J Clin Periodontol 2011; 38: 43–49 doi: 10.1111/j.1600-051X.2010.01632.x

Journal of Clinical Periodontology

Amoxicillin and metronidazole as an adjunctive treatment in generalized aggressive periodontitis at initial therapy or re-treatment: a randomized controlled clinical trial

Gareth S. Griffiths[1], Rasidah Ayob[2], Adrian Guerrero[3], Luigi Nibali[2], Jean Suvan[2], David R. Moles[4] and Maurizio S. Tonetti[5]

[1]University of Sheffield, Academic Unit of Restorative Dentistry, Sheffield, UK; [2]Unit of Periodontology and Eastman Clinical Investigation Centre, UCL Eastman Dental, Institute, London, UK; [3]Graduate Comprehensive Dentistry, University of Barcelona, and Private Periodontal Practice, Malaga, Spain; [4]Health Services Research, Peninsula Dental School, University of Plymouth, Plymouth, UK; [5]European Research Group on Periodontology (ERGOPerio), Berne, Switzerland

Griffiths GS, Ayob R, Guerrero A, Nibali L, Suvan J, Moles DR, Tonetti MS. Amoxicillin and metronidazole as an adjunctive treatment in generalized aggressive periodontitis at initial therapy or re-treatment: a randomized controlled clinical trial. J Clin Periodontol 2011; 38: 43–49. doi: 10.1111/j.1600-051X.2010.01632.x

Abstract

Background: Previously, we showed that systemic metronidazole and amoxicillin significantly improved the outcomes of non-surgical debridement in generalized aggressive periodontitis patients. This study aimed to observe whether re-treatment with adjunctive antimicrobials would give the placebo group benefits comparable with the test group.

Methods: Thirty-eight of 41 subjects, from the initial 6-month trial, completed the second phase, re-treatment of sites with remaining pockets $\geqslant 5$ mm. Subjects on placebo in phase one, received adjunctive antibiotics for 7 days. Clinical parameters were collected at 2 months posttreatment (8 months from baseline).

Results: Patients who received antibiotics at initial therapy, showed statistically significant improvement in pocket depth reduction and in the % of sites improving above clinically relevant thresholds, compared with patients who received antibiotics at re-treatment. In deep pockets ($\geqslant 7$ mm), the mean difference was 0.9 mm ($p = 0.003$) and in moderate pockets (4–6 mm) it was 0.4 mm ($p = 0.036$). For pockets converting from $\geqslant 5$ to $\leqslant 4$ mm, this was 83% compared with 67% ($p = 0.041$) and pockets converting from $\geqslant 4$ to $\leqslant 3$ mm was 63% compared with 49% ($p = 0.297$).

Conclusions: At 8 months, patients who had antibiotics at initial therapy showed statistically significant benefits compared with those who had antibiotics at re-treatment.

Key words: generalized aggressive periodontitis; antibiotics; treatment; randomized controlled clinical trial; human

Accepted for publication 14 September 2010

Conflict of interest and source of funding statement

There is no conflict of interest associated with the present study. This study was supported by the Periodontal Research Fund of the Eastman Dental Institute. L. N. was supported by a fellowship from the Italian Society of Periodontology, SIdP.

Generalized aggressive periodontitis (GAgP) affects a minority of the patients presenting with periodontal disease. However, it is highly significant because it is characterized by severe destruction of the supporting apparatus of the teeth, which may lead to edentulism early in life. Because of its relatively rare occurrence (Demmer & Papapanou 2010), few studies have evaluated how to treat this condition (Xajigeorgiou et al. 2006, Mestnik et al. 2010). The current notion is that, as with most forms of periodontitis, the first step in treatment of GAgP is a cause-related treatment phase aimed at the reduction and/or elimination

of the pathogenic microorganisms. In addition, it has been suggested that there may be adjunctive benefits from the use of systemic antimicrobials (Herrera et al. 2002, Haffajee et al. 2003).

In a previous study (Guerrero et al. 2005), we showed that a 7-day adjunctive course of systemic metronidazole and amoxicillin significantly improved the short-term clinical outcomes of non-surgical debridement in subjects with GAgP. However, because non-surgical therapy has been shown to be effective in treating periodontal diseases, most clinicians adopt a non-surgical approach without adjuncts and will review the situation before considering alternative treatments, which may include the use of systemic antimicrobials. Thus, antimicrobials are more likely to be used at re-treatment rather than as part of the initial therapy.

As the first patients from the study, by Guerrero et al. (2005) were completing the 6 months re-assessment it was clear that although there was an improvement in most subjects, there were still residual pockets $\geqslant 5$ mm. Further treatment was indicated and we planned extending the study to answer the question, ''If we performed further instrumentation and gave adjunctive antimicrobials to the group that had previously received placebo medication, would both groups end up with similar outcomes''? As both groups would have received similar treatments at this stage the null hypothesis would be that there was no difference in outcomes between the two groups. If differences were observed between the two groups, these may be attributable to the timing of when antibiotics were given.

