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Clinical changes following four different periodontal therapies for the treatment of chronic periodontitis: 1-year results

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Abstract

Objective: To compare clinical changes occurring in chronic periodontitis subjects receiving SRP alone or with systemically administered azithromycin, metronidazole or a sub-antimicrobial dose of doxycycline.

Material and Methods: 92 chronic periodontitis subjects were randomly assigned to receive SRP alone ($N = 23$) or combined with 500 mg azithromycin per day for 3 days ($N = 25$), 250 mg metronidazole tid for 14 days ($N = 24$) or 20 mg doxycycline bid for 3 months ($N = 20$). Gingival redness, bleeding on probing, suppuration, pocket depth and attachment level were measured at baseline and 3, 6 and 12 months post therapy. The significance of changes in clinical parameters within groups over time was sought using the Friedman test and among groups using ANCOVA or the Kruskal Wallis test.

Results: All groups showed clinical improvements at 12 months, with subjects receiving adjunctive agents showing a somewhat better response. Sites with initial pocket depth >6 mm showed significantly greater pocket depth reduction and greater attachment gain in subjects receiving metronidazole or azithromycin than subjects in the other groups. Some subjects showed attachment loss at 12 months in each group ranging from 15% to 39% of subjects in the SDD and SRP only groups respectively.

Conclusion: This study, demonstrated that periodontal therapy provides clinical benefits and that antibiotics provide a clinical benefit over SRP alone, particularly at initially deeper periodontal pockets.

Key words: antibiotics; attachment level; azithromycin; chronic periodontitis; metronidazole; periodontal therapy; pocket depth; scaling and root planing; subantimicrobial dose doxycycline

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There are numerous studies in the literature that have examined the effect of different periodontal therapies on clinical parameters of periodontal diseases, some of which are reviewed in Teles et al. 2006. In general, these studies have indicated that, on average, periodontal therapy provides an improvement in clinical parameters immediately after therapy and for extended periods after the completion of therapy. The adjunctive use of systemically administered antibiotics has been shown to provide a better clinical outcome, particularly in terms of pocket depth (PD) reduction and attachment-level (AL) gain, than scaling and root planing (SRP) not only in aggressive forms of periodontitis but also in chronic periodontitis subjects (Herrera et al. 2002, Haffajee et al. 2003).

The range of antibiotics used to treat periodontal infections is quite extensive. Antibiotics including the tetracyclines (Haffajee et al. 1995, Palmer et al. 1996, Ng & Bissada 1998, Feres et al. 1999, Ramberg et al. 2001, Akalin et al. 2004, Xajigeorgiou et al. 2006) metronidazole (MET; Loesche et al. 1991, 1992, Noyan et al. 1997, Soder et al. 1999, Xajigeorgiou et al. 2006) and the combination of MET and amoxicillin (Berglundh et al. 1998, Palmer et al. 1999, Lopez et al. 2000, Winkel et al. 2001, Rooney et al. 2002, Guerrero et al. 2005, Lopez et al. 2006, Xajigeorgiou et al. 2006) have been the most commonly used agents to treat different forms of periodontitis. However, other systemic antibiotics have been evaluated in smaller numbers of studies including Augmentin (Haffajee et al. 1995, Winkel et al. 1999, Purucker et al. 2001), azithromycin (AZ; Smith

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et al. 2002, Mascarenhas et al. 2005), clindamycin (Trieger et al. 1991, Sigusch et al. 2001), erythromycin (Helovuo & Paunio 1989), penicillin (Kunihira et al. 1985, Helovuo & Paunio 1989) and spiromycin (Al-joburi et al. 1989, Bain et al. 1994). Of these latter agents, AZ has a certain appeal, as it is taken once a day for 3 days and has limited side effects. The short dosage regime of this agent also improves patient compliance, which is often less than ideal when agents have to be taken for extended periods of time. The few studies that have examined the adjunctive use of AZ in the treatment of periodontitis demonstrated that this antibiotic provided additional clinical benefit over SRP alone. Smith et al. (2002) compared the clinical effects of SRP plus placebo or SRP combined with systemically administered AZ in 44 chronic periodontitis subjects. At 22 weeks post-therapy, subjects treated with AZ had a lower percentage of sites with PDs > 3 mm, fewer ''failing to improve'' teeth and fewer sites with bleeding on probing compared with the control group. In a study of 31 current smokers, treatment consisting of SRP and AZ provided significantly greater PD reduction and AL improvement at moderate (4–6 mm) and deep (>6 mm) pockets 6 months post-therapy than SRP alone (Mascarenhas et al. 2005).

For many decades, systemically administered tetracyclines have been used to treat different forms of periodontitis (Haffajee et al. 2003). Tetracycline has also been shown to be effective in improving clinical parameters and lowering bacterial counts when delivered locally into the periodontal pocket. One of the drawbacks of using systemically administered tetracycline is the emergence of resistant bacterial strains including species thought to be periodontal pathogens (Olsvik & Tenover 1993). Golub et al. (1983, 1990, 1994, 1995) determined that sub-antimicrobial doses of doxycycline (SDD) reduced gingival collagenolytic activity by inhibiting neutrophil matrix metalloproteinases. This property, in part, explained the demonstrated effectiveness of this agent in clinical studies of periodontitis subjects. Caton et al. (2000) randomly assigned 190 subjects to receive SRP and SDD given at the dosage of 20 mg bid for 9 months or SRP and placebo. The SDD group showed significantly greater reductions in PD and AL at sites with initial PD > 3 mm at the 3-, 6- and 9-month monitoring time points. In addition, there were no detrimental shifts in the periodontal microbiota or acquisition of antibiotic-resistant bacterial species or strains resistant to multiple antibiotics. A 12-month follow-up monitoring visit in the same subjects indicated that the improvements in clinical parameters observed at 9 months were maintained to 12 months with no ''rebound'' effect (Caton et al. 2001).

Other studies have also shown a greater clinical benefit of SDD and SRP when compared with SRP and placebo. Mohammad et al. (2005) examined the effect of a 9-month regimen of SDD at the dosage of 20 mg bid in 24 institutionalized subjects over 65 years of age. At 9 months, significantly greater reductions in bleeding on probing and in mean PD at initially moderate (4–5 mm) and deep (≥6 mm) sites were observed in the subjects receiving SRP plus SDD compared with the subjects receiving SRP and placebo. Similar greater improvements were seen in the SDD group for measures of clinical AL. Preshaw et al. (2005) performed a meta-analysis of two 9-month double-blind, placebo-controlled, randomized studies comparing the clinical effects of SRP and administration of SDD for 9 months and SRP and a placebo. A total of 392 subjects were enrolled in the two studies, 36.9% of whom were current smokers. The results indicated that smokers receiving the placebo exhibited the worst clinical outcomes, while non-smoking subjects who received SDD showed the best clinical outcomes. The authors concluded that the use of SDD improved clinical parameters in both non-smokers and smokers compared with subjects in each smoking category who received SRP and a placebo.

