Treatment of Periodontitis by Local Administration of Minocycline Microspheres: A Controlled Trial

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Background: Periodontitis is an inflammatory condition of tooth-supporting tissues that is usually treated by mechanical removal of plaque and microorganisms that adhere to teeth. This treatment, known as scaling and root planing, is not optimally effective. Adjunctive therapy with locally delivered antimicrobials has resulted in improved clinical outcomes such as probing depth reduction. This article reports on the efficacy and safety of locally administered microencapsulated minocycline.

Methods: Seven hundred forty-eight (748) patients with moderate to advanced periodontitis were enrolled in a multi-center trial and randomized to 1 of 3 treatment arms: 1) scaling and root planing (SRP) alone; 2) SRP plus vehicle; or 3) SRP plus minocycline microspheres. The primary outcome measure was probing depth reduction at 9 months. Clinical assessments were performed at baseline and 1, 3, 6, and 9 months.

Results: Minocycline microspheres plus scaling and root planing provided substantially more probing depth reduction than either SRP alone or SRP plus vehicle. The difference reached statistical significance after the first month and was maintained throughout the trial. The improved outcome was observed to be independent of patients' smoking status, age, gender, or baseline disease level. There was no difference in the incidence of adverse effects among treatment groups.

Conclusions: Scaling and root planing plus minocycline microspheres is more effective than scaling and root planing alone in reducing probing depths in periodontitis patients. *J Periodontol 2001;72:1535-1544.*

KEY WORDS

Minocycline/therapeutic use; periodontitis/drug therapy; multi-center studies; planing; scaling.

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Periodontitis is an inflammatory disease of the supporting tissues of the teeth caused by the presence of subgingival Gram-negative bacteria, including *Porphyromonas gingivalis, Bacteroides forsythus,* and *Treponema denticola*. These pathogens coexist with hundreds of other species in a highly organized plaque biofilm. The pathogenesis attributed to these bacteria may involve: 1) direct release of proteolytic enzymes; 2) production of toxins such as lipopolysaccharide that trigger the expression of degradable enzymes; and 3) stimulation of an immune response resulting in the release of cytokines from lymphocytes and macrophages that activate degradative pathways.[1] In susceptible individuals, the ongoing inflammatory process without intervention can cause loss of supporting tissue and, ultimately, teeth. In addition to causing local effects, plaque biofilms can serve as a reservoir for the entrance of Gram-negative bacteria, lipopolysaccharide, and other soluble

bacterial components into the general circulation.[2] As with chronic infections elsewhere in the body,[3-7] associations have been identified between periodontitis and various systemic complications including atherosclerosis/coronary heart disease,[8-12] cerebral vascular ischemia,[13,14] low birth weight,[15,16] and poor glycemic control in diabetes.[17-20] The United States Surgeon General's report on oral health[21] recently made note of these relationships.

Periodontitis affects approximately 15% of Americans over the age of 18[22] and at least that proportion in most other countries.[23-25] The Surgeon General reported the incidence in older Americans (65 to 74) to be 23%.[21] Periodontitis is usually treated with scaling and root planing (SRP), which removes subgingival plaque mechanically. This procedure, even when meticulously performed, improves periodontal status, but is rarely effective in the complete removal of plaque or periodontal pathogens.[26,27] Given that hundreds of millions of people worldwide have periodontitis, an approach that augments the effectiveness of SRP would have a major impact on managing this disease. Systemic antiobiotics have been prescribed for this purpose, but their widespread use is discouraged because of the concern over the development of resistant organisms. Locally delivered antimicrobials have also been used, but not extensively. This is due in part to difficulties in the delivery of some formulations.

A method of microencapsulating minocycline hydrochloride in a bioabsorbable polymer (polyglycolide-co-dl lactide) has been developed. The resulting microspheres are administered in powder form into diseased periodontal sites. Immediately upon contact with moisture, the polymer begins to hydrolyze and release minocycline. The administration results in a sustained local release of the antibiotic whereby concentrations of 340 µg per ml have been measured in human crevicular fluid after 14 days (unpublished data). These concentrations far exceed the minimum inhibitory concentrations (MICs) for periodontal pathogens. This article reports results from a controlled Phase 3 clinical trial that examined the efficacy and safety of minocycline microspheres when used as an adjunct to scaling and root planing.

MATERIALS AND METHODS

Patient Selection

Eighteen centers participated in this trial. A total of 748 patients with moderate (ADA Type III) to advanced (ADA Type IV) periodontitis were enrolled. To qualify for the study, participants were 30 or more years of age, in good general health, and presented with at least 4 teeth with probing depths of 6 to 9 mm and bleeding on probing. Exclusion criteria included: 1) pregnancy; 2) periodontal therapy within 6 months prior to enrollment; 3) antibiotic therapy within 3 months prior to enrollment; 4) allergy to tetracyclines; or 5) chronic therapy within 1 month prior to enrollment with medications that could affect periodontal status or healing. Patients received a verbal description of the study and provided written informed consent. Human subject review committees of the respective centers approved the trial.