Material and Methods

Experimental design

The first phase of the study was a randomized placebo-controlled, parallel design, double-blind clinical trial with 6-month follow-up, while the second phase study was a further 2-month follow-up on the same patient sample. During this second phase study, subjects who comprised the placebo group of the first phase study received re-treatment with the adjunctive use of antibiotics, while the subjects who comprised the first phase study test group received re-treatment alone. Throughout this second phase, the operator and examiner remained blinded to treatment assignment. As no placebo was used at this stage, the subjects were no longer blinded to the treatment received.

Ethical approval was obtained from the Eastman Dental Institute University College London Hospitals Joint Research and Ethics Committee and the study was conducted according to the principles outlined in the Declaration of Helsinki on experimentation involving human subjects.

Inclusion/exclusion criteria

The details of the initial study have been described previously (Guerrero et al. 2005) and are summarized in Fig. 1. Briefly, 51 subjects diagnosed with GAgP as per the 1999 classification (Armitage 1999) were considered eligible. The study included subjects (i) with at least 20 teeth present; (ii) in good general health; (iii) aged between 16 and 35 when first diagnosed with aggressive periodontal disease; (iv) exhibiting at least eight teeth presenting at least one site with probing pocket depth (PPD)

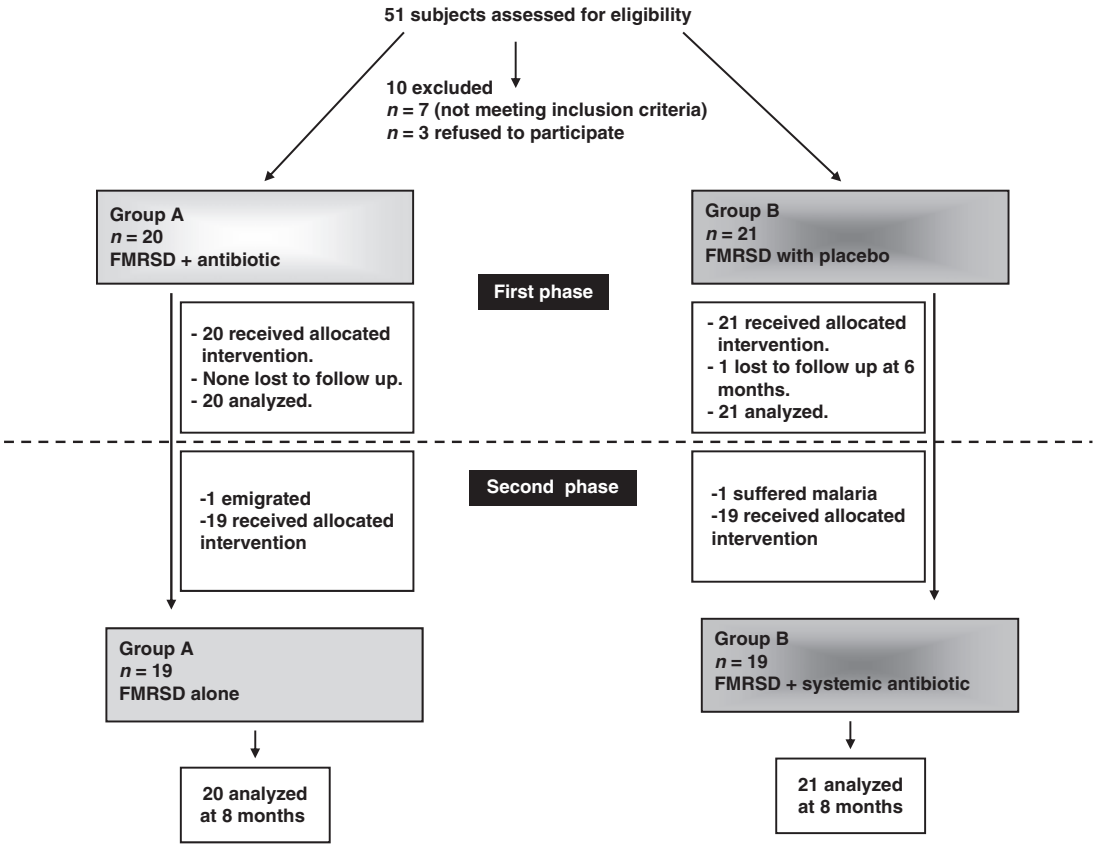

Fig. 1. Flow diagram showing recruitment, retention and the different phases of the study design. FMRSD, full-mouth root surface debridement.

and lifetime cumulative attachment loss (LCAL) $\geqslant$5 mm, with three or more being other than first molars or incisors. Subjects were excluded from the study if they: (i) were considered to have a diagnosis of chronic periodontitis (Armitage 1999); (ii) were pregnant or lactating females; (iii) were females of child-bearing age not using a standard accepted method of birth control; (iv) required antibiotic pre-medication; (v) had any other systemic diseases; (vi) had received antibiotic treatment in the previous 3 months; (vii) had received a course of periodontal treatment within the last 6 months; (viii) were allergic to penicillin or metronidazole and (ix) were not able or willing to consent to participating in the study. Informed consent was obtained from all the subjects to be entered in the study.

