Azithromycin buccal patch in treatment of chronic periodontitis

Sajith Abdul Latif, K. L. Vandana1, J. Thimmashetty2, Priyanka Jairaj Dalvi1

ABSTRACT

Aim: This study aims to explore the clinical, microbiological, and biochemical impact of azithromycin (AZM) buccal patch in chronic generalized patients as a monotherapy as well as an adjunct to nonsurgical therapy.

Materials and Methods: A parallel design was used forty periodontitis patients were randomly allocated into five groups, namely Group 1 scaling root planing (SRP) alone, Group 2 (SRP + AZM patch group), Group 3 (SRP + AZM tablet group), Group 4 (AZM patch monotherapy), and Group 5 (AZM tablet as monotherapy). Plaque index, gingival bleeding index, modified gingival index, probing pocket depth (PPD), and clinical attachment level (CAL) were assessed at baseline and 21 and 90 days. Subgingival pooled plaque sample was collected to assess periodontopathogens like Porphyromonas gingivalis and Prevotella intermedia (Pi) by anaerobic culture method. Tumor necrosis factor alpha (TNF-α) was also evaluated at baseline and 21 days. Periodontal maintenance was performed in Group 1 until 90th day, and clinical parameter was assessed at the end of 90th day.

Results: SRP + AZM tablets showed greater reduction in clinical parameters (P < 0.05) AZM as monotherapy did not offer clinical benefits over SRP. Baseline data were compared at the end, i.e., 90th day a significant reduction in plaque scores, gingival bleeding, and PPD was observed however no significant gain in the clinical attachment was observed.

Conclusion: The monotherapy resulted in no improvement of periodontal parameters, microbial parameters, and TNF-α level. It is safe to use AZM + SRP as a mode of nonsurgical treatment in periodontitis patients.

KEY WORDS: Antimicrobials, azithromycin, periodontitis, scaling root planing, tumor necrosis factor alpha

Introduction

There are several studies where in azithromycin (AZM) is used in the treatment of periodontitis in either tablet1,2 or gel form.3 The use of AZM buccal patch as a systemic route of drug administration has not been dealt in the literature so far. The tumor necrosis alpha (TNF-α) activity is not measured after AZM treatment in periodontitis patients which speaks about the immunomodulatory effect of AZM. The use of AZM in the treatment of periodontitis with known anti-inflammatory, immunomodulatory, and antimicrobial actions is a good venture to understand potential activity of AZM. In the literature, there are studies of AZM used in conjunction with periodontal therapy with inconsistent beneficial benefits. AZM can be administered either systemically or as local drug delivery. The buccal mucosa is permeable with a rich blood supply. A few drugs have been
Films of different periodontal disease. Various antimicrobials are used as an adjunct to enhance the effects of SRP considering multiple actions of the drug used either in the local drug delivery or systemic form. Administration via AZM buccal patch delivers the sufficient quantity of drug 90% to systemic circulation compared to oral administration of AZM (37%). The AZM effect on chronic periodontitis is not consistent in improving clinical and microbial parameter.

There is a need for definitive, properly controlled clinical periodontal studies that investigate the effects of AZM as a monotherapy and as an adjunct to nonsurgical periodontal treatment. Medline search using keywords AZM, periodontitis, buccal patch, and the tablet does not reveal similar studies. Hence, the aim of this pilot randomized control trial investigation was to evaluate AZM in the treatment of periodontitis, to compare the clinical, microbial, and biochemical parameters of chronic periodontitis before and after treatment with AZM and to evaluate effect of AZM on clinical parameters during supportive periodontal therapy (SPT) for SRP patients.

