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Azithromycin as an adjunctive treatment of aggressive periodontitis: 12-months randomized clinical trial

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Abstract

Aim: To assess the effect of systemic azithromycin as a supplement to scaling and root planing (SRP) in the treatment of aggressive periodontitis (AgP).

Material and Methods: Twenty-four individuals (13–26 years old) underwent a plaque control program, and then were treated with SRP. Subjects were assigned randomly into two groups; the test group used 500 mg azithromycin once a day for 3 days, whereas the control group used a placebo. Clinical variables were assessed at baseline, 3, 6, 9, and 12 months. The periodontal status at baseline and 12 months was compared using the Wald test, and adjusting for the effect of clustering of teeth within subjects.

Results: There were no significant differences in visible plaque, gingival bleeding, and supragingival calculus between groups throughout the study. Periodontal probing depth (PPD) and clinical attachment level improved significantly from baseline to 12 months in both groups, with the test group showing significantly more reduction in mean PPD compared with controls (2.88 mm *versus* 1.85 mm, respectively, $p = 0.025$). Subjects administering azithromycin showed a higher percentage of teeth with attachment gain $\geqslant 1$ mm (81.34 *versus* 63.63, $p = 0.037$), whereas the controls had higher percentage of teeth with attachment loss $\geqslant 1$ mm (11.57 *versus* 2.24, $p = 0.015$).

Conclusions: The adjunctive use of azithromycin has the potential to improve periodontal health of young patients with AgP.

Key words: adolescents/young-adults; antibiotics; azithromycin; periodontal disease; randomized controlled trial

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Aggressive periodontitis (AgP) is a rapidly progressive disease that affects otherwise healthy individuals (Armitage 1999), and has certain microbiologic (Ximenez-Fyvie et al. 2006) and immunologic characteristics (James et al. 2007, Nibali et al. 2008). This disease has a low prevalence in developed countries (Albandar & Tinoco 2002) but is more common in many developing countries (Albandar & Tinoco 2002, Susin & Albandar 2005).

The prevention and control of AgP is challenging (Albandar et al. 1995). Non-surgical periodontal therapy alone, although effective in the treatment of chronic periodontitis, seems less effective in patients with AgP (Slots & Rosling 1983, Christersson et al. 1985, AAP 2000). The effectiveness of systemic antibiotics as adjuncts to non-surgical treatment has been investigated, including tetracycline, amoxicillin, metronidazole, and combinations of these. Generally, studies show improved clinical outcomes following the adjunctive use of antibiotics (Herrera et al. 2002, Slots & Ting 2002, Walker & Karpinia 2002, Haffajee et al. 2003), although the results are sometimes inconsistent (Saxen et al. 1990, Saxen & Asikainen 1993, Palmer et al. 1996, Tinoco et al. 1998). Moreover, there are only a few studies

Conflict of interest and source of funding statement

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reporting longer-term results following controlled clinical trials of systemic antibiotics in young individuals with AgP.

Azithromycin is a macrolide antibiotic, similar to erythromycin, and has favourable pharmacological properties and few adverse effects. It has enhanced macrolide potency and a wide antimicrobial spectrum with in vitro activity against aerobic and anaerobic Gram-negative microorganisms (Retsema et al. 1987, Williams et al. 1992). Additionally, azithromycin has a long half-life that allows a once a day administration of 500 mg during 3 consecutive days (Foulds et al. 1990), thus improving patient compliance in administering the drug. In vitro studies have demonstrated its efficacy against *Aggregatibacter* (previously *Actinobacillus) actinomycetemcomitans* and *Porphyromonas gingivalis* (Pajukanta et al. 1992, Pajukanta 1993). Clinical studies have shown high concentrations in periodontal tissues (Blandizzi et al. 1999, Gomi et al. 2007), and significant reductions in periodontal probing depths (PPDs) (Smith et al. 2002) and clinical attachment gain (Haffajee et al. 2007) in individuals with chronic periodontitis. Its efficacy in the treatment of AgP is not well documented.

The aim of the present study was to compare the long-term clinical effect of the adjunctive use of azithromycin or placebo with non-surgical periodontal therapy in the treatment of AgP.

Material and Methods

Subjects

Twenty-eight AgP subjects, 13–26 years of age, consisting of 13 males and 15 females, participated in this study. Some of these subjects were identified in a large epidemiological survey of a sample representative of approximately 3 million people in the metropolitan area of Porto Alegre, Brazil (Susin & Albandar 2005). The rest of the cases were derived among patients that were awaiting treatment at the Department of Periodontology, the Federal University of Rio Grande do Sul, Porto Alegre, Brazil.