Figure 1.
Minocycline microspheres: unit-dose cartridge and handle.

Study Design

The trial was 9 months in duration and had 3 parallel arms: 1) control (SRP alone); 2) SRP plus vehicle; and 3) SRP plus minocycline microspheres.¶¶¶ At baseline, all patients were treated with full-mouth SRP. This treatment was unrestricted with respect to time or use of local anesthesia. Treatment group assignment was based on a predetermined randomization plan that included stratification for smoking status and study center.

Minocycline microspheres or vehicle was administered to all sites with probing depths ≥5 mm. Sites in the minocycline microspheres plus SRP group were given a unit dose of 4 mg of drug containing 1 mg of minocycline and 3 mg of polymer, while sites in the vehicle group received 3 mg of polymer only. The microspheres were dispensed subgingivally to the base of the periodontal pocket by means of a disposable plastic cartridge affixed to a stainless-steel handle (Fig. 1). Figure 2 shows an electron photomicrograph of the minocycline microspheres, and a photomicrograph of the microspheres in cross-section. At 3 and 6 months, patients randomized to either minocycline microsphere adjunctive therapy or vehicle received an additional application of the assigned treatment. Data were collected for all efficacy and safety assessments at baseline and at 1, 3, 6, and 9 months. Assessments were performed by the same examiner at each center, who was blinded with respect to the patient's treatment.

¶¶¶ OraPharma, Inc., Warminster, PA.

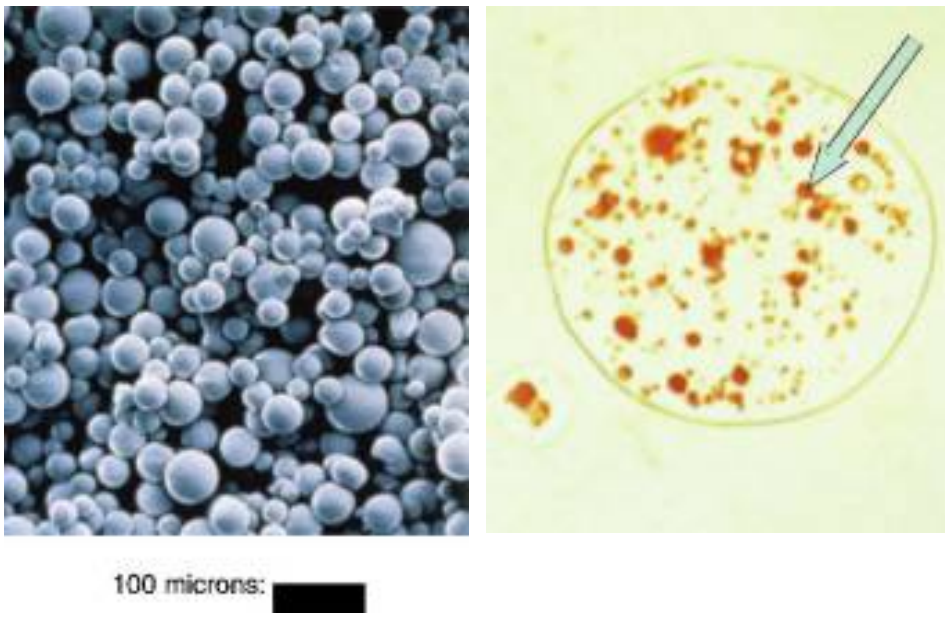

Figure 2.
Left: Electron photomicrograph of minocycline microspheres. Right: Cross-sectional photomicrograph of microspheres showing minocycline HCl particles (arrow).

Clinical Measurements and Assessments

Probing depth. Probing depth (PD) was measured from the gingival margin to the base of the periodontal pocket using a UNC #15 periodontal probe with 1 mm markings. Measurements were taken at 6 sites per tooth and recorded in whole millimeters using a rounding down convention if readings fell between markings. All sites with probing depths measuring ≥4 mm were measured a second time, and the average of the 2 readings was used as the site-specific probing depth endpoint. Prior to study initiation, clinicians were trained and calibrated to measure probing depths. Interexaminer reliability was high, with intraclass coefficients and percent agreement (within 1 mm) values ranging from 0.81 to 0.98 and 87.5% to 98.5%, respectively.

Clinical attachment level (CAL). Clinical attachment level was measured from the cemento-enamel junction or another fixed reference such as a crown margin to the base of the periodontal pocket. This measure was included as a safety assessment because it is theoretically possible to achieve a favorable probing depth outcome while actually compromising the clinical attachment level.

Bleeding on probing (BOP). Following the probing depth measurement, bleeding was recorded at 6 sites per tooth as "0" if no bleeding occurred within 10 seconds, and "1" if there was bleeding within 10 seconds.

Oral cavity examination. Oral and perioral hard and soft tissues were also examined. Findings were recorded as normal or abnormal at screening, and as changed or unchanged at subsequent visits.

Vital signs. Vital signs recorded included blood pressure, temperature, heart rate, and respiration rate.

