoke on the periodontium include an effect of nicotine on the periodontal tissues resulting in vasoconstriction in peripheral blood vessels and effects on the immune-inflammatory host response (Kinane & Chestnutt 2000). Exposure to cigarette smoke reduces the deformability of PMNs (Lannan et al. 1992) leading to abnormal function and phagocytosis (MacFarlane et al. 1992). Smoking has also been shown to reduce fibroblast function in vitro (Raulin et al. 1988), possibly contributing to impaired wound healing in smokers compared with non-smokers. Cigarette smoking has also been associated with increased cytokine production, with peripheral blood mononuclear cells from smokers secreting significantly greater levels of interleukin-1β compared with cells from non-smokers upon exposure to cigarette smoke (Ryder et al. 2002). Smokers have also been reported to have significantly higher GCF levels of tumour necrosis factor-α compared with non-smokers (Bostrom et al. 1998), and suppressed levels of protease inhibitors (Persson et al. 2001).

Thus, components of cigarette smoke result in increased release of pro-inflammatory mediators in the periodontal tissues. Furthermore, nicotine has been shown to alter gingival fibroblast function, resulting in decreased collagen formation and increased collagenase activity (Tipton & Dabbous 1995). Smokers have increased neutrophil elastase activity in their GCF compared with non-smokers (Soder 1999). Exposure of coronary endothelial cells to cigarette smoke condensate results in upregulation of genes involved in matrix degradation (MMP-1, MMP-8 and MMP-9) and increased production of cytokines, suggesting a complex pro-inflammatory response to cigarette smoke that likely involves recruitment of leukocytes, cytokine signaling and MMP upregulation (Nordskog et al. 2003).

The periodontal hyper-responsive phenotype has been postulated (Offenbacher 1996, Page & Kornman 1997) in which disease susceptible individuals mount an exaggerated inflammatory response to bacterial challenge, character-

ized by pathologically elevated levels of pro-inflammatory cytokines and MMPs in the periodontal tissues. Emerging research supports that cigarette smoking is a modifier of the inflammatory response, resulting in further exacerbation of destructive events in the inflamed periodontium. Thus, the use of a HMT such as SDD may be of benefit in the management of smokers with periodontal disease, who tend to demonstrate limited clinical improvements following conventional periodontal therapy. This premise is supported by the findings of a recently reported study in which subjects with severe, generalized CP received conventional non-surgical treatment and periodontal maintenance together with 9 months of adjunctive SDD or placebo (Novak et al. 2002). Nearly half of the subjects were smokers, and clinically and statistically significant improvements in PDs were reported in the adjunctive SDD group compared with the placebo group.

The present meta-analysis clearly shows the benefit of adjunctive SDD in smokers and non-smokers. It is perhaps not surprising that the best treatment response was consistently observed in non-smokers who received SDD, and the poorest treatment response was observed in the smokers who received placebo. All subjects derived benefit from participation in the studies, which reflects the clinical improvements that can be achieved by SRP alone. However, the increased benefit derived from the use of SDD in both the smokers and the non-smokers compared with SRP alone supports that SDD is a useful addition to the periodontal armamentarium in the management of disease. The treatment outcomes in smokers who received SDD were broadly equivalent to those seen in non-smokers who received placebo, suggesting that the use of adjunctive SDD improved the treatment response in smokers to a level comparable with that routinely seen in non-smokers who receive SRP alone. Treatment benefits with SDD were observed in all diseased sites, and particularly so in deep periodontal sites of 6 mm or greater. Given that smokers are among the most difficult periodontal patients to treat, in terms of limited improvements following therapy, then the use of SDD can be considered of benefit in this group of susceptible patients.