The subjects underwent a baseline clinical examination to determine their eligibility for the study, and were then interviewed to gather information about demographics, oral hygiene, smoking habits, systemic conditions, and medications history.

Study design

A randomized, double-blind, placebo-controlled, parallel design was used. Subjects were included in the study if they had a diagnosis of AgP and fulfilled the following criteria: presence of PPD and clinical attachment loss of $\geqslant 4$ mm, associated with bleeding on probing (BOP) in at least one incisor and one first molar. For stratification purposes the AgP cases were classified as having localized or generalized forms of disease (Albandar et al. 1997, Armitage 1999). Subjects with at least one incisor or first molar with clinical attachment loss $\geqslant 4$ mm and no more than two teeth other than first molars or incisor were classified as having localized AgP, whereas those with more than three non-incisor/first molar affected teeth were classified as having generalized AgP.

Patients with a previous history of SRP, surgical periodontal therapy, or antibiotic intake in the last 6 months were excluded. Other exclusion criteria included a history of allergic reactions to azithromycin or other macrolide antibiotic, and use of anti-acids containing aluminum or magnesium. Subjects were excluded from the study if they developed adverse reactions to medication.

The subjects were stratified by smoking status (smokers or non-smokers) and disease extent (localized or generalized) to allow a similar distribution of these factors in the sample. This resulted in four strata: smokers with localized AgP, smokers with generalized AgP, non-smokers with localized AgP, and non-smokers with generalized AgP. To ensure complete masking of the groups identities, an assistant not involved in the study was responsible for the randomization of the participants within each stratum. Participants were randomly assigned, by means of a draw, to one of the experimental groups. Test (azithromycin) and control (placebo) medications were stored in identical opaque-coloured bottles identified only by the respective code of each participant. Randomization codes were kept by the same assistant and were broken after statistical analyses had been performed. Both periodontists involved in the treatment and clinical examination were masked from the identity of the study participants throughout the experimental period.

Treatments

The subjects received a two-phase treatment (Fig. 1). Phase 1 consisted of two sessions of supragingival scaling and oral hygiene instructions. At day 15, a clinical examination was performed, and phase 2 started consisting of non-surgical periodontal therapy with subgingival hand scaling and root planing (SRP) under local anaesthesia using periodontal files and curettes. The treatment was conducted by one experienced periodontist (G. D. C.) and was carried out in multiple visits on a quadrant/sextant basis. Phase 2 was completed within a period of 14 days.

The subjects were given the medications (azithromycin or placebo) in the first treatment session of phase 2. Subjects in the test group received a bottle containing three azithromycin 500 mg coated tablets (EMS-SIGMA, São Paulo, Brazil). The control group received identical bottles containing three placebo tablets (Laboratory of Galenic Development, School of Pharmacy, Federal University of Rio Grande do Sul, Brazil). Test and control tablets were identical in colour, size, and weight. The subjects were instructed to take one tablet each day (24/24 h) orally for 3 consecutive days. Subjects took the first tablet just before the SRP session in the presence of the dental assistant not involved in the study. The dental assistant called each subject during the next 2 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 intake and occurrence of adverse events.

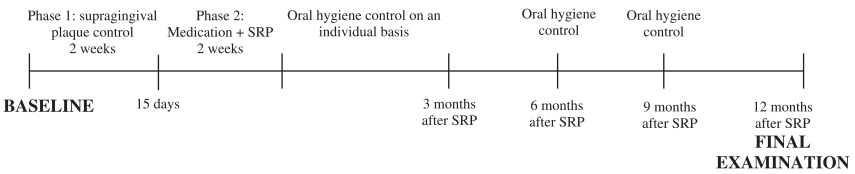

Fig. 1. Flowchart of treatments and examination schedules. SRP, scaling and root planning.