A series of studies carried out in Turkey used SDD at the dosage of 20 mg bid for 3 months. Gurkan et al. (2005) found, in a 6-month study of severe periodontitis subjects, that the 13 subjects in the SRP plus SDD group exhibited a significantly greater per cent of deep sites with resolution as determined by PD reduction ≥3 mm at 6 months compared with the 13 subjects receiving SRP and placebo. In a 12-month study of 30 subjects with chronic periodontitis by Emingil et al. (2004a, b), the subjects receiving SDD showed significantly greater improvement in clinical parameters compared with the placebo group. They also exhibited a greater reduction in the SDD group in the levels of MMP-8 in gingival crevicular fluid samples (Emingil et al. 2004a) and laminin 5 gamma 2 chain levels, which are involved in migration of epithelial cells during periodontal pocket formation (Emingil et al. 2004b).

The above studies suggest that systemically administered adjunctive agents provide better clinical outcomes than SRP without these agents. What is not clear is whether some of these agents are more effective than others in their long-term clinical efficacy. This manuscript presents the results of a randomized, single-blind study, in which subjects received SRP alone or in conjunction with systemically administered AZ, SDD (Periostat, Collagenex Pharmaceuticals, Newton, PA, USA) or MET. The hypothesis to be tested is that significant differences will be found in clinical parameters among treatment groups receiving SRP alone or in combination with systemically administered adjunctive agents with different mechanisms of action.

Material and Methods

Subject population

Ninety-eight subjects were recruited into the study. Subjects were >20 years of age, in good general health, had at least 20 natural teeth, including at least 1 molar tooth in each quadrant, and at least eight sites with PD > 4 mm. Subjects were excluded if they had any known allergies to the test antimicrobial agents, had received periodontal therapy in the previous 3 months, were pregnant or nursing or had systemic conditions that required antibiotic pre-medication or could influence the outcome of periodontal therapy. The 92 subjects included in the analyses had a mean age of 46 years (range 22–77 years), 36% were female, 63% were White, 26% were African American, 7% were Hispanic and 4% were Asian. The nature of the study was described thoroughly to all subjects and each provided signed informed consent before entry into the study.

Experimental design and treatment

In this single-blind study, subjects were randomized in blocks of four to one of four treatment groups using a random number table generated by Dr. Kent, the biostatistician. The assignment of subjects to the treatment groups was carried out by the clinic co-ordinator. The four treatment groups consisted of SRP alone or combined with systemically adminis-

tered AZ at the dosage of 500 mg once daily for 3 days or systemically administered MET at the dosage of 250 mg t.i.d. for 14 days or 20 mg doxycycline (SDD, Periostat) b.i.d. for 12 weeks. SRP was performed a quadrant at a time under local anaesthesia at approximately weekly intervals. The adjunctive agents were started at the first SRP visit. Subjects were clinically monitored at baseline (before therapy) and at 3, 6 and 12 months post-therapy. In addition, all subjects received maintenance SRP at the three post-therapy monitoring visits.

Clinical assessments

At each monitoring visit, overt gingivitis (0/1), bleeding on probing (0/1), suppuration (0/1), probing PD and probing AL were measured at six sites per tooth (mesiobuccal, buccal, distobuccal, distolingual, lingual and mesiolingual) at all teeth excluding third molars. The PD and AL measurements were repeated at each visit and the means of the pairs of measurements were used to determine change in these parameters. The PD and AL measurements were recorded to the nearest millimetre using a North Carolina periodontal probe (Hu-Friedy, Chicago, IL, USA). Measurements at all visits for a given subject were made by the same clinician. The clinician making the clinical measurements did not perform the therapy on that subject. A total of four clinicians performed the clinical monitoring and treatment for the subjects. They were randomized according to the different treatment groups so that each clinician examined or treated approximately the same number of subjects in each treatment group. The examiners participated in formal calibration studies conducted every 6 months involving probing the same half mouth of each of four subjects twice within 1 week. Intra-class correlations, within examiner, based on a single measurement at each site at each visit averaged 0.82 for PD and 0.78 for AL at the initial calibration study. Between-examiner pairwise correlations averaged 0.75 for PD and 0.62 for AL. The two more experienced examiners showed no differences $> \pm 1$ mm in PD measures between visits 1 and 2. The two less experienced examiners each showed differences $> \pm 1$ mm at 4/312 sites between visits. It should be noted that, while in this exercise each examiner made a single measure of each site at each visit, in the current investigation duplicate PD and AL measures were made by the same examiner at each site at each visit.

Data analysis

Of the 98 subjects recruited, 67 subjects had complete data for all four monitoring visits, while 16 and nine subjects had one and two missing visits, respectively. Intent-to-treat analyses were performed in the 23 subjects with missing data, whereby the last observation was carried forward, providing a total of 92 subjects with ''complete'' data that were included in the analyses. The remaining six subjects had baseline data only and their data were not included in the analyses.

The primary outcome variable in this study was mean AL change at 12 months at sites with baseline pocket depth (BPD) >6 mm. Secondary outcomes evaluated included change in mean PD at sites with BPD >6 mm as well as overall mean changes in PD and AL.

Clinical parameters including percentage of sites with gingival redness, bleeding on probing and suppuration as well as mean PD and AL were computed for each subject. The difference between baseline and each of the post-therapy monitoring visits was determined by subtracting the 3-, 6- and 12-month data from the baseline data. The subtracted values were then averaged across subjects in the four groups at each time point separately. The significance of differences over time in each group for each parameter was sought using the Friedman test, and the difference among groups at each time point was sought using ANCOVA adjusting for baseline values. These analyses were repeated for PD and AL change at sites with BPD values >6 mm. Overall differences among treatment groups at each time point were determined using ANCOVA adjusting for baseline values. If significant differences were found among the four groups, significance of differences between pairs of treatment groups was determined and the Bonferroni adjustment was used to adjust for multiple comparisons.

For some analyses, the data were subset into categories based on BPD categories of <4, 4–6 and >6 mm. Changes between baseline and 12 months were determined by averaging the clinical data at each time point within a subject for each BPD category and subtracting the baseline and 12 months data. The subtracted values were averaged across subjects for each PD category in the four treatment groups separately. Differences among treatment groups for the different BPD categories were sought using the Kruskal–Wallis test.

The percentage of sites exhibiting loss or ''gain'' of attachment >2 mm between baseline and each post-therapy time point was determined in each subject, averaged across subjects at each time point and in each treatment group separately.

Determination of sample size

It has been recognized that the major difference that occurs as the result of adjunctive systemic antibiotics takes place at sites with deeper BPDs (Haffajee et al. 2003). For this reason, the power calculations were based on sites with BPD >6 mm. It was felt that a difference of 1 mm between groups for AL change at these sites would be clinically significant. Further, it was determined that the standard deviation of AL change at sites with BPD >6 mm was 1.1 mm based on our earlier studies of subjects receiving SRP alone or combined with different adjunctive antibiotics. Based on these values, the study would require 20 subjects per group with an α of 0.05 and 80% power, a total of 80 subjects. Based on anticipated attrition of about 15%, 98 subjects were recruited.

