

## Azithromycin – the unsung hero in periodontics

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### Abstract

Azithromycin have been used in treatment of various systemic conditions. 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. This review explores the literature on the probable role of azithromycin in periodontal disease.

**Keywords:** Azithromycin periodontology local drug delivery, Probiotics, Periodontal disease, Antibiotic resistance

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### Introduction

Periodontal disease is a multifactorial disease. The most common cause of which is implicated to the presence of gram negative organisms in the periodontal pocket. Newer studies have revealed the penetration of these microorganisms into the deeper tissues. The presence of these organisms is not only of etiological significance but is also an indicator of progression of periodontal diseases. Majority of the cases respond well to the conventional periodontal therapy however, certain cases do not respond favorably to the mechanical therapy alone, for various reasons. The use of antimicrobial agents as an adjunct to periodontal therapy has become imperative due to the failure in reduction or elimination of the anaerobic organisms at the base of the pocket and inaccessible areas like the furcation, or within the gingival tissues.<sup>(1)</sup> Hence, the use of an appropriate adjunctive antimicrobial agents is considered and are often beneficial. Moreover, systemic antibiotic therapy can be essential in eliminating pathogenic bacteria that invade gingival tissue and also help control periodontal pathogens present in various niches in the oral cavity.

Various locally and systemically administered antimicrobials are currently being used for the management of periodontal diseases. The more commonly used chemical agents are tetracycline, doxycycline, chlorhexidine, clindamycin, and metronidazole, combination of metronidazole and amoxicillin and azithromycin.

Azithromycin falls under the second generation of macrolide group of drugs and has a favorable pharmacokinetic profile. It acts by inhibiting protein synthesis by binding to 50s ribosomal subunits thereby inhibiting translocation of amino acyl transfer RNA and inhibit polypeptide synthesis.<sup>(2)</sup> It has increased acid stability and tissue distribution along with decreased binding to plasma proteins and shows rapid

absorption.<sup>(3-6)</sup> It has enhanced activity against gram-negative pathogens and shows extensive systemic distribution following oral administration achieving a peak plasma concentration within 2 to 3 hours.<sup>(7)</sup> It also exhibits good penetration property and is sustained in remarkable concentration in tissues even after the levels in serum has decreased.<sup>(5)</sup> It's terminal half-life of 68 hours enables it to combat bacterial infections at a lower dosage<sup>(7)</sup> and shorter treatment regimens than other antibiotics. Short-course antibiotics may reduce the development of resistant bacterial species.<sup>(8)</sup> The most common dosage prescribed is 500mg orally once a day for 4-7 days. Usually the side effects is uncommon but can cause nausea, vomiting, diarrhoea. Rarely allergic reactions can occur.

### Properties of Azithromycin

Bacteria within the biofilm are thought to be protected from antibiotics. The ineffectiveness of the drug to penetrate the biofilm leads to the requirement of a higher dosage which may be almost 500 times the therapeutic dose of an antibiotic. Unlike other antibiotics, azithromycin is capable of efficiently infiltrating this biofilm, thus permitting more effective antimicrobial activity against microbes within it.<sup>(9)</sup> It is well tolerated and exhibits antimicrobial action against anaerobic organisms as well as gram negative bacilli. The effectiveness of azithromycin against periopathogens like *A.actinomycetemcomitans* and *P.gingivalis* has been seen during the treatment of various periodontal infections.<sup>(9-11)</sup> Hence, a long antibacterial half-life, ability to penetrate the biofilm and a short course makes it a viable option to be used as an adjunct in the management of various periodontal conditions.

The action of macrolides extend from the reduction of inflammation, regulation of neutrophil and macrophage activity along with the production of

cytokines. The gingival fibroblasts occupy the relatively large cellular compartment of the gingiva, so, accumulation of azithromycin by these cells could allow them to act as drug reservoirs that sustain therapeutic concentrations. It is rapidly taken up by neutrophils, macrophages and fibroblast.<sup>(4)</sup> Azithromycin is carried efficiently into inflamed tissues by neutrophils through chemotaxis while maintaining its activity. The effect is seen as rapid release of neutrophil granular enzymes, oxidative burst and oxidative protective mechanisms. Also a prolonged degranulation of circulating neutrophils could represent a potential anti-inflammatory effect in the treatment of subacute, non-infective inflammatory responses. It shows a potential for an adjunct in the treatment of periodontitis and gingival overgrowth.<sup>(12)</sup>

Significant immunomodulatory effects of azithromycin has been observed at varying concentrations in vitro; azithromycin was found to increase the number of actively phagocytosing alveolar macrophages and to decrease the expression of proinflammatory cytokines such as interleukin IL -1b, IL-6, IL-8 and tumor necrosis factor (TNF)-a along with growth factors such as granulocyte-macrophage colony stimulating factor. It changes the macrophage phenotype, thus suppressing the production of proinflammatory cytokines and increasing the production of anti-inflammatory cytokines. 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.

