Azithromycin in Periodontal Therapy: Beyond the Antibiotics

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ABSTRACT

Periodontitis is a multifactorial disease, in which microorganisms in plaque biofilm play a major role. Scaling and root planing is the primary mode of non-surgical treatment for periodontal disease. Adjunctive use of an antimicrobial is advocated in certain periodontal disease conditions. Azithromycin might be considered a promising adjunctive drug in the treatment for periodontal disease because of its distinguished characteristic of immunomodulation, anti-inflammatory and antibiotic property along with the accumulation in higher concentration into the acute reactant cells and sustained release at the site of infection. This antibiotic is popular for its very simple dosage regime and limited side effects. The objective of this literature review to highlight the mechanism and potential favourable role in the management of various form of the periodontal disease.

Keywords: Antibiotics; azithromycin; gingival overgrowth; macrolide; periodontal therapy.

INTRODUCTION

The complete elimination of tissue invasive microorganism is not possible with mere mechanical debridement in certain disease conditions. The systemic antimicrobials as an adjunctive mechanical therapy have been shown to enhance clinical benefits in these patients.[1]

Azithromycin (AZM) first synthesised in 1980, is a subclass of macrolides called azalides.[2] AZM is an antibiotic used extensively for the treatment of a wide range of infections such as upper respiratory tract infections, middle ear infections, sexually transmitted infections and trachoma. It is also effective against the most common periodontopathogens: Aggregatibacter actinomycetemcomitans (A. actinomycetemcomitans), and Porphyromonas gingivalis (P. gingivalis). These invasive periodontal pathogens are difficult to eliminate by mechanical debridement alone, but the adjunctive use of systemic antibiotics can enhance the therapeutic response to non-surgical periodontal therapy (NSPT).[1] AZM well plays 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.[3]

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Literature Search Methodology

An electronic search was conducted, for citations included till January 2017, to identify papers on azithromycin in periodontal therapy. Related studies and case reports written in the English language and published in major dental journals were included. Key words used for the search were the combination of "Azithromycin" and "Periodontal therapy" in surgical or non-surgical therapy.

Mechanism of Action

The mechanism of action of AZM is similar to other macrolide antibiotics.[4] AZM thought to bind to donor site, prevents translocation of aminoacyl transfer RNA and inhibit the growing peptide chain from the acceptor site to the donor site, by competing for this site. This may cause premature termination of the peptide chain.

AZM absorbs rapidly from gastrointestinal tract with bioavailability of about 40% and the peak plasma concentration is achieved 2-3 hours after the oral administration. The terminal half-life of AZM is 68 hours and average half-life is about 1-4 days.[5]

Dosage and Adverse Effects

The most common dosage regime for AZM (500 mg) orally once a day for three days, one hour before the food.[6,7] However, the approved dosage of ZM in the United States

(500 mg on the first day, followed by 250 mg daily for next five days) and in Europe (500 mg daily for three days) are different.[8] Shorter regimens are required because of long half-life, and this makes good patient compliance compared to other antibiotics.[9]

The single course of AZM rarely demonstrates any adverse reactions. Nausea, abdominal pain and diarrhoea are the most frequent adverse reactions (in approximately 5%). Rare, serious, allergic reactions, including angioedema and anaphylaxis (rarely fatal), have been reported in patients on AZM therapy. AZM is only contraindicated in combination with antacid, warfarin and cyclosporin. AZM interacts with the antacids and may potentiate the effect of warfarin. AZM should be avoided to prescribe in patients with known hypersensitivity to erythromycin.[10,11]

Antibiotic Spectrum

AZM is a broad spectrum antibiotic acting against both gram-positive and gram-negative bacteria and has bacteriostatic effects,[3] and effective against systemic, intraoral, and facial infections.[12] AZM demonstrates strong antibacterial activity against gram-negative anaerobic bacteria including Porphyromonas spp., Prevotella spp., and A. actinomycetumcomitans in comparison with earlier macrolides.

