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Incomplete adherence to an adjunctive systemic antibiotic regimen decreases clinical outcomes in generalized aggressive periodontitis patients: a pilot retrospective study

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Abstract

Aim: The objective of this study was to explore the effect of incomplete adherence to the prescribed antibiotic regimen, amoxicillin and metronidazole, in the non-surgical treatment of generalized aggressive periodontitis (GAP).

Methods: This retrospective study included 18 GAP subjects who received a conventional course of full-mouth non-surgical periodontal treatment using machine-driven and hand instruments and an adjunctive course of systemic antibiotics (500 mg amoxicillin and 500 mg metronidazole three times a day for 7 days). Clinical parameters were collected at baseline and at 2 months post-treatment. Self-reported adherence to the prescribed medication regimen was recorded at 2 months.

Results: All clinical parameters, except for the mean clinical attachment level (CAL) in sites with initial probing pocket depth (PPD) $\leqslant 3$ mm, improved at 2 months in all subjects. PPD reduction was 3.7 mm [95% confidence interval (CI) 3.2, 4.3 mm] in deep pockets ($\geqslant 7$ mm) and 2.2 mm (95% CI 1.9, 2.4 mm) in moderate pockets (4–6 mm), while CAL gain was 2.2 mm (95% CI 1.7, 2.6 mm) and 1.2 mm (95% CI 0.8, 1.5 mm), respectively. However, only 11 subjects (61.1%) reported full adherence to the medication. In deep pockets ($\geqslant 7$ mm), the difference between an adherent and non-adherent/partially adherent subject was 0.9 mm (95% CI 0.1, 1.7 mm, ANCOVA, $p = 0.027$) in PPD reduction and 0.8 mm (95% CI -0.2, 1.9, $p = 0.129$) in CAL gain at 2 months. In moderate pockets (4–6 mm) this difference was smaller in magnitude: 0.4 mm (95% CI 0.1, 0.9 mm, $p = 0.036$) in PPD reduction and 0.2 mm (95% CI -0.3, 0.9 mm, $p = 0.332$) in CAL gain.

Conclusions: Within the limits of this design, these data suggest that incomplete adherence to a 7-day adjunctive course of systemic metronidazole and amoxicillin is associated with decreased clinical outcomes in subjects with generalized aggressive periodontitis.

Key words: adherence/treatment; antibiotics; clinical outcomes; generalized aggressive periodontitis; human; retrospective study

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Conflict of interest and source of funding statement

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A recent study by Guerrero et al. (2005) presented results of a randomized placebo-controlled clinical trial in which the effect of the combination of amoxicillin and metronidazole as an adjunct to non-surgical cause-related periodontal therapy was evaluated in a group of generalized aggressive periodontitis (GAP) patients. The adjunctive antibiotic combination yielded clinically significant improvements.

Not unexpectedly, the adjunctive 7-day course of systemic antibiotics resulted in a higher prevalence – compared with placebo – of adverse events, especially at the gastrointestinal level. In fact, adverse events were named by participants as the main reason for early termination or missing doses. Nonetheless, reported full adherence to the prescribed course of antibiotics was high (80%) in the test group.

The microbiological effects of the lack of complete adherence to adjunctive systemic antibiotic have been previously assessed in a group of patients with advanced chronic periodontitis (Loesche et al. 1993). In that study, less-favourable improvements in microbiological parameters were observed in non-adherent patients. Whether or not lack of adherence to the adjunctive administration of amoxicillin and metronidazole has an impact on the clinical outcomes of non-surgical therapy of GAP is still an open question. Guerrero et al. (2005) used an ''intention to treat'' (ITT) analysis (Hollis & Campbell 1999). Besides portraying the benefits that are likely to arise with the actual use of the medication in clinical practice, this analysis avoids the difficulties related to excluding non-adherent subjects and/or subject's drop-outs. ITT analyses, on the other hand, tend to underestimate the size of the treatment effect with respect to ''on-drug'' analyses (Nagelkerke et al. 2000, Goetghebeur & Loeys 2002). A ''per protocol'' analysis (Dunn et al. 2005) (excluding those subjects who did not fully comply with the study medication protocol) of the study by Guerrero et al. (2005) did not provide a useful estimate of the effect of partial adherence as the number of non-adherant subjects was modest and the question of the benefits – expected from trying to complete the full-prescribed course in spite of the onset of mild to moderate adverse events – is open to debate.