Adverse events. Adverse events, both volunteered and solicited, were documented with respect to onset, duration, treatment, relation to study medication, and outcome.

Data Analysis and Statistical Methods

Primary, secondary, and subgroup efficacy analyses were all predetermined, and used the patient as the experimental unit. All sites with PD ≥5 mm at baseline were included in the analyses. The primary outcome measure was the average change in PD from baseline to 9 months. Site-specific PD changes from baseline were averaged to provide a mean change from baseline for each patient. To test for differences among the groups, patients' mean changes were analyzed using an analysis of covariance model adjusted for study site, baseline response, age, disease severity, and smoking status. Results presented in this paper are for adjusted means. All treatment comparisons were made using 2-sided tests with a 95% confidence interval. Analysis of covariance (ANCOVA) models were fitted using PROC GLM.### The F-tests based on Type III sums of squares**** was used for all hypothesis testing.

Clinical response was a secondary outcome measure, and was defined as the percentage of treatment sites that showed a prespecified level of improvement in PD at 9 months relative to baseline. The clinical response levels selected for this study were 1 and 2 mm since they are commonly used by clinicians to monitor disease progression. For each level, the patient-specific endpoint was computed as the percentage of treatment sites responding.

Bleeding on probing was also selected as a secondary outcome measure since it is a common approach for assessing the inflammatory state of periodontal sites. The percentage of treatment sites that demonstrated bleeding on probing was determined for each patient, and the average change from baseline was calculated. Clinical attachment level was assessed by calculating patient mean changes from baseline. Odds ratios with 95% confidence intervals were calculated *post hoc* to compare SRP plus minocycline

SAS Institute, Inc., Cary, NC.
**** Version 6.12, SAS Institute, Inc.

microspheres and SRP alone groups for reducing mean PD to <5 mm. An additional *post hoc* analysis compared the 2 groups for PD changes in patients' molar teeth. The ANCOVA model previously described was used for this analysis. Demographic and safety results (except CAL) were evaluated using descriptive statistics. In this study, the intent-to-treat sample population included all randomized patients. Last Observation Carried Forward and Worst Observation Carried Forward imputations were applied to missing data for each of the principal variables.

The relative responses to the study treatment were consistent across the investigators for each efficacy variable, and there was no evidence of a treatment-by-center qualitative interaction.

RESULTS

Efficacy

Of the 748 patients enrolled in the study at the baseline visit, 250 were randomized to SRP alone, 249 to SRP plus vehicle, and 249 to SRP plus minocycline microspheres. A total of 229 (91.6%), 230 (92.4%), and 237 (95.2%) patients in the control, vehicle, and minocycline microsphere groups, respectively, completed the study. All randomized patients were analyzed for efficacy and safety.

Demographic and baseline characteristics (Table 1) were similar across the 3 treatment groups. Most patients were male (54.8%) and Caucasian (75.8%). Mean ages were 47.7, 47.2, and 49.1 years (range, 29 to 79 years) for the control, vehicle, and minocycline microsphere patients, respectively. Severity of periodontal disease was moderate in 61.2% and advanced in 38.8% of patients, with similar distribution across treatment groups. Smokers were equally distributed across treatment groups and comprised 36.2% of total enrollment. Baseline mean PD, CAL, and number of treated sites were also similar for each treatment group. In this study, we evaluated an average of 30.7 sites per patient, resulting in a total of 22,987 sites. After 1 month of treatment, patients receiving SRP plus minocycline microspheres had a significantly greater mean reduction in PD when compared with vehicle and control groups (P<0.001). As shown in Figure 3, superiority for the SRP plus minocycline microsphere group was maintained throughout the study. At 9 months, the reduction in mean PD was 1.08 (SE 0.04) mm for the control group, 1.00 (SE 0.04) mm for SRP plus vehicle, and 1.32 (SE 0.04) mm for the SRP plus minocycline microsphere group. The difference between SRP plus minocycline microspheres and the other groups after 9 months was statistically significant at P<0.001.

Table 1.