Materials and Methods

Forty patients, aged 19–53 years (19 males and 21 females), who were diagnosed with chronic periodontitis from outpatient section of College of Dental Sciences, Davangere were enrolled in the study. Informed written consent was obtained from patients, and the Institutional Ethics Committee approved this Clinical Trial (Reference Number C0DS/2248/21010-2011). Systemically healthy subjects diagnosed with chronic periodontitis (probing pocket depth [PPD] = 5–7 mm) were included in the study. Patients who gave history of antibiotic or periodontal therapy in the last 6 months, patients with known or suspected allergy to the AZM other macrolides antibiotics, smokers, alcoholics, patients with diabetes, immunocompromised patients, and pregnant or lactating females were excluded from this study [Figure 1]. This pilot study was designed as a single center randomized, double-blind, parallel group study of 3 months duration. Forty patients were randomly assigned to each treatment group: SRP only (Group 1), SRP + AZM patch (Group 2), SRP + AZM tablet (Group 3), AZM buccal patch monotherapy (Group 4), and AZM Tablet monotherapy (Group 5). Oral hygiene instructions were given and the patients were advised a toothbrush (ICPA Health Products Ltd.) and toothpaste (SENSODENT-R® Warren Pharma, India). SRP was performed using ultrasonic (Gavitron® - Bobcat pro, dentsply USA) and hand instruments (Hu-Friedy, Chicago). Patients were advised not to use any kind of mouthwash or rinse during the study period. Patients were instructed to take AZM 500 mg (AZEE Cipla Global Ltd., India) one tablet/day for 3 days.

The clinical parameters recorded were: Plaque index (PI), gingival bleeding index (GBI), modified gingival index (MGI), PPD, and clinical attachment level (CAL); subgingival pooled plaque sample and pooled gingival crevicular fluid (GCF) was collected from selected sites on baseline day and 21 days. PPD, clinical attachment levels (CAL) were measured for the selected teeth using a standard manual probe Williams’s periodontal probe. A single clinician provided treatment to both groups, and all pre- and post-treatment clinical parameters were recorded by another examiner who was masked to the type of treatment received by the subjects.

All measurements were recorded by the same examiner. The clinical parameters were recorded at baseline, 21 days, and 90 days. The microbial parameters and TNF-α markers were recorded at baseline and 21 days. The microbiologist was blinded regarding coding of the plaque and the GCF samples. The outline of the study protocol is presented in Figure 2.

At baseline and 21st day, GCF sampling was pooled from 12 maxillary teeth using microcapillary pipettes was performed before recording the clinical parameters and performing microbiological sampling. TNF-α levels in the GCF samples were determined by ELISA (Sigma-Aldrich, India) according to the manufacturer’s instruction. Following sampling of GCF the subgingival plaque samples were collected using a sterile Gracey curette.

The general methods for the preparation of films were reported earlier. But the solvent casting method was followed in this study for preparation of films. Films of different composition of polymers were prepared. The films were observed for dispersion of drug, flexibility, and glossy structure. The “film” represents the one, which was prepared from the mould and was bigger in size (5 cm × 3 cm) and patch represents the one, which was obtained by cutting the film and was smaller in size (1 cm × 5 cm). The buccal mucoadhesive films of AZM were prepared using hydroxypropyl methyl cellulose (HPMC) polymer by solvent casting method. HPMC polymer (400 mg) was weighed accurately and placed in 4 ml of ethanol. The contents in the beaker were stirred on magnetic stirrer for 10 min for swelling of polymer. Further, 3 ml of ethanol was added to the above polymer solution and stirred the dispersion. Then, ten drops (25 mg) of dibutylphthalate were added to the polymer solution. AZM (300 mg) was weighed and dissolved in 3 ml of ethanol in another beaker. The drug solution was added to the polymer dispersion. The whole mixture was mixed thoroughly with the help of a magnetic stirrer. The glass mould of size 5 cm × 3 cm was placed over a flat surface. The drug-polymer mixture was poured into the glass mould. The mould was covered under inverted funnel overnight for drying and was allowed for slow evaporation to remove the solvent. The film was removed from the mould and packed in aluminum foil and stored in a dessic peace.

The AZM buccal patch administration was done during Phase I periodontal therapy and maintenance phase of those patients in the SRP group at 21 days and followed up to 42 days (3 weeks duration). The data recorded at 0, 21, and 90 days were subjected to statistical analysis.

