Adjunctive moxifloxacin in the treatment of generalized aggressive periodontitis patients: clinical and microbiological results of a randomized, triple-blind and placebo-controlled clinical trial


Abstract

Aim: The aim of the present study was to evaluate the clinical and microbiological efficacy of moxifloxacin (MOX) in one-stage scaling and root planing (SRP) in treating generalized aggressive periodontitis (GAgP).

Materials and Methods: Forty subjects were randomly allocated to two treatment groups. The two treatment groups consisted of SRP combined with systemically administered MOX at the dosage of 400 mg once daily for 7 days or SRP + placebo once daily for 7 days. Subgingival plaque samples were analysed for cultivable bacteria.

Results: Both groups resulted in significant reduction of probing depth (PD) and clinical attachment level (CAL) compared with baseline (p < 0.0001), and this difference was maintained at 6 months from baseline in both groups. However, subjects receiving MOX showed the greatest improvements CAL, and PD. Subjects in both groups at 6 months displayed the greatest reduction from baseline in frequency of sites with PD ≥6 mm (p < 0.001), favouring the MOX group. Adjunctive antibiotic protocol reduced subgingival Aggregatibacter actinomycetemcomitans to undetectable levels, after 3 and 6 months, and there was a significant reduction in the levels of Porphyromonas gingivalis and Tannerella forsythia in the MOX group compared to the placebo group.

Conclusions: The results from this study suggest that moxifloxacin as an adjunct to one-stage full-mouth SRP leads to a better clinical and microbiological advantages compared to mechanical treatment.

Conflict of interest and source of funding statement

The authors declare that they have no conflict of interest in relation to this investigation. The School of Dentistry of the Universidad de Antioquia, Medellín, Colombia financed the study. Clinical Trial Registration: NCT02125812.
It is commonly concluded that scaling and root planing (SRP) is a successful treatment for subjects with periodontitis, however, this procedure does not frequently lead to the microbiological changes necessary for maintaining the long-term stability of the clinical benefits achieved initially (Herrera et al. 2008a). The adjunctive use of systemically administered antibiotics has been shown to provide a better clinical outcome, particularly in terms of probing depth reduction and attachment-level gain than SRP in subjects with aggressive periodontitis. Periodontal pathogens such as Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Tannerella forsythia and Treponema denticola are more effectively reduced by the use of systemic antibiotics in aggressive periodontitis (Herrera et al. 2008a, Aimetti et al. 2012, Mestnik et al. 2012). Furthermore, adjunctive antimicrobial therapy with systemic antibiotics affects periodontal pathogens residing in non-periodontal mucosal surfaces (Müller et al. 1998).

Combinations of amoxicillin and metronidazole or doxycycline with mechanical treatment have essentially resolved the periodontal inflammation found in patients with generalized aggressive periodontitis (GAgP) (Aimetti et al. 2012, Moreno Villagran & Gómez Clavel 2012). Besides, the findings of a recent meta-analysis seem to support the efficacy and the clinical safety of one-stage, full-mouth disinfection protocol plus the systemic use of combined amoxicillin and metronidazole (Sgolastra et al. 2012). However, there is no a well-defined agreement on the method of action and efficacy of adjunctive use of antibiotics during the treatment of GAgP (Yek et al. 2010). Furthermore, amoxicillin and metronidazole should be administered with prudence because significantly higher levels of periodontal pathogen antibiotic resistance have been documented in the United States (Rams et al. 2013, 2014), Spain (van Winkelhoff et al. 2005) and Latin America (Ardila et al. 2010a). Thus, in the United States, amoxicillin and metronidazole resistance occurred in 43.3% and 30.3% of the patients respectively; in Spain amoxicillin resistance was found in 33% of the subjects, and in Colombia amoxicillin and metronidazole resistance (except for A. actinomycetemcomitans) was presented in 35% and 26% of the subjects, correspondingly.