Sample size calculation

The sample size calculation was based on the requirements of the first phase study and used data from the study by Sigusch et al. (2001). This determined that 17 subjects per treatment arm would provide 80% power to detect a true difference of 1.0 mm between test and placebo using PPD reduction in pockets $\geqslant$7 mm as the primary outcome variable, assuming that the common standard deviation is 1.0 mm. Accordingly, a sample of 21 subjects per arm (42 in total) were to be recruited to compensate for possible drop-out during the study period.

Population screening

Ten subjects were excluded as shown in Fig. 1, and 41 commenced the first phase study. Subject and clinical characteristics of the two groups at baseline are shown in Table 1. Baseline examinations were completed by an examiner (L. N.) and the operator (A. G.) completed all instrumentations within a 24 h period. Patients were then given identical bottles containing antibiotics or placebo according to the randomization. Only the study co-ordinator (J. S.) knew what was in the bottles; thus, the examiner, operator and the patient were blind to the medication given. Subjects were randomly assigned by a computer-generated table to receive one of the two treatments.

Before entering the second phase, one subject from the original test group and two from the placebo withdrew; one of these two later subjects was lost to follow-up between the 2- and 6-month visit (Fig. 1). These were viewed as random events and not study related. Consequently, 19 subjects entered each group for the second phase. However, data from the last observation of the three subjects who dropped out during the earlier phases of the study were carried forward until the end of the study.

Table 1. Subject and clinical characteristics of the two groups at baseline

Parameter	Antibiotic initially ($n = 20$)	Antibiotic at re-treatment ($n = 21$)
Age mean (95% CI)	31 (28, 34)	32 (29, 35)
Females nos (%)	16 (80%)	12 (57%)
Smokers nos (%)	5 (25%)	4 (19%)
Caucasians nos (%)	13 (65%)	10 (48%)
Mean nos of teeth at baseline (95% CI)	26 (25, 27)	26 (25, 27)
Baseline % of pockets $\geqslant$4 mm median (IQ range)	46 (38, 57)	46 (34, 60)

Mann–Whitney test, χ^2-test; and paired *t*-test showed no significant differences between groups. CI, confidence intervals; IQ, interquartile range; nos, numbers.

Clinical procedures and allocation concealment

All of these subjects had instrumentation within a 24-h period, by a single experienced therapist (R. A.), not the same individual as the first phase of the study. Randomization had occurred during the first phase of the study and allocation concealment was preserved as follows. The study coordinator prepared a closed envelope, which indicated whether or not subjects should have adjunctive antimicrobials. This envelope was opened by the therapist at the end of the instrumentation. Thus, the operator (R. A.) and examiner (L. N.) remained blind to treatment assignment. In order to keep the examiner masked from treatment assignment, self-reported adverse events were recorded by the therapist during the 1-week posttreatment control visit, and the subjects were asked not to mention to the examiner anything about adverse events or the medication taken. All 38 subjects completed the examination 2 months after the second phase of the study (8 months of the total study).

Clinical examination

Clinical parameters were assessed by the calibrated examiner (L. N.) using a UNC-15 periodontal probe, at six sites/tooth excluding third molars. The examiner recorded PPD and recession of the gingival margin (REC), and LCAL was calculated as the sum of PPD and REC. Ten non-study subjects with aggressive periodontitis were recruited and used for the calibration exercise, where the examiner showed 99.7% reproducibility within $\pm$ 2 mm in LCAL measurements. Details of the clinical examination were as described previously (Guerrero et al. 2005). Thus, the same information was recorded, by the same examiner at the baseline appointment of the first phase of treatment, at 2 months, at 6 months (second phase baseline) and at 8 months.

Non-surgical periodontal therapy

As in the first phase study reported by Guerrero et al. (2005), a standard cycle of periodontal therapy consisting of oral hygiene instructions, supra and subgingival mechanical instrumentation of the root surface was performed by a single experienced therapist (R. A.) using a piezoelectric instrument with fine tips (EMS, Nyon, Switzerland) and hand instruments as appropriate. The operator was not restricted by time, but completed the task until satisfied that each root surface to be treated had been adequately instrumented. The time taken for this instrumentation was recorded by the therapist. Local anaesthesia was used as necessary. The 19 subjects who took the antibiotics at re-treatment were provided with two bottles of medication. One bottle contained 21 capsules of 500 mg of amoxicillin, while the other contained 21 capsules of 500 mg metronidazole. Subjects were asked to take a pill of each medication three times a day during 7 days. All subjects used a 0.2% chlorhexidine rinse (supplied to improve and standardize initial plaque control compliance) for 2 weeks posttreatment and thereafter relied on standard oral hygiene methods as instructed at the commencement of the study.

