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Modulation of clinical expression of plaque-induced gingivitis

III. Response of "high responders" and "low responders" to therapy

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Abstract

Aim: The aim of the present study was to characterize the subject-based clinical behavior of the gingiva in response to a tooth-cleaning regimen in two subpopulations, ''high-responder'' (HR) and ''low-responder'' (LR) groups, presenting a different inflammatory response to plaque accumulation.

Material and Methods: The study population comprised of 96 systemically and periodontally healthy subjects, 46 males and 50 females, non-smokers, enrolled in an experimental gingivitis trial. At completion of the experimental gingivitis period (day 21), all subjects were prescribed the same 21-day treatment regimen of amine/stannous fluoride (AmF/SnF_2)-containing toothpaste and mouthrinse. Plaque index (PlI), gingival index (GI), gingival crevicular fluid volume (GCF), and angulated bleeding score (AngBS) were recorded on three selected teeth. Treatment efficacy was evaluated in the overall population as well as in HR and LR groups, separately.

Results: A statistically significant decrease of PlI was observed after treatment ($p < 0.001$), with PlI reversing to baseline levels. Changes in PlI revealed the same trend in both HR and LR groups, without differences between groups. Treatment also resulted in a significant decrease of all gingivitis parameters ($p < 0.001$ for all comparisons). After treatment, GI, AngBS, and GCF were comparable with baseline condition. However, when the two groups were compared, day 42-GCF was significantly higher in the HR group than the LR group.

Conclusions: A treatment regimen based on mechanical plaque control supplemented with AmF/SnF_2-containing toothpaste and mouthrinse is effective in reducing plaque accumulation and re-establishing healthy gingival conditions after experimentally induced gingivitis, even in subjects with different inflammatory response to plaque accumulation.

Key words: dental plaque/prevention and control; gingivitis/prevention and control; mouthwashes/therapeutic use; periodontal disease/gingivitis

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The rationale to develop treatment strategies to prevent or limit plaque accumulation is that dental plaque leads to the development of gingivitis and, as a final consequence, periodontitis (Robinson 1995). The epidemiology and natural history of gingivitis and periodontitis indicate that gingival inflammation is invariably a component of periodontitis and that gingivitis precedes periodontitis (Lindhe et al. 1973, Löe et al. 1986). However, it is also clear that all gingivitis cases do not progress to periodontitis (Goodson et al. 1982, Brown & Löe 1993, Prayitno et al. 1993). The reason for this is that plaque bacteria are necessary but not sufficient for the development of periodontitis; a susceptible host is necessary (Page & Schroeder 1982, Page 1999). At the present time, there are no reliable means to predict whether or not a gingivitis case will progress into periodontitis. In an effort to define the parameters that modulate individual susceptibility to gingivitis (Tatakis & Trombelli 2004), and perhaps, ultimately, to periodontitis, we have designed and implemented a series of studies employing the experimental gingivitis model (Trombelli et al. 2004).

Several studies and extensive clinical experience have demonstrated that mechanical procedures aimed at removing the supragingival plaque may prevent or reverse the inflammatory status of

gingival tissues. However, epidemiological data indicate that the majority of individuals do not control plaque accumulation to an extent sufficient to control the disease (Oliver et al. 1998, Sheiham & Netuveli 2002). Evidence exists that the degree of motivation and skill required for effective use of mechanical oral hygiene products may be beyond the ability of most patients (Lindhe & Koch 1966, 1967). Therefore, anti-microbial toothpastes and mouthrinses have been investigated and marketed to provide additional anti-plaque/anti-gingivitis activity when used daily as an adjunct to a mechanical oral hygiene regimen (Addy & Moran 1997).

The aim of the present single-blinded treatment study was to characterize the subject-based clinical behavior of the inflamed gingiva in response to a tooth-cleaning regimen supplemented by amine/stannous fluoride (AmF/SnF_2)-containing toothpaste and mouthrinse, i.e. agents with anti-microbial properties. The response of both the entire study population and the ''high-responder'' (HR) and ''low-responder'' (LR) groups (Trombelli et al. 2004) was evaluated.

Material and Methods

Experimental design and study population

A randomized, split-mouth, localized, experimental gingivitis clinical trial was recently reported (Trombelli et al. 2004). Briefly, a pretrial period of professional and supervised tooth cleaning was undertaken to obtain optimum gingival health and standardized gingival baseline conditions. Toothbrush, floss, and non-fluoridated toothpaste along with oral hygiene instructions were provided to all participants. Subjects were also prescribed a vitamin C supplement (ascorbic acid, 500 mg daily; Angelini, ACRAF, Ancona, Italy) to be taken for the entire pretrial and trial period in order to prevent subclinical ascorbate deficiency. According to a computer-generated randomization list, in each subject one maxillary quadrant was assigned as ''test'' (experimental gingivitis) and the contralateral quadrant as ''control''. Subjects were instructed to wear a customized stent prior to oral hygiene session throughout the experimental gingivitis period to prevent plaque removal during brushing of the remaining dentition. After 21 days of oral hygiene withdrawal in the test quadrant, the subjects were assigned to a self-performed oral hygiene regimen for 21 days.