On the other hand, as pointed out by Bozkurt et al. (2005), allergic reactions to amoxicillin and penicillin are commonly reported in the clinical practice. Beta-Lactams, the most important of which are amoxicillin and clavulanic acid, are involved in specific immunological mechanisms and hypersensitivity drug reactions mediated by IgE and T cells or they may be due to an immunological imbalance (Doña et al. 2014). Also, it is important to note that a systematic review evaluating the results of systemically administered antibiotics reported that 39% of subjects in the test group exhibited diarrhoea when provided with metronidazole alone or combined (Haffajee et al. 2003).

To our knowledge, no studies have looked at the microbiology and clinical efficacy of moxifloxacin (MOX) as adjunctive therapy in GAgP. MOX is a new oral 8-methoxy-quinolone with a wide spectrum of activity; it is active against Gram-negative and multi-resistant Gram-positive bacteria, aerobic and anaerobic bacteria and atypical microorganisms (Ardila et al. 2010b, Tsaoosoglou et al. 2014). Interestingly, Ardila et al. (2010a) suggested that MOX has potent antibacterial activity against periodontal pathogens, higher than that of metronidazole and amoxicillin. Moreover, in earlier randomized clinical trials MOX has shown microbiological and clinical efficacy in chronic periodontitis (Guentersch et al. 2008, Flemmig et al. 2011). The properties of MOX have been studied, showing excellent bioavailability, long half-life and good tissue penetration of this drug (Cachovan et al. 2009), and it has an excellent tolerability (Guentrsch et al. 2008). However, ciprofloxacin has been associated with rare but clinically important adverse events in patients with impaired renal function (Iannini 2007) and various cases of torsades de pointes have been reported in the United States (Frothingham 2001).

In addition, given the high incidence of hypersensitivity reactions to beta-lactam antibiotics, the use of MOX might represent a therapeutic alternative (Bozkurt et al. 2005). Nevertheless, because of the wide use of these drugs, the number of quinolone-resistant bacterial strains has been growing steadily since the 1990s (Aldred et al. 2014), but this problem is not relevant in periodontics due to the limited use at the moment.

On the other hand, the pharmacokinetic properties of MOX allow a single dose treatment per day. This reduces costs and enhances the patient’s compliance (Krassemann et al. 2001). This is an important fact, because incomplete adherence to a 7-day adjunctive course of systemic antibiotics is associated with decreased clinical outcomes in GAP (Guerrero et al. 2007). The above properties appear to make MOX an ideal candidate adjunctive antibiotic for using in association with SRP in treating GAgP.

Thus, the aim of the present study was to evaluate the clinical and microbiological efficacy of MOX in one-stage SRP in treating GAgP, comparing the outcomes of this treatment with those obtained with SRP + placebo, at 3 months and 6 months post-therapy.

Materials and Methods

Subjects

The patients had at least 20 teeth, excluding third molars and teeth indicated for extraction. Informed and written consent was obtained from each participant. The study design was approved by the Ethics Committee on the School of Dentistry of the Universidad de Antioquia according to the Declaration of Helsinki on experimentation involving human subjects. All subjects were informed individually about the objectives, probable risk and benefits of the protocol treatment and signed informed consent forms. Patients with a diagnosis of GAgP were considered candidates for the study. The diagnosis of GAgP was made based on criteria defined at the workshop sponsored by the American Academy of Periodontology (Armitage 1999).

Subjects were ≤30 years of age, minimum of six permanent teeth,
including incisors and/or first molars, with at least one site each with probing depth (PD) and clinical attachment level (CAL) ≥ 5 mm and a minimum of six teeth other than first molars and incisors with at least one site each with PD and CAL ≥ 5 mm. During the anamneses, the subjects were asked if they had at least one other member of the family presenting or with a history of periodontal disease in order to assess the familial aggregation (They were excluded if no familiar aggregation was referred). Exclusion criteria included diabetes, cardiovascular disease, immunological disorders or any other systemic disease that could alter the course of periodontal disease. Pregnant or nursing women, smoking, allergy to fluoroquinolones or MOX, consumption of systemic antimicrobials or anti-inflammatory drugs in the last 6 months, and periodontal therapy during the last 6 months also served as exclusion criteria.

