Probing Depth Changes Following 2 Years of Periodontal Maintenance Therapy Including Adjunctive Controlled Release of Chlorhexidine

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Background: Multicenter clinical trials have established that the adjunctive use of the subgingival controlled release of chlorhexidine, (CHX chip), significantly reduces probing depth (PD), improves clinical attachment levels, and reduces bleeding on probing compared to scaling and root planing (SRP) alone for periods of up to 9 months. The present report is based on a phase IV clinical trial to examine the adjunctive use of the CHX chip for routine periodontal maintenance therapy (RPMT) over 2 years.

Methods: Eight hundred thirty-five (835) patients were recruited into the study. At baseline a CHX chip was placed in pocket sites with PD ≥5 mm. The patients were scheduled to receive RPMT at 3-month intervals with repeated CHX chip placement at sites where the PD remained ≥5 mm. Patients who did not attend the 24-month recall visit or who failed to attend 2 consecutive time frame examinations were excluded from the analyses.

Results: The 595 patients included showed a continuous decrease in PD over 2 years of 0.95 mm. After 2 years, 23.2% of patients had at least 2 pockets showing a reduction in PD of 2 mm or more and 58.9% of the sites had been reduced to a PD of <5 mm. Only 2.9% (n = 57) of the sites showed an increase in PD of ≥2 mm. Adverse events were mild to moderate in nature and resolved spontaneously without medication.

Conclusion: The results of this Phase IV or follow-up trial indicate that the adjunctive use of the CHX chip is a clinically safe and effective treatment option for long-term management of chronic periodontitis. *J Periodontol 2003;74:420-427.*

KEY WORDS

Adjunctive therapy; chlorhexidine/therapeutic use; clinical trials, controlled; comparison studies; periodontal regeneration; planing; scaling.

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Traditionally periodontal disease therapy has been directed to altering the periodontal environment to one that is less conducive to the retention of bacterial plaque in the vicinity of the gingival tissues. With the increasing awareness of the bacterial etiology of periodontal diseases,[1-3] and in particular the hypothesis that specific bacteria are involved,[4] a more direct approach using antibacterial agents has become an integral part of the therapeutic armamentarium.

The delivery of antibacterial agents to the disease site has been carried out by systemic or topical administration. There is evidence that systemic administration of antibiotics[5,6] is effective in altering the progression of certain forms of periodontitis. However, the routine use of antibiotics over long periods of time is contra-indicated because of the development of resistant bacterial strains and possible systemic side effects. Topical administration of antibacterial agents in the form of mouthwashes has been shown to be effective in controlling supragingival plaque;[7] however, their access to the periodontal pocket and the subgingival flora is limited[8,9] and, therefore, ineffective in controlling disease progression. Local delivery of chemotherapeutic agents into the pockets via a syringe or irrigating device has been shown to have an effect on the subgingival flora but clinically it has not been effective in halting the progression of periodontal attachment loss.[10,11] The lack of clinical efficacy is probably because of

the short time the irrigating solution remains in contact with the pocket environment.[12]

The periodontal pocket provides a natural reservoir bathed by gingival crevicular fluid (GCF) and with easy access for inserting a delivery device. The GCF provides a leaching media for the release of a drug from the solid dosage form and its distribution throughout the pocket. These features, together with the fact that the periodontal diseases are localized to the immediate environment of the pocket, make the periodontal pocket a natural site for treatment with local sustained release delivery systems. The recent development of subgingivally placed delivery technology has made site-specific chemotherapeutic treatment of periodontal pockets possible. These technologies, which have recently been reported, have provided the profession with a new tool that has been shown in clinical trials to alter the subgingival flora and influence the healing of the marginal attachment apparatus.[13-18]

Chlorhexidine (CHX) is a highly effective antimicrobial agent that has been extensively studied and shown to be effective as a mouthrinse against supragingival plaque bacteria[19] in the prevention of gingivitis and as a treatment for gingivitis.[20]

Early studies on the controlled, subgingival, release of CHX, using a non-degradable delivery system,[21] presented evidence that it markedly suppresses the subgingival microflora for at least 11 weeks after administration. In addition, a study on a small cohort of adult periodontitis patients[22] compared routine periodontal maintenance therapy with therapy using the contolled release of chlorhexidine. The treatments were provided every 3 months over a 2-year period. The results of this study showed that the reduction in probing depth (PD), improvement in clinical attachment level (CAL), and reduction in bleeding on probing (BOP) was significantly greater for the CHX treated teeth than for the teeth receiving routine maintenance therapy.