The study design was approved by the local ethical committee and was found to conform to the requirements of the ''Declaration of Helsinki'' as adopted by the 18th World Medical Assembly in 1964 and subsequently revised (www.wma.net/e/policy/17-c_e.html). Written informed consent was provided by all participants.

Systemically and periodontally healthy volunteers, non-smokers, were recruited among current and permanent residents in the metropolitan area of Ferrara. Inclusion and exclusion criteria for subject enrollment were described in detail in a companion paper (Trombelli et al. 2004). Ninety-six subjects (mean age: 23.6 ± 1.7 years), 46 males (mean age: 23.9 ± 1.7 years), and 50 females (mean age: 23.3 ± 1.6 years), completed the study. From this study population, we identified two subpopulations presenting different severity of gingival inflammation after a 21-day period of plaque accumulation (Trombelli et al. 2004). According to GCF values, as recorded on day 21 in test quadrants and standardized on cumulative plaque exposure (CPE), we were able to discriminate two sets of individuals, defined as ''high-responder'' (HR) and ''low-responder'' (LR) groups, with significantly different severity of gingivitis to similar amount of plaque deposits. In particular, HR subjects showed significantly higher values for all clinical parameters of gingival inflammation compared with LR subjects, although no differences were found in the plaque index (PlI) and CPE between groups. The HR group comprised of 13 males and 11 females (mean age: 24.1 ± 1.6 years) and the LR group comprised of 11 males and 13 females (mean age: 23.4 ± 1.9 years).

Clinical parameters

The following clinical parameters were obtained in the order listed below from the selected sites:

- GI, according to a modification of the method of Löe & Silness (1963) without the bleeding on probing component.
- PlI, according to Silness & Löe (1964), recorded as reported by Furuichi et al. (1992).
- Gingival crevicular fluid volume (GCF), collected and measured according to Periotron® 8,000 manufacturer's instructions (OraFlow Inc., Plainview, NY, USA). Periotron® calibration was accomplished as previously described (Trombelli et al. 2004).
- Angulated bleeding score (AngBS) (Trombelli et al. 2004), which represents a modification of the angulated bleeding index as reported by van der Weijden et al. (1994).

In each test and control quadrant, clinical parameters were recorded on the following three maxillary teeth: lateral incisor; first premolar (if missing, replaced by second premolar); first molar (if missing, replaced by second premolar). For each tooth, clinical parameters were evaluated on two sites: the buccal and the mesiobuccal aspect.

All clinical parameters were recorded by two trained and calibrated examiners on days 0, 7, 14, 21 (at completion of the experimental gingivitis period), and day 42 (at completion of treatment regimen).

Before starting the trial, inter- and intra-examiner agreement for PlI and GI was assessed and evaluated by unweighted κ-statistics at both site-specific and subject levels. κ scores revealed good to excellent intra- and inter-examiner agreement for PlI, and good intra- and inter-examiner agreement for GI (Trombelli et al. 2004). During the course of the study, each subject was randomly assigned to one examiner. Attempt was made to ensure that the originally assigned examiner evaluated a particular subject throughout the trial, thus limiting inter-examiner variability. Of the 96 subjects completing the study, 88% were evaluated by the same examiner throughout the study.

Treatment regimen

At completion of the experimental gingivitis period (day 21), all subjects were prescribed the same treatment regimen based on AmF/SnF_2 toothpaste (meridol® toothpaste, GABA International AG, Münchenstein, Switzerland) and mouthrinse (10 ml t.i.d; meridol® mouthrinse, GABA International AG). Treatment was dispensed along with

written instructions to use. Toothpaste and mouthrinse were provided in unmarked containers so that subjects were blinded regarding the identity of the products received. After 21-day treatment period (day 42), all subjects were given further oral hygiene instructions, and professional tooth cleaning was provided.

Any adverse events occurring during the course of the study were reported and documented on a custom Adverse Reaction Report form. Development of tooth/tongue staining, presence of oral soreness or dryness, desquamation and burning sensation of the oral mucosa, and taste alteration were recorded. Subjects were also asked to rate the level of satisfaction derived from the use of the toothpaste and mouthrinse by using a scale ranging from 1 (''completely unsatisfied'') to 5 (''completely satisfied'').

Statistical analysis

The subject was regarded as the statistical unit. For each clinical parameter, the recordings from the six selected sites for either test and control quadrants were added and divided by six to give the mean value for each subject. Therefore, for each parameter at each observational period, the subject was represented by a single test and a single control value. Data were expressed by either median and inter-quartile range (IR) for non-parametric variables, or mean ± standard deviation (SD) for parametric variables.