Experimental design and treatment

The two treatment groups consisted of SRP combined with systemically administered MOX at the dosage of 400 mg once daily for 7 days (MOX test group) or SRP + placebo once daily for 7 days (Control group). MOX and placebo were indistinguishable in terms of consistency, colour, smell, packaging, and labelling. Patients were randomly assigned by a computer-generated table to receive one of the two therapies. A balanced random permuted block method was used to prepare the randomization table in order to elude inadequate balance between the two treatments. The randomization table was sent to a clinical coordinator apart from the study. The clinical coordinator applied the allocation. Operating this list, treatment assignments were issued to numbered opaque envelopes. The plastic bags including equal opaque bottles (20 bottles with moxifloxacin and 20 with placebo) and they were sent to the clinical coordinator. She opened the sealed envelope and marked the subject number on the neutral bottles containing the test or the placebo medications. A hygienist gave the plastic bag to each patient. The treatment codes of the study were not accessible to the investigators and to the examiner until the data were analysed by the statistician.

One-stage full-mouth SRP under local anaesthesia was performed (using manual instruments and ultrasonic debridement) in approximately 2 h and half by the same experienced clinician. The endpoint of SRP was a tactile smooth root surface. The adjunctive agent and placebo were started at the SRP visit. Subjects in the MOX and SRP + placebo groups were extensively informed about the intake of the prescribed medication.

Subjects were clinically and microbiologically monitored at baseline (before therapy) and at 3 and 6 months post-therapy. During the monitored sessions, oral hygiene was evaluated and home care instructions were re-emphasized. Additionally, all subjects were recalled monthly for oral hygiene instructions.

Compliance

A dental assistant called each subject during the next 6 days by telephone to remind him/her to take the remaining doses. The same dental assistant, not involved in the randomization process, recorded compliance with medication/placebo intake and the occurrence of adverse events. The subjects were asked to bring the boxes containing the medication/placebo the week after the SRP visit, when the pills were counted in order to check any inaccuracy in drug taking. They also answered a questionnaire about any self-perceived side effects of the medication/placebo.

Clinical evaluation

Medical history was taken and clinical and radiographic examinations were conducted for each patient. At each monitoring visit, visible plaque (0/1), bleeding on probing (BOP) (0/1), PD (in mm) and CAL (in mm) were measured at six sites per tooth (mesiobuccal, buccal, distobuccal, distolingual, lingual and mesiolingual) in all teeth excluding third molars. The PD and CAL measurements were recorded to the nearest millimetre by a calibrated standard probe (UNC-15, Hu-Friedy, Chicago, IL). CAL was determined at all sites by measuring the distance from the cemento-enamel junction (CEJ) to the free gingival margin (GM), adding the PD at the same site. CAL = PD + (CEJ to GM) (all measurements in millimetres). Therefore, CAL was determined as the sum of gingival recession plus probing pocket depth. Measurements at all visits for given subjects were made by the same blinded, trained and calibrated clinician. The clinician making the clinical measurements did not perform the therapy on the subjects (The examiner and the clinician were masked as to the nature of the treatment groups). The intra-examiner reproducibility was assessed before and during the experimental period. Repeated measurements were performed on a total of 10 periodontal patients (They were not participating in this study), five of whom were examined immediately before the clinical trial, and the other five during the experimental period. Duplicate measurements were conducted in groups of two patients with at least 2 h between each examination. The intra-class correlation coefficients for mean PD and CAL were 0.92 and 0.91 respectively. The examiner’s reproducibility of measurements made before and during the study was similar (0.93 and 0.92 respectively).

Primary and secondary outcome variables

It was defined that the primary outcome variable to determine the superiority of one treatment over the other would be differences between groups for means CAL changes at 6 months post-treatment. Secondary outcome variables included differences between therapies for the mean changes in the mean levels of PD and the proportion of BOP and the bacterial species analysed. PD, as well as the percentage of sites with PD changing from PD ≥ 6 mm.