Demographic and Baseline Characteristics of All Randomized Patients

Characteristic	Descriptive Statistic	SRP (250)	Vehicle (249)	Minocycline Microspheres (249)
Gender				
Male	n (%)	132 (52.8)	144 (57.8)	134 (53.8)
Female	n (%)	118 (47.2)	105 (42.2)	115 (46.2)
Age (years)	n	250	249	249
≥50	n (%)	167 (66.8)	168 (67.5)	142 (57.0)
<50	n (%)	83 (33.2)	81 (32.5)	107 (43.0)
	Mean	47.7	47.2	49.1
	SD	9.7	10	10.2
	Median	47	46	48
	Range	(29-76)	(29-79)	(29-76)
Race and ethnicity				
Caucasian	n (%)	191 (76.4)	181 (72.7)	195 (78.3)
Black	n (%)	29 (11.6)	39 (15.7)	30 (12)
Asian	n (%)	11 (4.4)	9 (3.6)	9 (3.6)
Hispanic	n (%)	14 (5.6)	17 (6.8)	12 (4.8)
Other	n (%)	5 (2.0)	3 (1.2)	3 (1.2)
Disease severity				
Moderate	n (%)	156 (62.4)	156 (62.7)	146 (58.6)
Advanced	n (%)	94 (37.6)	93 (37.3)	103 (41.4)
Smoking status				
Yes*	n (%)	91 (36.4)	90 (36.1)	90 (36.1)
No	n (%)	159 (63.6)	159 (63.9)	159 (63.9)
Number of baseline treatment sites	n	250	249	249
	Mean	29.5	31.7	31
	SD	17.9	19.9	20.3
	Median	24	27	26
	Range	(5-114)	(4-137)	(5-108)
Average probing depth	n	250	249	249
	Mean	5.8	5.9	5.8
	SD	0.4	0.5	0.4
	Median	5.7	5.7	5.7
	Range	(5.2-8.4)	(5-7.8)	(5.2-7.5)
Average clinical attachment level	n	250	249	249
	Mean (SD)	5.43 (1.44)	5.38 (1.43)	5.39 (1.38)
	Median	5.6	5.5	5.5
	Range	(2.11-10.19)	(2.13-9.50)	(2.21-9.05)

* Used tobacco product within the last 6 months.

The mean percentage of sites per patient with PD reductions of ≥1 mm was 60.07, 57.33, and 67.94 for control, SRP plus vehicle, and SRP plus minocycline microsphere groups, respectively, as presented in Table 2. Differences between SRP plus minocycline microspheres and the other 2 groups were statistically significant at $P<0.001$. The mean percentage of sites with PD reductions of ≥2 mm for the 3 respective groups was 32.87, 28.98, and 40.52. Differences between the SRP plus minocycline microsphere group and the other 2 groups were also significant at $P<0.001$.

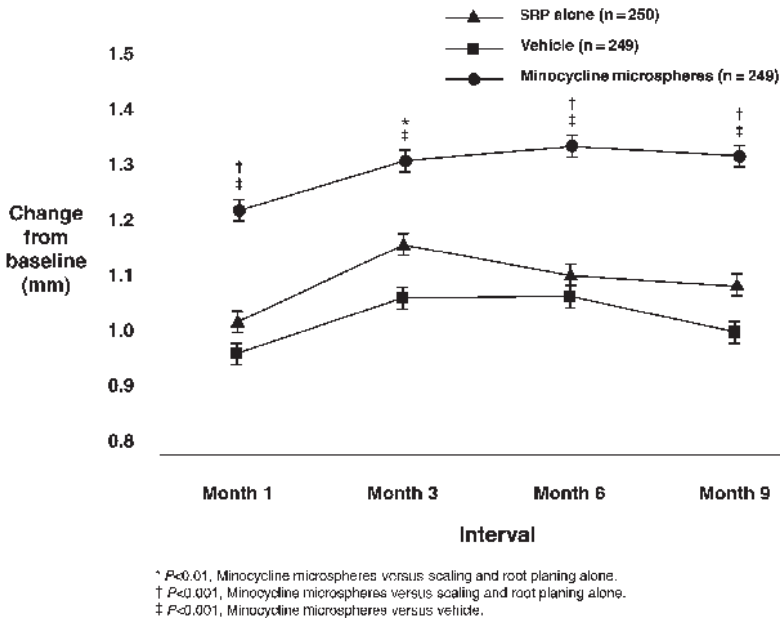

Figure 3.
Average probing depth reduction (adjusted means) from baseline.

Overall reduction in BOP was similar among treatment groups (data not shown). However, post hoc analysis of a subgroup of patients with more advanced disease (baseline mean PD ≥6 mm) showed significant differences among groups. In these patients, the percentage reduction in bleeding sites for the control group was 19.80 (SE 2.44), compared with 18.11% (SE 2.17) for SRP plus vehicle and 26.04% (SE 2.17) for SRP plus minocycline microspheres. These differences were significant at $P = 0.005$ and $P = 0.047$, respectively.

Results for subgroup analyses are presented only for SRP alone and SRP plus minocycline microsphere groups since the results for SRP plus vehicle and SRP alone were similar. Figure 4 shows mean PD reductions at 9 months for patient subgroups based on baseline PD. For patients with mean baseline PD ≥6 mm, mean reduction was 1.05 (SE 0.10) mm for the SRP group and 1.46 (SE 0.09) mm for SRP plus minocycline microspheres. The difference between groups (0.41 mm) was significant at $P \leq 0.01$. For patients with baseline PD ≥7 mm, mean reduction was 0.98 (SE 0.29) mm for SRP compared with 1.99 (SE 0.31) mm for SRP plus minocycline microspheres. The difference between treatment groups was the greatest in these patients (1.01 mm), and despite the small sample size, a P value of 0.06 suggests that this sample is representative of the population. Figure 5 shows the percentage difference in PD reduction between these patient groups. For patients with mean PD ≥5 mm, ≥6 mm, and ≥7 mm, the percentage differences in favor of SRP plus minocycline

Table 2.