We hypothesized the treatment regimen would result in significant changes in test quadrants for all clinical parameters, as recorded in the overall population. We also hypothesized that HR and LR groups would present differences in response to treatment. Three observation intervals were considered: baseline (day 0), before treatment (day 21), and after treatment (day 42). Therefore, to test the effect of ''time'' and ''quadrant'' on response variables, ANOVA for repeated measures and Friedman's test for parametric and non-parametric variables, respectively, were used. Paired *t*-test and Wilcoxon matched-pairs test were used to explore intra- and inter-quadrant differences within groups. Between-group comparisons were performed by using unpaired *t*-test and Mann–Whitney *U*-test. The level of significance was set at 5%.

Results

Protocol deviations

All subjects completed the study and stated they had properly complied with study instructions, including treatment regimen. Fifteen of the 96 subjects presented for evaluation on day 42 ± 3 days. All subjects from both HR and LR groups were available for evaluation on days 21 and 42.

Plaque accumulation

In the overall population, a statistically significant effect of ''treatment'' ($F = 522.2$; $p < 0.001$) on PlI score was observed. On day 21, PlI was 1.69 ± 0.35 in test quadrants and 0.51 ± 0.33 in control quadrants. A statistically significant decrease of PlI was observed in test quadrants (Fig. 1) at completion of treatment regimen ($p < 0.001$). In contrast, PlI remained similarly low in control quadrants before and after treatment (Fig. 1). No differences in PlI were noted between test and control quadrants after treatment (day 42-PlI equal to 0.55 ± 0.36 and 0.52 ± 0.36 in test and control quadrants, respectively). However, when PlI on day 42 was compared with baseline (day 0-PlI equal to 0.42 ± 0.30 and 0.43 ± 0.31 in test and control quadrants, respectively) significant differences were found in both test and control quadrants.

Table 1 shows PlI in test and control quadrants for HR and LR groups, respectively, as recorded on days 0, 21, and 42. A statistically significant decrease of PlI was observed in test quadrants after treatment for both groups. PlI significantly decreased from 1.73 ± 0.33 on day 21 to 0.58 ± 0.36 on day 42 for HR group ($p < 0.001$), and from 1.65 ± 0.37 on day 21 to 0.52 ± 0.29 on day 42 for LR group ($p < 0.001$). On day 42,

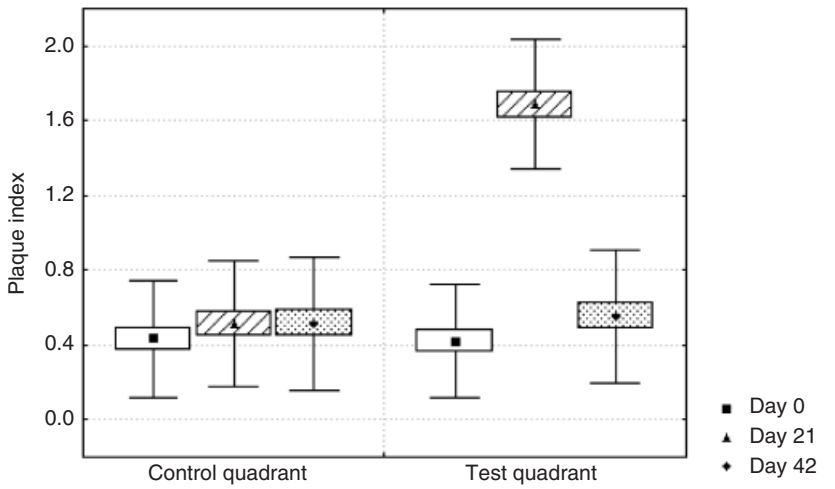

Fig. 1. Box–Whisker plot for plaque index at baseline (day 0), before treatment (day 21), and after treatment (day 42) in test and control quadrants in the overall population (mean; Box: ± 95% CI; Whisker: ± SD; $n = 96$).

Table 1. Descriptive statistics and comparisons among mean levels of plaque index measured in ''low-responder'' (LR) and ''high-responder'' (HR) groups at different observation intervals in test and control quadrants

	LR		HR		*t*-test (*p*-value)
	N	mean ± SD	*N*	mean ± SD	
Test quadrant					
day 0	24	0.34 ± 0.25	24	0.42 ± 0.32	0.32
day 21	24	1.65 ± 0.37	24	1.73 ± 0.33	0.41
day 42	24	0.52 ± 0.29	24	0.58 ± 0.36	0.56
Control quadrant					
day 0	24	0.35 ± 0.24	24	0.47 ± 0.37	0.23
day 21	24	0.42 ± 0.30	24	0.49 ± 0.37	0.48
day 42	24	0.47 ± 0.33	24	0.54 ± 0.37	0.45