Microbial sampling

Microbial sampling on periodontitis patients was performed on pockets ≥5 mm. The deepest six pockets were selected for sampling. After removing supragingival plaque with curettes and isolating the area with
cotton pellets, the paper points (Maillefer, Ballaigues, Switzerland) were inserted into each periodontal pocket for 20 s. The paper points were transferred to a test tube containing 1 ml of the VMGA III transport medium under anaerobic conditions and immediately sent to the microbial laboratory. Generally, isolation of microorganisms was carried out by methods previously reported (D’Ercole et al. 2008). The samples were analysed using microbial culture techniques for the presence of periodontopathic bacteria according to Slots (1986). All samples were processed immediately at room temperature and immediately incubated in CO2 and anaerobic culture systems. Brucella blood agar medium was incubated at 35°C in an anaerobic jar for 7 days. The trypticase-soy with serum, bacitracin, and vancomycin medium was incubated in 10% CO2 in air at 37°C for 4 days. Presumptive identification was performed according to the methods described (Slots & Reynolds 1982, Slots 1986) and using a commercial identification micromethod system (RapID ANA, Remel, Norcross, GA, USA) for A. actinomycetemcomitans, P. gingivalis and T. forsythia. Each patient provided a pooled subgingival plaque sample. Equal numbers of isolates were used from each subject.

Statistical analysis

Data were entered into an Excel (Microsoft Office 2007) database and were proofed for entry errors. The subject was the unit for the basic statistical analysis. Mean values ± SD and the proportions of sites within various categories of scoring units were calculated for data description. Normal distribution of continuous variables was verified with the Kolmogorov-Smirnov test. Categorical data were analysed with the \( \chi^2 \) test, and independent \( t \)-test was used to determine the differences between groups regarding changes in clinical parameters and the number of residual pockets. For clinical parameters, a repeated-measures ANOVA was used to detect intra group differences in clinical parameters.

Although only sites with initial PD ≥4 mm received SRP and shallower sites were treated with subgingival scaling (instrumentation of the crown and root surfaces of the teeth to remove plaque, calculus, and stains from these surfaces) (The American Academy of Periodontology 2001), all sites were included in the statistical analyses.

Data concerning sites with PD ≥6 mm were analysed separately with the site as the observational unit. At each time point, for each group, the number of sites ≥6 mm was calculated and changes of these numbers from baseline between groups were compared using the independent \( t \)-test.

Microbiological data were analysed with the subject as the observational unit, applying the chi-square test except when expected counts were less than five where the Fisher’s exact test was used. The data were evaluated using intention-to-treat analysis with last observation carried forward. The significance level was set at 0.05 for all tests. All data handling and statistical testing were performed with a software package (SPSS, Statistical Package for the Social Sciences, version 18, Chicago, IL, USA).

Sample size calculation

Study sample size calculations were based on subject level analyses as the study randomized individuals. The ideal sample size to assure adequate power to this clinical trial was calculated considering differences of at least 1 mm for CAL and a standard deviation of 1 mm between groups (Varela et al. 2011). Based on these calculations, it was determined that ≥12 subjects per group would be necessary to provide an 80% power at a \( \alpha \) of 0.05. To compensate for possible dropouts 20 patients were recruited per treatment group.

Results

This was a triple-blinded (examiner, biostatisticians and participants), randomized placebo-controlled clinical trial, with 6 months of follow-up. Forty subjects (23 women and 17 men in good general health), who attended the dental clinics of the Universidad de Antioquia, Medellín, Colombia, were recruited from February 2012 to August 2013.

Subject retention

Sixty-eight subjects were assessed for their eligibility before entering the study. Of these, 28 subjects were excluded because they did not meet the inclusion criteria. Of the 40 subjects recruited, 36 patients had complete data for all three monitoring visits, while four subjects had one missing visit (three patients missed one follow-up at 3 months and one at 6 months). Intent-to-treat analyses were performed in the four subjects with missing data, whereby the last observation was carried forward, providing a total of 40 subjects with complete data that were included in the analyses. One subject (SRP + placebo) had baseline data and 3 months data only and their data were included in the analyses. The subject did not return for unknown reasons. Participation of individuals during the study is illustrated in Fig. 1.

