

Effect of Systemically Administered Azithromycin in Early Onset Aggressive Periodontitis

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Azithromycin is a macrolide which possesses a strong antimicrobial activity against Gram-positive and Gram-negative pathogens. In the present study, we studied the effect of azithromycin as an adjunct to non-surgical treatment in early onset aggressive periodontitis. Initial treatment consisting of oral instructions and full-mouth scaling and root planing was performed over a 2-month period. Patients were then administered with azithromycin, 500 mg per os, 1x/day, for 3 days. Professional mechanical tooth cleaning was performed once every two weeks during the initial preparation. Initial treatment was considered as completed when the gingival index was < 1. The probing pocket depth, percentage of periodontal pockets with depth ≥ 4 mm, and the rate of bleeding on probing improved following treatment. The duration of the treatment was 4.7 ± 3.2 months. Another group of patients received the same initial treatment but without azithromycin. The duration of the treatment for this group was 11.2 ± 4.9 months. These results indicate that azithromycin may be useful for the treatment of early onset periodontitis.

Key words: azithromycin, early onset periodontitis, systemic administration

INTRODUCTION

Periodontal disease comprises a group of infections that lead to the inflammation of the gingiva and that are accompanied by the loss of alveolar bone with eventual exfoliation of the teeth in severe cases (Haffajee and Socransky, 1994). The oral cavity is colonized by a variety of different bacterial species. Over 300 different bacteria have been identified in subgingival plaque samples from periodontally diseased sites (Moore and Moore, 1994). Only few of these species, either alone or in combination, are implicated in the initiation of the disease as they reach critical levels (Marsh, 1989). It has been suggested that tissue destruction is host-mediated and results for the activation of the immune-inflammatory response by lipopolysaccharides released by periodontopathic bacteria (Wang and Ohura, 2002). It is generally accepted that periodontal disease is an infectious disorder that occurs in susceptible individuals

and that particular forms of periodontal disease such as aggressive periodontitis, chronic periodontitis, and necrotizing periodontitis, are associated with certain groups of bacteria (Socransky and Haffajee, 1994). The goals of periodontal treatment are to reduce/eliminate the load of periodontal pathogens in the subgingival area and to reduce the size of the habitat, i.e. the pocket, which allows colonization by periodontal pathogens. Various non-surgical and surgical techniques for the treatment of periodontitis were shown to be effective to reduce/eliminate periodontal pockets and to maintain alveolar bone and periodontal attachment levels over time (Cobb, 1996; Palkanis, 1996).

Various systemic antibiotic regimens, including the use of tetracycline, amoxicillin, metronidazole, or a combination of amoxicillin and metronidazole have been proposed as adjuncts to mechanical treatment in patients with aggressive forms of periodontal disease or in patients who do not respond

well to treatment (Slots, 2002; Walker and Karpina, 2002). However, only few reports are available on the effect of macrolide antibiotics in periodontal disease (Haffajee et al, 2003). Several terms have been used to describe the rapid loss of connective tissue and alveolar bone in apparently healthy young individuals: juvenile periodontitis, rapidly progressive periodontitis, and early onset periodontitis. Recently, it was proposed to replace early onset periodontitis by aggressive periodontitis (Armitage, 2002). To date, although tetracycline and metronidazole have been used in the treatment of early onset aggressive periodontitis (Smith et al, 2002; Walker and Karpina, 2002) there is limited information on the effect of macrolide antibiotics in patients with this form of disease. Azithromycin (AZM), a macrolide, has a strong antibiotic effect on a wide variety of oral bacteria; furthermore, AZM is taken up by phagocytes and is released over a long period of time in inflamed tissue (Lode et al, 1996). The purpose of the present study was to investigate the effectiveness of AZM in the non-surgical treatment of early onset aggressive periodontitis.

STUDY DESIGN

Patient Population

The study population consisted of 2 groups of patients: a group of 5 individuals (age range 23–34 years, 1 male and 4 females) and a second group of 6 individuals (age range 16–34 years, 2 males and 4 females) who were referred to the Institute of Medical Science, Health Science University of Hokkaido for the treatment of severe periodontitis. Patients were diagnosed as early onset aggressive periodontitis in our clinic. Complete medical and dental history was documented for each patient. We also checked that the patient: 1) was in good general health; 2) had not taken any antibiotics within the previous 3 months; and 3) was not allergic to AZM.