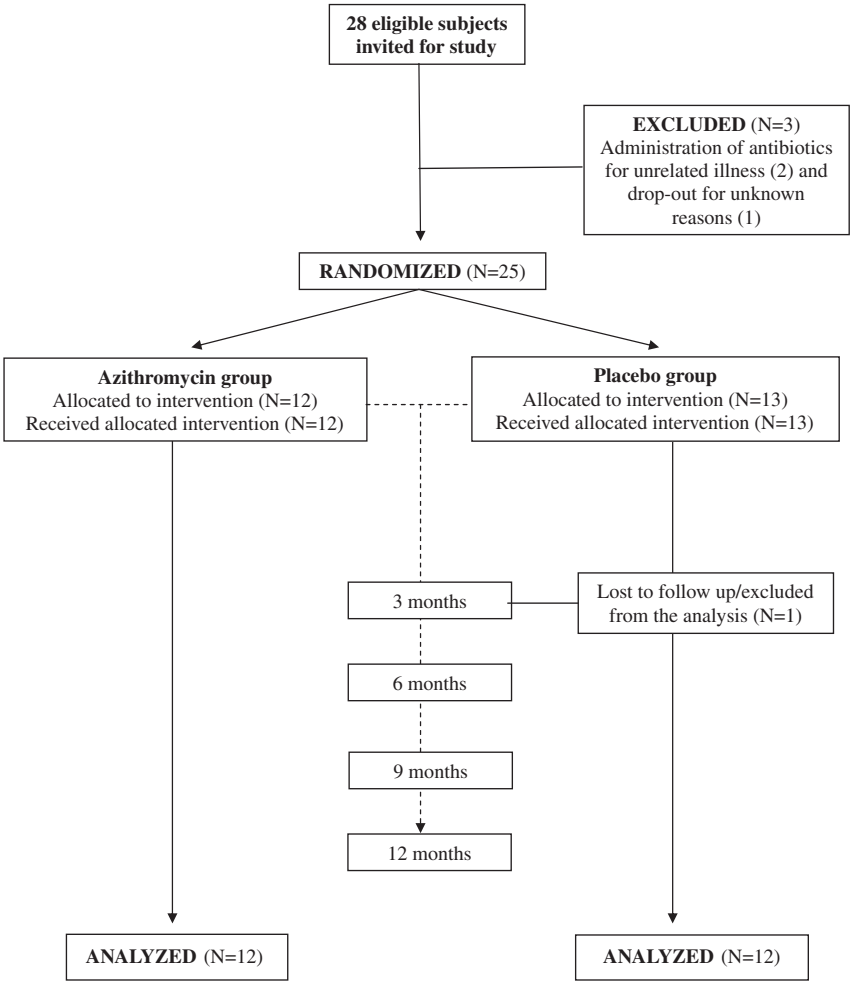

Fig. 2. Flowchart of participation in the study.

Subjects were asked to return the bottles of medication 2 days after the last tablet had been taken and the number of missing tablets was registered. At the same moment, participants were asked about the occurrence of any adverse event that could be associated with the use of the medication.

During the treatment sessions, oral hygiene was evaluated and home care instructions were re-emphasized. All subjects came for recall visits and received oral prophylaxis and oral hygiene evaluations. The recall visits were on a 3-week interval during the first 3 months after treatment, once a month during 3 and 6 months post-operatively, and once every 3 months in the last 6 months of the study (Fig. 2).

Clinical examination

Dental plaque, supragingival calculus, gingival marginal bleeding, periodontal probing depth (PPD), gingival recession, and bleeding on probing (BOP) were assessed for all participants at baseline, 15 days after supragingival plaque control, and 3, 6, 9 and 12 months after subgingival SRP. One periodontist (A. N. H.) performed all measurements on six sites per tooth, excluding third molars. First, visible plaque was scored as present if a film of plaque was visible to the naked eye after drying the tooth with a blast of air. Gingival bleeding was then recorded and scored as present/absent by running the probe 1–2 mm into the gingival crevice. The presence of supragingival calculus was assessed supragingivally and up to 1 mm below the gingival margin, following which, the patient rinsed with water. Consecutively, PPD and gingival recession were assessed using a manual periodontal probe (CP10SE, HuFriedy, Chicago, IL, USA). Clinical attachment level (CAL) was calculated as the sum of probing depth and gingival recession if gingival recession was present, or as the difference between the two if the gingival margin was located coronal to the cementoenamel junction. The cementoenamel junction was detected by probing the cervical area of each tooth. BOP was recorded as present/absent after PPD measurements.

Power analysis

Based on a preliminary analysis, a sample size of 24 subjects was estimated to be necessary to achieve 80% power to detect a difference of 1 mm (SD 0.85) between the two groups mean PPD reduction. This mean difference was chosen for being regarded as clinically relevant for an adjunct treatment (Greenstein 2003) and greater than the measurement error of the examiner. A two-sided two-sample *t*-test with a significance level of 5% was used for the sample size calculation. An attrition rate of 15% was assumed, yielding a total number of 28 recruited subjects.

