Review Article

Azithromycin – A Novel Anti-Microbial Agent in Periodontal Therapy

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ABSTRACT

Azithromycin, a macrolide has been used broadly in medicine in the treatment of an extensive array of diseases which includes middle ear infections, upper respiratory tract infections and also sexually transmitted infections. Its effectivity against most common periodontopathogens has been studied in detail. This drug could play a triple fold role for the resolution and treatment of diseases of the supporting structures of the tooth. High concentrated levels of the drug have been reported in neutrophils, macrophages and even fibroblasts, which are considered as prime players in the pathologic process of periodontal diseases. With the advent of increasing research regarding periodontal therapy the future could bring further confirmation of these properties, and azithromycin can become a treasured host-modulator for treating periodontal diseases. Thus, this review will explore on possible roles of azithromycin for treating periodontal diseases.

Key words: Antimicrobial, azithromycin, macrolide, periodontal disease

INTRODUCTION

Chronic periodontitis has been defined as an infectious disease resulting in inflammation within the supporting tissues of the teeth, progressive attachment loss, and bone loss.[1] The pathogenesis of this inflammatory condition can be attributed to the exaggerated immune and inflammatory response of the host system against the presence of multiple microbial communities which adhere on to the soft as well as hard tissues of the periodontium and the oral cavity. Socransky *et al.*[2] had described the presence of several species of bacteria in the subgingival plaque indicating that periodontitis is a polymicrobial infection. *Porphyromonas gingivalis* along with other red complex species is a late colonizer in biofilm establishment and is a key periodontal pathogen most commonly observed in severe forms of periodontitis.[3,4]

A plethora of evidence has been reported regarding the efficacy of azithromycin and its role in the treatment of periodontal lesions, due to its pharmacological properties. Anti-microbial action of azithromycin observed against periodontopathogens such as *P. gingivalis*[5,6] *Tannerella forsythia,*[5,6] *Treponema denticola,*[6] and *Aggregatibacter actinomycetemcomitans*[7] makes it a reliable antibiotic for reduction in bacterial load among the periodontal tissues. Recently, inhibitory effect of azithromycin has been reported against adherence property of *P. gingivalis* on soft and hard tissues of the oral cavity indicating usage of the drug in reduction of biofilm formation in reduced concentrations.[8]

The aim of this paper is to review the periodontal applications of azithromycin and the indication for its eligibility as a prophylactic agent. This paper will also review the available evidence on its acceptability as a therapeutic agent for the treatment of periodontal diseases.

HISTORICAL BACKGROUND

Grouped under subclass azalides of macrolides, azithromycin (9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A) has gained popularity very recently. It is one of the greatest inventions of Croatia. A team of researchers Pliva, a pharmaceutical company located in Zagreb, Croatia, namely, Gabrijela Kobrehel, Gorjana Radobolja-Lazarevski, Zrinka Tamburasev, led by Dr. Slobodan Dokic, set out to discover a semi-synthetic derivative of erythromycin in the late 1970's.[9] By 1980, azithromycin become a member of the subclass, Azalides which is a part of Macrolides. Trials presented the drug to remain in tissues for a longer duration and to be highly effective. Pliva issued for a patent application for Azithromycin in late 1980. In 1986, the drug is licensed to Pfizer in the United States, a company which had apparently already discovered and patented the same drug almost concurrently.[10] As Pliva had already submitted their application in 1980 at least 1 ½ year ahead of the multinational pharmaceutical company, Pfizer was forced to negotiate with Pliva. Pliva maintained the right to sell

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in Central and Eastern Europe under the brand name "Sumamed" in 1988. Pfizer launched azithromycin under Pliva's license selling worldwide including United States and Western Europe under the brand name "Zithromax" in 1991 after FDA approved in the same year.[11]

Pajukanta *et al.* in 1992[12] conducted the first *in vitro* trial of azithromycin to assess the susceptibility of *A. actinomycetemcomitans* when compared with erythromycin. Results indicated that azithromycin was highly effective *in vitro* against the bacteria.

Sefton *et al.* in 1996[13] employed azithromycin as an adjunct to non-surgical periodontal treatment (NSPT) in chronic periodontitis individuals. Patients who received azithromycin exhibited a decrease in black pigmented anaerobes. The authors recommended a study with a larger sample size and of a longer duration along with comparison with other antibiotics such as metronidazole or tetracycline.

Increased penetration was seen in normal as well as pathological periodontal tissues by azithromycin which was prescribed by Blandizzi *et al.* in 1999[14] in patients requiring surgical therapy for treating periodontitis. This was the first surgical trial done in the field of Periodontology utilizing azithromycin as a prophylactic remedy.[14]

MECHANISM OF ACTION

Azithromycin, a second-generation macrolide has a pleasing pharmacokinetic profile. It inhibits protein synthesis by binding to 50 s ribosome subunits thus impeding translocation of amino acyl t-SRNA and inhibits polypeptide synthesis.[15] It presents with improved acid stability and tissue distribution along with quick tissue absorption. It achieves peak plasma concentration in 2–3 h and acts extensively against gram negative pathogens after systemic delivery. Azithromycin's commendable penetration property and sustained concentration in tissues after decrease in serum levels are remarkable. With a half-life of 68 h, it is efficient in eradicating microbes at low doses and may reduce the progress of resistant bacterial species.[16] Common dosage prescribed is 500 mg orally once a day for 4–7 days.