1 week posttreatment controls

The objectives of the posttreatment appointments were to control and rein-

force the oral hygiene habits of the subject, to monitor the early healing events, and report on any adverse events or additional medications taken. In addition, the 1-week posttreatment visit served as a compliance control, because subjects were asked to return any medication not taken and/or the empty bottles. The number of pills not taken by the subject was documented.

Re-assessment examinations

Re-assessment visit occurred at 2 months after the completion of the second phase treatment, 8 months since the baseline examination. During this appointment, the examiner recorded any medical history changes and the clinical periodontal parameters recorded at the baseline visit were repeated.

Primary and secondary outcome measures

The primary outcome measure of the study was PPD reduction at sites with initial PPD $\geqslant$7 mm. Secondary outcomes included differences between groups for (i) changes in mean PPD and LCAL at different initial PPD categories; (ii) changes in percentage of sites with PPD reduction of $\geqslant$2 mm; (iii) percentage of sites with PPD changing from $\geqslant$5 to $\leqslant$4 mm and the percentage of sites with PPD changing from $\geqslant$4 to $\leqslant$3 mm; (iv) description and frequency of adverse events; (v) instrumentation time and (vi) compliance with the systemic medication.

Data management and statistical analysis

Data were entered into an Excel (Microsoft Office 2000) database and were proofed for entry errors. The database was subsequently locked, imported into SPSS for Windows (SPSS Inc. version 11.0) formatted and analysed. A subject-level analysis was performed by computing a subject-level variable (at different PPD categories) for each of the parameters. Numerical data were summarized as means and 95% confidence intervals, and the percentage-based measures were summarized as the median of the percentage and inter-quartile range. Significance of differences between test and placebo groups in terms of numerical data was evaluated via univariate analysis using the independent sample *t*-test. The percentage data between the two groups were compared with the Mann–Whitney test. The significance of the treatment option (antibiotics initially or antibiotics at re-assessment) on the dependent variables PPD reduction and LCAL gain at different initial PPD categories was estimated by analysis of covariance (ANCOVA). The models were adjusted for baseline values and controlled for smoking. The final model was then selected by including significant factors only. Model estimates included adjusted means and 95% confidence intervals. An intention-to-treat, last observation carried forward analysis was performed (Hollis & Campbell 1999). In addition, a per protocol analysis excluding those subjects who did not fully comply with the medication regimen, or that were lost to follow up, was also performed on the primary outcome variable (Dunn et al. 2005).

Results

Subject characteristic accountability

Figure 1 indicates what happened to all potential subjects throughout the study from possible recruitment to completion. None of the demographic parameters (age, ethnicity, gender and smoking) showed a statistically significant difference between groups at baseline (Table 1).

Figure 2 shows the mean differences in PPD change for 0–2 months, 0–6 months and 0–8 months in deep pockets ($\geqslant$7 mm). The solid red line (antibiotics at the re-treatment phase) shows instrumentation alone in the first phase, which at 0–2 months gives a mean reduction in PPD of 2.1 mm. The solid blue line (antibiotics at initial therapy) shows that the adjunctive use of antimicrobials gave an additional 0.9 mm mean reduction of PPD. At 0–6 months, the instrumentation alone (placebo group) shows some rebound, while the adjunctive antimicrobials show continued improvement. This magnifies the differences between the treatment groups, which at this stage was a mean difference of 1.4 mm. These data were reported previously in a tabular form by Guerrero et al. (2005). At 0–8 months, there was a big improvement in the red line, as this group had now received instrumentation plus antibiotics. There was a slight improvement of the blue line as this had undergone further instrumentation. The blue line still showed a 0.9 mm mean PPD improvement over the red line.

Multivariate models based on linear regression analysis of covariance (ANCOVA) were constructed taking into account potential sources of variability such as smoking status and baseline pocket depth. Table 2 shows the analysis of covariance for PPD reduction and LCAL gain at sites with baseline PPD classified as moderate (4–6 mm), or deep ($\geqslant$7 mm). The highlighted band for PPD reduction in sites with initial PPD $\geqslant$7 mm (primary outcome variable) represents the statistical analysis related to the data presented in Fig. 2 and shows that the differences were highly significant statistically. Furthermore, a per protocol analysis on this primary outcome variable (excluding subjects who did