Examiner reproducibility

The intra-examiner reproducibility of probing depth, CAL, and dental plaque measurements were assessed before and during the experimental period. Repeated measurements were performed on a total of 12 periodontal patients, six of whom were examined immediately before the clinical trial, and the other six during the experimental period. Duplicate measurements were conducted in groups of two patients with at least 1 h between each examination.

The weighted κ coefficients (± 1 mm) of PPD and CAL were 0.92 and 0.85, respectively, and the κ value for dental plaque was 0.65. The intra-class correlation coefficients for mean PPD and CAL were 0.98 and 0.94, respectively. The measurement error for PPD was 0.63 mm and for CAL was 0.83 mm. The examiner's reproducibility of measurements made before and during the study was similar.

Statistical analysis

The percentage of sites with visible plaque, gingival marginal bleeding, and supragingival calculus were calculated for each subject taking into consideration all examined teeth. Only teeth presenting, concomitantly, clinical attachment loss and PPD of 4 mm or more at baseline were considered in the

analyses of changes in CAL, PPD, and BOP, comprising a total of 294 eligible teeth for analysis. The worst site of each tooth was selected for analysis.

The mean change in BOP, PPD, and CAL was compared between the treatment groups, and the analysis was performed separately by subgroups defined by the magnitude of PPD at baseline: moderate (4–6 mm) and deep pockets (7 mm or more). The percentage of sites showing changes in attachment levels and probing depths from baseline to 12 months was calculated for different thresholds.

The present analysis used a per protocol strategy because one patient who did not take the third dose of the placebo and dropped out of the study after 3 months was not included in the analysis (see 'Results' for further information). Another subject from the control group moved out of town and missed the 12-months examination. A carry-forward strategy was employed to account for the missing information, and the 9-months data was used (Hollis & Campbell 1999).

Data analysis was performed using STATA software (Stata 9.2 for Windows, Stata Corporation, College Station, TX, USA). Comparisons of differences between the 12-months after SRP and baseline examinations between test and control groups were made using commands that take into account clustering of teeth within individuals. Linear models were used to calculate point estimates (i.e. means and percentages) and a robust variance estimator (Huber/White/sandwich estimator of variance) was used to adjust the standard errors for the correlation in the data. Wald tests were used to estimate *p*-values and the level of significance was set at 5%. Adjusted *p*-values were used for multiple comparisons.

Ethical consideration

The study protocol was approved by the Committee of Ethical Affairs of the Faculty of Dentistry of the Federal University of Rio Grande do Sul, and was conducted according to the principles outlined in the Declaration of Helsinki on experiments involving human subjects. The subjects read and signed an informed consent before entering the study.

Results

Participation of individuals during the study is illustrated in Fig. 2. Two patients were excluded because they received additional antibiotics for the treatment of unrelated systemic illnesses before randomization. One subject dropped out of the study before randomization for unknown reasons. Regarding compliance with medication use, all participants returned the bottles and a 100% compliance was achieved. One participant reported having a headache following administration of the medication and stopped using it after the second dose. Despite this lack of compliance with the study protocol the patient was periodontally treated and followed up to the 3-months examination. This subject later dropped out of the study for unknown reasons. Subsequent analysis after unveiling the randomization code showed that this patient was using placebo. No side effects related to azithromycin were reported during the study. Data were available for a total of 24 subjects (85.7%) initially recruited for this study.

There were no significant differences at baseline between the test and control groups regarding demographic, behavioural, and periodontal characteristics (Table 1). All participating subjects were enrolled in an oral hygiene programme, which resulted in significant reductions ($p \leqslant 0.001$) in visible plaque, gingival marginal bleeding, and supragingival calculus during the 1-year experimental period (Fig. 3). The azithromycin and placebo groups showed similar patterns of plaque accumulation and GB during the study ($p > 0.05$).