Statistical analysis was done with SPSS (SPSS version 17.0, SPSS, Chicago, IL) data comparison was done by applying specific statistical tests to find out the statistical significance of the results. Since the data were continuous type, parametric tests were used for analysis. Mean and standard deviation were calculated. Statistical tests employed for the obtained data in our study. One-way analysis of variance test was used.
Results

All subjects reported full adherence to the prescribed course of the antibiotic treatments. No adverse events were reported by subjects from the test groups. All subjects reported that the medications did not cause any major disturbance in their daily routine and that they would start the treatment again if necessary. No statistically significant differences were observed between groups for any parameter evaluated at baseline. No adverse reactions were observed for both AZM patch and tablet throughout the study period. On intergroup comparisons [Table 1], the plaque scores, gingival bleeding, gingival inflammation, PPD reduction, and CAL improvement were similar in SRP and SRP + AZM patch group. However, there was a statistically significant reduction in plaque and gingival bleeding scores in SRP + AZM tablet group, PPD and CAL did not show any significant improvement.

Although more than five hundred different types of bacteria have been isolated from the oral cavity, only a small fraction of these bacteria has the potential to cause destruction of periodontal tissues. All subjects were colonized by *Porphyromonas gingivalis* (Pg) and *Prevotella intermedia* (Pi) which are most commonly associated with chronic periodontitis and no statistically significant differences were observed in the individual mean counts evaluated between groups at baseline. Both therapies elicited a statistically significant reduction in microbial parameters in SRP + AZM tablet groups which showed no improvement in microbial parameters [Table 2]. All the groups had similar GCF TNF-α level amount at baseline. The SRP and SRP + AZM patch treatment demonstrated similar reduction for TNF-α level. TNF-α level showed marked improvements at 3 weeks in both SRP and SRP + AZM patch groups [Table 3]. No statistically significant differences were observed between groups for any parameter evaluated at
Table 1:
Intergroup comparison of clinical parameters from 0 to 21st day between treatment groups

| Groups                     | SRP versus SRP + AZM patch | SRP versus SRP+AZM tablet |
|----------------------------|----------------------------|---------------------------|
|                            | PI  | GBI  | MGI  | PPD  | CAL | PI  | GBI  | MGI  | PPD  | CAL |
| SRP (mean±SD)              | 37.2±15.6 | 14.4±6.9 | 21.2±12.8 | 1.7±3.0 | 2.40±1.1 | 37.2±15.6 | 14.4±6.9 | 21.2±12.8 | 2.40±1.1 |
| SRP + AZM patch            | 32.8±18.4 | 16.5±6.4 | 28.5±10.3 | 1.76±2.0 | 0.67±2.5 | -0.45±4.7 | 0.62±8.1 | -1.52±6.5 | -1.52±6.5 | 0.00±0.00 |
| Mann-Whitney U-test        | 44.5 | 42.0 | 29.9 | 42.5 | 42.0 | 0.0 | 4.0 | 0.0 | 0.0 | 12.5 |
| P                          | 0.677 (NS) | 0.545 (NS) | 0.112 (NS) | 0.566 (NS) | 0.542 (NS) | P | 0.002 (S) | 0.010 (S) | 0.002 (S) | 0.002 (S) | 0.097 (NS) |

Mann-Whitney U-test, P<0.05, P<0.01 - S, P<0.001 - HS, P>0.05 - NS. Group 1=SRP, Group 2=SRP + AZM patch, Group 3=SRP + AZM tablet, Group 4=AZM patch, Group 5=AZM tablet. Pg=Porphyromonas gingivalis, PI=Plaque index, GBI=Gingival bleeding index, MGI=Modified gingival index, CAL=Clinical attachment level, P=Plaque index, SRP=Scaling root planing, AZM=Azithromycin, S=Significant, HS=highly significant, NS=Nonsignificant, SD=Standard deviation