Thus, the aim of this retrospective study was to explore the effects of incomplete adherence to the prescribed adjunctive antibiotic regimen (consisting of a 1 week course of amoxicillin and metronidazole) on the short-term clinical outcomes of non-surgical cause-related periodontal therapy in a group of consecutively treated GAP subjects.

Material and Methods

This study was a retrospective study. Consecutive subjects suitable for the study were identified from the population treated in a specialist periodontal private practice in Malaga, Spain. At baseline, all subjects had a complete periodontal examination including a full medical and dental history, an intra-oral examination and full-mouth periodontal charting. A radiographic examination was performed using periapical films. The study included consecutive subjects who had been treated by non-surgical means with the adjunctive use of systemic amoxicillin (500 mg TID for 7 days) and metronidazole (500 mg TID for 7 days). Subjects were included in the retrospective study if they (i) had been diagnosed with GAP according to the criteria of the 1999 international classification (Lang et al. 1999); (ii) had at least 20 teeth present; (iii) were in good general health; (iv) preferably had an age between 16 and 35 when first diagnosed with aggressive periodontitis; (v) had a complete baseline and 2-month full-mouth periodontal examination; and (vi) had a recorded adherence report to the prescribed medication.

Clinical parameters were assessed by a single examiner using an electronic periodontal probe that recorded in 0.2 mm increments (Pocket Depth Probe, Florida Probe, FP32 version 4, Florida Probe Corporation, Florida, USA) at six sites/tooth excluding third molars. The probe tip and the outside straight sleeve had a diameter of 0.45 and 0.96 mm, respectively. A full-mouth percentage bleeding score (FMBS) was calculated after assessing dichotomously the presence of bleeding on probing (BOP) from the bottom of the pocket when probing with the Florida Probe at a force of 0.2 N. (Tonetti et al. 2002). Full-mouth plaque score (FMPS) was recorded by assigning a binary score at four sites/tooth (one for plaque present, zero for absent) and calculating the percentage of total surfaces that revealed the presence of plaque detected by the use of the electronic periodontal probe. Similarly, full-mouth probing pocket depth (PPD) and clinical attachment level (CAL) were recorded at each site. The tip of the Florida Probe was inserted towards the base of the periodontal pocket/gingival sulcus until tissue resistance was noticed, then the edge of the sleeve was brought to the gingival margin and the PPD value was recorded. Immediately thereafter, the probe tip was left at the base of the sulcus/pocket while the edge of the sleeve was moved, in an apical or coronal direction, to detect the CEJ – or an anatomical landmark in case a restoration margin was present – to record the CAL. Consequently, the value of the recession of the gingival margin (REC) was calculated as CAL – PPD by the Florida probe software. If the gingival margin occurred apical to the CEJ, the Florida Probe recorded REC as a positive value, whereas if it occurred coronal to the CEJ it was recorded as a negative value. In this later case, the edge of the probe's sleeve was used to detect the CEJ.

Non-surgical periodontal therapy was delivered as described below. An initial visit included a case presentation to each subject related to specific features of his/her disease. In addition, oral hygiene instructions were delivered as necessary.

All subjects received a conventional cycle of periodontal therapy consisting of supra and subgingival mechanical instrumentation of the root surface (scaling and root planing). These treatment visits were performed by three different experienced dental hygienists, under the supervision of a periodontist (AG), using a sonic instrument with fine tips (Titan S, Star Dental, USA) and hand instruments as appropriate. This treatment was delivered during four different 1-h appointments (one per quadrant) separated by 1 week. Local anaesthetic was used as necessary. At the end of the last treatment visit, a prescription with the medication was given to all subjects. They received instructions to take an adjunctive course of systemic antibiotics

consisting of 500 mg of amoxicillin and 500 mg of metronidazole three times a day for 7 days (Guerrero et al. 2005). All subjects used a 0.12% chlorhexidine rinse (supplied to improve adherence) twice a day for 2 weeks post-treatment and relied on standard oral hygiene methods as instructed during the treatment visits.