Figure 4 illustrates changes in PPD during the experimental period for azithromycin and placebo groups. There was a significant reduction in PPD in

Table 1. Characteristics of study subjects at baseline*

Variable	Statistics	Azithromycin ($n = 12$)	Placebo ($n = 12$)
Gender (male)	*N*	5	8
Age (years)	Mean ± SD	22.5 ± 3.6	20.1 ± 3.6
Smokers	*N*	3	2
Localized disease	*N*	5	6
Generalized disease	N	7	6
Tooth loss	Mean ± SD	1.8 ± 1.7	1.4 ± 1.9
Number of teeth with CAL and PPD ⩾4 mm at baseline (294 eligible teeth)	Mean ± SD	13.0 ± 2.1	11.5 ± 1.9
Whole-mouth clinical parameters†			
Visible plaque (% sites)	Mean ± SD	56 ± 33	72 ± 29
Gingival bleeding (% sites)	Mean ± SD	15 ± 19	23 ± 22
Calculus (% sites)	Mean ± SD	21 ± 27	37 ± 33
PPD (mm)	Mean ± SD	4.8 ± 2.1	4.7 ± 1.9
CAL (mm)	Mean ± SD	3.5 ± 2.6	3.1 ± 2.5
BOP (% sites)	Mean ± SD	42.5 ± 33.1	53.7 ± 33.3
Eligible-teeth clinical parameters‡			
Visible plaque (% sites)	Mean ± SD	62 ± 32	82 ± 22
Gingival bleeding (% sites)	Mean ± SD	16 ± 20	27 ± 24
Calculus (% sites)	Mean ± SD	33 ± 30	51 ± 32
PPD (mm)	Mean ± SD	6.7 ± 1.5	6.3 ± 1.6
CAL (mm)	Mean ± SD	5.9 ± 1.8	5.7 ± 1.8
BOP (% sites)	Mean ± SD	65.9 ± 24.5	76.4 ± 21.8

*No significant differences between azithromycin and placebo groups were observed for any of the variables.

†Means calculated considering all examined teeth.

‡Means calculated considering 294 eligible teeth for analysis (baseline PPD and CAL ⩾4 mm).

PPD, periodontal probing depth; CAL, clinical attachment level; BOP, bleeding on probing; SD, standard deviation.

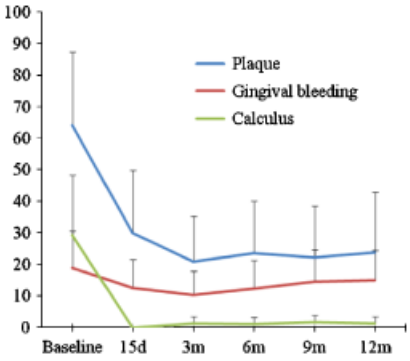

Fig. 3. Visible plaque, gingival marginal bleeding and supragingival calculus, considering all examined teeth, for all study subjects during experimental periods ($N = 24$); bars represent standard deviations.

both groups during the study. Additionally, initially moderate pockets demonstrated smaller reductions compared with deep pockets in both groups. Small changes were observed from baseline to 15 days after supragingival plaque control, whereas the greater amount of change occurred during the first 3 months in both groups with little variation after this period. Regarding CAL changes, test and control groups also demonstrated significant improvement during the 1-year follow-up period (Fig. 5). From 6 to 12 months post-operatively, the group treated with azithromycin showed a continued improvement in CAL, whereas the control group demonstrated a trend to increase clinical attachment loss.

The use of azithromycin resulted in a significantly higher reduction in mean probing depth of approximately 1 mm, compared with placebo ($p = 0.025$) (Table 2). The additional reduction in PPD was similar in sites that at baseline had deep ($\geqslant 7$ mm) or moderate probing depths (4–6 mm) (0.77 and 0.73 mm, respectively). The azithromycin group showed higher CAL improvement than the control group when all eligible sites were considered in the analysis, with a borderline p value ($p = 0.05$). There were no significant differences in mean CAL gain between groups in sites with moderate or deep PPD at baseline. The two treatment groups showed similar changes in BOP, with both groups showing a decrease of approximately 45% of bleeding sites ($p = 0.91$). The PPD at baseline did not have a significant effect on the reduction in BOP.

Table 3 shows the percentage of teeth according to thresholds of change in PPD and CAL. Compared with the placebo group, the azithromycin group had significantly higher percentages of teeth with a PPD reduction of $\geqslant 1$ and $\geqslant 2$ mm from baseline to 12-months post-operatively. Additionally, patients taking azithromycin had a significantly higher percentage of teeth with $\geqslant 1$ mm decrease in CAL than those taking the placebo. The same pattern was observed for the percentage of teeth gaining $\geqslant 2$ mm of attachment; however, the difference between groups did not reach statistical significance. Patients in the placebo group had an increase in the percentage of teeth showing loss of attachment $\geqslant 1$ mm during the study period.