A biodegradable, controlled-release, chlorhexidine delivery system has been developed[23] and tested in a number of multicenter clinical trials. The controlled release chlorhexidine delivery system‡ (CHX chip) was tested as an adjunct to scaling and root planing (SRP) during a 6-[12] and 9-month study period.[24] The CHX chip, used in conjunction with SRP, resulted in improved PD, CAL, and BOP compared to patients treated with SRP alone.[12,24] The purpose of the present report is to present the final results of a 2-year open-label, phase IV clinical trial. The study was carried out in a private dental practice setting, using the CHX chip in conjunction with routine periodontal maintenance in patients who had completed definitive periodontal therapy. Phase IV studies are Food and Drug Administration approval studies carried out to provide additional information on the use, prescribing information, safety, and quality of a drug. The purpose of this study was to provide evidence for the efficacy and safety of the repeated use of the CHX chip for the long-term maintenance of patients after definitive treatment.

A preliminary report describing the results obtained from the first 72 completed patients from this study has been reported previously.[25]

Table 1.

Number of Subjects from Each Dental Office

Office	Number
1	9
2	21
3	15
4	10
5	10
6	8
7	748
8	14
Total	835

MATERIALS AND METHODS

This study was designed as an open-label, 2-year clinical trial to evaluate the long-term effect of the adjunctive use of the CHX chip during routine periodontal maintenance therapy (RPMT). The study protocol was approved by the Institutional Review Board-Helsinki Committee of the Hebrew University-Hadassah Medical Center. It was carried out at 8 centers in Israel each of which was a privately run dental office (Table 1). Prior to the start of the study, examiners from each office participated in a prestudy calibration exercise to ensure reliability and reproducibility of PD measurements using a manual University of North Carolina (UNC) 15 mm periodontal probe. PD was recorded to the nearest millimeter. Except for the largest center which provided 3 examiners, each center used a single examiner. Intra- and interexaminer calibrations were carried out using the same examiner (AS) as the standard. Each center provided 4 patients with at least 5 sites with a PD ≥5 mm for the purpose of calibration. A correlation coefficient of ≥0.7 was required for examiner participation. Examiners were recalibrated at least once a year, and the patients were seen by the same examiner throughout the study period.

Enrolled patients included men and women in good general health, 30 years of age or older, with the pres-

‡ PerioChip, Dexcel Pharma Technologies Ltd., Jerusalem, Israel; distributed in the U.S. by Dexcel Pharma Inc., Edison, NJ.

ence of periodontal pockets with PD ≥5 mm. Subjects enrolled were recruited from patients attending the private dental offices who had not had definitive periodontal therapy (defined as periodontal surgery or SRP performed by a periodontist) within the 2 years prior to entrance into the study. Patients were divided into 2 groups: 1) SRP group: those who needed a thorough SRP prior to study entry. The SRP was carried out and completed 1 month prior to the study baseline and 2) non-SRP group, patients who did not require SRP because they were actively enrolled in a RPMT program.

