Review Article

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Azithromycin in Periodontics

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ABSTRACT

Azithromycin is an azalide, a subclass of macrolide antibiotics. Azithromycin is used to treat many different infections, including acute otitis media, nonstreptococcal bacterial pharyngitis, gastrointestinal infections such as traveler's diarrhea, respiratory tract infections such as pneumonia, cellulitis, babesiosis, bartonella infection, chancroid cholera, donovanosis, leptospirosis, lyme disease, malaria, mycobacterium avium complex disease, neisseria meningitis, pelvic inflammatory disease, pertussis, scrub typhus, toxoplasmosis, and salmonellosis. It is used to prevent bacterial endocarditis and some sexually transmitted infections including those from unprotected sex or sexual assault. Azithromycin could have a triple role in the treatment and resolution of periodontal diseases: suppressing periodontopathogens, anti-inflammatory activity and healing through persistence at low levels in macrophages and fibroblasts in periodontal tissues, even after a single course of three tablets. If future periodontal research confirms these properties, it could become a valuable host-modulator in periodontal treatment.

Keywords: Anti-Bacterial agents, Azithromycin, Periodontitis, Peri-implantitis.

INTRODUCTION

Dr. Slobodan Dokic discovered azithromycin in 1980. After several years, the U.S. Food and Drug Administration (FDA) approved Azalite, an opthalmic formulation of azithromycin for the treatment of eye infections[1].

Azithromycin is an azalide, a subclass of macrolide. It is derived from erythromycin, with a methyl-substituted nitrogen atom incorporated into the lactone ring[2]. Azithromycin is used to treat many different infections, including acute otitis media to respiratory tract infections such as pneumonia to pelvic inflammatory disease [3,4].

It is effective against localized dental infections. It is also effective against the most common periodontopathogens[5]. The versatility of the macrolides extends beyond their antibiotic properties as a result of their well-documented immune-modulating/anti-inflammatory effects.

Antibacterial properties of azithromycin

Azithromycin has bacteriostatic effect against a wide range of bacteria in vitro, including gram-positive bacteria such as Staphylococcus aureus and Streptococcus pyogenes. It has particularly strong antibacterial

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activity against gram-negative anaerobic bacteria in comparison with earlier macrolides such as erythromycin and clarithromycin[5].

Furthermore, azithromycin has a wide antimicrobial spectrum of action towards anaerobic bacteria as well as against gram negative bacilli including porphyromonas, prevotella and actinobacillus actinomycetemcomitans which plays an important role in periodontal pathogenesis[6].

Immunomodulatory properties of azithromycin

The spectrum of action of macrolides extends from the reduction of inflammation, regulation of neutrophil and macrophage activity and production of cytokines, to altering fibroblast activity and host immunity.

Azithromycin is carried efficiently into inflamed tissues by neutrophils through chemotaxis[7], while maintaining its activity. When azithromycin (500 mg once daily for 3 days) was taken by healthy volunteers, it persisted in neutrophils for 28 days after the last dose, presumably as a result of accumulation in neutrophil precursor cells[8].

A study of human gingival fibroblasts stimulated with lipopolysaccharide (LPS) derived from P. gingivalis and treated with azithromycin showed a dose-dependent increase in the production of IL-8[9], whereas azithromycin was found to reduce LPS-induced IL-8 production in an oral epithelial cell line, thereby modifying innate immunity and exerting an anti-inflammatory effect on human oral epithelial cells [10].

When azithromycin (500 mg followed by 250 mg per day for the next 2 days) was given to periodontally healthy subjects, a marked decrease in the volume of gingival crevicular fluid was observed on the day of the last dose; a return to baseline levels of gingival crevicular fluid had occurred after 14 days. The amounts of proinflammatory cytokines IL-8, TNF-α and vascular endothelial growth factor decreased significantly on day 4 of the study [11].

MECHANISM OF ACTION

Like all macrolide antibiotics, azithromycin reversibly inhibits bacterial protein synthesis by targeting the 23S ribosomal RNA of the 50S ribosomal subunit in susceptible organisms [12]. while having a long half-life and good periodontal tissue penetration[13]. Its long terminal half-life[14] enables azithromycin to combat bacterial infections at a lower dosage and shorter treatment regimes than other antibiotics.

Due to its high concentration in phagocytes, azithromycin is actively transported to the site of infection. During active phagocytosis, large concentrations are released. Azithromycin's half-life allows a large single dose to be administered and yet maintain bacteriostatic levels in the infected tissue for several days. The concentrations of azithromycin in tissue specimens from periodontal lesions are significantly higher than that of normal gingiva. The azithromycin is actively transported to sites of inflammation by phagocytes and then released directly into the sites of inflammation as the phagocytes rupture during phagocytosis.

METABOLISM

According to Davis' Drug Guide for Nurses, following a single 500 mg dose, the half-life of azithromycin is 11–14 hours. The longer half-life of 68 hours is achieved only when multiple doses are consumed. Biliary excretion of azithromycin, predominantly unchanged, is a major route of elimination. Over the course of a week, approximately 6% of the administered dose appears as unchanged drug in urine.

SIDE EFFECTS

Most common side effects are gastrointestinal: diarrhea (5%), nausea (3%), abdominal pain (3%) and vomiting. Less than 1% of patients stop taking the drug due to side effects. Nervousness, dermatologic reactions and anaphylaxis have been reported. As with all antimicrobial agents, pseudomembranous colitis can occur during and up to several weeks after azithromycin therapy[15,16].