Table 2:
Intergroup comparison of microbial parameters from 0 to 21st day between various treatment groups

| Microorganisms          | SRP versus SRP + AZM patch | SRP versus SRP + AZM tablet |
|-------------------------|----------------------------|-----------------------------|
| Pg (mean ± SD)          | Porphyromonas gingivalis    | Porphyromonas gingivalis    |
| SRP                     | 39.63±13.56 (SRP)           | 48.86±10.05 (SRP)           |
| 50.97±7.45 SRP + AZM patch | 43.72±16.87 SRP + AZM patch | -5.04±14.58 SRP + AZM tablet |
| Mann-Whitney U-test     | 24.5                        | 42.5                        |
| P                       | 0.053 (NS)                  | 0.568 (NS)                  |

Mann-Whitney U-test, P<0.05, P<0.01 - S, P<0.001 - HS, P>0.05 - NS. Group 1=SRP, Group 2=SRP + AZM patch, Group 3=SRP + AZM tablet, Group 4=AZM patch, Group 5=AZM tablet. Pg=Porphyromonas gingivalis, PI=Prevotella intermedia, SRP=Scaling root planing, AZM=Azithromycin, S=Significant, HS=highly significant, NS=Nonsignificant, SD=Standard deviation

Table 3:
Intergroup comparison of tumor necrosis alpha from 0 to 21st day between various treatment groups

| Groups                     | SRP versus SRP + AZM patch | SRP versus SRP + AZM tablet |
|----------------------------|----------------------------|-----------------------------|
| Mean±SD                    | 20.93±25.92 (SRP)          | 20.93±25.92 (SRP)           |
|                         | 24.98±46.76                | -49.66±34.57                |
| (SRP+AZM patch)           | (SRP+AZM tablet)           | (SRP+AZM tablet)           |
| Mann-Whitney U-test       | 44.0                       | 2.0                         |
| P                         | 0.650 (NS)                 | 0.005 (S)                   |

Mann-Whitney U-test, P<0.05, <0.01 - S, P<0.001 - HS, P>0.05 - NS. Group 1=SRP, Group 2=SRP + AZM patch, Group 3=SRP + AZM tablet, Group 4=AZM patch, Group 5=AZM tablet. SRP=Scaling root planing, AZM=Azithromycin, S=Significant, HS=Highly significant, NS=Nonsignificant, SD=Standard deviation

Baseline. The monotherapy groups showed no improvement in clinical parameters at any of the intervals (0, 21, and 90 days) monotherapy did not show any improvement in microbial parameters. There was no reduction in the TNF-α level among the monotherapy groups from baseline to 21 days. Periodontal maintenance therapy was performed only in SRP group. The patients were given AZM 500 mg tablet orally once daily for 3 days, and the clinical and microbiological were assessed [Graph 1a and 1b]. There was a significant reduction in plaque gingival bleeding and pockets depth however no significant gain in the clinical attachment was observed. Baseline 0th day data were compared at the end, i.e., 90th day a significant reduction in plaque scores, gingival bleeding, and PPD however no significant gain in the clinical attachment was observed [Graph 2].

Discussion

The concentration of AZM in the tissues can be over fifty times higher in plasma. Bioavailability is 37% following oral administration, and its pKa is 8.74. As the bioavailability is 37% the drug available in the systemic circulation and oral administration of 500 mg was 185 mg of AZM. Based on these calculations, buccal films were designed at a concentration of 300 mg/15 cm² using 3 cm × 5 cm in situ developed glass molds. A film of 15 cm² is divided into two patches, each measuring 1.5 cm width and 5 cm length and oral administration of 500 mg of AZM tablet is equivalent to buccal administration of two patches measuring 1.5 cm × 5 cm on either side of buccal mucosa. AZM is a well-established drug used in the treatment of periodontitis. The results of the present study are discussed as follows: At baseline, no significant difference was observed in clinical, microbial, and TNF-α parameters. On intergroup comparisons [Table 1], the plaque scores, gingival bleeding, gingival inflammation, PPD reduction, and CAL improvement were similar in SRP and SRP + AZM patch group. However,
there was a statistically significant reduction in plaque and gingival bleeding scores in SRP + AZM tablet group. AZM patch in the treatment of periodontitis has been tried for the 1st time in periodontal literature; however, this type of treatment showed similar results as of SRP. Hence, the authors recommend AZM tablet as an adjunct to scaling and root planing. On intergroup comparison, there was no significant difference in Pg and PI reduction in SRP versus SRP + AZM patch group. However, there was a statistically significant reduction in the periodontopathogens in SRP + AZM tablet group suggesting the adjunctive use of AZM to SRP.