Results

Subject retention

As described above, 67 of 98 subjects had clinical data for all four visits, 15 subjects had data for three visits, nine subjects had data for two visits and six subjects had baseline data only. All of the subjects started the treatment protocol. Of the subjects with only baseline data, two exited the study due to systemic illness; one subject was diagnosed with diabetes and the other with cancer of the liver. One subject left the country and three subjects were too busy with work and did not wish to continue. Four of these subjects had been assigned to the SDD group and one each to the MET and SRP groups. Of the subjects with one or two missing visits, 4, 8, 6 and 7 were assigned to the AZ, MET, SDD and SRP groups, respectively. Despite valiant efforts, nine of these subjects could not be contacted by phone or mail to reschedule missed appointments. The most common reason given by the remaining subjects for missing visits was that they were too busy.

Table 1. Mean (± SD) clinical and demographic features of subjects with data for the four monitoring visits in the four treatment groups at baseline

	Treatment group				Kruskal–Wallis (*p*)
	azithromycin	metronidazole	periostat	SRP	
N	25	24	20	23	
Age	47 ± 14	44 ± 11	47 ± 11	43 ± 15	0.51086
Number of missing teeth	2.40 ± 2.50	2.58 ± 2.12	2.35 ± 2.62	1.83 ± 2.44	0.50788
N males	15	18	10	16	0.33237
N current smokers	3	3	1	2	0.66845
Percentage of sites with					
Plaque accumulation	62.49 ± 23.49	65.98 ± 20.90	66.52 ± 25.61	64.26 ± 22.27	0.86874
Gingival redness	64.32 ± 29.14	73.90 ± 21.38	66.09 ± 24.57	63.95 ± 27.04	0.62136
Bleeding on probing	34.29 ± 26.04	39.37 ± 28.02	41.11 ± 24.78	32.62 ± 26.20	0.61425
Suppuration	0.94 ± 1.45	0.85 ± 2.05	2.52 ± 4.16	0.21 ± 0.68	0.00246
Mean pocket depth (mm)	3.11 ± 0.64	3.00 ± 0.45	3.33 ± 0.92	2.92 ± 0.37	0.52465
Mean attachment level (mm)	3.42 ± 0.88	3.21 ± 0.78	3.47 ± 0.93	3.03 ± 0.56	0.34108

SRP, scaling and root planing.

Patient compliance

Compliance with taking the medication was determined by pill counts. These were performed at 1 week (second SRP visit), 2 weeks (third SRP visit) and for the SDD group at 3 weeks (final SRP visit) and at 3 months. Twenty-four of 25 subjects completed the course of AZ. One subject reported an allergy to the medication and stopped after 1 day. Sixteen of 24 subjects assigned to the MET group took the medication for at least 12/14 days; four subjects took the medication for at least 10 days, while one subject took the medication for 1 week only. Three subjects indicated that they took the complete course of medication, but this was not confirmed by pill counts. Seventy five per cent of subjects receiving SDD took at least 171/180 tablets (95%); two subjects took 161 and 127 tablets, respectively. Two subjects indicated that they took ''most of the tablets'', but this was not confirmed by pill counts. One subject appeared to have taken more than two tablets on some days, thus finishing the course of medication before 3 months.

Teeth lost during the study

A total of seven teeth were extracted during the course of the study: two in one subject in the AZ group, one tooth in each of three subjects in the MET group and one tooth in two subjects in the SDD group. Five of the teeth were extracted during the treatment phase, and their data were not included in the analyses. The remaining two teeth, both in the MET group, were extracted between the 6- and 12- month monitoring visits and the 6-month data for these teeth were carried forward to the 12-month visit.

Adverse events

Two subjects in the AZ group reported adverse events: one had an allergic reaction to the study medication and the second had difficulty swallowing the tablets, although this latter subject completed the course of medication. One subject in the MET group reported dizziness and a second subject described diarrhoea associated with the use of the study medication. Two subjects in the SDD group reported adverse events including dizziness/tachycardia with the administration of local anaesthetic for SRP and a possible interaction between the study medication and OTC vitamins and calcium supplements. The subject stopped taking the latter for the duration of the SDD administration. No adverse events were reported in the SRP-only group. Four severe adverse events not considered related to the study included the diagnosis of diabetes, cancer of the liver, hospitalization for allergic pneumonia and hospitalization due to a ''bad fall''.

Table 1 presents the baseline clinical and demographic characteristics of the 92 subjects subset into the four treatment groups. There were no statistically significant differences among treatment groups for any of the parameters, with the exception of the percentage of sites with suppuration, which was the highest in the SDD group due to two subjects with 9% and 16% of suppurating sites, respectively.

Figure 1 presents the mean change in clinical parameters from baseline to each of the post-therapy monitoring visits in the four treatment groups. There were statistically significant improvements over time for most parameters, irrespective of treatment group, with the greatest improvements between baseline and 3 months post-therapy. In general, the subjects receiving the adjunctive agents exhibited greater clinical improvement than the subjects receiving SRP only. This was particularly noticeable for PD and AL. There was an increase in mean PD and an increase in the mean AL in the SDD group that occurred after 3 months, the time point at which the subjects ceased taking this medication.

The analyses were repeated for mean PD and mean AL change at sites with BPDs >6 mm (Fig. 2). All treatment groups showed statistically significant reductions in mean PD and AL measurements over time. Subjects receiving either systemically administered AZ or MET showed greater mean PD reduction post-therapy compared with subjects in the SDD- and SRP-only groups (Fig. 2, left panel). The differences among treatment groups were statistically significant at 6 and 12 months. After adjusting for multiple comparisons, MET was significantly different from SDD at $p<0.05$ at 12 months and the MET group was also significantly different from the SRP group at 6 months ($p<0.05$) and 12 months ($p<0.01$). A similar pattern was observed for change in mean AL post-therapy (Fig. 2, right panel). The greatest improvement in mean AL post-therapy at initially deeper sites was observed for the MET group, and the antibiotic groups showed greater improvement than the SDD and SRP groups. Differences among treatment