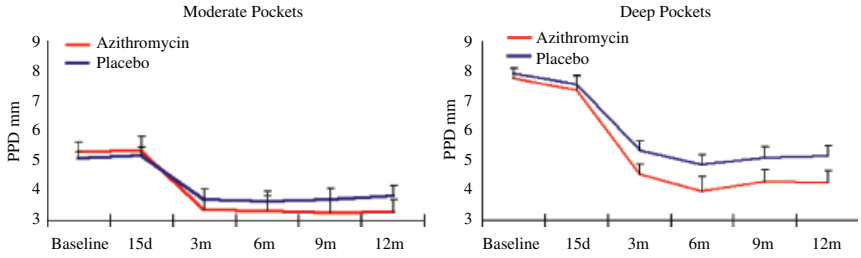

Fig. 4. Mean periodontal probing depth in study groups during experimental periods for sites with baseline probing depths 4–6 mm (left) and $\geqslant 7$ mm (right) (bars represent standard errors).

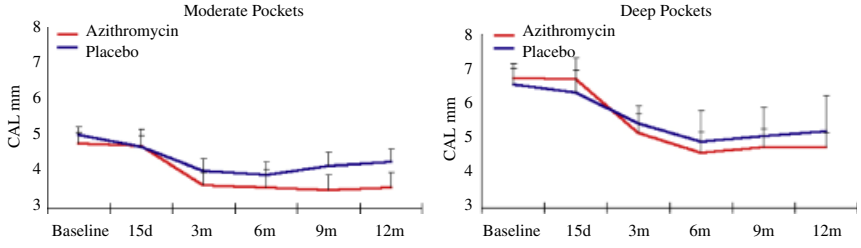

Fig. 5. Mean clinical attachment level in study groups during experimental periods for sites with baseline probing depths 4–6 mm (left) and $\geqslant 7$ mm (right) (bars represent standard errors).

Discussion

The aim of the present randomized controlled trial was to assess the effect of adjunctive use of azithromycin with non-surgical treatment of AgP in young patients. SRP combined with a 3-day regimen of azithromycin resulted in significantly better clinical outcome parameters, including PPD and CAL, compared with SRP. To the best of our knowledge, this is the first study showing the clinical efficacy of azithromycin 1 year following non-surgical treatment of AgP in young individuals.

Few randomized controlled trials have been conducted to evaluate the effects of adjunctive systemic antibiotics in the treatment of AgP (Saxen et al. 1990, Saxen & Asikainen 1993, Palmer et al. 1996, Tinoco et al. 1998). Perhaps one of the reasons for this scarcity of studies is the low prevalence of AgP (Albandar & Tinoco 2002) and the consequent difficulty in recruiting cases for studies. Furthermore, oftentimes AgP is diagnosed at an advanced stage of the disease, at which time the prognosis for

Table 2. Changes (mean ± SE) in probing depth (PPD), clinical attachment level (CAL), and bleeding on probing (POB) in the test (azithromycin) and control (placebo) groups during 12 months, by baseline probing depth

	Baseline PPD								
	moderate (4–6 mm)			deep ($\geqslant 7$ mm)			all ($\geqslant 4$ mm)		
	placebo	azithromycin	p	placebo	azithromycin	p	placebo	azithromycin	p
PPD reduction (mm)	1.25 ± 0.17	2.02 ± 0.14	0.003	2.76 ± 0.51	3.49 ± 0.23	0.21	1.85 ± 0.36	2.88 ± 0.23	0.025
CAL gain (mm)	0.74 ± 0.28	1.21 ± 0.16	0.16	1.35 ± 0.34	2.01 ± 0.23	0.125	0.97 ± 0.29	1.68 ± 0.20	0.05
BOP reduction (%)	44.74 ± 4.34	38.30 ± 3.95	0.29	44.41 ± 6.67	49.83 ± 2.91	0.47	44.46 ± 3.89	45.04 ± 3.32	0.91

Table 3. Percentage of teeth (± SE) by treatment group and thresholds of changes in PPD and CAL during the 1-year study period

	Changes in PPD and CAL during 1 year											
	increased ⩾1 mm			no change			decreased ⩾1 mm			decreased ⩾2 mm		
	placebo	azithromycin	*p*	placebo	azithromycin	*p*	placebo	azithromycin	*p*	placebo	azithromycin	*p*
PPD	4.13 ± 1.40	0	0.007	13.22 ± 4.03	2.99 ± 1.81	0.03	82.64 ± 4.76	97.01 ± 1.81	0.010	57.85 ± 8.21	81.34 ± 4.00	0.017
CAL	11.57 ± 3.43	2.24 ± 0.97	0.015	24.79 ± 6.51	16.42 ± 2.94	0.25	63.63 ± 7.29	81.34 ± 3.28	0.037	36.36 ± 7.95	51.49 ± 7.19	0.17

PPD, periodontal probing depth; CAL, clinical attachment level.

non-surgical treatment may not be favourable.