Clinical Parameters

Initial examination included measurements of probing depth (PD), gingival index as well as bleeding on probing (BoP). Six sites per tooth (3 on the

facial side, 3 on the lingual) were examined using a PCP-11 periodontal probe (HU-FRIEDY, Chicago, IL, USA). Data were collected on all teeth with the exception of third molars. We also calculated the change in the percentage of periodontal pockets ≥ 4 mm (PoR).

Therapy

All patients were given specific toothbrushing technique instructions and received full-mouth scaling and root planing over a 2 month period. The first group of patients was then administered with azithromycin, 500 mg per os (Zithromac®, Pfizer Japan Inc., Tokyo, Japan), 1x/day, for 3 consecutive days. The other group was used for comparison. Patients were re-examined every 2 months. Professional mechanical tooth cleaning (PMTTC) was performed at each visit during the follow-up period. Photographs were taken before treatment, after the completion of AZM therapy and at the time of maintenance. Initial treatment was considered as completed when the gingival index was < 1 .

Data Analyses

Results were expressed as mean \pm standard deviation. The significance of differences was assessed by the two-tailed Student's *t*-test or one-way analysis of variance followed by estimation of the least significant difference.

RESULTS AND DISCUSSION

In the present study, we examined the effect of systemically administered AZM in the treatment of early onset aggressive periodontitis. Clinical parameters including PD, PoR, and BoP were recorded at each re-examination. In the AZM treated group, the time span for the initial treatment to be completed was 4.7 ± 3.2 months. All clinical parameters showed a significant improvement between the initial examination and the last re-evaluation: PD decreased from 3.8 ± 0.7 mm to 2.1 ± 0.1 mm ($P < 0.01$) (Fig. 1A); the PoR decreased from $48 \pm 18\%$ to $6 \pm 3\%$ ($P < 0.01$) (Fig. 1B); and the BoP decreased from $66 \pm 28\%$ to $14 \pm 11\%$ ($P < 0.05$) (Fig. 1C). Figure 2 shows photographs of the gingivae of a patient at the time of initial diagnosis and after completion of

therapy with AZM. In contrast, in the group of patients who did not receive AZM, the time span for initial treatment was 11.2 ± 4.9 months.

These data indicate that AZM dramatically reduced the time of the initial phase of treatment and suggests that systemically administered AZM may be useful in the treatment of early onset (aggressive periodontitis).

AZM is a macrolide antibiotic that is closely related to erythromycin. AZM is a drug that has a similar spectrum of activity as erythromycin but has enhanced potency against Gram-negative organisms. Upon administration of AZM, the molecule becomes concentrated in fibroblasts as well as in phagocytes (McDonald and Pruul, 1991). As a result of chemotactic effects exerted on the phagocytes (Schentag and Ballow, 1991), the drug is transported and delivered to the inflamed sites. It has been shown that the concentration of AZM in inflamed tissues greatly exceeds serum level by 10–100 fold (Foulds et al, 1990). In addition, the release of AZM from tissues is slow, leading to prolonged excretion. Lalak and Morris (1993) reported that AZM was still detectable in the tonsils for over one week after a single 500 mg dose. AZM is usually given once a day for 3–5 days. In addition, AZM is an antibiotic that has a strong effect against a wide variety of oral bacteria. Williams et al (1992) demonstrated that AZM was the most active among the five antibiotics tested in vitro against oral Gram-negative anaerobes. Thus, AZM appears to have excellent pharmacological properties which make it suitable for the treatment of periodontal disease.

Other antibiotics such as tetracycline, amoxicillin, and metronidazole have several disadvantages. These antibiotics usually need to be administered 3–4 times per day over 7–14 days in order to obtain effective concentrations in the serum or in periodontal tissues (Greenberg, 1984). Administration of an antibiotic for a long period of time not only is inconvenient, but also increases the chance of appearance of resistant microbes as well as the severity of side effects.