Immunomodulation

Immune-modulator properties of AZM is favourable over other macrolides, characterised by its significantly higher uptake by fibroblasts and acute reactant cells, like neutrophils, macrophages, monocytes, and lymphocytes,[13] with a high degree of retention.[14] AZM is carried efficiently into inflamed tissues by neutrophils through chemotaxis[15] while maintaining its activity. AZM exerted acute effects by prolonged degranulation of circulating neutrophils and the release of neutrophil granular enzymes, through oxidative burst and oxidative protective mechanisms; which could represent a potential anti-inflammatory effect in the treatment of subacute, noninfective inflammatory responses.[16]

AZM was demonstrated to decrease the expression of proinflammatory cytokines [interleukin (IL)-1β, IL-6, IL-8 and tumour necrosis factor (TNF)-α], growth factors such as granulocyte–macrophage colony-stimulating factor and also increases the number of actively phagocytosing alveolar macrophages.[17] Downregulation of the proinflammatory cytokines results into its anti-inflammatory property.[3]

Bacterial Resistance

AZM has significantly less bacterial resistance to subgingival microflora of adult periodontitis compared to other commonly prescribed oral antibiotics.[18] It was noticed that after 12 months the percentage of resistant species were reduced to levels approaching those detected before periodontal therapy.[19]

FAVOURABLE ROLE OF AZITHROMYCIN IN PERIODONTAL THERAPY

Bacteraemia Incidences

The prevalence of scaling and root planing (SRP)-triggered bacteraemia in patients with periodontitis was reported 80.9% and it occurred more frequently immediately after treatment. AZM prophylaxis is beneficial in both reducing the bacteraemia incidence and the improvement of the effect of periodontal therapy.[20]

Effect on Biofilm

In vivo, bacteria within the biofilm are thought to be protected from antibiotics.[19] AZM demonstrated to reduce the formation of biofilm by interfering with the signals of quorum sensing.[3,21,22] AZM permitting more effective antimicrobial activity against microbes within the biofilm by efficiently infiltrating this barrier.[23] AZM is likely to be useful for the treatment of diseases caused by P. gingivalis biofilms.[24]

Accumulation in Gingival Crevicular Fluid (GCF)

Drugs that enter the interstitial fluid seep through gingival connective tissue and eventually cross the junctional epithelium into the gingival crevice. However,

Table 1: Effect of azithromycin in periodontal treatment.

Bacteraemia	Decreased incidences
Biofilm	Infiltrate barrier, Decrease in thickness
GCF	Higher concentration than serum
Smokers	Rapid wound healing
Non-surgical therapy	Improvement in the gingival inflammation Pocket reduction and improve clinical attachment level in aggressive and chronic periodontitis
Surgical therapy	Decrease in pocket depth and enhance clinical attachment gain Bone regeneration recently reported on periapical radiographs.
Gingival overgrowth	Inhibition on Cyclosporin-A induced gingival overgrowth

Table 2: Clinical studies used azithromycin as an adjunct to periodontal therapy.