Summary of Clinical Response Level Using Baseline Treatment Sites

Patient's Percent of Baseline Treatment Sites With	Descriptive Statistic	SRP (250)	Vehicle (249)	Minocycline Microspheres (249)	Treatment Comparison (*P* Values) Minocycline Microspheres Versus SRP	Vehicle
PD reduction ≥1 mm at month 9	N	250	249	249	<0.001*	<0.001*
	LS mean (SE)	60.07 (1.40)	57.33 (1.40)	67.94 (1.40)		
	Mean (SD)	64.18 (28.30)	61.32 (27.41)	71.90 (25.90)		
	Median	67.96	62.16	76.92		
	Range	(0,00, 100.00)	(0.00, 100.00)	(0.00, 100.00)		
PD reduction ≥2 mm at month 9	N	250	249	249	<0.001*	<0.001*
	LS mean (SE)	32.87 (1.39)	28.98 (1.39)	40.52 (1.39)		
	Mean (SD)	36.62 (28.09)	32.75 (27.35)	44.63 (28.73)		
	Median	31.58	25.00	42.11		
	Range	(0.00, 100.00)	(0.00, 100.00)	(0.00, 100.00)		

* *P* value from ANCOVA for the null hypothesis that the response is equal between the 2 treatment groups.

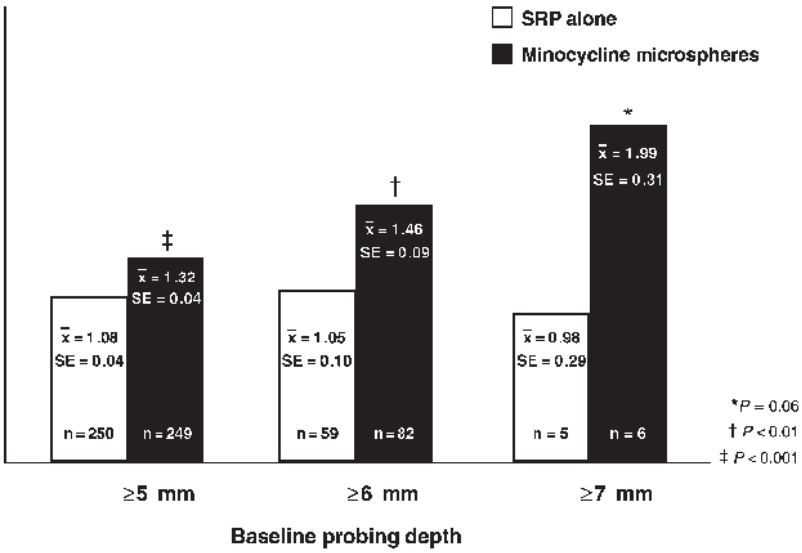

Figure 4.
Mean probing depth reduction at 9 months based on baseline probing depth.

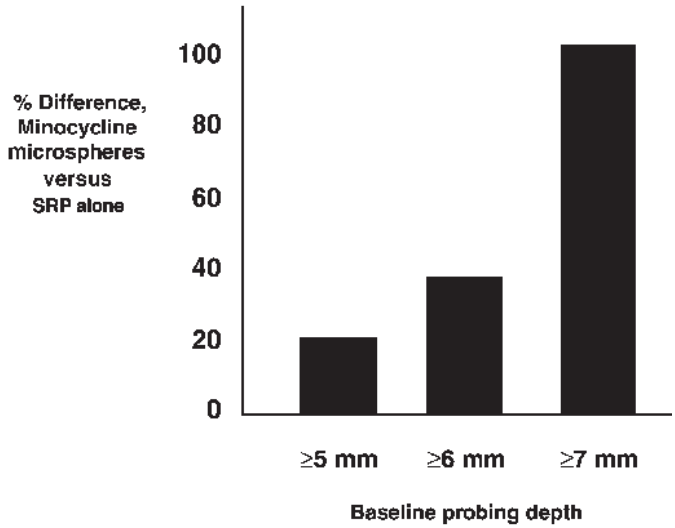

Figure 5.
Percent difference in probing depth reduction at month 9 by baseline probing depth.

Table 3.

Odds Ratio for Reducing Patient Mean Probing Depth to <5 mm; Minocycline Microspheres Versus SRP Alone

Baseline Probing Depth	Odds Ratio	N	95% Confidence Interval
≥5	1.59	499	1.08, 2.35
≥6	2.86	141	1.45, 5.66

microspheres were 22.2, 39.0, and 103.1, respectively. Table 3 presents odds ratios comparing minocycline microsphere adjunctive therapy with SRP alone for reducing mean PD to <5 mm in patients with mean baseline PD ≥5 mm and ≥6 mm. Odds ratios were significant at 1.59 and 2.86 for patients with baseline PD ≥5 mm and ≥6 mm, respectively. With an odds ratio of 2.86, minocycline microsphere therapy would be nearly 3 times more likely to reduce mean probing depths from ≥6 mm to <5 mm than SRP alone.