HMT is combined with conventional periodontal treatment with the aim being to create the most optimal conditions for stabilization of the periodontium by reducing destructive processes and increasing wound healing. SRP and HMT target different aspects of periodontal pathogenesis. The aims of SRP are to remove subgingival plaque and calculus, and disrupt the biofilm to create a local environment more commensurate with wound healing. HMT aims to reduce destructive inflammatory host responses, and SDD downregulates MMP activity in the tissues. In smokers with periodontitis, there is another treatment strategy that should be considered, and that is smoking cessation therapy. Smoking cessation therapy can be undertaken either within the dental practice (if staff members are appropriately trained), or through collaboration with the patient's medical doctor or specialist smoking cessation clinics. Given the evidence that smokers have worse periodontal disease than non-smokers (Stoltenberg et al. 1993, Wouters et al. 1993), and that the magnitude and predictability of clinical improvements following treatment is significantly reduced in smokers (Preber & Bergstrom 1990, Ah et al. 1994), smoking cessation counselling should form a major part of treatment for smokers with periodontitis.

In summary, this meta-analysis demonstrated the benefits of adjunctive SDD for 9 months in both smokers and non-smokers. A hierarchical treatment response was observed: non-smokers who received adjunctive SDD demonstrated the best treatment response and smokers who received placebo demonstrated the poorest treatment response. Outcomes following treatment were intermediate and broadly similar in smokers who received SDD and non-smokers who received placebo. These data support the use of adjunctive SDD in periodontal therapy in both smokers and non-smokers.

Acknowledgements

This study was supported by a grant from CollaGenex Pharmaceuticals Inc. (Newtown, PA, USA). We would like to acknowledge the invaluable contribution made by the lead investigators in the original research: J. G. Caton, S. G. Ciancio, T. M. Blieden, R. J. Crout, J. M. Massaro, A. M. Polson, J. Thomas, C. B. Walker, M. J. Novak, B. S. Michalowicz, B. L. Pihlstrom, R. Schoor, C. L. Trummel, J. Dean, T. E. Van Dyke.

References

Ah, M. K., Johnson, G. K., Kaldahl, W. B., Patil, K. B. & Kalkwarf, K. L. (1994) The effect of smoking on the response to periodontal therapy. *Journal of Clinical Periodontology* **21**, 91–97.

Alpagot, T., Wolff, L. F., Smith, Q. T. & Tran, S. D. (1996) Risk indicators for periodontal disease in a racially diverse urban population. *Journal of Clinical Periodontology* **23**, 982–988.

Bergstrom, J. & Eliasson, S. (1987) Noxious effect of cigarette smoking on periodontal health. *Journal of Periodontal Research* **22**, 513–517.

Bostrom, L., Linder, L. E. & Bergstrom, J. (1998) Clinical expression of TNF-alpha in smoking-associated periodontal disease. *Journal of Clinical Periodontology* **25**, 767–773.

Caton, J. G., Ciancio, S. G., Blieden, T. M., Bradshaw, M., Crout, R. J., Hefti, A. F., Massaro, J. M., Polson, A. M., Thomas, J. & Walker, C. (2000) Treatment with subantimicrobial dose doxycycline improves the efficacy of scaling and root planing in patients with adult periodontitis. *Journal of Periodontology* **71**, 521–532.

Caton, J. G., Ciancio, S. G., Blieden, T. M., Bradshaw, M., Crout, R. J., Hefti, A. F., Massaro, J. M., Polson, A. M., Thomas, J. & Walker, C. (2001) Subantimicrobial dose doxycycline as an adjunct to scaling and root planing: post-treatment effects. *Journal of Clinical Periodontology* **28**, 782–789.

Cobb, C. M. (2002) Clinical significance of non-surgical periodontal therapy: an evidence-based perspective of scaling and root planing. *Journal of Clinical Periodontology* **29** (Suppl. 2), 6–16.

Crout, R. J., Lee, H. M., Schroeder, K., Crout, H., Ramamurthy, N. S., Wiener, M. & Golub, L. M. (1996) The ''cyclic'' regimen of low-dose doxycycline for adult periodontitis: a preliminary study. *Journal of Periodontology* **67**, 506–514.

Golub, L. M., Ciancio, S., Ramamurthy, N. S., Leung, M. & McNamara, T. F. (1990) Low-dose doxycycline therapy: effect on gingival and crevicular fluid collagenase activity in humans. *Journal of Periodontal Research* **25**, 321–330.