The first periodontal clinical study on AZM was performed in 1996. There are two groups of results on adjunctive AZM drug trial in periodontal disease treatment. Those authors who reported AZM is an effective drug in combination with SRP are Smith et al., Mascarenhas et al., Gomi et al., Yashima et al., and Oteo et al. The current study also supports adjunctive use of AZM tablet 500 mg to SRP. Few authors who reported AZM did not improve the periodontal parameters are Sampaio et al. and Emingil et al. The reasons for inconsistent report in the literature could be due to variation in study designs that requires to be analyzed. The microbiological goal of periodontal therapy has been achieved in the present study, although adjunctive systemic AZM did not result in any additional effect on the microbial levels given the antimicrobial activity of AZM in vitro.

There are several in vitro reports on the immunomodulatory effects of AZM. The anti-inflammatory and immunomodulatory properties of AZM and its concentration in neutrophils, macrophages, and fibroblasts are well documented, but it is not known how long these effects persists after a single course and what intracellular concentration of the drug is required to exert its immunomodulatory effect. In the present study, TNF-α was evaluated to assess the immunomodulatory effects of AZM. The GCF TNF-alpha levels reduction was similar in SRP and SRP + AZM patch group, whereas SRP group showed higher TNF-α reduction than the SRP + AZM tablet group. The TNF-α level estimation in chronic generalized periodontitis patients does not exist. However, de Oliveira et al. reported a significant reduction in TNF-α levels after nonsurgical treatment in aggressive periodontitis.

Monotherapy in the form of AZM buccal patch and tablet were used without SRP for the 1st time in literature. In the present study, clinical parameters within the group (AZM patch and AZM tablet) had no significant improvement in PI, GBI, MGI, PPD, and CAL from baseline. Both the patch and tablet did not significantly reduce the Pg and PI. The TNF-alpha levels reduction in monotherapy groups was not significantly affected. The role of TNF-alpha to represent the immunomodulant effect of AZM did not show any significant results.

Monotherapy per se would be useful in those patients where mechanical debridement would be contraindicated. AZM was tried as monotherapy based on its triple action as anti-inflammatory, antimicrobial, and immunomodulatory that are required for treatment of periodontal disease unlike antimicrobials such as amoxicillin and others that have restricted antimicrobial property. Authors like Lopez and Gamonal (1998) and Lopez et al. (2006) have supported the use of systemic antimicrobials as monotherapy. The current study AZM did not provide any beneficial effects either as an adjunct neither as monotherapy. The nonsurgical therapy with and without AZM demonstrates significantly lower TNF-α levels as compared to monotherapy. The results of the study indicate that the increased TNF-α levels at 21 days in the drug alone groups (AZM patch and AZM tablet) are alarming which requires to be elucidated. Only one study by Ho et al. reported the increase of TNF-α levels in periodontally healthy patients. He reported that with AZM treatment, GCF volume decreased significantly on days 2 through 7 (P < 0.05) but increased toward baseline levels on day 14. The possible reasoning could be that the AZM-induced suppression of TNF-α production from diseased periodontium cells would have exaggerated the production of TNF-α after the cessation of the 14th day action of AZM. The exact reason for increased TNF-α level in periodontitis patients at 21 days during monotherapy requires to be elucidated.