A re-assessment visit occurred at 2 months after the completion of treatment. During this appointment the examiner recorded the same clinical periodontal parameters documented at the baseline visit. Likewise, the examiner recorded self-reported adherence to the antibiotic regimen. If a subject had missed one or more pills, they were categorized as non-adherent. On the contrary, if they had completed the full-prescribed course of antibiotics they were categorized as adherent. At the end of the appointment a session of supragingival debridement was performed as necessary and the need for further treatment was determined.

The primary outcome measure of the study was the effect of adherence to the medication (yes or no) on PPD reduction in sites with initial PPD $\geqslant$ 7 mm (Guerrero et al. 2005). In addition, the changes in mean full-mouth PPD and the changes in PPD and CAL at different initial PPD categories were also analysed.

Data management and statistical analysis

Data were entered into an Excel (Microsoft office 2003) database and were proofed for entry errors. The database was subsequently locked, imported into SPSS for Windows (SPSS Inc., version 12.0) formatted and analyzed. A subject-level analysis was performed by computing a subject-level variable (full-mouth or at different PPD categories) for each of the parameters. Numerical data were summarized as means and 95% confidence intervals (CI), categorical data were summarized as frequency distribution and the percentage-based measures (e.g. FMPS) were summarized as the median of the percentage and interquartile range. For numerical data, significance of difference within each group before and after treatment was evaluated with the paired samples *t*-test. The significance of adherence to the medication (yes or no) on the dependent variables PPD reduction and CAL gain at different initial PPD categories was estimated by analysis of covariance (ANCOVA). The models were adjusted for baseline values and smoking (yes or no). Model estimates included adjusted means and 95% CIs. In addition, the potential effect of the therapists' variability was assessed with a one-way ANOVA. Comparisons between adherent and non-adherent subjects were performed with the Mann–Whitney test, for percentage-based data; with the independent samples *t*-test, for numerical data; and with the χ^2 test, for categorical data.

Results

Subject accountability

The records of 54 generalized aggressive periodontitis subjects, who had been consecutively treated in a private periodontal practice in Spain between November 2004 and April 2006, were reviewed. Then, assessment for eligibility according to the inclusion criteria took place. Eighteen of them fulfilled all the criteria and were included in this study.

Subject characteristics at baseline

The baseline characteristics of the 18 subjects who were treated non-surgically with the adjunctive use of amoxicillin and metronidazole are displayed in Table 1. Full adherence was reported by 11 subjects (61%). The mean age of the participants was 34.8 years of age [95% (CI) 32.1, 37.4]. Females represented 61.1% of the sample and smokers accounted for 33.3% of the subjects [two adherent subjects (18.2%) and four non-adherent subjects (57.1%), χ^2 test, $p = 0.087$]. The self-reported level of smoking determined that the two adherent subjects smoked 20 and 30 cigarettes/day, respectively, while the four non-adherent subjects reported smoking 5, 15, 20 and 20 cigarrettes/day respectively (χ^2 test, 0.392).

None of the baseline demographic parameters showed a statistically significant difference between the adherent and non-adherent subjects (data not shown).

Clinical characteristics

The baseline examination revealed that the subjects had retained most of their teeth [25.1, 95% (CI): 23.9, 26.2], but had a 28.8 median percentage [interquartile range (IQ): 16.6, 47.63] of sites with PPD $\geqslant$ 5 mm. Additionally, both plaque and bleeding scores were high. None of these clinical parameters showed a statistical significant difference between the adherent and non-adherent subjects (data not shown).