Golub, L. M., Lee, H. M., Greenwald, R. A., Ryan, M. E., Sorsa, T., Salo, T. & Giannobile, W. V. (1997) A matrix metalloproteinase inhibitor reduces bone-type collagen degradation fragments and specific collagenases in gingival crevicular fluid during adult periodontitis. *Inflammation Research* **46**, 310–319.

Golub, L. M., Ryan, M. E. & Williams, R. C. (1998) Modulation of the host response in the treatment of periodontitis. *Dentistry Today* **17**, 1–6.

Golub, L. M., Sorsa, T., Lee, H. M., Ciancio, S., Sorbi, D., Ramamurthy, N. S., Gruber, B., Salo, T. & Konttinen, Y. T. (1995) Doxycycline inhibits neutrophil (PMN)-type matrix metalloproteinases in human adult perio-

dontitis gingiva. *Journal of Clinical Periodontology* **22**, 100–109.

Grossi, S. G., Zambon, J. J., Ho, A. W., Koch, G., Dunford, R. G., Machtei, E. E., Norderyd, O. M. & Genco, R. J. (1994) Assessment of risk for periodontal disease. I. Risk indicators for attachment loss. *Journal of Periodontology* **65**, 260–267.

Haber, J. (1994) Smoking is a major risk factor for periodontitis. *Current Opinion in Periodontology* **2**, 12–18.

Haber, J., Wattles, J. & Crowley, M. (1993) Evidence of cigarette smoking as a major risk factor for periodontitis. *Journal of Periodontology* **64**, 16–23.

Jette, A. M., Feldman, H. A. & Tennstedt, S. L. (1993) Tobacco use: a modifiable risk factor for dental disease among the elderly. *American Journal of Public Health* **83**, 1271–1276.

Kinane, D. F. & Chestnutt, I. G. (2000) Smoking and periodontal disease. *Critical Reviews in Oral Biology and Medicine* **11**, 356–365.

Lannan, S., McLean, A., Drost, E., Gillooly, M., Donaldson, K., Lamb, D. & MacNee, W. (1992) Changes in neutrophil morphology and morphometry following exposure to cigarette smoke. *International Journal of Experimental Pathology* **73**, 183–191.

MacFarlane, G. D., Herzberg, M. L., Wolff, L. F. & Hardie, N. A. (1992) Refractory periodontitis associated with abnormal polymorphonuclear leukocyte phagocytosis and cigarette smoking. *Journal of Periodontology* **63**, 908–913.

Machtei, E. E., Dunford, R. G., Hausmann, E., Grossi, S. G., Powell, J., Cummins, D., Zambon, J. J. & Genco, R. J. (1997) Longitudinal study of prognostic factors in established periodontitis patients. *Journal of Clinical Periodontology* **24**, 102–109.

Mariotti, A. (1993) The extracellular matrix of the periodontium: dynamic and interactive tissues. *Periodontology 2000* **3**, 39–63.

McGuire, M. K. & Nunn, M. E. (1996) Prognosis versus actual outcome. III. The effectiveness of clinical parameters in accurately predicting tooth survival. *Journal of Periodontology* **67**, 666–674.

Nordskog, B. K., Blixt, A. D., Morgan, W. T., Fields, W. R. & Hellmann, G. M. (2003) Matrix-degrading and pro-inflammatory changes in human vascular endothelial cells exposed to cigarette smoke condensate. *Cardiovascular Toxicology* **3**, 101–117.

Novak, M. J., Johns, L. P., Miller, R. C. & Bradshaw, M. H. (2002) Adjunctive benefits of subantimicrobial dose doxycycline in the management of severe, generalized, chronic periodontitis. *Journal of Periodontology* **73**, 762–769.

Offenbacher, S. (1996) Periodontal diseases: pathogenesis. *Annals of Periodontology* **1**, 821–878.

Page, R. C. & Kornman, K. S. (1997) The pathogenesis of human periodontitis: an introduction. *Periodontology 2000* **14**, 9–11.