Periodontal maintenance regular follow-up is required for long-term prognosis. AZM as a chemotherapeutic agent in the maintenance phase has been tried for the 1st time. During SPT, when the clinical parameters of periodontitis are stabilized by SRP considerably were provided with AZM tablet/once daily at 21st post-SRP to evaluate if there could be any beneficial role of AZM during this phase. At the end of the 60th day, there was a significant improvement in all the clinical parameters of SRP growth when compared from baseline to 60th day and from 21st to 60th day except for no significant changes in CAL. To discuss the results of the current study, considering the AZM effect on the 0–21st day phase. It is unlikely that AZM has any role to play during SPT most probably the significant parameter reduction at the end of 60 days can be attributed directly to the continued effects of SRP. The compliance was good for both AZM buccal patch and tablet. The films did not cause any discomfort to the
volunteers. Thus, buccal patch claims the potential clinical usefulness in delivering the drug.  

**Conclusion**

AZM offers good patient compliance. This is the first report of AZM usage as a buccal patch of AZM compared to tablet form and as monotherapy in the treatment of periodontitis. Considering the results of the study, it is safe to use AZM along with SRP. Further larger sample sizes are required to reassess the outcome of AZM as monotherapy. Studies are required to investigate the concentration and kinetics of AZM present in gingival tissue and GCF. Further studies are warranted to evaluate the efficacy and safety of AZM patch in patients with periodontitis whose tissue defenses are compromised and in patients with GIT disorders.

**Financial Support and Sponsorship**

Nil.

**Conflicts of Interest**

There are no conflicts of interest.