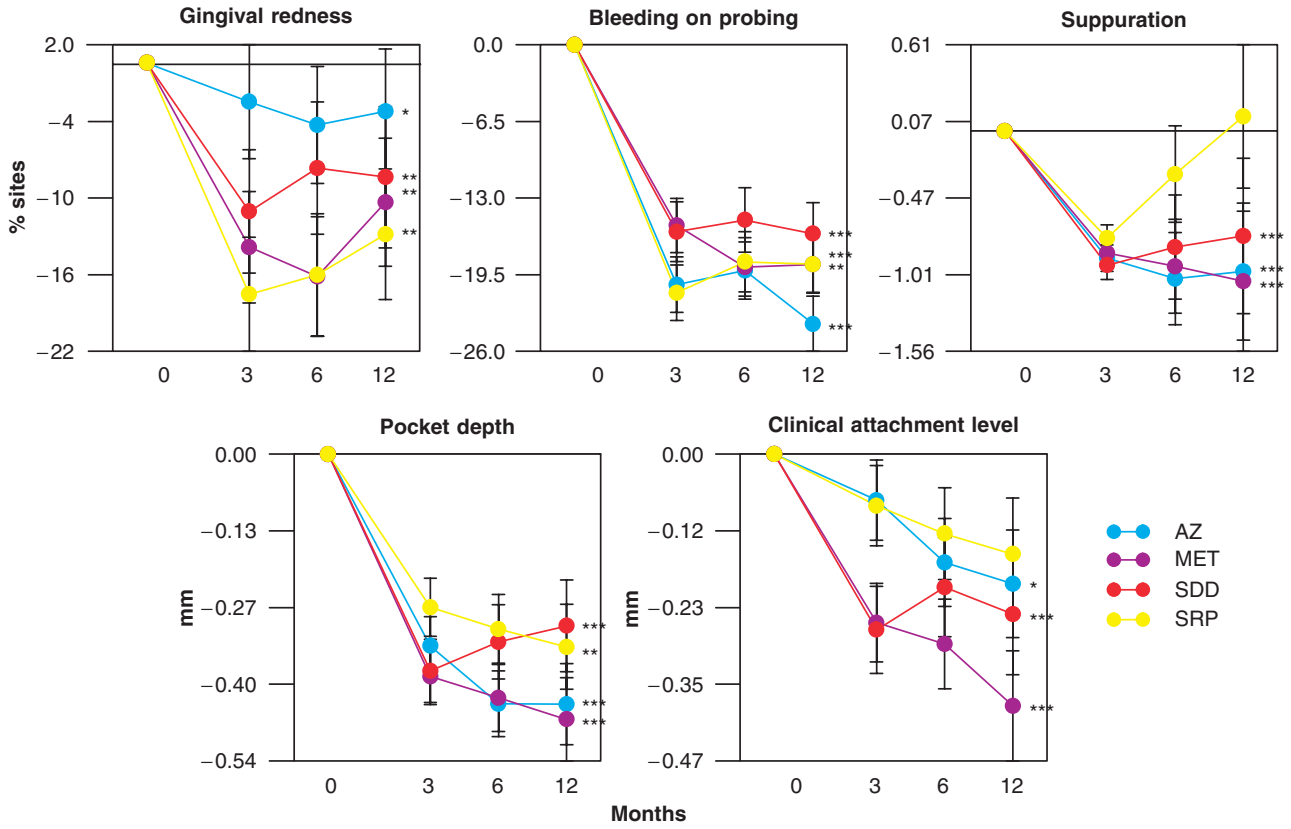

Fig. 1. Mean change (± SEM) from baseline to 3, 6 and 12 months post-therapy in the percentage of sites with gingival redness, bleeding on probing, suppuration as well as change in mean pocket depth and attachment level in each of the four treatment groups. The data for each parameter were measured at up to 168 sites in each subject, averaged within a subject and the 3-, 6- and 12-month data were subtracted from the baseline data. The subtracted values for each parameter were averaged across subjects in each treatment group at each time point separately. Significance of differences among treatment groups at each time point was determined ANCOVA and significance of differences over time determined using the Friedman test; $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$.

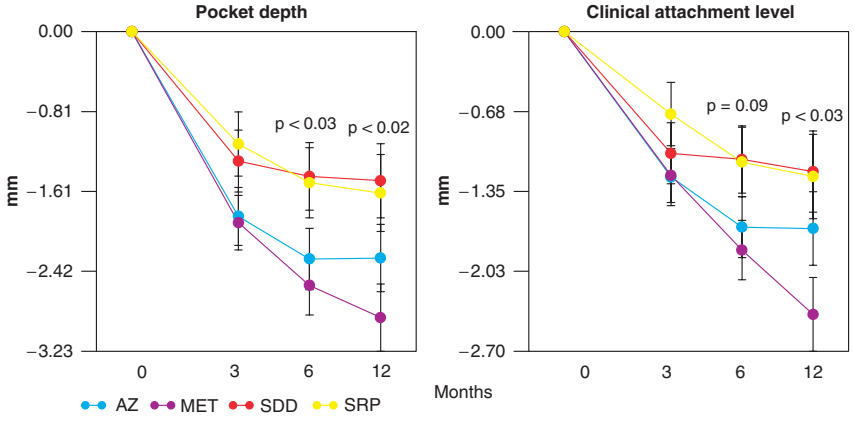

Fig. 2. Mean change (± SEM) from baseline to 3, 6 and 12 months post-therapy in mean pocket depth (PD) and attachment level in each of the four treatment groups at sites with baseline PD > 6 mm. Data were averaged as described for Fig. 1. Differences among treatment groups were determined using ANCOVA adjusting for baseline values.

groups were significant at 12 months and approached significance at 6 months. MET was significantly different from SRP ($p<0.05$) at 12 months after adjusting for multiple comparisons.

Figure 3 presents the mean baseline and 12-month data for PD and AL in each subject in the four treatment groups. In accord with the data from the previous figures, the majority of the subjects in each group showed an improvement in both PD and AL at 12 months. Only three of 25 subjects (12%) showed an increase in PD in the AZ group, while 15–22% of subjects in the other three treatment groups exhibited an increase in the mean PD at 12 months. More subjects showed loss of attachment at 12 months post-therapy. The best response was observed in the MET and SDD groups where four of 24 (16.6%) and three of 20 (15%) subjects showed mean attachment loss at the end of the study. A larger proportion of subjects in the AZ and SRP groups exhibited attachment loss. Indeed, 39% of subjects exhibited attachment loss at 12 months in the SRP group, more than twice the proportion of subjects seen in the SDD and MET groups.

Figure 4 presents the mean percentage of sites in each treatment group that exhibited gain or loss of attachment > 2 mm at each post-therapy monitoring visit. The increase in the mean percentage of sites showing attachment gain > 2 mm post-therapy was statistically significant in the AZ and MET groups. Subjects receiving AZ exhibited the largest percentage of sites showing attachment gain > 2 mm at 12 months