DOSAGE

Therapeutic use requires a single dose of 250 mg/day for 5 days after an initial loading dose of 500 mg.

DISCUSSION

The most extensively studied periodontal antibiotic regimen is the combination of amoxicillin (375 mg) and metronidazole (500 mg), both taken three times a day for 7 days[17] in conjunction with periodontal therapy. To date, no comparative trial has shown the superiority of any other antibiotic regimen over amoxicillin/metronidazole in any clinically or microbiologically defined variant of periodontal disease[20]. Short-course antibiotics may reduce the development of resistant bacterial species [21]. Side effects are very common with the amoxicillin/metronidazole regimen (42%)[18] and compliance is therefore compromised. Amoxicillin is not noted for immunomodulatory or anti-inflammatory properties that are distinct from its antibiotic effects. Metronidazole suppressed the production of proinflammatory cytokines by human periodontal ligament cells[19], but there is sparse evidence of specific immunomodulatory action. First, azithromycin when given as a single course of three 500mg tablets could well play a triple role in the treatment of moderate to advanced periodontitis. Its effectiveness against gram-negative bacteria, the ability to penetrate biofilm and a long antibacterial half-life and short course make it an attractive antibiotic option as an adjunct to the management of advanced inflammatory periodontitis.

Second, the uptake of azithromycin by neutrophils and macrophages allow it to target and be concentrated at sites of periodontal inflammation and exert its anti-inflammatory properties. As hyper-responsive macrophages are considered to be determinants of susceptibility to periodontitis by producing large quantities of proinflammatory cytokines in response to LPS and bacterial products, a possible beneficial role of azithromycin is to down-regulate proinflammatory cytokine production[20].

Third, azithromycin appears to exert a long-term healing influence on the periodontal tissues. This property may be related to its effect on changing the macrophage phenotype (to M2), thus increasing the production of anti-inflammatory cytokines[21] and favouring healing. If an agent was being specifically designed to treat inflammatory forms of periodontitis, it would have these distinct and temporally overlapping activities (Figure 1). The strategic use of azithromycin may become useful in primary periodontal therapy of patients with a poor treatment response, with respect to both its antibacterial and immune modulating action[22].

Azithromycin may prove to be a more effective host modulator in the treatment of periodontitis than low dose doxycycline [which requires patients to take two tablets a day for 3 months or longer and is accompanied by side effects[23]]. It may be possible to develop a subantimicrobial azithromycin dosing regimen that avoids potential bacterial resistance. Of interest, the development of a nonantibiotic macrolide derived from azithromycin has recently been reported[24]. After a single course of azithromycin in the treatment of periodontitis, antibacterial phase of the drug's most studied and understood activity; it is known to be active against periodontopathogens for at least 14 days. The anti-inflammatory properties of azithromycin and its concentration in neutrophils, macrophages and fibroblasts are well documented. Finally, there is evidence of the ability of azithromycin to cause regression of cyclosporine A-induced gingival overgrowth over time as well as of periodontal healing and bone regeneration for up to 12 months after a single course of azithromycin[25].

Azithromycin can be used in periodontics in patients with

- Advanced/ terminal chronic periodontitis
- Aggressive periodontitis [23]
- Patients not responding to supportive periodontal therapy (SPT)[21]
- Moderate- severe gingival overgrowth related to calcium channel blocker medications[24]
- Peri-implantitis[21]
- Periodontal or gingival abscess[25]
- Local drug delivery agent[26]

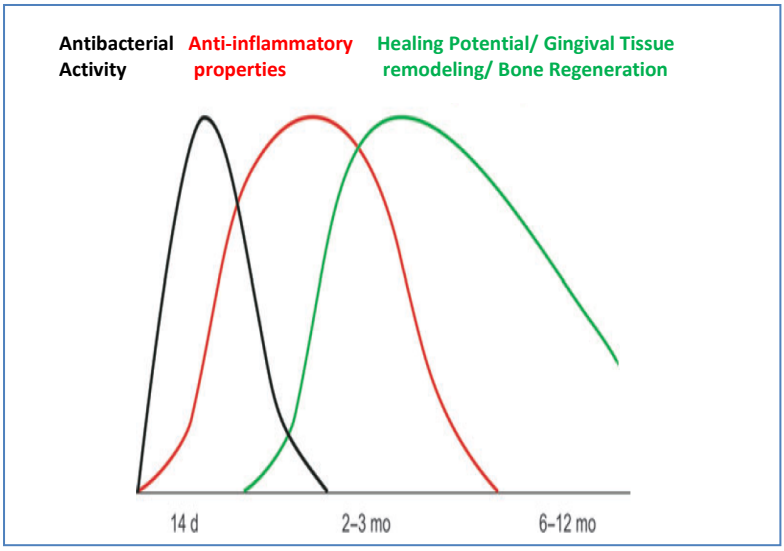

Figure 1: Temporal model of the three overlapping phases of periodontal activity

Conclusion and future prospective

Azithromycin could have a triple role in the treatment and resolution of periodontal diseases: suppressing periodontopathogens, anti-inflammatory activity and healing through persistence at low levels in macrophages and fibroblasts in periodontal tissues, even after a single course of three tablets. If future periodontal research confirms these properties, it could become a valuable host-modulator in periodontal treatment.

CONFLICT OF INTEREST

Authors declare no conflict of interest

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