Adverse events

All subjects who completed the study reported full adherence to the prescribed course of antibiotics/placebo and none reported any adverse event at any time point associated with the therapy. Patients were asked to return the bottles of medications the day after the intake of the last capsule and the remaining pills were counted. All subjects returned the medication bottles. Twenty subjects (100%) in the test group and 20 subjects (100%) in the placebo group completed the course of systemic medication as indicated.

Clinical findings

Table 1 presents the baseline clinical and demographic characteristics of the 40 patients subdivided into the two treatment groups. There were no statistically significant differences among treatment groups for any of the parameters.

Table 2 displays descriptive statistics and comparisons for both groups concerning the percentage of sites with plaque accumulation, BOP, PD and CAL. Plaque and BOP decreased significantly in both groups at the end of 3 months and 6 months compared to baseline (\( p < 0.0001 \)). However, no differences...
Differences were observed between the groups (ANOVA).

Differences were observed among the three time points (ANOVA).

Deviation; NS, no differences were observed between groups (independent test p.

PD, probing depth; CAL, clinical attachment level; BOP, bleeding on probing; SD, standard

development; 'v, v-test for independent samples.

Clinical parameters of the two groups during the experimental period

Table 2.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>MOX group, N = 20</th>
<th>SRP + placebo group, N = 20</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age years (mean±SD)</td>
<td>28.4 ± 0.9</td>
<td>26.4 ± 1.1</td>
<td>NS†</td>
</tr>
<tr>
<td>Gender, Females</td>
<td>11 (47.8%)</td>
<td>12 (52.2%)</td>
<td>NS†</td>
</tr>
<tr>
<td>PD mm (mean ± SD)</td>
<td>4.27 ± 0.4</td>
<td>4.34 ± 0.5</td>
<td>NS†</td>
</tr>
<tr>
<td>CAL mm (mean ± SD)</td>
<td>4.92 ± 0.5</td>
<td>4.93 ± 0.4</td>
<td>NS†</td>
</tr>
<tr>
<td>BOP (%±SD)</td>
<td>44 ± 10</td>
<td>47 ± 16</td>
<td>NS†</td>
</tr>
<tr>
<td>Plaque (%±SD)</td>
<td>41 ± 15</td>
<td>46 ± 12</td>
<td>NS†</td>
</tr>
<tr>
<td>% sites PD ≥ 6 mm</td>
<td>50.5</td>
<td>49.4</td>
<td>NS†</td>
</tr>
</tbody>
</table>

PD, probing depth; CAL, clinical attachment level; BOP, bleeding on probing; SD, standard deviation; NS, difference between groups is not statistically significant.

†t-test for independent samples.

‡t² test.

 lorsque comparisons were made within each group, both groups resulted in significant reduction of PD and CAL compared with baseline (p < 0.0001), and this difference was maintained at 6 months from baseline in both groups. No differences were observed within the groups between 3 months and 6 months after baseline. The differences between treatments were statistically significant at months 3 and 6, favouring the MOX group (p < 0.0001).

Additional differences concerning the effect of different treatments on PD were sought with the site instead of the subject as the observational unit, analysing the subset of pockets with PD ≥ 6 mm (Table 3). According to the findings, subjects in both groups at 6 months displayed the greatest reduction from baseline in frequency of sites with PD ≥ 6 mm (p < 0.001). Differences were observed between the subjects who received adjunctive MOX or SRP + placebo (p < 0.001) favouring the MOX group.

Microbiological findings

The proportions of subjects positive for studying species are presented in Table 4. At baseline no differences were observed between both groups, however, MOX group presented a significantly greater decrease in the frequency of patients colonized by all the periodontal pathogens studied, at 3 months and 6 months (p = 0.002). Significantly, adjunctive antibiotic protocol reduced subgingival A. actinomycetemcomitans to undetectable levels, after 3 and 6 months.

