Scholars Journal of Applied Medical Sciences (SJAMS) **ISSN 2320-6691 (Online)**
Sch. J. App. Med. Sci., 2014; 2(5E):1843-1847 **ISSN 2347-954X (Print)**

(An International Publisher for Academic and Scientific Resources)
www.saspublishers.com **DOI:** 10.36347/sjams.2014.v02i05.072

Review Article

Azithromycin: Not Just an Antibiotic Anymore

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Abstract: Azithromycin (AZI), prototype of a novel class of macrolide named azalide,is a congener of erythromycin . Macrolides including azithromycin are used for wide range of infections such as upper respiratory tract infections, sexually transmitted diseases, skin and soft tissue infections. In dental practice, azithromycin is frequently used in odontogenic infections because of its capability to penetrate into soft tissue, longer half life and higher uptake by fibroblasts, macrophages, neutrophils which are main players of inflammation. Several evidences also confirm thats its concentration is high in saliva and gingival tissue than in plasma. This review article provides information that azithromycin is not only used as an antibiotic but also as an antiinflammatory agent to resolve gingival overgrowth or to suppress periodontal pathogens. If in future, more research occurs to evaluate the effectiveness of azithromycin it will provide more insight into the promising action of it as a valuable modulator in periodontal therapy. Azithromycin shows a potential for eventual use as an adjunct in the treatment of periodontitis and gingival overgrowth. This article throws a light on its properties mentioned from past literature to present arena for the sames.
Keywords: Azithromycin, Gingival overgrowth, Periodontal therapy.

INTRODUCTION

As many as 700 different species of bacteria that colonize the oral cavity can affect the delicate balance of host-bacterial interactions, leading to health or disease. The periodontal infection is initiated by specific invasive oral pathogens that colonize dental plaque biofilms on the tooth surface.

This chronic challenge of virulent microorganisms leads to destruction of tooth -supporting soft and hard tissues of periodontium including alveolar bone, tooth-root cementum, and periodontal ligament.

Inflammation is the central pathological feature of periodontal disease and bacterial plaque which contains mainly microorganisms in the etiological factor resposible for inducing the host inflammatory process [1]. Microorganism play a crucial role in the initiation and progression of periodontitis .The subgingival microfloras are complex and compromise a lot of gram negative anaerobic and facultative anaerobic microorganisms. In a susceptible host, microbial virulence factors trigger the release of host derived enzymes and pro-inflammatory cytokines that can lead to periodontal destruction. Hence the extent and degree of periodontal destruction varies widely from patient to patient. Antibiotics have been used as an adjunct in the treatment of chronic and aggressive periodontitis from a very long time. With the increased use of antibiotics, there is a rising incidence of developing resistance against the antibiotic both in animals and humans. There are evidences which clearly indicate the increased use of antibiotics in humans and developing resistance in bacteria. These issues have taken into consideration in the treatment of periodontal therapy. Commonly used drugs are penicillin and macrolides.

The most common regimen used extensively is the combination of amoxicillin (375mg) and metronidazole (500mg) thrice a day for 7 days [27]. Till date , no evidence is present which can show the superiority of any other antibiotic regimen against amoxicillin and metronidazole [2] but with the increase chances of development of resistant bacteria short course of antibiotics are prescribed.

On the other hand macrolide antibiotics proved to be a valuable new addition to the field of anti-infective as it offered activity against emerging penicillin pathogens and could be used in those patients who show B-lactam intolerance. However resistance to erythromycin appeared quite rapidly in staphylococci, streptococci, pneumococci and enterococci. A number of semisynthetic derivatives of erythromycin such as clarithromycin and azithromycin have emerged. These

second generation macrolide have a more favourable pharmacokinetic profile than erythromycin.

The most common dosage regimen prescribed is 500mg orally once a day for 4-7days.Usually the side effects from this drug is uncommon but can be nausea, vomiting, diarrhoea [3]. Rarely allergic reactions can be occurred.

MECHANISM OF ACTION

Azithromycin has a wide antimicrobial spectrum of action towards anerobic bacteria as well as against gram negative bacilli including *Porphyromonas spp.*, *Prevotella spp., Actinobacillus actinomycetemcomitans*. They inhibit protein synthesis by binding to 50s ribosomal subunits thereby inhibiting translocation of amino acyl transfer Rna and inhibit polypeptide synthesis [4].