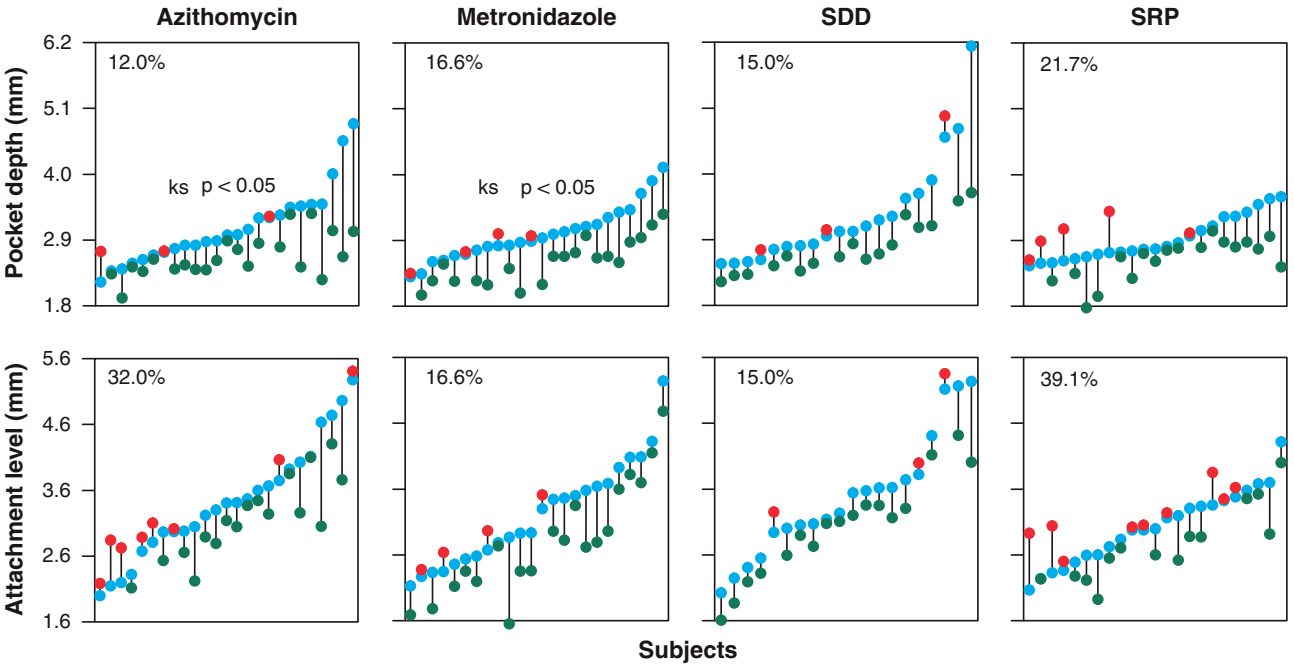

Fig. 3. Plots of mean pocket depth (PD) (top row) and mean clinical attachment level (AL) (bottom row) values at baseline and 12 months in subjects in the four treatment groups. The blue circles represent the mean baseline PD orAL values, measured at six sites per tooth for up to 28 teeth in each subject and have been ordered from the subject with the lowest mean baseline PD orAL value to the subject with the highest values pre-therapy. The red and green circles represent the 12-month mean data for each subject. The red circles represent subjects who exhibited a mean increase in the PD or AL measurements, and the green circles represent subjects who exhibited a mean decrease in PD or AL measurements at 12 months. The baseline and 12-month PD distributions were significantly different for both the azithromycin ($p < 0.05$) and the metronidazole ($p < 0.05$) treatment groups (Kolmogorov–Smirnov test). The percentage of subjects showing either an increase in the mean PD or an increase in mean AL at 12 months in each group is indicated in the top left corner of each graph.

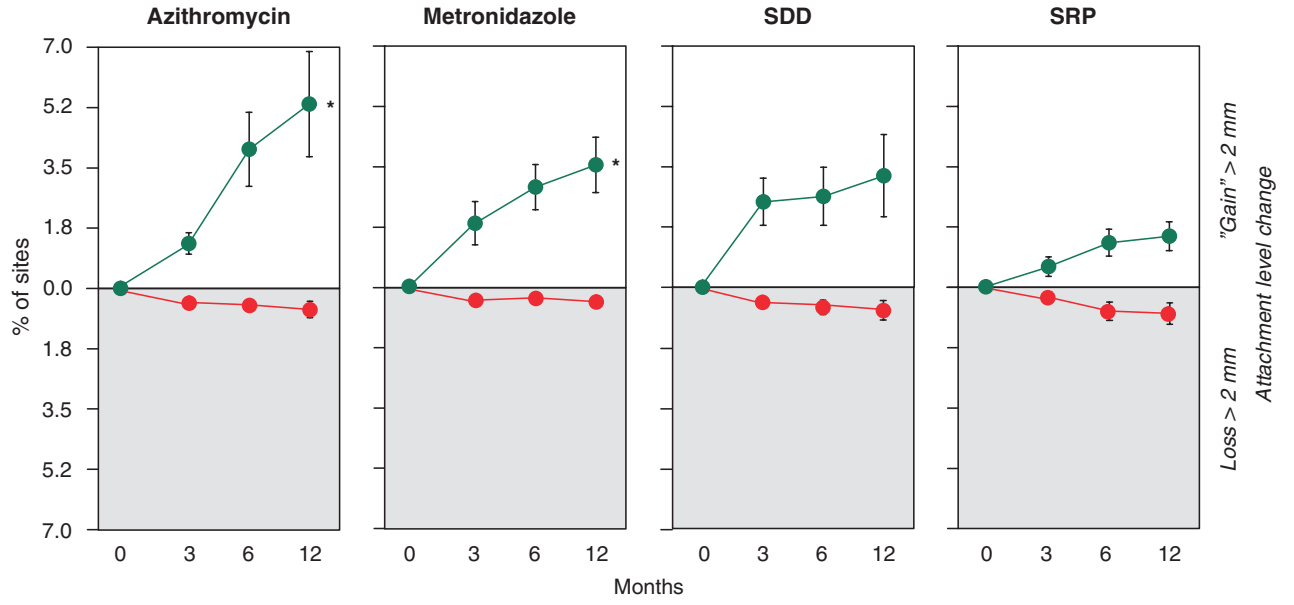

Fig. 4. Mean percentage of sites (± SEM) exhibiting either a ''gain'' in clinical attachment level (AL) >2 mm (green lines) or loss of attachment >2 mm (red lines) from baseline to 3, 6 and 12 months post-therapy in each of the four treatment groups. The percentage of sites exhibiting AL change >2 mm was computed in each subject and averaged across subjects in each treatment group at the 3-, 6- and 12-month time points. Significance of differences over time was determined using the Friedman test; $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

(5.3%), while the MET group showed the lowest percentage of sites showing loss of attachment >2 mm (0.41%). All groups exhibited a greater percentage of sites gaining attachment than losing attachment >2 mm. However, the difference between percentage of gaining and losing sites at 12 months was the smallest in the SRP group (1.48% *versus* 0.76%). The difference in the percentage of gaining sites among treatment groups at 3, 6 and 12 months

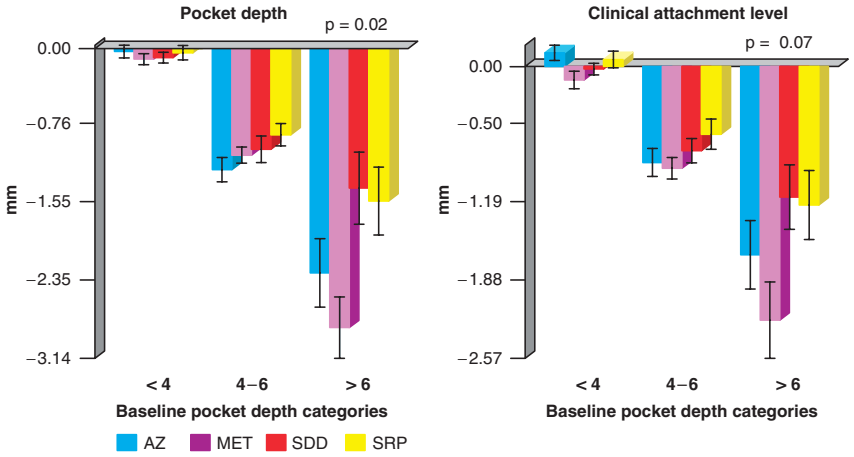

Fig. 5. Bar plots of the mean change (± SEM) in pocket depth (PD; (left panel) and attachment level (right panel) in the four treatment groups at sites with initial PDs of < 4, 4–6 and > 6 mm. The difference in mean PD and mean attachment between baseline and 12 months was computed for each baseline pocket depth (BPD) category within each subject and then averaged across subjects in each treatment group for each PD category separately. The significance of differences among treatment groups within each BPD category was determined using the Kruskal–Wallis test.