Discussion

Aggressive periodontitis comprises a group of rapidly progressing form of periodontal disease that occurs in otherwise clinically healthy individuals (Armitage 1999). Particularly, this disease has a higher prevalence in developing countries than in developed countries (Albandar & Timoco 2002). The ultimate goal of treatment is to create a clinical condition that is conducive to retaining
as many teeth as possible for as long as possible. The disease responds less predictably to conventional mechanical periodontal therapy than chronic periodontitis (Teughels et al. 2014).

This randomized, clinical trial evaluated the clinical and microbiological effects of MOX in one-stage SRP in treating GAgP, comparing the outcomes of those obtained with SRP + placebo. To the best of our knowledge, the present study is the first clinical study comparing MOX as an adjunct to SRP in aggressive periodontitis.

Our data showed that the adjunctive MOX therapy achieved significantly greater improvement in clinical parameters than SRP + placebo. MOX group subjects in the present study exhibited a greater reduction in BOP, PD and clinical attachment gains; our results are in agreement with Guentsch et al. (2008) that showed an enhanced clinical response when MOX was combined with SRP in the treatment of chronic periodontitis. On the other hand, plaque levels were maintained at a low level (< 12%) through the 6 months in both groups. Similar results were reported by Aimetti et al. (2012), Guerrero et al. (2005) and Sgolastra et al. (2012), focused on the additional effects of adjunctive amoxicillin-metronidazole in aggressive periodontitis patients; significantly greater improvements in probing depth and clinical attachment levels were demonstrated.

Meta-analyses by Herrera et al. (2002) and Haffajee et al. (2003) have suggested that the adjunctive benefit expected from antibiotic usage may be greater in aggressive periodontitis patients. An additional gain in CAL of 0.7 mm was observed in seven studies including 231 subjects receiving the antibiotic adjunctively to non-surgical or surgical root instrumentation. In the present study, the use of adjunctive antimicrobials resulted in an additional benefit of 1.8 mm in CAL gain compared with the 6-month outcomes reported by Aimetti et al. (2012). Our test patients showed a mean PD reduction of 1.19 mm at 6 months. These results are slightly inferior but comparable with the 6-month outcomes reported by Mestnik et al. (2012) with the use of adjunctive amoxicillin and metronidazole.

A particular finding in this study was that the full-mouth CAL gain was higher than the full-mouth PD reduction. Comparable results were described recently in 59 individuals with localized aggressive periodontitis (Shaddox et al. 2013). Similarly, Mestnik et al. (2012) showed a higher CAL gain than a PD reduction in the SRP group and equal values for the experimental group in 30 patients with generalized aggressive periodontitis. A straight comparison of these measures of clinical results is unworkable because of divergence among study designs, particularly concerning the programme for debridement, time of clinical measurements, prescription and scheduling of antibiotic management (Aimetti et al. 2012).

In order to eliminate the inconvenience related to the timing of antibiotic administration during quadrant-wise SRP (Killoy 2002), the administration of MOX commenced on the same day of one-stage full-mouth SRP, indicating that all quadrants were proportionately benefited by the antimicrobial treatment.

Although in the present study, smokers were excluded, a previous study in GAgP demonstrated that less PD reduction and less CAL gain occur in smokers as compared with non-smokers (Guerrero et al. 2005).

When analysing data at a site level, and in particular, the proportion of sites with PD ≥ 6 mm, a similar pattern was observed between groups. However, MOX group exhibited a significant reduction of the percentages of sites ≥ 6 mm (p < 0.001). This finding indicates a beneficial effect of MOX on deep pockets. The conclusions of the present study agree with a randomized clinical trial by Guentsch et al. (2008). These authors have shown that a 7-day adjunctive course of systemic MOX resulted in an additional reduction of PD in deep pockets (>6 mm) at 6 months in chronic periodontitis. Also, comparable findings were demonstrated by Aimetti et al. (2012) and Mestnik et al. (2012) with the adjunctive administration of systemic antibiotics in patients with aggressive periodontitis. Both the systematic reviews evaluating the effects of systemically administered antibiotics suggested