Results for predetermined subgroups based on smoking status, age, and gender are presented in Figure 6. The difference in PD reductions between treatments in both smokers and non-smokers was significant ($P \leq 0.01$), with a greater difference between treatments in smokers (0.29 mm) than in non-smokers (0.20 mm). The difference between treatment groups was significant in older (>50) and younger (≤50) patients ($P \leq 0.05$), but was greater in patients >50 years (0.33 mm versus 0.18 mm in patients ≤50 years). Minocycline microsphere therapy worked similarly in men and women, and at 9 months reached statistical significance in each ($P \leq 0.004$). An additional predetermined analysis was conducted for patients with a history of cardiovascular disease (data not shown). Despite a small sample size (n = 36), the difference in PD reduction between SRP plus minocycline microspheres and SRP alone groups was highly significant ($P < 0.001$) in favor of minocycline microspheres.

Results for molar teeth are presented in Figure 7. Probing depth reduction was significantly greater for the SRP plus minocycline microsphere group at all examinations, and at 9 months was 0.99 (SE 0.05) mm for SRP alone compared with 1.26 (SE 0.05) mm for SRP plus minocycline microspheres. The numerical difference in PD reduction between the 2 groups at 9 months (0.27 mm) was slightly greater than the difference observed for all teeth.

Safety

Adverse events were reported by 62.4%, 71.9%, and 68.3% of patients in the control, vehicle, and combination therapy groups, respectively. The incidence of these adverse events was similar among treatment groups. The most common adverse events (Table 4) included headache, dental infection, increased periodontitis, tooth sensitivity, tooth caries, dental pain, gingivitis, and stomatitis.

No clinically significant changes in vital signs or oral hard or soft tissues were noted in these studies. All groups experienced a mean gain in clinical attachment at 9 months, but the minocycline microsphere group showed a greater gain.

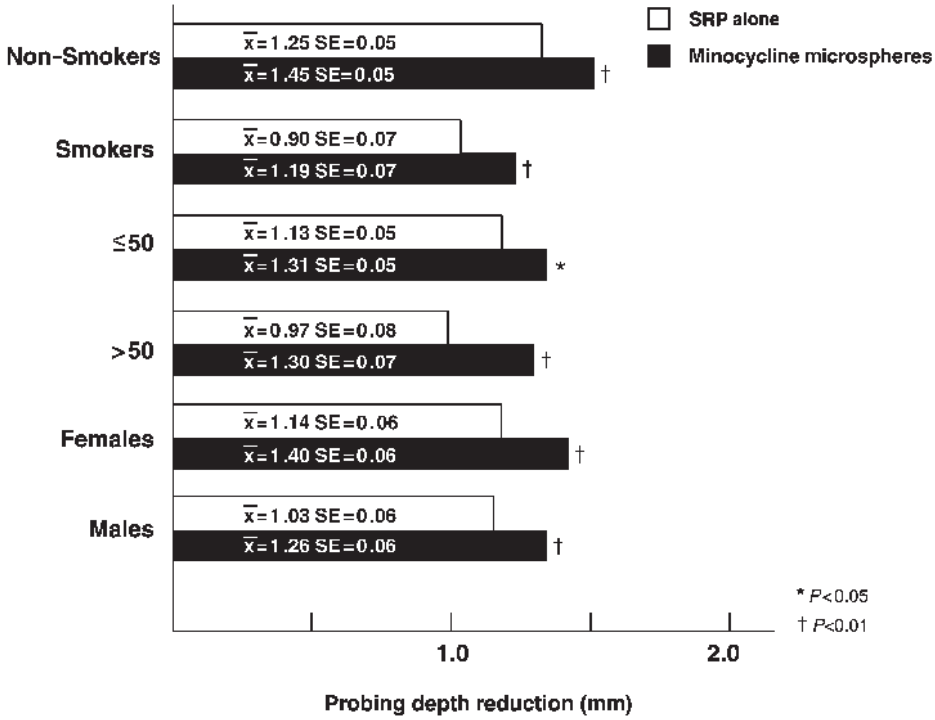

Figure 6.
Probing depth reduction at 9 months based on gender, age, and smoking status.

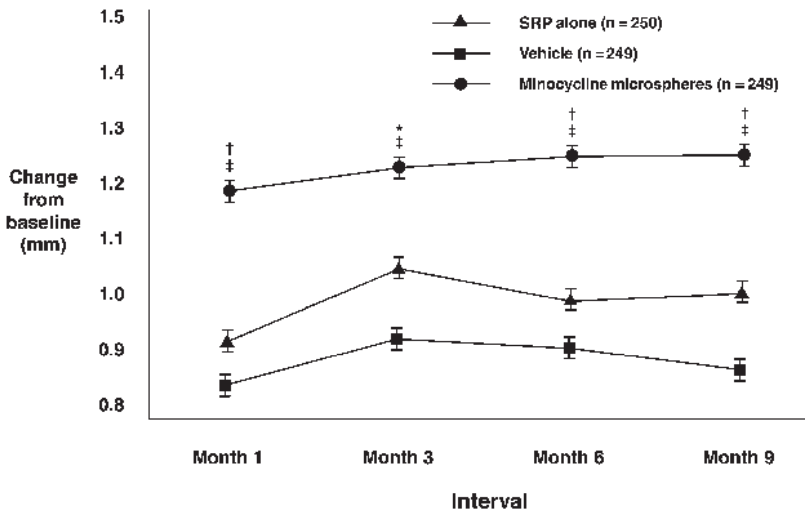

Figure 7.
Average probing depth reduction (adjusted means) from baseline: molar teeth.