It is rapidly absorbed from GIT with bioavailability is about 40%.Its peak plasma concentration is achieved 2-3 hour after oral administration.It has a terminal half life of 68 hour and average half life is 1-4 days [5].

ADVANTAGES OF AZITHROMYCIN OVER OTHER ANTIBIOTICS

- It has increased acid stability, increased tissue distribution and decreased binding to plasma proteins and rapid absorption.
- Azithromycin has enhanced activity against gram-negative pathogens compared with its predecessors (e.g. erythromycin).
- Azithromycin showed extensive systemic distribution following oral administration, leading to good penetration and sustained concentrations in tissues, even after the levels in serum had decreased, making it a favourable immune-modulator over other macrolides [6].
- Azithromycin also has significant immunomodulatory properties and, for this reason, is used to treat diseases distinct from infections.
- Increased concentration found in cells such as neutrophils,macrophages,fibroblasts,monocytes and epithelial cells which may explain the high level of azithromycin in infected tissues.
- Its long terminal half-life enables azithromycin to combat bacterial infections at a lower dosage and shorter treatment regimes than other antibiotics [5].
- Patient compliance is good because of the short course of administration and the low incidence of side effects [3].
- In vivo, bacteria within biofilm are thought to be protected from antibiotics; however, unlike other macrolides and tetracyclines, azithromycin is capable of efficiently infiltrating this barrier , thus permitting more effective antimicrobial activity against microbes within the biofilm.

IMMUNOMODULATORY PROPERTIES

The action of macrolides extend from the reduction of inflammation, regulation of neutrophil and macrophage activity and production of cytokine. It is rapidly taken up by neutrophils, macrophages and fibroblast [13-15]. Azithromycin is carried efficiently into inflammed tissues by neutrophils through chemotaxis while maintaining its activity. Azithromycin exerted acute effects on the release of neutrophil granular enzymes, on oxidative burst and on oxidative protective mechanisms; there was a prolonged degranulation of circulating neutrophils, which could represent a potential anti inflammatory effect in the treatment of subacute, non-infective inflammatory responses.

Significant immunomodulatory effects of azithromycin have 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 pro-inflammatory cytokines [interleukin (IL)-1b, IL-6, IL-8 and tumor necrosis factor (TNF)-a] and growth factors such as granulocyte-macrophage colony stimulating factor. Azithromycin changes the macrophage phenotype, shifting macrophage polarization towards alternatively activated phenotype, thus suppressing the production of proinflammatory cytokines and increasing the production of anti-inflammatory cytokines. In a study of human gingival fibroblasts stimulated with lipopolysaccharides (LPS) derived from P. gingivalis and treated with azithromycin showed a dose dependent increase in the production of IL-8, whereas azithromycin was found to reduce LPS induces IL-8 production in oral epithelial cells. These authors concluded that treatment with azithromycin at an early stage in periodontal therapy would be a useful way to enhance the reduction of IL-8 levels.

Hirsch *et al*. [28] reported that in chronic periodontitis patient receiving azithromycin treatment without periodontal therapy have alveolar bone regeneration, thus raising the possibility that it can help in bone formation once inflammation is subsided.

Various evidences proves the immunomodulatory effect of azithromycin :

- 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,long anti-bacterial half life and short course make it an attractive antibiotic option as an adjunct to the management of advanced inflammatory periodontitis .
- The uptake of azithromycin by neutrophils and macrophages allows it to be concentrated at sites of periodontal inflammation.

- It exert its anti-inflammatory properties by down regulating the proinflammatory cytokine production.[25]

CLINICAL AND MICROBIOLOGICAL STUDIES

For an antibiotic to be effective, a basic assumption is that it should be present in the infected site in adequate concentration. The first reported periodontal clinical study of azithromycin was performed in 1996. A study was conducted in which concentration of azithromycin in plasma, saliva, normal gingival and pathological tissues were assessed after administration of azithromycin 500mg/day orally for three consecutive days. Azithromycin levels were measured by microbiological plate assay using micrococcus luteus and it was found that azithromycin levels were higher than minimum inhibitory concentration in pathological tissues than those in normal gingiva suggesting that azithromycin represents a promising option in both adjunctive and prophylactic treatment of chronic periodontal disease [16].