Study Procedures

A flow chart of the study procedure is shown in Figure 1. At screening, all patients provided a medical history and their study eligibility was ascertained. Each patient then received a full-mouth PD charting. Full-mouth SRP was provided and completed 1 month prior to baseline for the SRP group while the non-SRP group proceeded immediately into the study. At the baseline visit the inclusion/exclusion criteria were verified and all eligible target sites (PD ≥5 mm) were reprobed. A CHX chip was placed in all pocket sites with PD ≥5 mm (1 chip per tooth regardless of the number of eligible sites noted for the tooth). The study design required that patients receive RPMT at their respective study centers every 3 months following the baseline visit. All target sites that had received a CHX chip at baseline were then reprobed and a new CHX chip placed if the PD measured ≥5 mm. Sites with PD <5 mm at any 3-month return visit did not receive a chip at that visit but continued to be monitored, with a CHX chip placed subsequently only if the pocket site again showed PD ≥5 mm. If a site showed an increase in PD from baseline of ≥3 mm, it was exited from the study and treated as deemed necessary by the principal investigator. The remaining target sites within the same patients continued to be evaluated and treated within the study protocol. As would be expected from a study carried out under general dental practice conditions, the compliance of the patients with the 3 monthly study time-schedule was poor. In order to standardize the examination time intervals over the course of the 2-year study period, "time frames" were created. Each time frame was defined as an interval of days post-baseline centered around a post-baseline time point corresponding to a nominally-scheduled follow-up examination (e.g., 12 weeks ± 6 weeks). In this manner time frames were established corresponding to the nominal 3, 6, 9, 12, 15, 18, 21, and 24 month visits, each one of 3-month duration. Data from patients who failed to attend an examination during 2 consecutive time frames were excluded from all summaries and analyses. For each study time frame the PD, and whether or not a chip was placed, was recorded. If more than one examination took place during a time frame, the highest PD score per site was recorded (worst case scenario). In general the therapists carrying out the RPMT and CHX chip placement were hygienists.

Statistical Methods

Descriptive data only are presented for site-wise scores. Statistical analyses were performed using the mean PD per patient as the unit score. Comparisons of baseline and follow-up PD scores were investigated using the paired *t* test. For all statistical tests, $P \leq 0.05$ was considered statistically significant.

RESULTS

A total of 835 patients from 8 different dental offices were enrolled in the study. The large majority 748 were from one single office (Table 1). The data obtained at each patient visit were then placed into a time frame according to the number of days post-baseline. Five-hundred ninety-five patients (595) who had been examined during the 24-month time frame and fulfilled the other inclusion criteria were included in the data analysis (completed patients). Two hundred forty (240) patients were excluded from the analysis because they were not examined during the final study

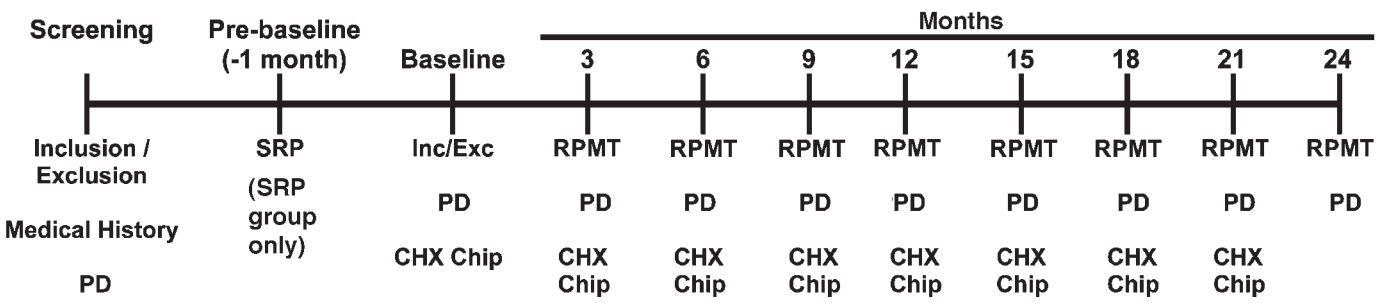

Figure 1.
Flow chart indicating the chronological order of the study procedures.

Table 2.

Baseline Patient Demographics

	Total Population	Completed Patients	Excluded Patients
Number	835	595 (71.3%)	240 (28.7%)
Age (range)	50.76 (24-85)	51.19 (29-85)	49.74 (24-76)
Males	36%	35%	37%

Table 3.