Azithromycin concentrations in gingiva reportedly persist for up to 14 days after systemic administration. 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, thus increasing the production of anti-inflammatory cytokines and favor the healing process. Evidence also confirms that azithromycin concentration is higher in saliva and gingival crevicular fluid than in plasma.<sup>(8)</sup> It's concentrations in gingival tissue are up to 25-fold higher than in the blood.<sup>(10)</sup> It's role in regenerative therapy has been investigated by Hirsch *et al.* for alveolar bone regeneration.

Various modes of administering azithromycin as an adjunct in the treatment of periodontal conditions has been evaluated using various clinical, microbiological and biochemical methods. The use of azithromycin in the field of periodontics is vast, from a local drug delivery agent<sup>(13)</sup> to the management of advanced chronic periodontitis & aggressive periodontitis.<sup>(14)</sup> It has also been used in patients who do not respond well to supportive periodontal therapy (SPT).<sup>(8)</sup> More recently, its use in the treatment of moderate- severe gingival overgrowth related to calcium channel

blockers and cyclosporine,<sup>(15)</sup> cases of peri-implantitis<sup>(8)</sup> and periodontal or gingival abscess<sup>(16)</sup> are remarkable.

### Systemic

The first reported clinical study of azithromycin in periodontics was conducted by Blandizzi et al in 1996.<sup>(17)</sup> The concentration of azithromycin in plasma, saliva, normal gingival and pathological tissues were assessed after systemic administration for three days. The level of azithromycin were higher than the minimum inhibitory concentration in pathological tissues when compared to those in normal gingiva. Thus suggesting importance of azithromycin as an adjunctive as well as a prophylactic treatment for chronic periodontal disease.

Haffajee et al.<sup>(18)</sup> studied the clinical changes occurring in subjects with chronic periodontitis after the use of SRP alone or combined with systemically administered AZM, metronidazole, or subantimicrobial-dose doxycycline. Delivering the antimicrobial agent directly into the periodontal pocket, high intrasulcular drug levels can be achieved with minimum systemic exposure.<sup>(19)</sup>

In a clinical and microbiological study,<sup>(20)</sup> thirty four patients with chronic periodontitis were prescribed azithromycin 500mg once daily for three days. The aim was to measure the azithromycin concentration in the tissues lining the periodontal pocket. On the 14<sup>th</sup> day, azithromycin was detectable in inflamed periodontal tissue with improvement in the clinical and microbiological parameters with marked effectiveness against *P. intermedia* and *A. actinomycetemcomitans*.

Another study<sup>(7)</sup> was conducted to compare the effects of conventional SRP with azithromycin administration orally 3 days before full-mouth SRP. The clinical parameters, total number of bacteria, and number of black pigment-producing rods (BPRs) were evaluated at baseline and 5, 13, and 25 weeks after baseline. All clinical parameters improved in the test group more than in the control group and BPRs were not detected until 13 weeks. This study showed that full-mouth SRP using systemically administered azithromycin was a useful basic periodontal treatment for severe chronic periodontitis.

Twenty-nine patients harbouring *P. gingivalis* were randomized into test and placebo groups to evaluate the clinical and microbiological effects of systemic azithromycin as an adjunct to scaling and root planing (SRP) in the treatment of Porphyromonas gingivalis-associated chronic periodontitis. The six month followup study demonstrated significant clinical and microbiological benefits when compared with SRP plus placebo.<sup>(21)</sup>

A double blind study in which azithromycin was compared with placebo in patients with chronic periodontitis, as an adjunct to scaling and root planing. The clinical and microbiological effects were favorable

for azithromycin particularly in the presence of deep periodontal pockets.<sup>(22)</sup>