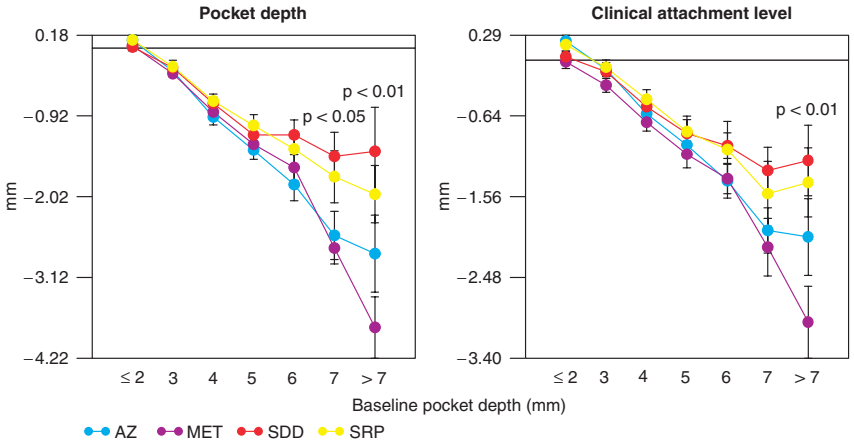

Fig. 6. Mean change (± SEM) in pocket depth (PD; left panel) and attachment level (AL; (right panel) in the four treatment groups from baseline to 12 months for baseline pocket depth (BPD) categories of ⩽2, 3, 4, 5, 6, 7 and > 7 mm. Change in PD and AL between baseline and 12 months was computed for each BPD category within a subject and then averaged across subjects in each treatment group and BPD category separately. Significance of differences among treatment groups for each BPD category was determined using the Kruskal–Wallis test.

approached statistical significance ($p = 0.06$ for each time point)

Sites were subset into the traditional BPD categories of < 4, 4–6 and > 6 mm. Figure 5 presents the mean change in PD and AL from baseline to 12 months in each PD category in each treatment group. On average, there was a reduction in PD in all treatment groups for each BPD category, with the least reduction at shallow sites and the greatest reduction at the deep sites. There was a significant difference in PD reduction among treatment groups in the > 6 mm BPD category with the systemic antibiotics, AZ and MET, providing the greatest reduction. A similar pattern was observed for AL gain, although the shallow sites in the AZ- and SRP-treated subjects, on average, lost attachment at 12 months. Once again the sites with initial PD > 6 showed the best response, with the AZ and MET groups exhibiting the greatest gain.

Figure 6 presents the mean PD and AL change at each BPD of ⩽2, 3, 4, 5, 6, 7, > 7 mm. There was little difference in mean PD or AL change among the four treatment groups at sites with BPD ⩽ 2, 3, 4 and 5 mm. However, there were significant differences among groups in PD reduction at sites with BPD 7 and > 7 mm and for AL change at sites with BPD > 7 mm. Subjects receiving systemically administered AZ or MET showed greater reductions in mean PD and AL at sites with initially deeper pockets compared with the subjects receiving SRP alone or SDD.

The reason for the differences in PD reduction and AL change at the sites with different BPDs or AL was explored further. The nature of the changes that were induced by each of the therapies at the sites with different BPD (Fig. 7) or AL values (Fig. 8) was evaluated. Figure 7 demonstrates that the post-therapy distributions of PDs at sites with BPD < 6 were quite similar among treatment groups. In contrast, at sites with BPD > 5 mm, the majority of sites in the group receiving SRP only showed modest reductions in PD, typically 1–3 mm, while the sites receiving adjunctive agents showed many sites that were reduced 3 mm or more. A similar pattern was observed for AL change at different baseline ALs (Fig. 8). In the SRP-only group, the magnitude of AL reduction was less, particularly at the sites with initially more attachment loss, compared with the other three treatment groups.

Discussion

The goal of the present investigation was to evaluate the clinical effects of four different periodontal therapies, SRP alone or in combination with systemically administered AZ, MET or SDD over a 12-month post-therapy monitoring period. The adjunctive treatments were chosen because of their reported efficacy in the literature and because of the quite different dosage regimes and mechanisms of action of the test agents. The results indicated that periodontal therapy, irrespective of treatment group, on average, significantly improved the clinical parameters examined. Further, treatment improved PD and clinical AL in the majority of subjects in each treatment group. However, there were differences among treatment groups regarding the magnitude of the clinical improvement. Although not statistically significant, overall, subjects receiving the adjunctive agents exhibited greater improvement in mean PD and those receiving MET exhibited greater improvement in mean AL at 6 and 12 months post-therapy. Further, subjects receiving adjunctive therapy exhibited a greater