Page, R. C., Offenbacher, S., Schroeder, H. E., Seymour, G. J. & Kornman, K. S. (1997) Advances in the pathogenesis of periodontitis: summary of developments, clinical implications and future directions. *Periodontology 2000* **14**, 216–248.

Persson, L., Bergstrom, J., Ito, H. & Gustafsson, A. (2001) Tobacco smoking and neutrophil activity in patients with periodontal disease. *Journal of Periodontology* **72**, 90–95.

Preber, H. & Bergstrom, J. (1985) The effect of non-surgical treatment on periodontal pockets in smokers and non-smokers. *Journal of Clinical Periodontology* **13**, 319–323.

Preber, H. & Bergstrom, J. (1990) Effect of cigarette smoking on periodontal healing following surgical therapy. *Journal of Clinical Periodontology* **17**, 324–328.

Preshaw, P. M., Hefti, A. F., Novak, M. J., Michalowicz, B. S., Pihlstrom, B. L., Schoor, R., Trummel, C. L., Dean, J., van Dyke, T. E., Walker, C. B. & Bradshaw, M. H. (2004) Subantimicrobial dose doxycycline enhances the efficacy of scaling and root planing in chronic periodontitis: a multi-center trial. *Journal of Periodontology* **75**, 1068–1076.

Raulin, L. A., McPherson, J. C. III, McQuade, M. J. & Hanson, B. S. (1988) The effect of nicotine on the attachment of human fibroblasts to glass and human root surfaces in vitro. *Journal of Periodontology* **59**, 318–325.

Ryder, M. I., Saghizadeh, M., Ding, Y., Nguyen, N. & Soskolne, A. (2002) Effects of tobacco smoke on the secretion of interleukin-1beta, tumor necrosis factor-alpha, and transforming growth factor-beta from peripheral blood mononuclear cells. *Oral Microbiology and Immunology* **17**, 331–336.

Salvi, G. E., Lawrence, H. P., Offenbacher, S. & Beck, J. D. (1997) Influence of risk factors on the pathogenesis of periodontitis. *Periodontology 2000* **14**, 173–201.

Scott, D. A., Palmer, R. M. & Stapleton, J. A. (2001) Validation of smoking status in clinical research into inflammatory periodontal disease. *Journal of Clinical Periodontology* **28**, 715–722.

Soder, B. (1999) Neutrophil elastase activity, levels of prostaglandin E2, and matrix metalloproteinase-8 in refractory periodontitis sites in smokers and non-smokers. *Acta Odontologica Scandinavica* **57**, 77–82.

Stoltenberg, J. L., Osborn, J. B., Pihlstrom, B. L., Herzberg, M. C., Aeppli, D. M. & Wolff, L. F. (1993) Association between cigarette smoking, bacterial pathogens and periodontal status. *Journal of Periodontology* **64**, 1225–1230.

Tipton, D. A. & Dabbous, M. K. (1995) Effects of nicotine on proliferation and extracellular matrix production of human gingival fibroblasts in vitro. *Journal of Periodontology* **66**, 1056–1064.

Tomar, S. L. & Asma, S. (2000) Smoking-attributable periodontitis in the United States: findings from NHANES III National Health and Nutrition Examination Survey. *Journal of Periodontology* **71**, 743–751.

Walker, C., Thomas, J., Nango, S., Lennon, J., Wetzel, J. & Powala, C. (2000) Long-term treatment with subantimicrobial dose doxycycline exerts no antibacterial effect on the subgingival microflora associated with adult periodontitis. *Journal of Periodontology* **71**, 1465–1471.

Wouters, F. R., Salonen, L. E., Frithiof, L. & Hellden, L. B. (1993) Significance of some variables on interproximal alveolar bone height based on cross-sectional epidemiological data. *Journal of Clinical Periodontology* **20**, 199–206.

Address:
Philip M. Preshaw
Department of Periodontology
School of Dental Sciences
University of Newcastle upon Tyne
Framlington Place
Newcastle upon Tyne NE2 4BW
UK
E-mail: p.m.preshaw@ncl.ac.uk