DISCUSSION

The objectives of this study were to: 1) determine whether the administration of minocycline microspheres would enhance the therapeutic effect of scaling and root planing in patients with chronic periodontitis, and 2) determine whether the compound was safe and well tolerated. Our results show that adjunctive treatment with SRP plus minocycline microspheres reduces probing depths significantly more than SRP alone. Adjunctive therapy with minocycline microspheres showed a 22% greater therapeutic effect than the commonly practiced scaling and root planing, while, as anticipated, the vehicle had no potentiating effect. The results reported here are at the higher end of the range of probing depth reductions reported for other locally delivered agents, which included sustained release of doxycycline[28] and chlorhexidine.[29]

Because clinically relevant assessments are not always possible when analyzing overall mean differences between treatment groups,[30] this trial was specifically designed for such assessments. A parallel design, rather than split mouth, that treated all sites with PD ≥5 mm was employed and yielded sufficient numbers of sites and teeth to evaluate specific local variances that can have a profound effect on therapeutic outcomes. This design also allowed for testing the ease of use of the delivery system. Administering minocycline microspheres to over 7,500 sites provided a wide distribution of the number of sites treated in each patient. This enabled us to detect whether there was a trend toward a fatigue factor that affected efficacy in patients with numerous sites treated.

"Clinical response" has become a common means for presenting clinically relevant data. In particular, the 2 mm threshold is a level clinicians use to monitor disease progression and evaluate therapeutic success. Patients' mean percentage of treatment sites with probing reductions ≥2 mm was significantly higher for the SRP plus minocycline microsphere group. In addition to threshold reduction levels, reducing probing depths to less than 5 mm is also important. Odds ratio calculations revealed that SRP plus minocycline microspheres was almost 3 times as likely as scaling and root planing alone to reduce mean probing depths to <5 mm in patients with baseline probing depths ≥6 mm. This finding may have a significant impact on the course of therapy, since a 5 mm

Table 4.

Adverse Events (AE) Reported by ≥3% of Patients

Event	Treatment Group		
	SRP (N = 250)	Vehicle (N = 249)	Minocycline Microspheres (N = 248)
Total number of AE	543	589	594
Number (%) of patients	156 (62.4)	179 (71.9)	170 (68.3)
Periodontitis	64 (25.6)	70 (28.1)	54 (21.7)
Tooth sensitivity	30 (12.0)	34 (13.7)	39 (15.7)
Tooth caries	23 (9.2)	28 (11.2)	32 (12.9)
Infection	20 (8.0)	24 (9.6)	27 (10.8)
Dental pain	22 (8.8)	22 (8.8)	24 (9.6)
Gingivitis	18 (7.2)	22 (8.8)	24 (9.6)
Headache	18 (7.2)	29 (11.6)	17 (6.8)
Stomatitis	21 (8.4)	17 (6.8)	12 (4.8)
Flu syndrome	8 (3.2)	16 (6.4)	10 (4.0)
Dental infection	10 (4.0)	9 (3.6)	11 (4.4)
Accidental injury	8 (3.2)	9 (3.6)	6 (2.4)

probing depth is often considered in the decision to proceed to further therapy such as surgery.

SRP plus minocycline microsphere therapy was more effective than SRP plus vehicle or SRP alone in all subgroups. Substantially greater treatment effects were noted in subgroups with increased baseline probing depths. This observation was not unexpected. Since scaling and root planing has been shown to be less efficient in removing plaque and microorganisms from deeper sites,[31] a locally delivered antibiotic should be particularly effective in these sites. Other work has reported similar findings.[32]

In this study, non-smokers showed greater improvement than smokers. This is in agreement with prior reports of a reduced response to periodontal therapy in smokers.[33] Smokers in the SRP plus minocycline microsphere group, however, showed significantly greater probing depth reduction than smokers in the SRP alone group. In fact, the proportional treatment effect for adjunctive therapy with minocycline microspheres was greater in smokers. SRP plus minocycline microspheres showed a 32.2% increase in mean probing depth over scaling and root planing for smokers, compared to 16.0% in non-smokers. One possible explanation for the enhanced treatment effect of SRP plus minocycline microspheres in smokers is the antimetalloproteinase properties of minocycline that could counteract the increased protease activity associated with smoking. The effects of nicotine on metalloproteinase activity are well known. It has been shown, for example, that nicotine can increase collagenase activity in vitro using human gingival fibroblasts.[34] In the smoker's lung, it was shown that the inhibitory effect of α_1-antitrypsin on elastase released from neutrophils is compromised.[35] A second possible explanation is that smokers may harbor higher proportions of certain periodontal pathogens,[36] making them more likely to benefit from the antibiotic.