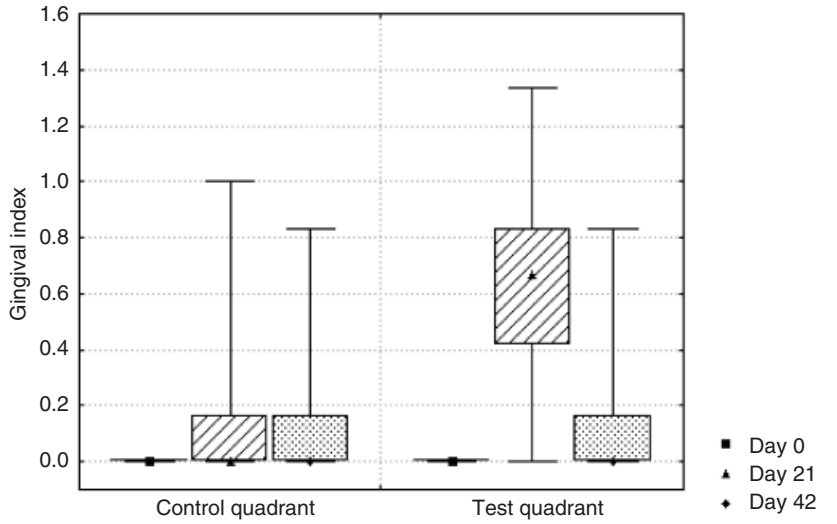

Fig. 2. Box–Whisker plot for gingival index at baseline (day 0), before treatment (day 21), and after treatment (day 42) in test and control quadrants in the overall population (median; Box: 25–75%; Whisker: min–max; $n = 96$).

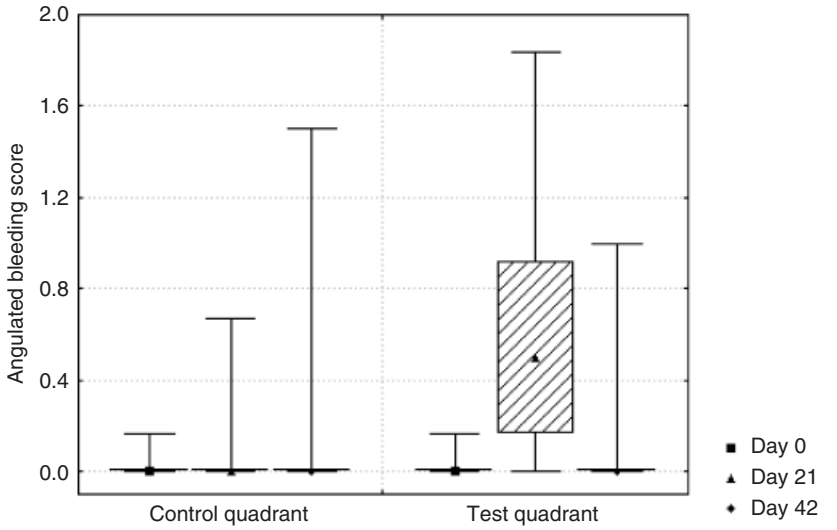

Fig. 3. Box–Whisker plot for angulated bleeding score at baseline (day 0), before treatment (day 21), and after treatment (day 42) in test and control quadrants in the overall population (median; Box: 25–75%; Whisker: min–max; $n = 96$).

PlI was similarly low in test compared with control quadrants for both groups ($p = 0.99$ and $p = 0.94$ for HR and LR, respectively). Moreover, no significant differences in PlI were found between days 0 and 42 in both groups ($p = 0.18$ and $p = 0.05$ for HR and LR, respectively). In control quadrants, PlI remained similar to baseline condition on days 21 and 42 for both groups ($p > 0.40$ for all comparisons).

When the two groups were compared, no significant differences in PlI were noted on days 0, 21, and 42 in either test or control quadrants (Table 1).

Gingival inflammation

In the overall population, treatment resulted in a statistically significant decrease of GI (Friedman ANOVA $\chi^2 = 157.2$; $p < 0.001$), AngBS (Friedman ANOVA $\chi^2 = 132.2$; $p < 0.001$), and GCF ($F = 413.5$; $p < 0.001$) in test quadrants (Figs. 2–4). GI shifted from 0.67 (IR: 0.42–0.83) on day 21 to 0.00 (IR: 0.00–0.17) on day 42, AngBS from 0.50 (IR: 0.17–0.92) to 0.00 (IR: 0.00–0.00), and GCF from $0.33 \pm 0.12\,\mu$l to $0.09 \pm 0.06\,\mu$l. After treatment GI, AngBS, and GCF were similarly low in test and control quadrants. However, significant differences were noted between days 0 and 42 for all clinical parameters in test quadrants ($p < 0.001$ for all comparisons).