Early studies of systemic antibiotic treatment of AgP used tetracycline. Significantly higher improvements have been reported in PPD and CAL 3 months following treatment in subjects using tetracycline compared with controls (average: 0.49 mm for PPD and 0.46 mm for CAL) (Palmer et al. 1996). It should be noted that in the latter study the clinical benefit attributed to tetracycline amounts to approximately half of the improvement in clinical parameters observed in the present study in the group using azithromycin. However, the study by Palmer et al. (1996) did not exclude sites with shallow pockets from the data analysis, and this may partly explain the lower mean change. Other studies also reported a beneficial effect of using tetracycline in the treatment of AgP (Slots & Rosling 1983, Christersson & Zambon 1993); however, these studies did not have control groups. In addition, these studies used non-surgical and/or surgical treatment methods, and therefore their findings are not directly comparable.

Other studies in Finnish subjects have used doxycycline or metronidazole (Asikainen et al. 1990, Saxen et al. 1990, Saxen & Asikainen 1993). Doxycycline did not result in significant changes in the percentage of sites with ⩾4 mm PPD compared with the placebo. Metronidazole resulted in a small increase in crestal bone height after 18 months compared with SRP alone, but statistical analysis was not performed due to the small sample size. Tinoco et al. (1998) used a combination of metronidazole and amoxicillin in a Brazilian sample, and they reported approximately 74% of sites demonstrating PPD reduction and 35% sites showing CAL gain ⩾2 mm, compared with 41% and 16% in the placebo group, respectively. The corresponding changes in clinical parameters in the present study were 81% and 51%, respectively, suggesting that the effect of azithromycin is somewhat similar to the use of a combination of metronidazole and amoxicillin.

More recent studies have addressed the use of systemic antibiotics in the treatment of aggressive periodontitis (Guerrero et al. 2005, Xajigeorgiou et al. 2006). In general, these studies showed that the adjunctive use of antibiotics resulted in some additional clinical benefit in PPD and CAL compared with SRP alone.

Azithromycin has certain characteristics that make it an attractive agent for use in the treatment of young patients with AgP. Two important microorganisms associated with AgP, *A. actinomycetemcomitans* and *P. gingivalis*, are sensitive to azithromycin in vitro (Pajukanta et al. 1992, Pajukanta 1993, Muller et al. 2002). Minimal inhibitory concentrations of azithromycin for these periodontopathogens are also reached and maintained in the serum and gingivae for a period of 7–14 days (Foulds et al. 1990, Blandizzi et al. 1999, Gomi et al. 2007). Moreover, compared with tetracycline that has to be administered for a period of 14–21 days, and other agents that are prescribed for 7–10 days, azithromycin is administered in one dose of 500 mg every 24 h for only 3 consecutive days, hence increasing patient compliance. Consequences of incomplete adherence to the antibiotic regimen were recently evaluated, demonstrating worst clinical results when full compliance with medication intake is not achieved (Guerrero et al. 2007). Additionally, adverse events are reported in only 0.7% of the patients taking azithromycin (Contopoulos-Ioannidis et al. 2001). In the present study no side effects related to azithromycin intake were reported.

Azithromycin used with SRP has been shown to be effective in the treatment of chronic periodontitis when compared with SRP alone (Smith et al. 2002, Mascarenhas et al. 2005, Haffajee et al. 2007). Azithromycin improved the efficacy of SRP, and its effects on PPD and CAL seem to last longer than other antibiotics.

In the present study, initially deep pockets had greater PPD reduction than moderate pockets in both experimental groups. On the other hand, the additional PPD reduction observed in subjects using azithromycin was similar in initially moderate and deep sites when compared with placebo (approximately 0.8 mm). Previous studies have demonstrated that the additional benefit of antibiotics is more evident in deep sites (Guerrero et al. 2005, Haffajee et al. 2007). These contradictory findings may be partly explained by the greater PPD reduction observed in the control group in the present study as compared with control groups from previously published reports. SRP alone resulted in a mean PPD reduction of 2.8 mm in the present study, whereas others reported reductions ranging from 1.5 to 1.8 mm in initially deep pockets (Herrera et al. 2002, Guerrero et al. 2005, Haffajee et al. 2007). Another interesting finding of the present clinical trial is that mean PPD was higher than mean CAL at baseline, indicating that gingival recession was not frequent (Table 1). At the end of the 12-months period, mean values for CAL and PPD became similar (Figs 4 and 5), indicating that both treatments resulted in some gingival recession.