Recently, there is general consensus that dental plaque functions as a biofilm (Marsh and Bradshaw, 1995; Socransky and Haffajee, 2002) and caries and periodontal disease have been termed biofilm infections (Costerton et al, 1999). The concept of biofilm has important clinical implications (Costerton et al, 1995) as the

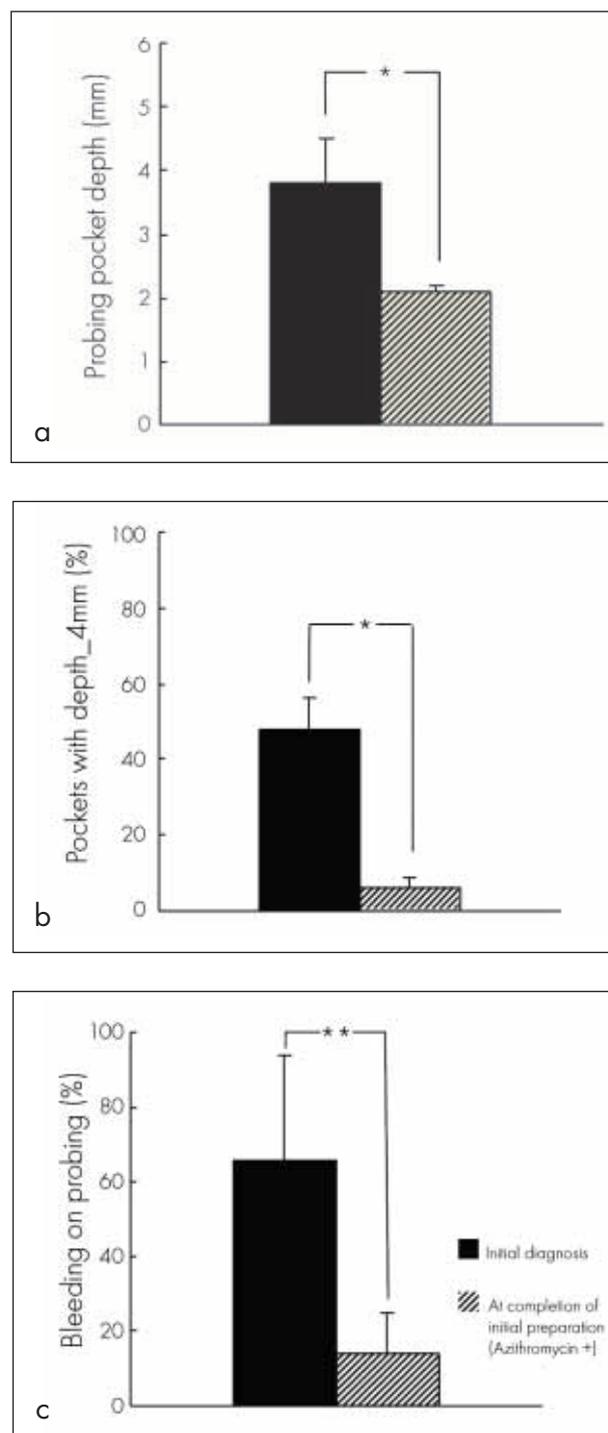


Fig. 1 Comparison of various clinical parameters at the time of initial diagnosis of early onset periodontitis and at the time of completion of initial preparation among patients who received azithromycin (AZM).

(A) Probing pocket depth (PD) (mm);
(B) Percentage of pockets with a depth ≥ 4 mm (PoR) (%);
(C) Percentage of teeth with bleeding on probing (BoP) (%). Each bar represents the mean \pm S.D (n = 5).

* P < 0.01

** P < 0.05 compared with the respective value at the time of initial diagnosis



Figs 2a-c Photographs of gingival tissue (A) at the time of initial diagnosis; (B) after completion of treatment with AZM in a patient who received therapy with AZM during the initial preparation; and (C) at the time of maintenance.

bacteria have been shown to be more resistant to antimicrobial agents (Brown et al, 1988; Socransky et al, 1999). In this context, it is interesting to note that AZM inhibits biofilm formation and possesses good activity against dental infection (Sasaki, 2000).

Treatment of periodontal disease usually consists of plaque control by the patient and scaling and root planing. However, in severe forms of disease such as early onset aggressive periodontitis treatment may require the use of antibiotics. In the present study, the use of AZM improved clinical parameters and shortened the time span of the initial treatment phase. These results suggest that AZM, a macrolide antibiotic, is effective for the treatment of early onset aggressive periodontitis.

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