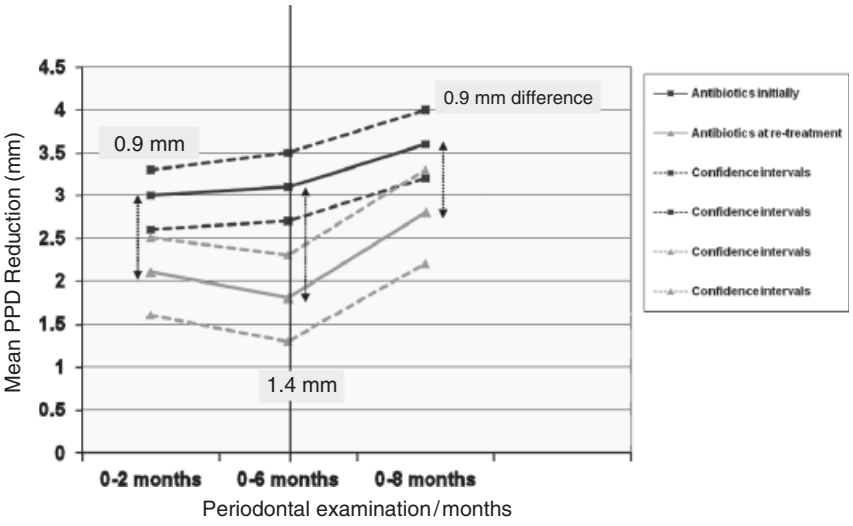

Fig. 2. Mean probing pocket depth (PPD) reduction and confidence intervals between 0–2, 0–6 and 0–8 months at sites probed as $\geqslant$7 mm at baseline. The differences between the two groups in mean PPD reduction at each time interval are highlighted within the figure.

Table 2. Analysis of covariance (ANCOVA) for probing pocket depth reduction (PPD) and gain in lifetime cumulative attachment loss (LCAL), at 0–2, 0–6 and 0–8 months

Multivariate ANCOVA models	Differences 0–2 months		Differences 0–6 months		Differences 0–8 months	
	estimate (95%, CI)	*p* value	estimate (95%, CI)	*p* value	estimate (95%, CI)	*p* value
Mean PPD reduction in pockets 4–6 mm	0.5 (0.2, 0.8)	0.001	0.4 (0.1, 0.7)	0.005	0.4 (0.0, 0.7)	0.036
Mean PPD reduction in pockets ⩾7 mm	0.9 (0.4, 1.5)	0.001	1.4 (0.8, 2.0)	<0.001	0.9 (0.3, 1.5)	0.003
Mean gain in LCAL at sites with initial PPD 4–6 mm	−0.2 (−0.4, 0.0)	0.605	0.5 (0.2, 0.8)	<0.001	0.3 (0.1, 0.5)	0.077
Mean gain in LCAL at sites with initial PPD⩾7 mm	0.6 (0.2, 0.9)	0.002	1.0 (0.7, 1.3)	<0.001	0.7 (0.2, 1.6)	0.007

Differences were calculated as ''antibiotics during initial therapy-antibiotics at re-assessment and data are presented as mean and confidence intervals (95% CI)''. The highlighted bar represents the statistical analysis related to Fig. 2.

Table 3. Subset analysis showing clinically relevant changes in probing pocket depth (PPD) presented at median and interquartile range (IQ) using Mann–Whitney test

Clinical measure	Timing of antibiotic	0–2 months	*p* value	0–6 months	*p* value	0–8 months	*p* value
% of sites with ⩾2 mm of PPD reduction	Initially	29 (24, 44)	0.029	30 (21, 47)	0.021	31 (24, 46)	0.179
	Re-treatment	21 (11, 33)		21 (9, 33)		27 (19, 39)	
% of pockets converting from ⩾5 to ⩽4 mm	Initially	71 (63, 78)	0.039	74 (64, 84)	0.008	83 (74, 86)	0.041
	Re-treatment	57 (30, 73)		54 (29, 76)		67 (45, 85)	
% of pockets converting from ⩾4 to ⩽3 mm	Initially	49 (43, 61)	0.112	55 (39, 65)	0.038	63 (48, 65)	0.297
	Re-treatment	42 (21, 58)		37 (18, 56)		49 (36, 72)	

not fully comply with the medication or that were lost to follow up) showed a very similar result as compared with the one obtained in the intention-to-treat analysis The difference at 0–8 months for mean PPD reduction was 0.8 mm (95% CI, 0.1, 1.4, $p = 0.023$). Table 2 shows similar patterns for LCAL with highly significant differences, but a lower magnitude of difference. However, it is still a mean difference in LCAL of 0.7 mm at 0–8 months ($p = 0.007$). This also showed that for moderate pockets there was a statistically significant difference at 0–6 months, but the magnitude was smaller (0.4 mm, $p = 0.005$). At 0–8 months, the level of significance is much lower ($p = 0.036$) and for LCAL in moderate pockets it is no longer statistically significant (0.3 mm, $p = 0.077$).