Mean PD ±SD per Patient of Treated Pockets by Time Frame

Time Frame	All Completed Patients (N)	SRP Patients (N)	Non-SRP Patients (N)
Baseline	5.72 ± 0.81 (595)	6.13 ± 0.86 (55)	5.67 ± 0.80 (540)
Month			
3	5.32 ± 0.88 (540)	5.58 ± 1.06 (50)	5.29 ± 0.85 (490)
6	5.14 ± 0.95 (504)	5.40 ± 1.11 (50)	5.11 ± 0.93 (454)
9	5.06 ± 0.97 (477)	5.20 ± 1.15 (45)	5.04 ± 0.95 (432)
12	4.98 ± 1.01 (513)	5.03 ± 1.11 (52)	4.98 ± 1.00 (461)
15	4.91 ± 1.06 (483)	5.00 ± 1.14 (41)	4.90 ± 1.05 (442)
18	4.89 ± 1.01 (492)	4.91 ± 0.81 (41)	4.89 ± 1.02 (451)
21	4.84 ± 1.12 (446)	4.97 ± 1.16 (43)	4.82 ± 1.11 (403)
24	4.77 ± 1.05 (595)	4.78 ± 1.13 (55)	4.77 ± 1.05 (540)

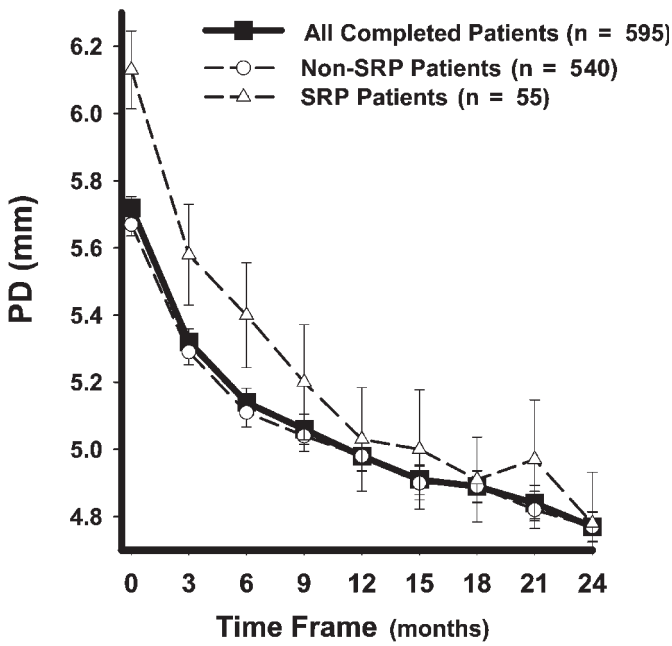

Figure 2.
Mean probing depths per patient of the treated pockets at each time frame.

time frame (24 ± 1.5 months) or they had not been examined during 2 or more consecutive time frames. The excluded group had the same baseline demographics as the completed patients (Table 2). In addition the mean baseline PD for the excluded and the completed groups were similar (5.79 ± 0.85 and 5.72 ± 0.81, respectively).

Of the 595 completed patients, 540 belonged to the non-SRP group and were enrolled from a single practice. The remaining 55 belonged to the SRP group and were from the 7 other private offices. Of these 563 (94.62%) attended at least 6 visits during the 8 time frames established for the study period. The remaining patients attended 5 visits (5.38%) with one patient attending only 4 visits (0.17%).

All analyses were performed using data from only those sites to which chips had been dispensed at baseline. The average number of pockets per subject, with a baseline PD of ≥5 mm, was 4.54 ± 3.24 SD.

The mean PD scores for the completed patients are shown in Table 3 and Figure 2. A continuous decrease in the mean PD from baseline (5.72 mm ± 0.81 SD) to 24 months (4.77 mm ± 1.05 SD) was observed providing a mean reduction in PD over the 2 years of 0.95 mm. This improvement followed an exponential-like curve over the 24-month study period. Changes in PD of the non-SRP patients over the study period reflect the changes in PD of the total population. However, although the PD scores over the study period were very similar, the SRP group had a significantly higher mean baseline PD than the non-SRP group (6.13 mm versus 5.67 mm; $P < 0.0001$). The reduction in the mean PD over the 2 years was also significantly greater in the SRP group than in the non-SRP patients (1.35 mm versus 0.90 mm; $P < 0.0001$).

A total of 2,484 pockets were evaluated at both the baseline and 24-month visits. By the end of the study 58.9% of the sites had a PD of <5 mm. The percent of patients showing a reduction in PD of ≥2 mm are shown in Table 4. Patients with one or more pockets showing a reduction in PD of ≥2 mm increased from 21.3% at the 3-month time frame to 51.3% at the 24-month time frame. Patients with 2 or more pockets showing a decrease of ≥2 mm increased from 6.1% at the first post treatment time frame (3 months) to 23.2% at the final examination (24 months).