**References**

1. Gomi K, Yashima A, Iino F, Kanazashi M, Nagano T, Shibukawa N, et al. Drug concentration in inflamed periodontal tissues after systemically administered azithromycin. J Periodontal 2007;78:918-23.
2. Yashima A, Gomi K, Maeda N, Arai T. One-stage full-mouth versus partial-mouth scaling and root planing during the effective half-life of systemically administered azithromycin. J Periodontal 2009;80:1406-13.
3. Pradeep AR, Sagar SV, Daisy H. Clinical and microbiologic effects of subgingivally delivered 0.5% azithromycin in the treatment of chronic periodontitis. J Periodontal 2008;79:2125-35.
4. Thimmasetty J, Pandey G, Babu P. Design and in vivo evaluation of carvedilol buccal mucoadhesive patches. Pak J Pharm Sci 2008;21:241-8.
5. Cobb CM. Microbes, inflammation, scaling and root planing, and the periodontal condition. J Dent Hyg 2008;82 Suppl 3:4-9.
6. Armitage GC. Development of a classification system for periodontal diseases and conditions. Ann Periodontol 1999;4:1-6.
7. Sillness J, Loe H. Periodontal disease in pregnancy. II. Correlation between oral hygiene and periodontal condition. Acta Odontol Scand 1964;22:121-35.
8. Ainamo J, Bay I. Problems and proposals for recording gingivitis and plaque. Int Dent J 1975;25:229-35.
9. Lobene RR, Weatherford T, Ross NM, Lamm RA, Menaker L. A modified gingival index for use in clinical trials. Clin Prev Dent 1986;8:3-6.
10. Lai PC, Ho W, Jain N, Walters JD. Azithromycin concentrations in blood and gingival crevicular fluid after systemic administration. J Periodontal 2011;82:1352-6.
11. Griffiths GS. Formation, collection and significance of gingival crevicular fluid. Periodontal 2000;2003;31:32-42.
12. Jervøe-Storm PM, Alahdab H, Koltzschzer M, Fimmers R, Jepsen S. Comparison of curet and paper point sampling of subgingival bacteria as analyzed by real-time polymerase chain reaction. J Periodontal 2007;78:909-17.
13. Syed SA, Svanberg M, Svanberg G. The predominant cultivable dental plaque flora of beagle dogs with gingivitis. J Periodontal Res 1980;15:123-36.
14. Paster BJ, Boches SK, Galvin JL, Ericson RE, Lau CN, Levanos VA, et al. Bacterial diversity in human subgingival plaque. J Bacteriol 2001;183:3770-83.
15. Socransky SS, Haffajee AD, Ximenez-Fyvie LA, Feres M, Mager D. Ecological considerations in the treatment of Actinobacillus actinomycetemcomitans and Porphyromonas gingivalis periodontal infections. Periodontol 2000 1999;20:341-62.
16. Selton AM, Maskeil JP, Beighton D, Whitey A, Shain H, Foyle D, et al. Azithromycin in the treatment of periodontal disease. Effect on microbial flora. J Clin Periodontal 1996;23:998-1003.
17. Smith SR, Foyle DM, Daniels J, Joyston-Bechal S, Smale SC, Selton A, et al. A double-blind placebo-controlled trial of azithromycin as an adjunct to non-surgical treatment of periodontitis in adults: Clinical results. J Clin Periodontol 2002;29:54-61.
18. Mascarenhas P, Gapski R, Al-Shammari K, Hill R, Soehren S, Fenno JC, et al. Clinical response of azithromycin as an adjunct to non-surgical periodontal therapy in smokers. J Periodontal 2005;76:426-36.
19. Gomi K, Yashima A, Nagano T, Kanazashi M, Maeda N, Arai T. Effects of full-mouth scaling and root planing in conjunction with systemically administered azithromycin. J Periodontal 2007;78:422-9.
20. Oto A, Herrera D, Figuero E, O’Connor A, González I, Sanz M. Azithromycin as an adjunct to scaling and root planing in the treatment of Porphyromonas gingivalis-associated periodontitis: A pilot study. J Clin Periodontal 2010;37:1005-15.
21. Sampao E, Rocha M, Figueiredo LC, Faveri M, Duarte PM, Gomes Lira EA, et al. Clinical and microbiological effects of azithromycin in the treatment of generalized chronic periodontitis: A randomized placebo-controlled clinical trial. J Clin Periodontal 2011;38:836-46.
22. Emming G, Han B, Ozdemir G, Tervahartiala T, Vural C, Atilla G, et al. Effect of azithromycin, as an adjunct to nonsurgical periodontal treatment, on microbiological parameters and gingival crevicular fluid biomarkers in generalized aggressive periodontitis. J Periodontal Res 2012;47:729-39.
23. Haffajee AD, Teles RP, Socransky SS. The effect of periodontal therapy on the composition of the subgingival microbiota. Periodontal 2000 2006;42:219-58.
24. Pajukanta R. In vitro antimicrobial susceptibility of Porphyromonas gingivalis to azithromycin, a novel macrolide. Oral Microbiol Immunol 1993;8:325-6.
25. Bosnar M, Bosnjak B, Cuzic S, Hvicac B, Marjanovic N, Goljarnic I, et al. Azithromycin and clarithromycin inhibit lipopolysaccharide-induced murine pulmonary neutrophilia mainly through effects on macrophage-derived granulocyte-macrophage colony-stimulating factor and interleukin-1beta. J Pharmacol Exp Ther 2009;331:104-13.
26. Hodge S, Hodge G, Brozyna S, Jersmann H, Holmes M, Reynolds PN. Azithromycin increases phagocytosis of apoptotic bronchial epithelial cells by alveolar macrophages. Eur Respir J 2006;28:486-95.
27. Hirsch R, Deng H, Laochhrai MN. Azithromycin in periodontal treatment: More than an antibiotic. J Periodontal Res 2012;47:137-48.
28. de Oliveira RR, Schwartz-Filho HO, Novaes AB, Garlet GP, de Souza RF, Taba M, et al. Antimicrobial photodynamic therapy in the non-surgical treatment of aggressive periodontitis. Cytokine profile in gingival crevicular fluid, preliminary results. J Periodontal 2009;80:98-105.
29. Herrera D, Alonso B, León R, Roldán S, Sanz M. Antibacterial therapy in patients with periodontitis whose tissue defenses are compromised and in patients with GIT disorders.
30. Ho W, Eubank T, Leblebioglu B, Marsh C, Walters J. Azithromycin decreases crevicular fluid volume and mediator content. J Dent Res 2010;89:831-5.