### Table 3. Change of proportions of sites with probing depth ≥ 6 mm of the two groups during the experimental period

<table>
<thead>
<tr>
<th>Observation</th>
<th>MOX, %</th>
<th>SRP + placebo, %</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>50.5†</td>
<td>49.4†</td>
<td>NS</td>
</tr>
<tr>
<td>3 months</td>
<td>11.4</td>
<td>16.6</td>
<td>†</td>
</tr>
<tr>
<td>6 months</td>
<td>8.7</td>
<td>13.4</td>
<td>†</td>
</tr>
</tbody>
</table>

NS, no differences were observed between groups (independent test p > 0.05).
†Differences were observed among baseline and 3 months and baseline and 6 months (p < 0.001).
‡Differences were observed between the groups (independent test p = 0.002).

### Table 4. Number of subjects positive for *Aggregatibacter actinomycetemcomitans* (A.a), *Porphyromonas gingivalis* (P.g) and *Tannerella forsythia* (T.f) during the experimental period

<table>
<thead>
<tr>
<th>Microorganisms</th>
<th>Group</th>
<th>Baseline</th>
<th>3 months</th>
<th>6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>A.a</td>
<td>MOX</td>
<td>11†</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>SRP + placebo</td>
<td>9†</td>
<td>3‡</td>
<td>4‡</td>
</tr>
<tr>
<td></td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P.g</td>
<td>MOX</td>
<td>16†</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>SRP + placebo</td>
<td>17†</td>
<td>7‡</td>
<td>8‡</td>
</tr>
<tr>
<td></td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T.f</td>
<td>MOX</td>
<td>10†</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>SRP + placebo</td>
<td>13†</td>
<td>6‡</td>
<td>11‡</td>
</tr>
</tbody>
</table>

NS, no differences were observed between groups (p > 0.05).
†Differences were observed among baseline and 3 months and baseline and 6 months (p < 0.001).
‡Differences were observed between the groups (p < 0.05).
that antibiotics provided greater benefit in subjects with more periodontal disease and at deeper periodontal sites (Haffajee et al. 2003, Herrera et al. 2008a).

The authors focused on determination of three periodontopathogens: A. actinomycetemcomitans, P. gingivalis and T. forsythia. These bacterial species are known to relate strikingly to clinical measures of periodontal disease and are predictors for treatment outcome (Fujise et al. 2002).

Related to clinical results, MOX group presented a significantly greater decrease in the number of patients colonized by all the periodontal pathogens studied, at 3 months and 6 months after baseline. The most marked decrease in prevalence occurred between the baseline visit and the 3 months sampling. These results are in agreement with other studies that also demonstrated the adjunctive effects of these antibiotics, in reducing red complex species (Guentsch et al. 2008, Haffajee et al. 2008). Interestingly, in the current study, adjunctive antibiotic protocol reduced subgingival A. actinomycetemcomitans to undetectable levels, after 3 and 6 months. This observation is consistent with the findings described by Guentsch et al. (2008) who found that A. actinomycetemcomitans were reduced to undetectable levels after adjunctive MOX in chronic periodontitis. Consistent with these results, Müller et al. (2002) showed that all tested strains of A.actinomycetemcomitans were susceptible to moxifloxacin at 0.032 μg/ml. Furthermore, concentrations in saliva and capillary plasma narrowly reflect equivalent concentrations in venous plasma, but primarily surpass plasma levels (Conway et al. 2000). Quinolones are recognized for their modulation of the immune reaction, permitting the in vitro extermination of A. actinomycetemcomitans by polymorphonuclear leucocytes (Dalhoff 2005). Thus, Weiss et al. (2004) demonstrated that MOX inhibits the production of IL-8, TNF-α and IL-β in lipopolysaccharide-stimulated human peripheral blood monocytes and in the THP-1 monocytic cell line. In correspondence with these findings, it is important to point that MOX could be considered an important antibiotic in the treatment of aggressive periodontitis.