As shown in Table 5, it is evident that there is a

Table 4.

Patients (%) with Sites Showing a Reduction in PD ≥2 mm

Time Frame	Total N	≥1 Sites	≥2 Sites
Baseline	595	0	0
Month			
3	540	21.30	6.11
6	504	32.14	11.90
9	477	40.25	17.40
12	513	42.88	17.93
15	483	50.10	20.95
18	492	48.78	20.77
21	446	49.55	23.99
24	595	51.26	23.19

Table 5.

Number of Sites, by Initial PD, Showing an Improvement ≥2 mm Over 24 Months

Baseline PD (mm)	Total Sites Examined	N Sites with PD Improvement ≥2 mm (%)
5.0-6.0	2,005	415 (20.70)
6.5-7.0	243	127 (52.26)
7.5-8.0	97	48 (49.48)
>8	139	56 (40.29)
Overall	2,484	646 (26.01)

relationship between baseline PD and the tendency for a site to show a reduction in PD of ≥2 mm. Of the shallower pockets with a baseline PD of 5.0 to 6.0 mm only 20.7% showed an improvement of 2 mm or more after 24 months, whereas over 40% of the sites with a deeper initial PD showed more than 2 mm improvement. Improvement was most marked among pockets with an initial PD in the 6.5 to 7.0 mm range (52.3%).

Table 6 shows the number of pockets showing increasing PD, no change, or reduction in PD over different time periods of the study. At the termination of the study, 73% of the sites showed improvement in PD, 18.8% showed no change and 8.2% showed worsening (Fig. 3). Only 2.9% (n = 57) of the worsening sites showed an increase in PD of ≥2 mm. The results achieved in the first year clearly reflect the results achieved over the total 2 years although they are slightly less marked.

The study sites were categorized according to their baseline PD and their change in PD over the 24 months. In Table 7, the mean number of chips placed, per categorized site, over the study period is provided. Among the sites showing a reduction in PD over the study period, there was a direct relationship between the initial probing depth and the number of chips used to achieve this result; i.e., the shallower pockets at baseline requiring fewer chips than the deeper pockets. Sites that showed an increase in PD over the study period did not show this relationship, receiving, on average, more than 6 chips per pocket irrespective of the initial PD.

During the 2 years of the study, 281 (35%) of the 835 patients entered into the study reported a total of 571 adverse events. Only 300 of these events (52.5%), reported by 140 (16%) of the patients, were considered to be treatment related (i.e., affect the teeth and oral tissues). These 300 events followed a total of 4,920 patient visits at which chips were placed, representing an incidence of 6.1%. Of the patients entering the study, 9.0% were 65 years of age or older, whereas only 3.6% of the patients who reported adverse events were 65 years or more. The adverse events were mostly mild to moderate in nature and resolved spontaneously without medication (Table 8).

Table 6.

Number of Sites Showing PD Changes During Year 1 and Total Period

Time Frame	Worsened N (%)	No Change N (%)	Improved N (%)	Total
0-12 months	201 (9.1)	568 (25.8)	1,437 (65.14)	2,206
0-24 months	204 (8.2)	467 (18.8)	1,813 (73.0)	2,484

DISCUSSION

The results of this study demonstrate that patients with chronic periodontitis can achieve clinically significant benefits from the use of locally-delivered, sustained-release chlorhexidine (CHX) chip when used as an adjunct to RPMT, at sites with a PD ≥5 mm. In order to assess these benefits, in relationship to those obtained from RPMT alone, we compared our study results to reports in the literature of studies that examine the effect of RPMT on PD associated with periodontal pockets. These studies[26-34] indicate that after the initial healing of the gingival tissues (which generally occurred within approximately 3 months of completing definitive periodontal therapy), no further improvement in the mean PD was seen.