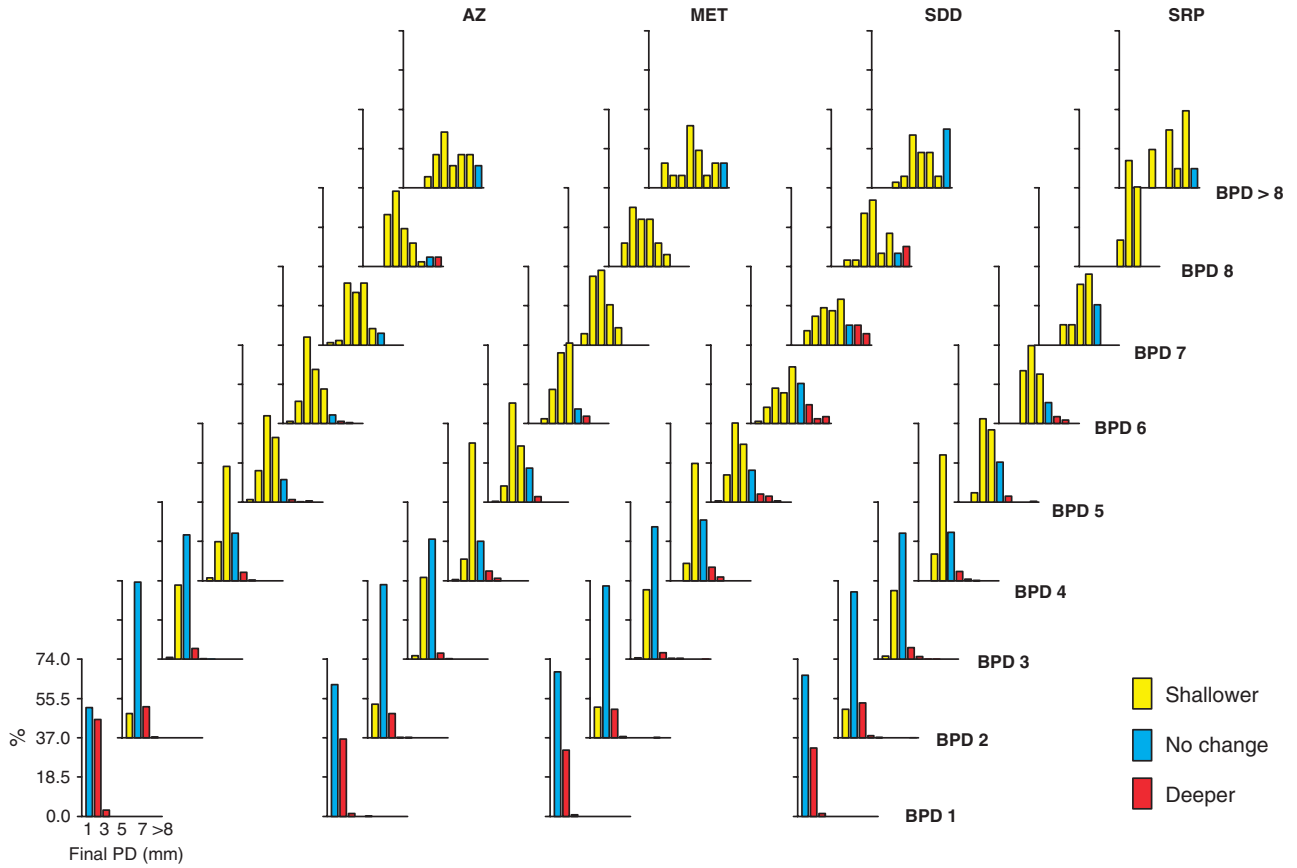

Fig. 7. Percentage of sites with different pocket depths (PDs) at 12 months post-therapy for sites with different baseline PDs in the four treatment groups. Each bar graph represents a different initial PD category ranging from 1 to >8 mm. The *x*-axis on each graph represents the final PD and the *y*-axis the percentage of sites. The colour of the bars indicates whether the PD at sites became shallower, deeper or did not change at 12 months.

reduction in the percentage of sites with suppuration at all post-therapy time points than subjects receiving SRP alone. Examination of AL change from pre-therapy to 12 months post-therapy in individual subjects indicated that a greater proportion of subjects receiving adjunctive therapy showed a ''gain'' of attachment than subjects receiving SRP only. The percentage of subjects receiving adjuncts who showed loss of attachment 12 months post-therapy ranged from 15% to 32%, while in the SRP-only group this number was 39%.

When examining changes on a site level, subjects receiving SRP only exhibited the lowest per cent of sites with AL gain >2 mm. In all groups, the proportion of sites showing AL gain >2 mm exceeded the percentage of sites with attachment loss >2 mm. However, the difference between losing and gaining sites at 12 months was the least in the SRP only group.

The results of the current investigation are in accord with studies in the literature that suggest that systemically administered antibiotics and a SDD can lead to better clinical outcomes compared with SRP alone (Caton et al. 2000, 2001, Haffajee et al. 2003). However, in the current investigation, the overall improvements in clinical parameters beyond that achieved by SRP alone were quite modest. The major reason for this finding was that, although subjects entering the study had at least eight sites with PD >4 mm, the mean BPD and AL values were quite low suggesting that most of the subjects had mild to moderate levels of periodontitis. Both the systematic reviews evaluating the effects of systemically administered antibiotics suggested that antibiotics provided greater benefit in subjects with more periodontal disease and at deeper periodontal sites. The data from the study by Caton et al. (2000, 2001) also suggested that SDD provides a greater benefit at sites with BPD>3 mm. Indeed, the results of the current investigation indicated that when sites were subset into different BPD categories, a better clinical response was seen at the initially deeper PD sites in terms of PD reduction and AL ''gain'' in subjects receiving adjunctive antibiotics. In subjects receiving either MET or AZ, sites with initial PDs of 6 mm or more exhibited significantly greater PD reduction and greater AL ''gain'' when compared with similar sites in subjects receiving SDD or SRP only. In particular, the mean difference between the MET and both the SRP and SDD groups for PD reduction and between MET and SRP for AL change, at initially deeper sites, were statistically significant. These differences should also be considered clinically significant, as the differences between groups exceeded, on average, more than 1 mm. Thus, the studies in the literature and the results of the current investigation indicate that the use of systemically administered antibiotics or SDD should be limited to subjects who would receive the maximum benefit from these agents, i.e. subjects with more severe periodontal destruction.