Some studies evaluated the efficacy of administering systemic antibiotics at the same time with SRP (Lindhe & Liljenberg 1984, Saxen et al. 1990, Ramberg et al. 2001), whereas others used the antibiotics after the SRP was completed (Saxen & Asikainen 1993, Palmer et al. 1996, Tinoco et al. 1998, Smith et al. 2002). There seems to be no consensus about which of the two methods is more effective. Pharmacological studies have demonstrated that azithromycin remains at high concentrations up to 14 days in serum (Foulds et al. 1990)

and periodontal tissues (Blandizzi et al. 1999, Gomi et al. 2007). In this study, the administration of azithromycin started in the first SRP session. The subsequent SRP treatment sessions were completed within a period of 14 days, when the concentration of the antibiotic is high, aiming to achieve a better adjunctive effect of azithromycin on a recently disrupted biofilm (Kaner et al. 2007).

Smoking is a strong predictor of unsuccessful periodontal therapy, because it has been demonstrated that smokers have a less favourable clinical response than non-smokers (Grossi et al. 1996, Van der Velden et al. 2003, Hughes et al. 2006). Other factors that are believed to influence the response to mechanical therapy include disease severity/extent at the beginning of treatment, and the adequacy of supragingival plaque control (Kaldahl et al. 1993, Kornman et al. 1994, Tomasi et al. 2007). In this study we took measures to minimize these confounding effects. Individuals were stratified by smoking status and disease extent before randomization to reduce the imbalance between test and control groups regarding these variables. Additionally, all individuals received a strict supragingival plaque control as part of the treatment and no significant differences were observed between groups in the amount of plaque deposition over the study period.

The occurrence of antimicrobial resistance has increased dramatically since penicillin was discovered, and this is also true for the periodontal microbiota (Walker 1996, van Winkelhoff et al. 2000). It has also been demonstrated that macrolides elicit microbial resistance in the oral streptococcal flora (Malhotra-Kumar et al. 2007). The findings from the present study indicate that SRP alone was an effective treatment for young patients with AgP, yielding similar clinical results to those obtained after SRP alone in chronic periodontitis patients found in previously published meta-analyses (Cobb 1996, Hung & Douglass 2002, Van der Weijden & Timmerman 2002). Thus, the indiscriminate use of antimicrobial agents should be avoided in the treatment of AgP patients. Additionally, it still remains difficult to identify those patients who would benefit the most with the use of systemic antibiotics.

Among the strengths of the present study are the uniqueness of testing a short-duration and easy to comply with medication in the treatment of young individuals with AgP. Moreover, the use of a randomized double-blind placebo-controlled parallel design, a stratified randomization of the sample for important factors (disease extent and smoking) and a 12-months follow-up improve the methodological quality of the present research. A possible shortcoming of this study is that the statistical analysis used a per protocol strategy. One patient that did not take the third dose of the placebo and dropped out of the study after 3 months was not included in the analysis. An evaluation of the 3-months clinical results showed that this patient did not respond well to the treatment. In this regard, the inclusion of this subject in the analysis as required by the intention to treat strategy (Hollis & Campbell 1999) would have the potential to overestimate the benefits associated with the use of azithromycin.

In this study, better clinical outcomes including higher PPD reduction and CAL gain were obtained with the adjunctive use of azithromycin than placebo. In addition, the suitable administration schedule makes this agent a better alternative than other antibiotics. It can be concluded from the present study that the adjunctive use of azithromycin has the potential to improve periodontal health of young patients with AgP.

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Clinical Relevance

Scientific rationale for the study: Clinical management of aggressive periodontitis is challenging, and the use of systemic antibiotics may enhance the effects of SRP. Azithromycin has antimicrobial activities against AgP-associated periodontopathogens, and its administration schedule is more favourable than other antibiotics, which could improve patient compliance.
Principal findings: The adjunctive use of azithromycin resulted in additional clinical benefits compared to SRP alone. Test subjects showed significant decrease in PPD and higher attachment gain 12 months postoperatively.
Practical implications: Systemic azithromycin may be used together with mechanical periodontal therapy in the treatment of AgP.