Descriptive statistics of GI, AngBS, and GCF in test and control quadrants for HR and LR groups at different observation intervals are shown in Tables 2–4, respectively. In test quadrants, all clinical parameters significantly decreased from day 21 to day 42 ($p < 0.001$ for all comparisons), and were similarly low when compared with control quadrants ($p > 0.20$ for all comparisons) for both HR and LR groups. After treatment, AngBS and GCF reversed to baseline condition in test and control quadrants for both groups, while no differences were noted in control quadrants throughout the study. GI on day 42 remained significantly higher than baseline score in test quadrants for both groups ($p < 0.01$) and in control quadrants for HR group ($p = 0.002$).

When the two groups were compared, GI, AngBS, and GCF in test quadrants were significantly higher in the HR group than the LR group on day 21. Treatment produced similarly low scores for GI and AngBS in the test and control quadrants for both groups (Tables 2 and 3). In contrast, GCF remained significantly higher in the HR group than the LR group even after treatment (Table 4).

Adverse effects and level of satisfaction

No serious adverse events to treatment regimen were recorded. Development of extrinsic tooth staining was noted in three subjects on day 42, which was removed during the final prophylaxis session. One subject presented with desquamation of the oral mucosa, while six subjects reported mild burning sensation without any detectable clinical changes. Three subjects experienced slight taste alterations. All symptoms completely recovered within 1 week after treatment cessation. Level of satisfaction from the use of meridol® toothpaste and meridol® mouthrinse was 4.0 (IR: 3.0–5.0) and 3.0 (IR: 3.0–4.0), respectively.

Discussion

The aim of the present study was to evaluate the effectiveness of an oral hygiene regimen based on mechanical

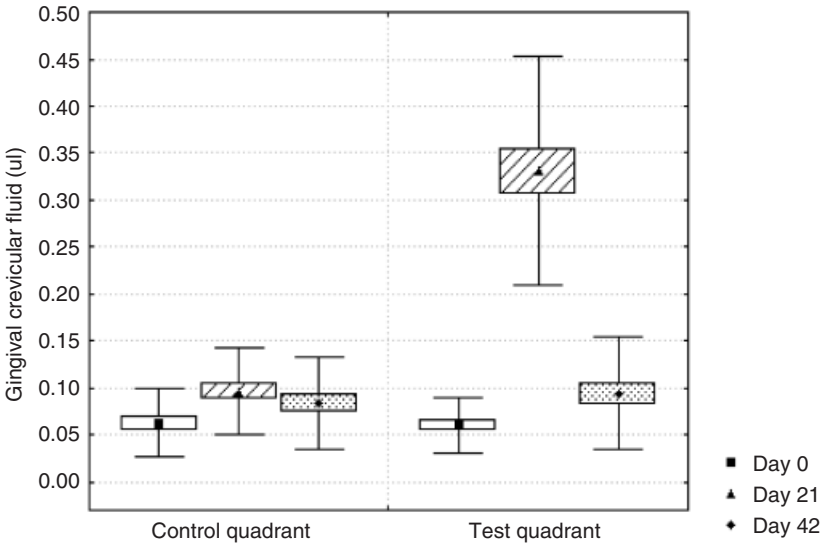

Fig. 4. Box–Whisker plot for gingival crevicular fluid volume (in μl) at baseline (day 0), before treatment (day 21), and after treatment (day 42) in test and control quadrants in the overall population (mean; Box: $\pm$ 95% CI; Whisker: $\pm$ SD; $n = 96$).

Table 2. Descriptive statistics and comparisons among median levels of gingival index measured in ''low-responder'' (LR) and ''high-responder'' (HR) groups at different observation intervals in test and control quadrants

	LR		HR		Mann–Whitney test (p-value)
	N	median (interquartile range)	N	median (interquartile range)	
Test quadrant					
day 0	24	0.0 (0.0–0.0)	24	0.0 (0.0–0.0)	0.805
day 21	24	0.50 (0.33–0.58)	24	0.83 (0.67–1.0)	<0.001
day 42	24	0.0 (0.0–0.17)	24	0.08 (0.0–0.33)	0.338
Control quadrant					
day 0	24	0.0 (0.0–0.0)	24	0.0 (0.0–0.0)	0.621
day 21	24	0.0 (0.0–0.17)	24	0.0 (0.0–0.17)	0.829
day 42	24	0.0 (0.0–0.17)	24	0.17 (0.0–0.17)	0.110

Table 3. Descriptive statistics and comparisons among median levels of angulated bleeding score measured in ''low-responder'' (LR) and ''high-responder'' (HR) groups at different observation intervals in test and control quadrants