Author	Study design	Periodontal Status	Sample size	Study duration	Treatment/AZM regimen	Outcomes
Smith et al (2002)[33]	RCT	Chronic Periodontitis	44	22 weeks	SRP+AZM-500 mg x 3 days / control-SRP+ Placebo	Significantly more reduction in pocket depth in AZM group, even with poor plaque control.
Mascarenhas et al (2005)[39]	RCT	Chronic Periodontitis in smoker	31	6 month	SRP+ AZM 250 mg 1st day and one 250 mg for next 4 days. Control-SRP	Improved the efficacy of non-surgical periodontal therapy in smokers with moderate to advanced attachment loss.
Gomi et al (2007)[34]	Case -control	Severe chronic periodontitis	34	25 weeks	SRP+ AZM 500 mg x 3 days. Control-SRP	Shortened the duration of periodontal treatment.
Dastoor et al (2007)[47]	RCT	Chronic periodontitis, Heavy smoker	30	6 months	Surgical AZM-500 mg x 3 days. Control-Placebo	Sustained reduction in periodontal pathogens and rapid wound healing. No difference in clinical outcome.
Haas et al (2008)[41]	RCT	Aggressive periodontitis	24	12 months	SRP+AZM 500 mg x 3 days, Control-SRP+Placebo	Significantly more reduction in mean PPD. Potential to improve periodontal health
Pradeep et al (2008)[28]	RCT	Chronic periodontitis	80	3 months	SRP+0.5% AZM (controlled drug delivery system). Control-SRP	Enhanced the clinical result, and improved microbiological parameter.
Yashima et al (2009)[7]	Case -control	Chronic periodontitis	30	12 months	AZM 500 mg x 3 days before SRP. FM-SRP (single visit), PM-SRP (3 visit over 7 days), Control: SRP (6 visit over 6 weeks)	Improvement in clinical parameters, with no significant differences between the two test groups. Different treatments for test and control groups make results difficult to compare.
Oteo et al (2010)[38]	RCT	P. gingivalis associated Chronic periodontitis	29	6 month	SRP+ AZM 500 mg x3 days. Control-SRP	Significant improvement in clinical parameter and reduction in frequency of pathogenic microbes.
Sampaio et al (2011)[40]	RCT	Chronic periodontitis	40	12 months	SRP+AZM 500 mg x 5 days. Control- SRP	No adjunctive benefit.
Han et al (2012)[8]	RCT	Chronic periodontitis	36	6 months	SRP+ AZM 500 mg x 3 days. Control-SRP	No additional benefit on the periodontal pathogen investigated except decrease in F. nucleatum and reduction in GCF MMP-8 level.
Haas et al (2012)[45]	RCT	Aggressive periodontitis	24	12 months	SRP+ AZM 500 mg x 3 days Control- SRP	Ineffective in lowering the subgingival level of important putative periodontal pathogens.
Haas et al (2012)[45]	RCT	Aggressive periodontitis	17	12 months	SRP+ AZM 500 mg x 3 days Control-SRP+Placebo	No significant radiographic bone label change compared to placebo.
Pradeep et al 2013[29]	RCT	Chronic periodontitis in smokers	54	9 months.	SRP+0.5% AZM Control-SRP+placebo gel	Significant improvement in clinical outcome in the treatment of chronic periodontitis among smokers.
Ercan et al 2015[42]	RCT	Aggressive periodontitis	45	3 months	SRP+AZM, SRP+ Metronidazole +Amoxcilline, Control-SRP,	A non-significant improvement in periodontal parameter in the AZM and Metronidazole+Amoxicilline groups. Good Healing tendency in the AZM group despite the baseline plaque scores. AZM might be active against the bacteria in dental biofilms.
Saleh et al 2016[35]	RCT	Chronic periodontitis, Non-smoker	37	3 months	SRP+AZM, SRP+Metronidazole +Amoxicillin, Control-SRP	Amoxicillin+Metronidazole showed a higher reduction in PPD compared to AZM in the all sites analysis.
Latif et al 2016[36]	RCT	Chronic periodontitis	40	90 days	Group 1: SRP only, Group 2: SRP + AZM patch, Group 3: SRP + AZM tablet, Group 4: AZM buccal patch monotherapy, Group 5: AZM tablet 500 mg x 3 days monotherapy.	SRP + AZM tablets showed greater reduction in clinical parameters, however no significant gain in the clinical attachment was observed.
Martande et al 2016[43]	RCT	A. actinomycetemcomitans associated moderate to severe periodontitis	70	12 months	SRP+AZM (500 mg x 3 days), Control-SRP+Placebo	Significantly improved the clinical and microbiological parameters.

a substantial amount of macrolide antibiotics may be taken up from interstitial fluid and concentrated inside macrolide reservoirs (fibroblasts, epithelial, inflammatory, and immune cells).[13,25] They are thought to enhance macrolide distribution to gingiva and account for the large concentration difference between blood serum and gingival crevicular fluid[26] (Table 1).

A study found AZM level in GCF, above the minimal inhibitory concentrations for the several periodontal pathogens after two weeks suggested, that AZM could produce beneficial antimicrobial and anti-inflammatory activity, even in patients who fail to complete the standard 1.5 gm regimen.[27]

Application in Local Drug Delivery

Topical administration of AZM (0.5%) in systemically healthy chronic periodontitis patients demonstrated improvement in the clinical parameter as well as in subgingival microflora in both non-smokers[28] and smokers.[29] The authors hypothesised that the local application of AZM at the site of inflammation facilitated the penetration of the drug into the periodontal tissues, resulting in a high drug concentration and enhancing the bactericidal effect. The dual effect of the drug on the local microflora as well as on the invading pathogens may result in clinical improvement without systemic side effects or the development of bacterial resistance.