Mean values for clinical parameters

Mean full-mouth clinical outcomes and mean clinical outcomes at shallow ($\leqslant$ 3 mm) moderate (4–6 mm) and deep ($\geqslant$ 7 mm) pocket categories for baseline, and the differences between baseline – 2 months are displayed in Table 2. As this is a non-randomized study, the tables are presented as one group of consecutively treated subjects. However, when considering the sample as two different groups (adherent group and non-adherent group), the baseline values of all clinical parameters did not show any statistically significant difference between them.

All parameters, with the exception of mean CAL gain at initially shallow pockets, showed a statistically significant improvement between baseline and 2 months.

The impact of adherence to the medication regimen on clinical parameters evaluated at 2 months (difference between adherent and non-adherent subjects in mean PPD reduction and mean CAL gain at different pocket categories) is displayed in Table 3. Multivariate models based on linear regression

Table 1. Subjects characteristics at baseline

Parameter	Subjects $N = 18$
Age, mean (95% CI)	34.8 (32.1, 37.4)
Full adherence at 2 months (percentage)	11 (61.1%)
Smokers (%)	6 (33.3%)
Females (%)	11 (61.1%)
Teeth at baseline mean (95% CI)	25.1 (23.9, 26.2)
% of pockets $\geqslant$ 5 mm median (IQ)	28.8 (16.6, 47.63)
Full-mouth plaque score median (IQ)	58.5 (49.0, 76.5)
Full-mouth bleeding score median (IQ)	45.5 (30.0, 62.7)

CI, confidence interval; IQ, interquartile range.

Table 2. Mean clinical outcome variables at baseline and differences between 0 and 2 months

Mean (95% CI)	Baseline	Difference 0–2 months	*p*-value Paired *t*-test
Full-mouth mean PPD	3.7 (3.3, 4.0)	1.3 (1.0,1.6)	<0.001
Mean PPD at pockets ⩽3 mm	2.2 (2.0, 2,3)	0.2 (0.0, 0.3)	0.016
Mean PPD at pockets 4–6 mm	4.9 (4.7, 5.0)	2.2 (1.9, 2.4)	<0.001
Mean PPD at pockets ⩾7 mm	7.5 (7.2, 7.7)	3.7 (3.2, 4.3)	<0.001
Full-mouth mean CAL	4.4 (3.9, 4.9)	0.5 (0.2, 0.8)	0.001
Mean CAL at sites with initial pockets ⩽3 mm	2.9 (2.6, 3.3)	−0.2 (−0.5, 0.0)	0.116
Mean CAL at sites with initial pockets 4–6 mm	5.6 (5.3, 5.8)	1.2 (0.8, 1.5)	<0.001
Mean CAL at sites with initial pockets ⩾7 mm	8.0 (7.6, 8.4)	2.2 (1.7, 2.6)	<0.001

CI, confidence interval; PPD, probing pocket depth; CAL, clinical attachment level.

Table 3. Analysis of covariance for PPD reduction and CAL gain at 2 months in different pockets categories

Multivariate ANCOVA models	Parameter	Difference 0–2 months	
		estimate (95% CI)	*p*-value
Full-mouth Mean PPD reduction	Adherence (yes–no)	0.3 (−0.0, 0.6)	0.052
	Smoking (no–yes)	0.3 (0.0, 0.6)	0.052
Mean PPD reduction in pockets 4–6 mm	Adherence (yes–no)	0.4 (0.1, 0.9)	0.036
	Smoking (no–yes)	0.4 (0.0, 0.8)	0.052
Mean PPD reduction in pockets ⩾7 mm	Adherence (yes–no)	0.9 (0.1, 1.7)	0.027
	Smoking (no–yes)	0.3 (0.5, 1.1)	0.436
Full-mouth Mean CAL gain	Adherence (yes–no)	0.4 (−0.0, 0.9)	0.061
	Smoking (no–yes)	0.4 (0.0, 0.9)	0.070
Mean CAL gain in sites with initial PPD 4–6 mm	Adherence (yes–no)	0.2 (−0.3, 0.9)	0.332
	Smoking (no–yes)	0.5 (0.0, 1.2)	0.086
Mean CAL gain in sites with initial PPD ⩾7 mm	Adherence (yes–no)	0.8 (−0.2, 1.9)	0.129
	Smoking (no–yes)	0.3 (0.6, 1.3)	0.446

CI, confidence interval; PPD, probing pocket depth; CAL, clinical attachment level; ANCOVA, analysis of covariance.