In another 14 days study, thirty four patients with chronic periodontitis were prescribed azithromycin 500mg once daily for three days [26]. Control group was not taken which was the limitation of this study. The following clinical parameters (probing depth, bleeding on probing, gingival index and gingival crevicular fluid level) were recorded. The aim of the study was to measure the azithromycin concentration in the tissues lining the periodontal pocket by agar diffusion bioassay. Subgingival plaque was collected for bacteriological examination like *P. intermedia* and *A. actinomycetemcomitans*. On day 14, azithromycin was detectable in inflammed periodontal tissue after systemic administration at a concentration which was effective against *P. intermedia* and *A. actinomycetemcomitans*. Clinical and microbiological improvement was reported with this drug [17].

A double blind study was conducted in patients of adult periodontitis in which azithromycin was compared with a placebo both of which was given as an adjunct to scaling and root planing. Both clinical and microbiological effects were evaluated. The results indicated that azithromycin may be a useful adjunct in the treatment of adult periodontitis particularly where deep pockets were present [18].

INFLUENCE OF AZITHROMYCIN ON GINGIVAL OVERGROWTH

Drug induced gingival enlargement is done by three groups of drugs i.e calcium channel blockers,immunosuppressants and antiepileptic drugs. Initially azithromycin was used only as an antibiotic but recently another important advantage came into light that it can reduce or resolve the gingival overgrowth induced by these drugs. This was first addressed in a letter to the New England Journal of Medicine in 1995 which stated that azithromycin reduced the gingival overgrowth induced by cyclosporine A [19]. In support of this there is a study in which partial regression of gingival overgrowth occurred in a 19 year old woman taking cyclosporine therapy, azithromycin was given 500mg once daily for 3 days [20].

Two patients were encountered with inflammatory gingival overgrowth taking cyclosporineA therapy. They were prescribed azithromycin because of chest infections. After 3-4 months patients reported that gingival bleeding was stopped with resolution of gingival overgrowth in one patient and regression in other without any periodontal treatment or altering the dose of cyclosporine A.

A study was conducted to compare the efficacy of local and systemic azithromycin therapy in the treatment of gingival overgrowth induced by cyclosporineA in kidney transplant patients. It was reported that systemic azithromycin was more effective than local administration in reducing the gingival overgrowth [21].

In a study efficacy of metronidazole and azithromycin was evaluated in cyclosporine induced gingival overgrowth. The patients were randomly divided into two groups, one group was prescribed five days of azithromycin and 7 days of metronidazole to another group. The results showed that azithromycin offers an effective alternative in the management of cyclosporine induced gingival enlargement [22].

A study was done to examine the efficacy of local azithromycin in cyclosporine induced gingival enlargement. Azithromycin was applied in toothpaste form, control group was taken for comparison and gingival index was measured. 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 [23].

Inspite of existing evidences about azithromycin in resolution of drug induced gingival enlargement, this property of azithromycin is still unknown in periodontal therapy and clinical practice .Definitive clinical and microbiological studies are required whether azithromycin alone or as an adjunct to the periodontal therapy can enhance the management of gingival overgrowth induced by calcium channel blockers, immunosuppressants and anti- epileptic drugs .

CONCLUSION

Azithromycin has been found useful in the treatment of periodontal infections, because of its increase concentration found in cells such as neutrophils, macrophages, fibroblasts, monocytes and epithelial cells, which may explain the high level of azithromycin found in the infected tissue. As a result of chemotactic

effect exerted on the phagocytes, this drug is transported to the site of inflammation [29]. Also among all macrolides azithromycin is most effective against gram negative anaerobes i.e. fusobacterium species, bacteroid species, actinobacillus actinomycetemcomitans, selemonas species [11].

Furthermore, GCF concentration achieved by locally delivered azithromycin gel is 2041 ug/ml retained in site for upto 28 days [30, 31] tissue concentration greatly exceed the concomitant serum levels by 10- 100 fold.

Gingival overgrowth improvement with the use of azithromycin might be related to the antibiotic effect of this drug, eliminating oral bacteria, reducing local inflammation, and decreasing the extracellular matrix by fibroblasts. In fact, some researchers observed a decrease in the growth of aerobes and spirochetes with the use of AZI. Kim et al. have shown in their in vitro study that AZI blocked fibroblast proliferation and collagen synthesis (initiated by cyclosporine) and activated fibroblast MMP-2.

Since very limited number of studies and evidences are present which can confirm the use of azithromycin in periodontitis and gingival overgrowth.If the various properties as mentioned earlier in this article like prolonged retention, good bioavailability, immunomodulatory effects & resolution of gingival overgrowth are proved in near future, we can use it not only just as an antibiotic but also in host modulation, periodontitis, & gingival overgrowth.

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