A subset analysis was carried out to test the changes of some clinically relevant parameters at 2, 6 and 8 months (Table 3.) These were defined as a PPD reduction of large magnitude ⩾2 mm, or reducing the number of pockets that were in need of treatment. This latter outcome was variously defined as either PPD⩾5 mm, which it is often suggested requires surgery, or any sites with PPD⩾4 mm at initial therapy, which are usually viewed as being in need of some instrumentation. At 0–6 months, the initial treatment showed an additional improvement of 9% of sites for PPD reduction ⩾2 mm, 20% for sites converting from PPD ⩾5 to ⩽4 mm and 18% of sites converting from PPD ⩾4 to ⩽3 mm. At this stage, the differences were statistically significant, whereas this was not always the case for the data at 0–2 months. The biggest % improvement was always the change from 0 to 8 months, but at this time the differences between the two groups were smaller, and they were no longer statistically significant apart from pockets ⩾5 mm converting to ⩽4 mm ($p = 0.041$).

There was a high incidence of adverse events, affecting 42% of subjects who took the medication as part of the re-treatment phase (Table 4). The majority

Table 4. Reported adverse events following antibiotic treatment at re-treatment phase (8 months)

Type of adverse event	Number $n = 19$ (%)	Severity of event
Nausea	3 (16%)	Two mild, one moderate*
Vomiting	1 (5%)	Mild
Diarrhoea	1 (5%)	Mild
Rashes	2 (10.5%)	One mild, one severe*
Headaches/drowsy	1 (5%)	Mild
Metallic taste	1 (5%)	Mild
Total events	9	Seven mild, one moderate and one severe
% of subjects with one or more event	8 (42%)	

*Patients who did not complete the antibiotic therapy as prescribed.

were minor events, but serious adverse events sufficient to withdraw the medication occurred in two patients. One subject developed a severe rash at 3 days and another discontinued at 5 days because of nausea, diarrhoea and drowsiness. All other patients complied with the medication regime. The clinical results of these subjects were included in the intention-to-treat analysis

The mean time for instrumentation after the 6 months evaluation (second phase of the study) was 76.9 min. for the original placebo group and 63.3 min. for the initial test group.

Discussion

In this study, patients who previously received placebo in the first study of the randomized placebo-controlled clinical trial design (Guerrero et al. 2005) had the antibiotics 6 months after the initial full-mouth root surface debridement (FMRSD). The second phase of the study was designed as the first few patients completed the 6 months evaluation, in the first study, before masking was broken. At this stage, a decision needed to be made on the need for further treatment and an additional research question arose. ''If we performed a further instrumentation and gave adjunctive antimicrobials to the group that had received placebo medication previously, would both groups end up with similar outcomes''? This represents one of the dilemmas in the current use of antibiotics. Namely should antibiotics be given as part of initial therapy, or only in patients who have not been successfully treated by mechanical cleaning alone?

At both phases, we implemented FMRSD within 24 h to reduce the load of periodontal pathogens in a short period of time (Herrera et al. 2008) and prevent cross-contamination of the treated sites (Quirynen et al. 2001). Each treatment was followed by chlorhexidine (0.2%) mouth rinse for 2 weeks for anti-plaque activity while the patient's home care cleaning could be compromised.

This present investigation consisted of 41 patients – three of which were lost to follow-up at different time points during the study – with a mean age of 31 years (Table 1) and clear features of GAgP according to the criteria of the 1999 International Classification (Armitage 1999). They had severe generalized disease as evidenced by the 46% pockets $\geqslant$4 mm that needed treatment at baseline (Table 1). Good compliance and acceptable retention of patients to the end of the 8 months evaluation enabled this study to be at least 80% powered to detect a true difference of 1.0 mm between groups using our primary outcome variable. Although three patients from the initial phase did not continue with the re-treatment phase, they appeared to be largely random events and we did not suspect any presence of attrition bias. At baseline, randomization was performed and both groups were matched, with no difference between the groups in terms of clinical characteristics

Both treatments resulted in improvement of the mean PPD and LCAL, which continued to show improvement such that the maximum improvement was evident at 8 months. Initial PPD category of $\geqslant$7 and 4–6 mm were selected as our primary and secondary outcome measures respectively, as treatment is normally provided in these categories of pockets.