Table 4. Analysis on FMPS and FMBS at baseline and differences between 0 and 2 months.

Median of percentage (IQ)	Baseline	Difference 0–2 months	*p*-value Wilcoxon's signed-ranks test
Full-mouth plaque score	58.5 (49.0, 76.5)	24.5 (16.2, 35.0)	<0.001
Full-mouth bleeding score	45.5 (30.0, 62.7)	25.5 (19.5, 43.0)	<0.001

FMPS, Full-mouth plaque score; FMBS; FMBS, full-mouth percentage bleeding score; IQ, interquartile range.

ANCOVA were constructed taking into account smoking status and baseline PPD as potential sources of variability. When examining pockets ⩽3 mm no differences were observed between adherent and non-adherent subjects for either CAL or PPD. For ease of presentation, these analyses have been omitted from Table 3.

There were significant effects of adherence for PPD reduction at 4–6 mm pockets, and PPD reduction at ⩾7 mm pockets at 2 months, with the outcomes favouring the adherent subjects. For PPD reduction in 4–6 mm pockets, the adjusted differences between adherent and non-adherent subjects were 0.4 mm (95% CI, 0.1, 0.9), while in sites with initial PPD⩾7 mm, the difference in PPD reduction was 0.9 mm (0.1, 1.7). On the contrary, no statistically significant differences were detected comparing adherent and non-adherent subjects in terms of full-mouth PPD reduction, full-mouth CAL gain or CAL gain in any of the different pocket categories. In this small sample, the effect of smoking on PPD reduction and CAL gain at different pocket categories did not reach statistical significance.

In addition, when the effect of the different therapists was explored for the dependent variables, PPD reduction at ⩾7 mm pockets and PPD reduction at 4–6 mm pockets at 2 months, no significant effects of the different therapists were detected ($p = 0.107$ and 0.662, respectively; one-way ANOVA).

Oral hygiene and BOP

FMPS and FMBS at baseline, and the reduction (difference baseline – 2 months) within each group, are displayed in Table 4. Both plaque and bleeding scores decreased from baseline to 2 months and the differences were statistically significant ($p<0.001$). There were no statistically significant differences between adherent and non-adherent subjects either for the improvement in plaque score ($p = 0.425$) or for the improvement in bleeding score ($p = 0.375$) (Mann–Whitney test, data not shown).

Discussion

The results of this retrospective study suggest that the full benefit of the adjunctive administration of amoxicillin and metronidazole during non-surgical treatment of periodontitis may require full adherence to the prescribed regimen. No definitive conclusions, however, should be drawn from this preliminary investigation as: (i) the results obtained in a retrospective study are highly susceptible to bias (Schulz & Grimes 2002); and (ii) self-reported adherence to the prescribed regimen may underestimate non-adherence or partial adherence (Bachmann et al. 1999). Nonetheless, to the best of our knowledge, this was the first study specifically aimed at estimating the clinical effects of adherence to an adjunctive antibiotic regimen in the periodontal literature.

Although unavoidable in this retrospective study, dichotomization of adherence does not reflect the fact that a dose-dependent effect of non-adherence may be anticipated. Future prospective trials may address this shortcoming by using ''electronic medication event monitoring'' (eMEM) (Urquhart 1997). The eMEM has been used in clinical trails aimed at obtaining an unbiased estimation of adherence and/or compliance (de Klerk et al. 2003, Charpentier et al. 2005).