Patients of all ages showed significantly more probing depth reduction with adjunctive minocycline microsphere therapy compared with SRP alone, but the treatment effect was proportionally greater in older patients. As Figure 6 shows, the treatment effect was more pronounced in patients over 50 due to that group's poorer response to scaling and root planing when compared with younger patients. The reason for this is unclear since age does not seem to have an effect on healing following periodontal therapy.[37] The observation that adjunctive therapy with minocycline microspheres was more effective in smokers and older patients may be particularly significant since periodontitis is more prevalent in these individuals, and because they are at risk for several systemic diseases. It is important to test this therapy in other groups that have periodontitis, such as diabetic and immunosuppressed individuals. Patients with a history of cardiovascular disease should probably be included as well, since our results suggest a greater effect with adjunctive minocycline microsphere therapy in that group versus SRP alone, albeit in a very small sample. Such studies are currently being planned.

The analysis on molar teeth showed that adjunctive SRP plus minocycline microsphere therapy maintained its effectiveness over SRP alone. This is clinically relevant since it has been shown that molar teeth do not respond as well as single-rooted teeth to mechanical therapy.[38] It would be of interest to further dissect this analysis by subgrouping sites in molar teeth based on baseline PD.

In this study, bleeding on probing was reduced to a greater extent in the SRP plus minocycline microsphere group (data not shown). Differences between treatment groups reached statistical significance only in patients with advanced disease. This is understandable given the insensitivity of assessing bleeding as present or absent. In addition, the assessment itself is quite subjective since bleeding can be influenced by probing pressure as well as the inflammatory state of the soft tissue.

The therapeutic benefit of minocycline microsphere therapy was accomplished without concern for systemic effects of minocycline. This statement is sup-

ported by results from a recent combined pharmacokinetic and bacterial resistance trial which showed relatively little systemic absorption of minocycline following local administration with minocycline microspheres, and no development of resistant bacteria in fecal samples.[39,40] The means for achieving the efficacy results with adjunctive minocycline microsphere therapy observed in this study could be attributed to a number of activities associated with the tetracycline family of drugs. It is likely, however, that the antimicrobial activity of minocycline played a major role, as evidenced by a separate independent study that showed minocycline microspheres to be highly effective against local periodontal pathogens.[41]

Supplementing the mechanical removal of subgingival microorganisms could have implications beyond protecting teeth, and includes reducing risk for systemic complications. Indeed, reports of associations between periodontitis and systemic complications are common. A review[13] of one study reported an association with fatal heart disease and stroke, with incidence odds ratios of 1.9 and 2.8, respectively, after adjusting for known risk factors. A study by Wu et al.[14] reported relative risks of 2.11 for incident nonhemorrhagic stroke in patients with periodontitis, and 1.66 for total cerebrovascular accident. Associations were also shown with hematological changes considered to be risk factors for cardiovascular disease. Specifically, patients with periodontitis have higher white blood cell counts[43] and higher levels of von Willebrand factor,[42] fibrinogen,[43] and acute-phase reactants.[44] Associations with systemic disorders other than cardiovascular disease have also been shown. Insulin requirements in type 1 and type 2 diabetics were reduced following treatment for periodontal disease which included systemic antibiotic administration.[17-20] A case-control study of pregnant or postpartum mothers showed that those with periodontitis were more than 7 times as likely to have a preterm low birth weight infant.[15] Evidence from these studies, coupled with a better understanding of the pathogenesis of periodontitis, suggests that this oral infection of epidemic proportion may be associated with several systemic complications.

The user friendliness of a locally delivered antimicrobial warrants some discussion in efficacy trials, particularly when the number of sites treated is large. Clinicians participating in this study found minocycline microspheres easy to administer, and were able to treat an average of approximately 30 sites per patient without appreciably prolonging the scaling and root planing visit. There was no evidence of a fatigue factor that impacted efficacy since there were no differences in PD reduction between patients with higher versus lower numbers of treated sites (data not shown). Since the powder, composed of minocycline microspheres, begins to hydrolyze upon contact with moisture, it immediately becomes bioadhesive and self-retentive. These attributes would be likely to favorably impact efficacy.

In conclusion, scaling and root planing plus minocycline microspheres provided significantly greater probing depth reduction than scaling and root planing alone. The therapeutic effect was even more pronounced in patients with compromising conditions at both systemic and local levels. Considering the limitations of scaling and root planing shown in this and other studies, along with evolving evidence that minimizing oral infections may contribute to patients' general well-being, it would appear that the use of locally delivered antimicrobial agents should be incorporated as part of an optimal non-surgical therapeutic regimen.

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