The primary outcome of mean PPD difference in deep pockets ($\geqslant$7 mm) demonstrated a statistically significant difference between the group who had antibiotics initially and the group that had antibiotics at the re-treatment phase and this was large enough to have clinical relevance (Fig. 2 and Table 2), with a difference of 0.9 mm ($p<0.001$) between groups at 2 months, 1.4 mm ($p<0.001$) at 6 months and 0.9 mm ($p=0.003$) at 8 months. A similar pattern was detected for PPD in sites with an initial PPD of 4–6 mm and for LCAL in moderate and deep pockets, but with a smaller magnitude of change compared with the initial PPD$\geqslant$7 mm. It is important to note that the results for FMRSD alone were in agreement with recent systematic reviews (Cobb 1996, 2002, Suvan 2005). Therefore, the differences in Fig. 2 with the adjunctive use of antimicrobials, which reached a maximum at 6 months, are additive to normal outcomes for FMRSD. Interestingly, the gap in clinical response between groups closed when antibiotics were given to the group that received placebo initially. The median percentage of sites with $\geqslant$2 mm pocket reduction and the percentage sites showing pocket reduction from a ''diseased'' to ''healthy'' status showed a similar pattern (Table 3). Although the best outcome was observed at 8 months, the largest change occurred between 0 and 2 months regardless of the treatment provided. This substantiates the observations from cited studies on the effect of non-surgical mechanical therapy, which suggest that the biggest changes occur during 1–3 months following the initial treatment (Cobb 1996, Adriaens & Adriaens 2004). At 8 months, 63% and 49% of pockets that were in need of treatment ($\geqslant$4 mm) at baseline had been converted to healthy sites ($\leqslant$3 mm) posttreatment, for the antibiotic initially group and the antibiotic at re-assessment group, respectively. Therefore, as suggested by others (Loesche et al. 1991, 1992), there may be less need for invasive treatments like surgery.

The observations of this study must be made with some caution, as the therapist between the first and second phase of the study changed. However, they are in agreement with findings from a retrospective study from Kaner et al. (2007), who reported that administration of amoxicillin/metronidazole at initial FMRSD may provide more clinical benefits than late administration at re-treatment. Kaner and colleagues suggested that differences in pharmacokinetics may account for the different magnitude of effect of the antibiotics if given at initial therapy or at re-treatment. In particular, perfusion and permeability of capillaries may be increased in cases of advanced inflammation (such as at initial presentation), thus increasing the local uptake and effect of antibiotics when the local inflammation is greater (Kaner et al. 2007). This speculation, if confirmed by further investigations, may have clinical repercussions.

Comparison of the time taken for instrumentation between groups was not possible because of the different therapists involved. However, in the first study at 6 months, the time taken for FMRSD for both groups was comparable (unpublished data). In the second phase, the time taken was shorter by 14 min. for FMRSD in the group that received the systemic antibiotic at the initial phase.

Generally, there were high percentages (42%) of patients reporting adverse events in the second phase (Table 4). Because no placebo was provided, the patients were not blinded and we do not know whether this is purely due to the antibiotic or some other effect. When we had blinding in the initial phase, due to the use of a placebo, some patients experienced adverse events with the placebo. Most of the reported incidents were considered as mild by patients and only two (10%) did not complete the medication as prescribed. The total percentage

was smaller compared with the subjects reporting adverse events by test group in the initial study (Guerrero et al. 2005), which occurred on 55% of subjects. Furthermore, these were more severe with three patients who were generally un-well. The percentage of subjects experiencing adverse events, if reported, in other studies has varied from patients that had no adverse events at all (Rooney et al. 2002), 5% (van Winkelhoff et al. 1989), 22% (Flemmig et al. 1998) to as high as 77% (Winkel et al. 1998). Therefore, clinicians must take account of this factor when weighing the risk-benefits of prescribing these antibiotics to patients.

Within the protocol of the current study, we can conclude that: patients that received the antibiotics at the initial therapy showed significant additional benefits compared with those who received the same regime at the re-treatment phase.

References

Adriaens, P. A. & Adriaens, L. M. (2004) Effects of nonsurgical periodontal therapy on hard and soft tissues. *Periodontology 2000* **36**, 121–145.

Armitage, G. C. (1999) Development of a classification system for periodontal diseases of conditions. *Annals of Periodontology* **4**, 1–6.

Cobb, C. M. (1996) Non-surgical pocket therapy, mechanical. *Annals of Periodontology* **1**, 443–490.

Cobb, C. M. (2002) Clinical significance of non-surgical periodontal therapy: an evidence-based perspective of scaling and root planing. *Journal of Clinical Periodontology* **23** (Suppl. 2), 6–16.

Demmer, R. T. & Papapanou, P. N. (2010) Epidemiologic patterns of chronic and aggressive periodontitis. *Periodontology 2000* **53**, 28–44.

Dunn, G., Maracy, M. & Tomenson, B. (2005) Estimating treatment effects from randomized clinical trials with noncompliance and loss to follow-up: the role of instrumental variable methods. *Statatistical Methods in Medical Research* **14**, 369–395.

Flemmig, T. F., Milian, E., Karch, H. & Klaiber, B. (1998) Differential clinical treatment outcome after systemic metronidazole and amoxicillin in patients harbouring *Actinobacillus actinomycetemcomitans* and/or *Porphyromonas gingivalis*. *Journal of Clinical Periodontology* **25**, 380–387.

Guerrero, A., Griffiths, G. S., Nibali, L., Suvan, J., Moles, D. R., Laurell, L. & Tonetti, M. S. (2005) Adjunctive benefits of systemic amoxicillin and metronidazole in non-surgical treatment of generalised aggressive periodontitis: a randomized placebo-controlled clinical trial. *Journal of Clinical Periodontology* **32**, 1096–107.