An unexpected finding from the present investigation was the increase in

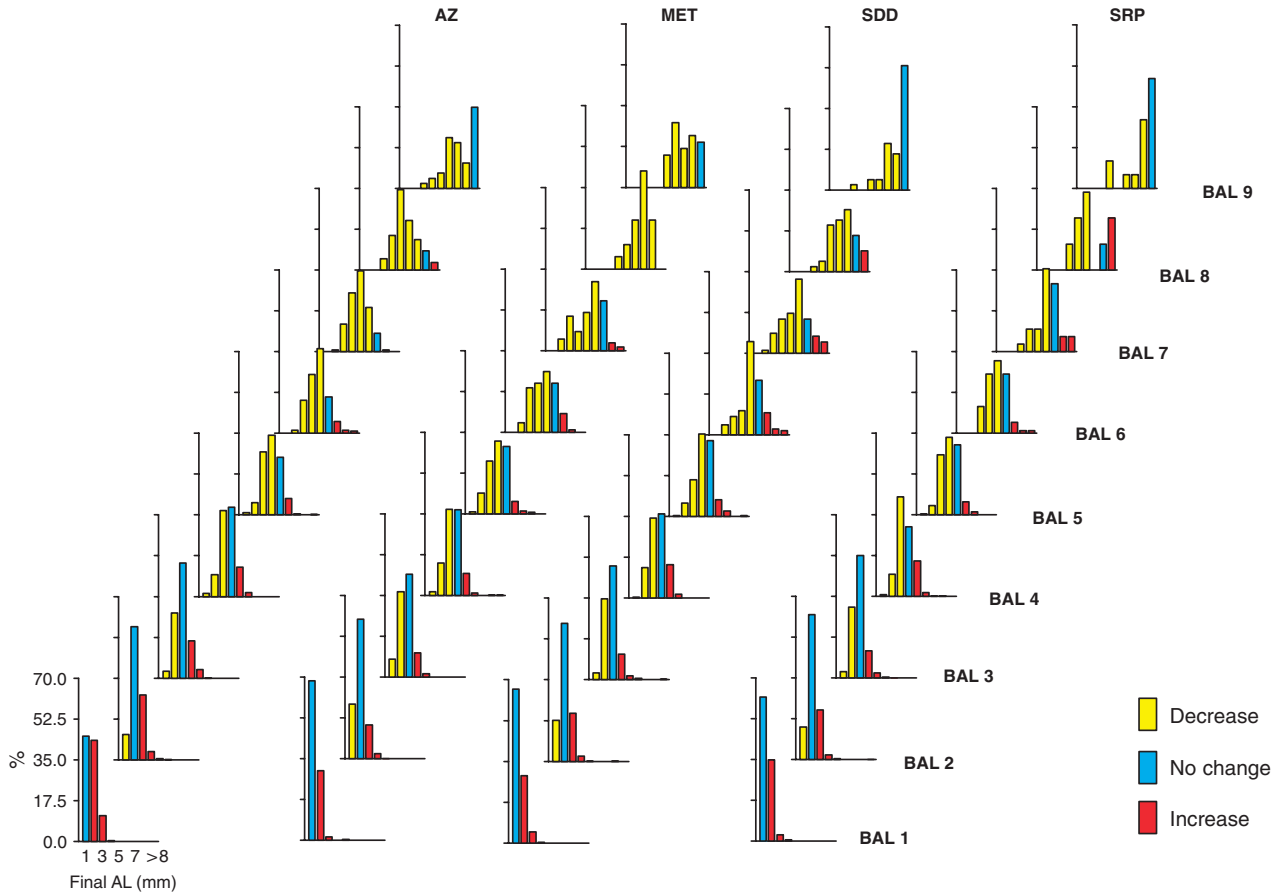

Fig. 8. Percentage of sites with different clinical attachment levels (ALs) at 12 months post-therapy for sites with different baseline ALs in the four treatment groups. Each bar graph represents a different initial AL category ranging from 1 to >8 mm. The *x*-axis on each graph represents the final AL and the *y*-axis the percentage of sites. The colour of the bars indicates whether the AL at sites decreased, increased or did not change at 12 months.

mean PD, mean AL and percentage of sites with gingival redness, after the 3-month post-therapy monitoring visit in subjects in the SDD group. The timing of this worsening occurred in the time period immediately after the subjects stopped taking the medication. Examination of the individual subject data indicated that 7/20 and 8/20 subjects showed a worsening for PD and AL, respectively, at the 6-month monitoring visit compared with the 3-month visit. Further, 12/20 subjects showed an increase in the percentage of sites with gingival redness between the 3- and 6-month monitoring visits. In the current study, SDD was given for 3 months and not the 9-month dosage used in the initial investigations of this agent (Caton et al. 2000, 2001). In the studies by Caton et al. (2000, 2001), SDD was prescribed for 9 months and at 12 months, i.e. 3 months after the cessation of the SDD, no relapse in clinical parameters was observed. However, the data emphasized in these studies were sites with BPD > 3 mm. When only sites with initially deep pockets were examined in the current investigation, the increase in clinical parameters at 6 months was not seen.

The 9-month regimen of SDD may be more effective in maintaining the initial benefits obtained from using the agent than the 3-month regimen. However, the 3-month SDD regimen has been used by some investigators and provided a significant decrease in mean PD and ALs post-therapy, although the results were limited to sites with initially deeper pockets (Emingil et al. 2004a, b, Gurkan et al. 2005). In a 6-month study, Gurkan et al. (2005) found a significant reduction in mean PD and AL at sites with BPD or AL of 4–6 and >6 mm in the placebo and SDD groups at both 3 and 6 months. There was no significant difference between groups and no increase in these parameters at the 6-month monitoring visit. Emingil et al. (2004a, b), in a 12-month study, also demonstrated a significant reduction in mean PD and mean AL in both the placebo and SDD groups post-therapy at the study sites that had initial mean PDs of about 7 mm. No increase in mean PD was observed at the 6-, 9- and 12-month monitoring visits. A significant decrease in mean AL was observed at 3 months at the study sites in both treatment groups with an increase at 6 months and decreases at 9 and 12 months. The pattern of AL change in that study was very similar to the pattern of change observed for AL for the overall data in the current investigation.

Overall, the different therapies provided an improvement in clinical parameters. However, no treatment was ideal for all subjects in any treatment group. An obvious question is why did some subjects show excellent PD reduction and AL gain, while other subjects in the same treatment group showed a poor clinical response. One reason, at least in the groups receiving an adjunctive agent, could have been the non-compliance of the subjects in taking the medications. Based on pill counts and questioning of

the subjects, it appeared that the majority of the subjects in each treatment group took the majority of the medications prescribed. However, it was clear that subjects assigned to the AZ group were the most compliant. This finding was presumably due to the short course of administration and the few reported side effects of this agent, both important considerations when utilizing systemically delivered agents. Another reason for the difference among subjects could have been the initial level of disease. An expectation would be that subjects with more disease before therapy would show greater PD reduction and AL gain than subjects with less initial periodontal destruction, particularly in the treatment groups receiving an adjunctive agent. However, with perhaps the exception of the MET group, subjects with a wide range of initial mean ALs showed subsequent loss of attachment post-therapy (Fig. 3). Indeed, in the AZ group, the subjects with the lowest and highest mean AL measurements at baseline showed attachment loss 12 months post-therapy. Other factors impacting treatment response could include systemic factors and habits such as smoking. As far as we could ascertain, the subjects were systemically healthy and systemic illness was an exclusion criterion for the study. Only eight of the 92 subjects in the population were current smokers and of the 24 subjects who showed attachment loss 12 months post-therapy, only two were current smokers. Both were in the SRP-only group and showed a very modest full-mouth mean loss of attachment of 0.08 and 0.14 mm, respectively. As periodontal diseases are infections, it is likely that the sub-gingival microbial profile of the subject would play a role in the treatment outcome (Haffajee et al. 2006). The effect of therapy on the subgingival microbiota as well as the impact of a subject's baseline microbial profile on treatment outcomes in this population will be examined in a second manuscript.

There were limitations to the current study. It was a randomized, single-blind study, but it was not placebo controlled. The issue of providing placebo tablets was contemplated, but with the different dosing regimes and the different types of tablets/capsules involved, creating a standard placebo presented some difficulty. It was therefore decided not to use placebos. However, the examining clinicians were unaware of the treatment group to which subjects were assigned. Randomization led to similar number of subjects in the four treatment groups initially. However, there were a larger number of subjects with only baseline data in the SDD group, resulting in fewer subjects in this group being included in the final analyses compared with the other three treatment groups.

Despite its limitations, the study demonstrated that periodontal therapy in general does provide clinical benefits and that adjunctive systemically administered antibiotics do provide a clinical benefit over SRP alone, particularly at initially deeper periodontal pockets. However, many of the subjects showed a good clinical response after SRP only. These findings underscore the need to use adjunctive agents judiciously, reserving their use for subjects with moderate to advanced periodontal disease in whom such agents would provide the maximum benefit. The study also showed that not all subjects receiving a specific treatment responded clinically in the same fashion, indicating the importance of determining factors that impact treatment outcome so that the the most appropriate therapy can be provided to individual subjects.

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Clinical Relevance

Scientific rationale for the study: Little is known regarding the comparative clinical efficacy of different systemically administered agents with different modes of action and length of administration in the treatment of periodontal diseases.

Principal findings: Overall, all subjects showed improvement in clinical parameters as a result of therapy; however, subjects receiving systemically administered AZ or MET demonstrated significantly greater PD reduction at sites with initially deeper pockets. Not all subjects responded equally well to a given therapy, suggesting that local and systemic factors could impact therapeutic outcomes.

Practical implications: Subjects with moderate to advanced periodontitis would demonstrate added clinical benefit if systemically administered antibiotics were included as part of the treatment protocol.