The patients in this study had been on RPMT for an extended period of time prior to entering the study or had had SRP at least 1 month prior to the baseline PD recordings. It would, therefore, be reasonable to assume

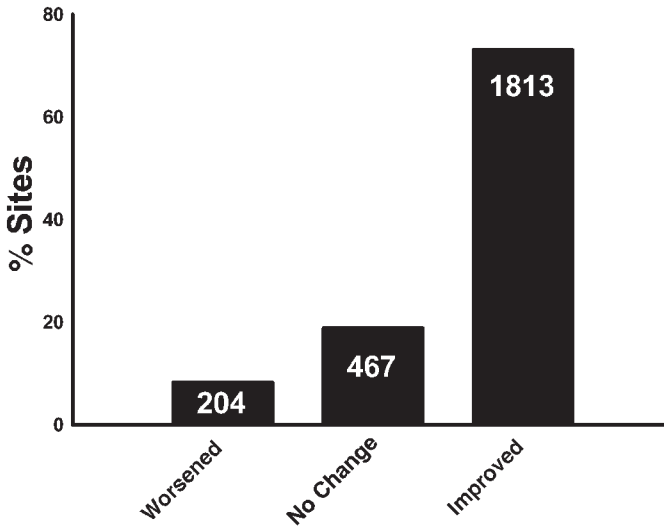

Figure 3.
The percentage of sites in which PD showed improvement, had no change, or worsened over 2 years.

that the PD were stable at the baseline visit. The subsequent reduction in the mean PD from 5.72 mm ± 0.81 at baseline to 4.77 mm ± 1.05 at 24-months therefore represents a mean improvement of 0.95 mm during a period of time in which only a stable mean PD had been achieved in previous studies. It is important to note that the improvement was continuous, following an exponential-like curve (Fig. 2), over the whole 24-month study period. The continuing reduction in PD seen in our study, therefore, suggests that the adjunctive use of the CHX chip together with RPMT provides additional clinical benefits compared to RPMT alone. This finding is further supported by a study using a minocycline containing gel as part of RPMT.[35] That study showed that after stabilization of the clinical parameters by SRP a further reduction in PD of 0.7 mm was obtained over the rest of the 15-month study period. The control group, treated with a placebo gel, showed no further reduction in PD, behaving as might be predicted. This adjunctive effect of the minocycline gel may have been due to its antibacterial or anti-collagenolytic activity. These observations support the conclusion that the adjunctive use of chemotherapeutic agents confers additional long-term clinical benefits to those obtained by RPMT alone. The greater reduction in the PD scores seen in the SRP group compared to the non-SRP group (Fig. 2) could be interpreted as being due to a more pronounced response of the deeper pockets to the treatment. However it may also be due to the short healing period between the active treatment (SRP) and the commencement of the study. Had these patients been enrolled 3 or more months after the active therapy, the extended healing time post-SRP may have resulted in a similar magnitude of response as that seen in the non-SRP group. In fact the mean PD scores achieved in both groups were identical at the end of the study (SRP group = 4.78 ± 1.13 mm; non-SRP group = 4.77 ± 1.05 mm).

A PD reduction of 2 mm or more has previously been considered as a clinically meaningful change, one that may have a real impact on tooth prognosis or the periodontal treatment plan.[24] The increase in the percentage of patients with 2 or more pockets showing a reduction in PD of ≥2 mm (from 6.11% at 3 months to 23.19% by the end of the 2 years) is strong evidence that a continual improvement in the periodontal status of patients is achieved using CHX chip supported RPMT. Moreover, the reduction of more than 50% of the pockets to a PD <5 mm is further evidence for the therapeutic effect of the treatment.

The frequency of chip placement is an interesting finding. In Table 7 we see that the number of chips required to achieve a ≥2 mm improvement in PD over 24 months is directly related to baseline PD. Pockets with baseline PD of ≤6 mm needed an average of 2.79 ± 1.77 chips. With increasing baseline PD the mean

Table 7.