Susceptibility to Periodontal Pathogens

Various microorganisms including the A. actinomycetemcomitans, P. gingivalis, P. intermedia, and Pseudomonas aeruginosa are susceptible to AZM.[3] This suggested that adjunctive AZM can potentially enhance the elimination of A. actinomycetemcomitans from patients with periodontitis[30] especially under conditions in which neutrophils are greatly outnumbered by bacteria in gingival epithelial cells. A. actinomycetemcomitans has shown susceptibility to a low dose of AZM,[31] which are resistant to high dosage of erythromycin, clarithromycin and roxithromycin. AZM is highly effective against P. gingivalis.[32]

Non-surgical Periodontal Therapy

AZM has a wide spectrum of antibiotic action against periodontopathic bacteria as well as availability for a long duration, in periodontal lesions or in regions of surgical stress such as SRP may be an advantage for NSPT.[5] The shift of bacterial flora from the elimination of the anaerobic environment to healthy state induce a tendency to heal, which is responsible for the improvement of inflammation and decrease in the periodontal pocket depth (PPD). The high concentration of AZM was maintained in inflamed tissues after uptake by phagocytic cells, which seems to make AZM ideal for the treatment of periodontitis.[33]

Multiple randomised controlled trial (RCTs), conducted ranges from three to 12 months duration in chronic periodontitis patients including non-smokers[7,28,33–37] and smokers[29,38,39] investigated the effect of systemic AZM (500 mg x 3 days) in adjunct to SRP demonstrated the improvement in the efficacy of NSPT in reducing PPD and/or improving attachment levels in chronic periodontitis (Table 1, 2).

However, contrary to these reports, few clinical studies found no additional benefit in the improvement of clinical parameters as well as a reduction in periodontal pathogens, with adjunctive use of AZM with SRP in chronic periodontitis patients in non-smoker[7] and smoker.[8,40]

Systemic antimicrobials have been advocated as a possible alternative to achieve better outcomes in the treatment of Aggressive periodontitis (AgP) in adjunct to SRP. The results from the clinical trials, demonstrate the improvements in periodontal clinical parameters at three months,[41] and at 12 months[42,43] as well as reduction in A. actinomycetemcomitans positive subjects.[43] However one study found that AZM was ineffective in lowering the subgingival levels of putative periodontal pathogens in young AgP subjects, although periodontal health was achieved,[44] another RCT[45] also failed to show any change in radiographic bone level compared to placebo (Table 1, 2).

Surgical Periodontal Treatment

The only available RCT[46] using the AZM adjunct to surgical periodontal therapy in heavy smokers showed rapid wound healing, short-term gingival inflammation and less plaque formation in AZM group, but failed to demonstrate any difference in PPD or clinical attachment with placebo. (Table 1, 2)

Bone Regeneration

In addition to the resolution of inflammation, remodelling and significant periodontal healing of the gingival tissues over time, regeneration of bone has been reported in few case reports[47,48] in patients with severe localised and generalised periodontitis, following a single course of AZM. Bone formation was noted on periapical radiographs after the patients took two additional courses of AZM in the treatment of periodontal abscesses in conjunction with SRP.[49] The results from these case reports raise the possibilities of bone formation with the use of AZM (Table 1).

Drug Induced Gingival Overgrowth

Clinically, AZM has been reported to be highly effective in treating Cyclosporin-A (CsA) induced gingival

overgrowth.[50,51] These results imply that AZM has an inhibitory effect on CsA induced gingival overgrowth[50,52] (Table1). Three possible mechanisms[53] could be inferred, i) the inherent drug effect of AZM on gingival overgrowth might be related to its antibiotic activity, killing of oral bacteria, reducing local inflammation, and suppressing protein synthesis in fibroblasts;[51] ii) AZM inhibits the inherent effects of CsA, The interaction between AZM and CsA is controversial, but no studies has been found to support this second mechanism; iii) AZM is associated with the inhibition of phagocytosis induced by CsA. Phagocytosis was thought to be the principal pathway of collagen degradation in CsA induced gingival overgrowth. Moreover, treatment with AZM appears to restore part of the phagocytosis mechanism.

SUMMARY

AZM represents a promising option for the adjunctive treatment of chronic inflammatory periodontal diseases, due to its various properties such as prolonged retention, good bioavailability, immunomodulation, accumulation in GCF, infiltrating the biofilm and marked penetration into both normal and pathological periodontal tissues. Evidence from the various studies supported the improvement in periodontal health with the adjunctive use of 500 mg AZM, in the NSPT. However, if future well-designed studies confirm these breakthrough findings, AZM could prove a valuable unique drug, not only as antibiotic but also as host modulating agent in the treatment of moderate to severe form of periodontitis and gingival overgrowth.

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