A randomized trial was designed to determine the efficacy of azithromycin (AZM) when combined with scaling and root planing (SRP) for the treatment of moderate to severe chronic periodontitis in smokers. At baseline and 3 and 6 months, clinical measurements, GCF bone marker assessment (C-telopeptide [ICTP] as well as BANA test analyses) were performed. The utilization of AZM in combination with SRP improves the efficacy of non-surgical periodontal therapy in reducing probing depth and improving attachment levels in smokers with moderate to advanced attachment loss.<sup>(23)</sup>

Conversely, Dastoor et al. in a pilot study,<sup>(24)</sup> evaluated the adjunctive effect of systemic AZM in combination with periodontal surgery in smokers and demonstrated that in heavy smokers, adjunctive AZM in combination with periodontal surgery did not significantly enhance PD reduction or CAL gain.

The study comparing the local antimicrobial and anti-inflammatory effects<sup>(25)</sup> resulting from a single dose of azithromycin 500mg or amoxicillin 2gm prior to surgical placement of one-stage dental implants. Peri-implant crevicular fluid (PICF) samples from the new implant and gingival crevicular fluid (GCF) from adjacent teeth were sampled on postoperative days 6, 13 and 20. Inflammatory mediators in the samples were analyzed by immunoassay and antibiotic levels were measured by bioassay. Thus, preoperative azithromycin may enhance resolution of postoperative inflammation to a greater extent than amoxicillin.

The administration of systemic azithromycin was also found to be effective in reducing the drug induced gingival overgrowth caused by cyclosporine A.<sup>(26)</sup>

A study conducted to compare the efficacy of local and systemic azithromycin therapy in the treatment of gingival overgrowth induced by cyclosporine A in kidney transplant patients reported that systemic azithromycin was more effective than local administration in reducing the gingival overgrowth.<sup>(27)</sup>

In a comparison study<sup>(28)</sup> for the efficacy of metronidazole and azithromycin in reducing the cyclosporine induced gingival overgrowth, azithromycin was found to be superior.

## Local

The long-term use of systemic antibiotics may lack patient compliance and lead to potential side effects such as development of resistant strains and superimposed infections.<sup>(29)</sup> Therefore, the local administration of antimicrobials provides an alternative to prevent these complications while being effective. Local drug delivery can provide 100-fold higher therapeutic doses of the agent in subgingival areas than systemic therapy.<sup>(30,31)</sup> Furthermore, GCF concentration achieved by locally delivered azithromycin gel is 2041 ug/ml retained in site for upto 28 days<sup>(31,13)</sup> tissue

concentration greatly exceed the concomitant serum levels by 10- 100 fold.

Recent developments suggest that the local delivery of antimicrobials into periodontal pockets can improve periodontal health. For an antibiotic to be effective, a basic assumption is that it should be present in the infected site in adequate concentration.

A study<sup>(13)</sup> was undertaken to investigate the clinical and microbiologic effectiveness of azithromycin (AZM) at 0.5% concentration in an indigenously prepared bio-absorbable controlled release gel as an adjunct to non-surgical mechanical therapy in the treatment of chronic periodontitis categorized into two treatment groups. Three months follow up microbiologic assessment was done to assess the percentage of morphologically different microorganisms using dark field microscopy. Although both treatment strategies seemed to benefit the patients, the adjunctive use of 0.5% AZM as a controlled drug delivery system enhanced the clinical and microbiologic results as shown by the intergroup comparison.

The adjunctive use of 0.5% AZM subgingivally<sup>(32)</sup> as a controlled drug delivery system was found to enhance the clinical outcome for treating chronic periodontitis in patients with type 2 diabetes as compared to the placebo.

A study was done to examine the efficacy of local azithromycin in cyclosporine induced gingival enlargement. Azithromycin was applied in toothpaste form. The results showed that gingival overgrowth decreased significantly in the azithromycin containing toothpaste group than control group. Azithromycin containing toothpaste is an effective, simple and non-invasive treatment for cyclosporine induced gingival enlargement.<sup>(33)</sup>

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.<sup>(34)</sup> 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.<sup>(16)</sup>

## Conclusion

Azithromycin in both the local and systemic forms has shown a promising effect in enhancing the periodontal conditions along with impressive antibacterial activity. More study in this field in future can be helpful in establishing it as a subantimicrobial local drug delivery agent.

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