	LR		HR		Mann–Whitney test (p-value)
	N	median (interquartile range)	N	median (interquartile range)	
Test quadrant					
day 0	24	0.0 (0.0–0.0)	24	0.0 ((0.0–0.0)	0.322
day 21	24	0.33 (0.0–0.75)	24	0.67 (0.42–1.0)	0.035
day 42	24	0.0 (0.0–0.0)	24	0.0 (0.0–0.17)	0.095
Control quadrant					
day 0	24	0.0 (0.0–0.0)	24	0.0 (0.0–0.0)	0.621
day 21	24	0.0 (0.0–0.0)	24	0.0 (0.0–0.0)	0.621
day 42	24	0.0 (0.0–0.0)	24	0.0 (0.0–0.25)	0.257

plaque control in association with AmF/SnF_2-containing toothpaste and mouthrinse as prescribed after experimentally induced gingivitis. The single-blinded design (unmarked containers for both toothpaste and mouthrinse) of the study was chosen to eliminate subject bias (possibly originating from previous exposure to these commercially available products) and, in this manner, to enhance compliance regarding use of the materials supplied by the study (Chilton & Fleiss 1986). Treatment effects were also separately analyzed in two subpopulations of subjects (HR and LR groups) presenting with substantially different inflammatory response to similar plaque levels. The results of the study indicate that such oral hygiene regimen is effective in reducing the plaque deposits and improving the inflammatory status of the gingival tissues in the overall population, as well as in both HR and LR groups. However, the HR group demonstrated a statistically greater inflammatory condition, as determined by the amount of gingival crevicular fluid, following treatment when compared with the LR group.

In a companion paper (Trombelli et al. 2004), we investigated the validity of the randomized, split-mouth, localized, experimental gingivitis model to assess the impact of supragingival plaque on gingival status over a 21-day period. A statistically significant increase of plaque deposits and clinical parameters of gingival inflammation was observed in test quadrants compared with control quadrants over the course of the experimental gingivitis period. Consistently, the decreasing amount of supragingival plaque in test quadrants observed here was associated with a significant decrease of gingival inflammation after treatment.

Reinstitution of conventional toothbrushing and flossing after an experimental gingivitis trial has been demonstrated to be an effective means to reverse the plaque-induced inflammation of the gingiva (Löe et al. 1965, 1967, Theilade et al. 1966). Since the present trial did not include control treatment based on conventional mechanical plaque control alone, the results should not be regarded as an assessment of the effectiveness of AmF/SnF_2 for treating gingivitis. However, the adjunctive use of meridol® toothpaste and meridol® mouthrinse may have improved the anticipated reversal of gingival inflammation, by adding an active anti-bacterial chemical component to the mechanical oral hygiene regimen (Brecx et al. 1990, 1992, Zimmermann et al. 1993, Mengel et al. 1996, Hoffmann et al. 2001). In a recent investigation, it was demonstrated that mouthrinse containing AmF/SnF_2 was effective in reducing plaque accumulation and in maintaining healthy gingiva (Brecx et al. 1990). In addition, it was shown that a combination

Table 4. Descriptive statistics and comparisons among mean levels of gingival crevicular fluid (in μl) measured in ''low-responder'' (LR) and ''high-responder'' (HR) groups at different observation intervals in test and control quadrants

	LR		HR		*t*-test (*p*-value)
	N	mean ± SD	*N*	mean ± SD	
Test quadrant					
day 0	24	0.06 ± 0.02	24	0.08 ± 0.04	0.025
day 21	24	0.22 ± 0.07	24	0.46 ± 0.13	<0.001
day 42	24	0.07 ± 0.03	24	0.12 ± 0.07	0.002
Control quadrant					
day 0	24	0.05 ± 0.03	24	0.08 ± 0.05	0.015
day 21	24	0.08 ± 0.03	24	0.11 ± 0.05	0.006
day 42	24	0.07 ± 0.03	24	0.11 ± 0.07	0.011

of habitual self-performed and non-supervised oral hygiene with this mouthwash regimen is more beneficial for plaque control than the use of mechanical oral hygiene alone (Brecx et al. 1992, Hoffmann et al. 2001). In addition to the anti-microbial activity of the fluoride compounds, AmF and SnF_2 have been shown to enhance the oxygen-dependent anti-bacterial activity of neutrophils, with the combination of the two being far more effective than each one alone (Shapira et al. 1997). This effect may have contributed to the improvement of gingival status.

In a previous report based on a partial sample (39 subjects) of this study population, we have demonstrated that additional AmF/SnF_2 toothpaste and mouthrinse as an adjunct to oral hygiene regimen was effective in reducing plaque-associated gingivitis, regardless of preexisting severity of gingival inflammation. The level of improvement in gingival status, however, was dependent on the preexisting severity of inflammatory condition which, in turn, was associated to the amount of plaque deposits (Trombelli et al. 2003). In the present study, a similar reduction in plaque deposits with concomitant regression of clinical signs of gingival inflammation was observed for subjects presenting significantly different inflammatory response to similar plaque levels. Overall, these observations corroborate the well-established causal relationship between supragingival plaque and gingival inflammation. It is noteworthy that the self-administered oral hygiene regimen reversed the gingivitis condition to a level that eliminated pretreatment differences between the HR and LR groups. Based on this finding, and the evidence that subjects with severe gingival inflammation may have difficulty reducing such inflammation with mechanical plaque control alone (Hefti 1981), one can theorize that use of the oral hygiene regimen prescribed in the present study may have benefits even for subjects with a higher susceptibility to gingival inflammation. Testing of this hypothesis will necessitate specifically designed studies.