Haffajee, A. D., Socransky, S. S. & Gunsolley, J. C. (2003) Systemic anti-infective periodontal therapy. A systematic review. *Annals of Periodontology* **8**, 115–181.

Herrera, D., Alonso, B., León, R., Roldán, S. & Sanz, M. (2008) Antimicrobial therapy in periodontitis: the use of systemic antimicrobials against the subgingival biofilm. *Journal of Clinical Periodontology* **35** (Suppl. 8), 45–66.

Herrera, D., Sanz, M., Jepsen, S., Needleman, I. & Roldan, S. (2002) A systematic review on the effect of systemic antimicrobials as an adjunct to scaling and root planing in periodontitis patients. *Journal of Clinical Periodontology* **29** (Suppl. 3), 136–159.

Hollis, S. & Campbell, F. (1999) What is meant by intention to treat analysis? Survey of published randomised controlled trials. *British Medical Journal* **319**, 670–674.

Kaner, D., Christan, C., Dietrich, T., Bernimoulin, J. P., Kleber, B. M. & Friedman, A. (2007) Timing affects the clinical outcome of adjunctive systemic antibiotic therapy for generalized aggressive periodontitis. *Journal of Periodontology* **78**, 1201–1208.

Loesche, W. J., Giordano, J. R., Hujoel, P., Schwarcz, J. & Smith, B. A. (1992) Metronidazole in periodontitis: reduced need for surgery. *Journal of Clinical Periodontology* **19**, 103–112.

Loesche, W. J., Schmidt, E., Smith, B. A., Morrison, E. C., Caffesse, R. & Hujoel, P. P. (1991) Effect of metronidazole on periodontal treatment needs. *Journal of Periodontology* **62**, 247–257.

Mestnik, M. J., Feres, M., Figueiredo, L. C., Duarte, P. M., Lira, E. A. & Faveri, M. (2010) Short-term benefits of the adjunctive use of metronidazole plus amoxicillin in the microbial profile and in the clinical parameters of subjects with generalized aggressive periodontitis. *Journal of Clinical Periodontology* **37**, 353–365.

Quirynen, M., De Soete, M., Dierickx, K. & van Steenberghe, D. (2001) The intra-oral translocation of periodontopathogens jeopardises the outcome of periodontal therapy. A review of the literature. *Journal of Clinical Periodontology* **6**, 499–507.

Rooney, J., Wade, W. G., Sprague, S. V., Newcombe, R. G. & Addy, M. (2002) Adjunctive effects to non-surgical periodontal therapy of systemic metronidazole and amoxicillin alone and combined. A placebo controlled study. *Journal of Clinical Periodontology* **29**, 342–350.

Sigusch, B., Beier, M., Klinger, G., Pfister, W. & Glockmann, E. (2001) A 2-step non-surgical procedure and systemic antibiotics in the treatment of rapidly progressive periodontitis. *Journal of Periodontology* **72**, 275–283.

Suvan, J. E. (2005) Effectiveness of mechanical non-surgical pocket therapy. *Periodontology 2000* **37**, 48–71.

Van Winkelhoff, A. J., Rodenburg, J. P., Goene, R. J., Abbas, F., Winkel, E. G. & de Graaff, J. (1989) Metronidazole plus amoxicillin in the treatment of *A.a.* associated periodontitis. *Journal of Periodontology* **16**, 128–131.

Winkel, E. G., Van Winkelhoff, A. J. & van der Velden, U. (1998) Additional clinical and microbiological effects of amoxicillin and metronidazole after initial periodontal therapy. *Journal of Clinical Periodontology* **25**, 857–864.

Xajigeorgiou, C., Sakellari, D., Slini, T., Baka, A. & Konstantinidis, A. (2006) Clinical and microbiological effects of different antimicrobials on generalized aggressive periodontitis. *Journal of Clinical Periodontology* **33**, 254–264.

Address:
Gareth S. Griffiths
University of Sheffield
Academic Unit of Restorative Dentistry
Claremont Crescent
Sheffield S10 2TA
UK
E-mail: g.s.griffiths@sheffield.ac.uk

Clinical Relevance

Scientific rationale for the study: Management of aggressive periodontitis is challenging and the use of systemic antibiotics, such as the combination of amoxicillin and metronidazole has been suggested as beneficial. Antibiotics are frequently used after a course of non-surgical therapy. This study compared antimicrobials given at either initial therapy or the re-treatment phase of periodontal care.

Principal findings: In deep pockets, there was a significant benefit in the use of amoxicillin and metronidazole as an adjunct to non-surgical therapy. Antibiotics given at initial therapy resulted in significantly better outcomes than antibiotics given at re-treatment.

Practical implications: Amoxicillin and metronidazole have an adjunctive effect and this study suggests that the timing of antibiotic therapy may be important.