As was observed in previous studies, for P. gingivalis and T. forsythia a slight rebound was detected after 3 months (Guentsch et al. 2008, Haffajee et al. 2008). Subjects treated with adjunctive MOX in the current investigation, exhibited a good clinical response, suggesting that a rapid decrease in subgingival periodontopathogens may be crucial for successful periodontal therapy and long-term periodontal stability (Haffajee et al. 2008). The longitudinal follow-up of these subjects will help to clarify this hypothesis.

The occurrence of periodontopathogens observed in this study was similar to the previous investigation (Herrera et al. 2008b). D’Ercole et al. (2008) recently compared conventional culture methods and multiplex PCR for the detection of periodontopathogenic bacteria and observed that for both methods, there was a good degree of accuracy in the determination of A. actinomycetemcomitans and P. gingivalis. Similar results were obtained for T. forsythia (Boutaga et al. 2005). Both culture and PCR techniques introduced many methodological problems when applied in oral microbiology, but the ideal technique for accurate detection of pathogens in subgingival plaque samples has yet to be developed (D’Ercole et al. 2008).

Subjects from the MOX group did not report adverse events during this investigation, corroborating the results of Guentsch et al. (2008). In addition to antimicrobial activity studies, the properties of MOX have been studied, showing excellent bioavailability, long half-life and good tissue penetration of this drug (Cachovan et al. 2009). Some studies reported adverse effects of fluoroquinolones in young people, related to musculoskeletal effects. Most take the form of arthralgia and they seem to occur more frequently with levofloxacin than with other fluoroquinolones (1 child in 60 after 1 month and 1 child in 30 after 1 year of treatment) (Noel et al. 2007). Corroborating these results, a recent prospective, non-controlled, multicentre Phase IV observational cohort study of patients with acute bacterial rhinosinusitis, who were treated with moxifloxacin in clinical practice in 19 countries in Asia Pacific, Europe and the Middle East, reported MOX as an an effective and well-tolerated treatment option in the overall population. They included 150 subjects less than 20 years and the most frequently reported adverse events were nausea, followed by diarrhoea (Møsges et al. 2013).

Although the published data and clinical experience with MOX are limited, given their relatively recent entry into our market, this perspective attempts to provide an understanding of the potential role of moxifloxacin in the treatment of patients with aggressive periodontitis. As a final point, the study of the susceptibility of the subgingival microbiota in a particular country becomes pertinent to identify its possible impact on outcomes after treatment (Herrera et al. 2008b).

Because antibiotics are highly potent drugs, Herrera et al. (2008a) concluded that in specific clinical situations, such as with patients with deep pockets, patients with progressive or active disease, or with specific microbiological profiles, antimicrobial therapy adjunctive to SRP could be clinically relevant.

One limitation of the present study is the 6-month evaluation period. Definitely, longitudinal monitoring of these patients will be essential in order to conclude whether this therapy would produce persistent favourable changes in the subgingival microbial profile and periodontal clinical parameters over time.

In conclusion, the results from this study suggest that moxifloxacin as and adjunct to one-stage full-mouth SRP leads to a better clinical and microbiological advantages compare to SRP alone. After 3 and 6 months the adjunctive MOX approach resulted in undetectable levels of subgingival A. actinomycetemcomitans, and there was a significant reduction in the levels of P. gingivalis and T. forsythia.

References


### Clinical Relevance

*Scientific rationale for the study:* The adjunctive use of systemically administered antibiotics has been shown to provide a better clinical outcome, particularly in terms of probing depth reduction and attachment-level gain than SRP in subjects with aggressive periodontitis. No studies have looked at the microbiology and clinical efficacy of moxifloxacin as adjunctive therapy in GAgP.

*Principal findings:* Subjects receiving MOX showed the greatest improvements in clinical attachment level, and probing depth. Adjunctive antibiotic protocol reduced subgingival *A. actinomycetemcomitans* to undetectable levels.

*Practical implications:* These results support the administration of moxifloxacin in one-stage SRP in treating GAgP.