Mean Number of Chips ± SD (number of sites) Placed Over 24 Months According to Baseline PD and Changes in PD

			Decreasing PD	
Baseline PD (mm)	Increasing PD	Stable PD	<2 mm	>2 mm
5-6.0	6.57 ± 1.45 (141)	5.32 ± 1.89 (365)	3.34 ± 2.02 (1084)	2.79 ± 1.77 (415)
6.5-7.0	6.43 ± 1.50 (30)	6.53 ± 1.16 (43)	6.53 ± 1.03 (43)	4.83 ± 1.96 (127)
7.5-8.0	7.11 ± 0.88 (19)	6.63 ± 1.20 (16)	7.07 ± 0.73 (14)	5.98 ± 1.98 (48)
>8	6.71 ± 1.73 (14)	6.60 ± 1.38 (43)	7.08 ± 0.63 (26)	6.59 ± 1.20 (56)
Overall	6.61 ± 1.43 (204)	5.60 ± 1.84 (467)	3.59 ± 2.15 (1167)	3.76 ± 2.25 (646)

Table 8.

Frequency of Treatment-Related Adverse Events

Event	Number of Occurrences (%)
Gingival pain	174 (58)
Gingival swelling/inflammation	50 (16.6)
Abcess	10 (3.4)
Gingival discomfort	27 (9)
Pus discharge	10 (3.4)
Gingival sensitivity	12 (4)
Fistula	4 (1.3)
White spots on gingiva	4 (1.3)
Worsening tooth condition	9 (3)
Total	300

number of chips used increased and pockets with baseline PD >8 mm needed an average of 6.59 ± 1.20 CHX chips to achieve the ≥2 mm improvement. As most of the improvement in the PD noted in this trial occurred during the first 12 to 15 months it can be expected that the benefits of using the CHX chip as an adjunct to RPMT in clinical practice would also occur during this period. Little further improvement in PD would be expected by continuing the adjunctive use of the CHX chip with the RPMT. This provides the basis for a recommendation for the use of the CHX in periodontal maintenance therapy. If, after completing definitive periodontal therapy, there are still residual pockets of ≥5 mm remaining, and the goal of therapy is to reduce the PD to below 5 mm, combined RPMT together with the CHX chip should be effective within the first 12 months. If this expected improvement is not achieved within this time frame, little further advantage would be gained by continuing the adjunctive use of CHX chips with RPMT and other options to reduce the PD <5 mm should be considered. However the data also clearly indicate that once a reduction in PD has been achieved it can be maintained or even slightly improved by further continuing the combined RPMT/adjunctive CHX chip therapy. Therefore, one of the options that could be considered is the continuation of the combined therapy, over an extended time period, with the goal being to prevent deterioration of the PD achieved over the initial 12 months. If during this period pockets show signs of deterioration, surgical intervention should be considered.

In order to assess the adverse events all reports for the 835 intent-to-treat patients were considered irrespective of their compliance to the protocol. The total of 300 treatment related adverse events over the 2-year study period were reported to occur in 140 patients (16.7%). This is a 6.1% incidence of adverse events when related to the number of visits at which chips were dispensed. It should be kept in mind that multiple adverse events could be reported by one individual at a single visit and, therefore, the real incidence would be much lower. It is important to note that the incidence of patients over the age of 65 reporting adverse events was far less than their representation in the study population. This suggests that geriatric patients have less adverse events than the population as a whole. It can therefore be concluded that the repeated use of the chlorhexidine chip over an extended period of time is safe for use by the full range of adult patients and does not result in more adverse events than were reported in more restricted studies over a 6- to 9-month period.[24]

In conclusion this study indicates that RPMT together with the adjunctive use of the CHX chip results in a continual and clinically significant reduction in the PD over a 2-year period. The CHX chip is safe for repeated use over an extended period of time resulting in relatively few, minor, adverse events. In addition, the results suggest that these adverse events may occur less frequently in patients over the age of 65 years.

ACKNOWLEDGMENTS

The authors thank Drs. Dan Mahler, Lior Shapira, Yisrahel Gellman, Tirza Ramon, Eran Dolev, Michael Schwartz, and Lionel Berger in whose private offices the data for this study were collected. We would also thank Dr. Moshe Flushner and Ms. Brenda Kolatch for their invaluable input into the planning and execution of the study.

This study was supported by a grant from Dexcel Pharma Technologies Ltd., Jerusalem, Israel (formerly Perio Products Ltd., Jerusalem). Dr. W. Soskolne is a consultant to Dexcel Pharma Technologies Ltd., and Mr. Howard Proskin is the chief executive officer.

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Accepted for publication September 13, 2002.