Many factors have been related to a lack of adherence: misunderstanding of

medical guidelines (Hanchak et al. 1996), gastrointestinal adverse events (Kruse et al. 1993), dosing (Claxton et al. 2001) and/or duration (Paes et al. 1997) of medication regimen. The prescribed adjunctive course consisting of 500 mg TID for 7 days of amoxicillin and 500 mg TID for 7 days of metronidazole requires administration of a minimum of 42 pills/tablets (in countries where both medications are available in that dose) to be taken over seven consecutive days, during which there are high probabilities of experiencing some kind of gastrointestinal adverse event, as shown by Guerrero et al. (2005) in periodontitis patients. Thus, this drug regimen contains many features that make clinicians expect a less than ideal adherence in clinical practice (Rudd 1993). This was shown in our small patient sample, in which only 61.1% of the subjects reported complete adherence. However, in clinical research, Guerrero et al. (2005) showed that, in spite of the presence of adverse events, self-reported full compliance was high, bearing in mind that, as mentioned above, the method they used to assess compliance (pill count) overestimates that variable (Pullar et al. 1989). Different methods have been tested to improve compliance in clinical trials (Haynes et al. 2005), among them one may have direct relevance in clinical practice: a reduction in adverse events may lead to better adherence. Choice of antibiotic and/or the implementation of specific measures to limit morbidity with the chosen regimen may play an important role.

The clinical characteristics of our subjects at baseline were similar to those of the subjects in the study by Guerrero et al. (2005). Given that the measurements were taken by a single examiner using an electronic pressure-sensitive probe, the small difference between the two studies can be attributed to the different performances of manual and electronic probing (Barendregt et al. 2006).

The authors have used PPD reduction in sites with an initial PPD $\geqslant$ 7 mm as the primary outcome variable. The rationale for the selection of the deeper pockets as our primary outcome is at least twofold: the small sample size and the expected larger adjunctive benefit in deeper pockets (Guerrero et al. 2005). The results of the study have shown that for all consecutively treated subjects PPD reduction at deep pockets 2 months after treatment was 3.7 mm (95% CI 3.2, 4.3), whereas the difference between adherent and non-adherent subjects in mean PPD reduction at deep pockets was 0.9 mm (95% CI: 0.1, 1.7; $p = 0.027$). It must be emphasized that the outcomes of the whole group compare well with those reported in other studies (Sigusch et al. 2001, Guerrero et al. 2005). Our results, however, also suggest that self-reported full adherence was associated with even better clinical outcomes as compared with partial adherence. These results are in agreement with the fact that adherence to the prescribed regimen leads to better outcomes (DiMatteo et al. 2002, Simpson et al. 2006); in some infections, however, incomplete adherence did not seem to significantly affect clinical outcomes (Bachmann et al. 1999).

In this study, incomplete adherence to the medication regimen was not associated with incomplete adherence to oral hygiene instructions. Our results show that, for FMPS, there were no statistically significant differences, between groups, either for the baseline values or for the improvements after 2 months. Consequently, the differences in clinical outcomes observed between adherent and non-adherent subjects cannot be attributed to differences in oral hygiene performance (Magnusson et al. 1984). In the same context, smoking could have acted as a confounding factor as it was not balanced between groups at baseline, although this difference was not statistically significant. However, the multivariate analysis failed to show statistically significant effects of smoking on the evaluated clinical variables. The same applies to the potential variation in treatment outcomes due to the participation of different therapists.

In conclusion, the findings of this study agree with the hypothesis that generalized aggressive periodontitis subjects who do not fully adhere to the prescribed 7-day adjunctive course of systemic amoxicillin and metronidazole experience a decreased adjunctive benefit as compared with adherent subjects during the initial phase of periodontal treatment. Further controlled clinical trials need to be carried out to confirm or reject this hypothesis.

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Clinical Relevance

Scientific rationale for the study: Adjunctive systemic antibiotics during non-surgical therapy benefit aggressive periodontitis patients. However, the impact of adherence to the prescribed medication regimen on the clinical outcomes has not been explored.

Principal findings: In this pilot trial, subjects with generalized aggressive periodontitis who reported full adherence to the prescribed 7-day adjunctive course of systemic amoxicillin and metronidazole experienced a greater adjunctive benefit during the initial phase of periodontal treatment.

Practical implications: Adherence to the prescribed antibiotic regimen may play an important role in the optimization of treatment outcomes in generalized aggressive periodontitis patients. Further studies are needed.