Prior to treatment, the HR group presented a crevicular fluid level 110% greater than the LR group in test quadrants. Interestingly, test quadrant GCF levels remained significantly higher after treatment in the HR group compared with the LR group (HR was 71% greater than LR), even though the levels were very low in absolute value. Moreover, the HR group also presented elevated levels of crevicular fluid in control quadrants compared with the LR group both before and after treatment, despite similarly low plaque accumulation. These findings support further the hypothesis that the severity of gingival inflammatory response to plaque may be a patient trait (Tatakis & Trombelli 2004, Trombelli et al. 2004), a trait that apparently is not obliterated even after substantial reduction of the microbial challenge. Therefore, this raises the possibility that susceptibility to plaque-induced gingivitis might be clinically detectable even when optimum plaque control regimen is either maintained or re-established. Further investigations are needed to assess the effectiveness of local or systemic chemotherapeutic approaches shown to modulate host factors implicated in the pathogenesis of the gingival inflammatory process (Heasman & Seymour 1989, Johnson et al. 1990, Kornman et al. 1990, Heasman et al. 1994, Suresh et al. 2001) in controlling the gingival status of subjects with ''high'' or ''low'' susceptibility to gingivitis.

In conclusion, the results of the present study indicate that a treatment regimen based on mechanical plaque control supplemented with AmF/SnF_2-containing toothpaste and mouthrinse is effective in reducing plaque accumulation and re-establishing a healthy gingival condition after experimentally induced gingivitis. This treatment regimen was equally effective when subjects with different severity of gingivitis to comparable amounts of plaque deposits were considered.

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References

Addy, M. & Moran, J. M. (1997) Evaluation of oral hygiene products: science is true; don't be misled by the facts. *Periodontology 2000* **15**, 40–51.

Brecx, M., Brownstone, E., MacDonald, L., Gelskey, S. & Cheang, M. (1992) Efficacy of listerine, meridol and chlorhexidine mouthrinses as supplements to regular tooth cleaning measures. *Journal of Clinical Periodontology* **19**, 202–207.

Brecx, M., Netuschil, L., Reichert, B. & Schreil, G. (1990) Efficacy of listerine, meridol and chlorhexidine mouthrinses on plaque, gingivitis and plaque bacteria vitality. *Journal of Clinical Periodontology* **17**, 292–297.

Brown, L. J. & Löe, H. (1993) Prevalence, extent, severity and progression of periodontal disease. *Periodontology 2000* **2**, 57–71.

Chilton, N. W. & Fleiss, J. L. (1986) Design and analysis of plaque and gingivitis clinical trials. *Journal of Clinical Periodontology* **13**, 400–410.

Furuichi, Y., Lindhe, J., Ramberg, P. & Volpe, A. R. (1992) Patterns of de novo plaque formation in the human dentition. *Journal of Clinical Periodontology* **19**, 423–433.

Goodson, J. M., Tanner, A. C. R., Haffajee, A. D., Sornberger, G. C. & Socransky, S. S. (1982) Patterns of progression and regression of advanced destructive periodontal disease. *Journal of Clinical Periodontology* **10**, 298–310.

Heasman, P. A. & Seymour, R. A. (1989) The effect of a systemically-administered non-steroidal anti-inflammatory drug (flurbiprofen) on experimental gingivitis in humans.

Journal of Clinical Periodontology **16**, 551–556.

Heasman, P. A., Seymour, R. A. & Kelly, P. J. (1994) The effect of systemically-administered flurbiprofen as an adjunct to toothbrushing on the resolution of experimental gingivitis. *Journal of Clinical Periodontology* **21**, 166–170.

Hefti, A. (1981) Prospects of success with the papillary bleeding index for the motivation of children with pronounced gingivitis. *SSO Schweizerische Monatsschrift für Zahnheilkunde* **91**, 963–968.

Hoffmann, T., Bruhn, G., Richter, S., Netuschil, L. & Brecx, M. (2001) Clinical controlled study on plaque and gingivitis reduction under long-term use of low-dose chlorhexidine solutions in a population exhibiting good oral hygiene. *Clinical Oral Investigations* **5**, 89–95.

Johnson, R. H., Armitage, G. C., Francisco, C. & Page, R. C. (1990) Assessment of the efficacy of a nonsteroidal anti-inflammatory drug, Naprosyn, in the treatment of gingivitis. *Journal of Periodontal Research* **25**, 230–235.

Kornman, K. S., Blodgett, R. F., Brunsvold, M. & Holt, S. C. (1990) Effects of topical applications of meclofenamic acid and ibuprofen on bone loss, subgingival microbiota and gingival PMN response in the primate *Macaca fascicularis*. *Journal of Periodontal Research* **25**, 300–307.

Lindhe, J., Hamp, S. & Loe, H. (1973) Experimental periodontitis in the beagle dog. *Journal of Periodontal Research* **8**, 1–10.

Lindhe, J. & Koch, G. (1966) The effect of supervised oral hygiene on the gingiva of children. Progression and inhibition of gingivitis. *Journal of Periodontal Research* **1**, 260–267.

Lindhe, J. & Koch, G. (1967) The effect of supervised oral hygiene on the gingivae of children. *Journal of Periodontal Research* **2**, 215–220.

Löe, H., Anerud, A., Boysen, H. & Morrison, E. (1986) Natural history of periodontal disease in man. Rapid, moderate and no loss of attachment in Sri Lankan laborers 14 to 46 years of age. *Journal of Clinical Periodontology* **13**, 431–445.

Löe, H. & Silness, J. (1963) Periodontal disease in pregnancy. I. Prevalence and severity. *Acta Odontologica Scandinavica* **21**, 533–551.

Löe, H., Theilade, E. & Jensen, S. B. (1965) Experimental gingivitis in man. *Journal of Periodontology* **36**, 177–187.

Löe, H., Theilade, E., Jensen, S. B. & Schiott, C. R. (1967) Experimental gingivitis in man. 3. Influence of antibiotics on gingival plaque development. *Journal of Periodontal Research* **2**, 282–289.

Mengel, R., Wissing, E., Schmitz-Habben, A. & Flores-de-Jacoby, L. (1996) Comparative study of plaque and gingivitis prevention by AmF/SnF2 and NaF. A clinical and microbiological 9-month study. *Journal of Clinical Periodontology* **23**, 372–378.

Oliver, R. C., Brown, L. J. & Löe, H. (1998) Periodontal diseases in the United States population. *Journal of Periodontology* **69**, 269–278.

Page, R. C. (1999) Milestones in periodontal research and the remaining critical issues. *Journal of Periodontal Research* **34**, 331–339.

Page, R. C. & Schroeder, H. E. (1982) *Periodontitis in man and other animals. A comparative review*. New York, NY: Karger.

Prayitno, S. W., Addy, M. & Wade, W. G. (1993) Does gingivitis lead to periodontitis in young adults? *Lancet* **342**, 471–472.

Robinson, P. J. (1995) Gingivitis: a prelude to periodontitis? *Journal of Clinical Dentistry* **6**, 41–45.

Shapira, L., Schatzker, Y., Gedalia, I., Borinski, R. & Sela, M. N. (1997) Effect of amine and stannous fluoride on human neutrophil functions in vitro. *Journal of Dental Research* **76**, 1381–1386.

Sheiham, A. & Netuveli, G. S. (2002) Periodontal diseases in Europe. *Periodontology 2000* **29**, 104–121.

Silness, J. & Löe, H. (1964) Periodontal disease in pregnancy. II. Correlation between oral hygiene and periodontal condition. *Acta Odontologica Scandinavica* **22**, 121–135.

Suresh, D. K., Vandana, K. L. & Mehta, D. S. (2001) Intracrevicular application of 0.3% flurbiprofen gel and 0.3% triclosan gel as anti inflammatory agent. A comparative clinical study. *Indian Journal of Dental Research* **12**, 105–112.

Tatakis, D. N. & Trombelli, L. (2004) Modulation of clinical expression of plaque-induced gingivitis. I. Background review and rationale. *Journal of Clinical Periodontology* doi: 10.1111/j.1600-051X.2004.00477.x.

Theilade, E., Wright, W. H., Jensen, S. B. & Löe, H. (1966) Experimental gingivitis in man. II. A longitudinal clinical and bacteriological investigation. *Journal of Periodontal Research* **1**, 1–13.

Trombelli, L., Bottega, S., Orlandini, E., Scapoli, C., Tosi, M. & Tatakis, D. N. (2003) Response to a plaque control regimen on different levels of gingival inflammation. *Minerva Stomatologica* **52**, 75–79.

Trombelli, L., Tatakis, D. N., Scapoli, C., Bottega, S., Orlandini, E. & Tosi, M. (2004) Modulation of clinical expression of plaque-induced gingivitis. II. Identification of ''high responder'' and ''low responder'' subjects. *Journal of Clinical Periodontology* doi: 10.1111/j.1600-051X.2004.00478.x.

van der Weijden, G. A., Timmerman, M. F., Nijboer, A., Reijerse, E. & van der Velden, U. (1994) Comparison of different approaches to assess bleeding on probing as indicators of gingivitis. *Journal of Clinical Periodontology* **21**, 589–594.

Zimmermann, A., Flores-de-Jacoby, L. & Pan, P. (1993) Gingivitis, plaque accumulation and plaque composition under long-term use of meridol. *Journal of Clinical Periodontology* **20**, 346–351.

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