ROLE IN PERIODONTOLOGY

Non-surgical periodontal application

A great deal of literature has been published in context of the adjunctive application of azithromycin in periodontally compromised patients following scaling and root planning (SRP). Because of its property of being available in tissues for a longer duration, it can be used effectively as an adjunct to SRP in NSPT.

In 1996 Sefton *et al.*[13] conducted the 1st NSPT where 23 patients from one group who exhibited a CPITN score of four with at least 20 teeth and pocket depth of >6 mm, were provided with non-surgical care and azithromycin 500 mg once a day for 3 days. Microbiological evaluation of the affected sites was maintained for 22 weeks. A significant decrease in black pigmented microbes and spirochetes was noted. Although this was a microbiological analysis of the drug, a decrease in pocket depth was seen in azithromycin group.

Clinical trials performed in smokers[17,18] presenting with chronic periodontitis have evaluated AZM as an adjunct to NSPT and results have shown significant improvements in reduction of probing depth (PD) and gain in the clinical attachment level. Although contradictory results have been reported, indicating adjunctive use of AZM had no significant effect after NSPT.[19]

It is pertinent to mention the studies which administered AZM along with NSPT, have pondered on microbial analysis in which the decrease in the microbial load along with amelioration of the periodontal parameters has placed this drug as an effective antimicrobial agent [Table 1].[19-26]

APPLICATION IN PERIODONTAL SURGERY

Main aim of periodontal treatment is to diminish inflammation and to eradicate infection to bring about an environment beneficial for the repair and regeneration of lost tissues.

The penetration and potential therapeutic role of AZM in normal and diseased periodontal tissues was noted on 32 patients who had to undergo surgery for chronic marginal periodontitis, chronic periapical periodontitis or dentigerous cyst, were given 500 mg of AZM for 3 days. The drug concentration peaked 12 h after the final dose was administered and was seen to be present after 6.5 days, and was higher in diseased tissues than in normal tissues indicating marked penetration capacity of AZM.[14]

Dastoor *et al.*[18] conducted an RCT involving 30 patients (smokers) with generalized moderate to advanced chronic periodontitis who underwent surgical therapy for infected sites after SRP. After surgery, 15 patients (test) out of 30 received AZM (500 mg × 3 days, 1 tablet/day) and were asked to return for follow ups in 2 weeks and at 1, 3, and 6 months. Improvement observed in CAL gain, PD reduction, and BOP reduction but these cannot be attributed to adjunctive use of AZM. Rapid wound healing, less plaque formation within 3 months, less gingival inflammation and reduction in periodontopathogen bacteria by the usage of AZM which was observed in test group is an indication that the drug's benefits outweigh the risks.[18]

A comparative analysis between surgical (n = 19) and non-surgical therapy (n = 20) with adjunctive usage of AZM at the 6th month for a period of 36 months among patients with moderate to severe periodontitis was evaluated. Patients reporting with residual pockets ≥6 mm deep at the 6th month only were treated with for azithromycin in both groups. Additional therapy after 6 months yielded beneficial results as <2% residual pockets were observed at 36 months and betterment of periodontal indices. This study is limited by its financial outcomes.[30]

CONCLUSION

Increased tissue penetration, long half-life, greater tolerance to gram negative organisms, biofilm inhibition are just some of

Table 1: Summary of non-surgical periodontal therapy utilizing azithromycin as an adjuvant

Author	Study model	Subjects	Duration	Periodontal condition	Treatment	Outcome
Han *et al.*[19]	RCT	36	6 months	Chronic periodontitis	1. AZM+SRP 500 mg x 3 days 2. Control - SRP	Decrease in *F. nucleatum*, GCF MMP-8 level post operatively and at the end of 2 weeks
Botero *et al.*[27]	RCT	105	9 months	Moderate periodontitis (diabetes -typeI/II)	1. AZM 500mg/day (3 days) + subgingival scaling (AZ-Sca) 2. Placebo 500 mg/day (3 days) +subgingival scaling (PBSca) 3. AZM 500 mg/day (3 days) + supragingival prophylaxis (AZ-Pro)	Decrease in PD in (AZ-Sca) group, improvement in CAL in (AZ-Sca) group, improvement in glycemic levels in (AZ-Sca) group.
Hincapié *et al.*[22]	RCT	105	9 months	Chronic periodontitis (diabetes -type I/II)	1. AZM 500mg/day x 3 days (1/day) + subgingival scaling 2. Placebo 500 mg/day x 3 days (1/day) +subgingival scaling 3. AZM 500 mg/day x 3 days (1/day) + supragingival scaling	Pathogens count decreased in 3 months in all groups. After 3 months counts of *Tannerella forsythia* increased in all groups. Subgingival intervention with AZM showed no significant result
Agarwal *et al.*[28]	RCT	63	9 months	Moderate periodontitis (Type 2 diabetes)	1. SRP+Placebo 2. SRP+0.5% AZM (subgingival)	Group 2 showed reductions in PI, GI, PD, gain in CAL. No microbial analysis was performed
Yashima *et al.*[24]	RCT	63	6 weeks	Moderate – severe periodontitis	1. Full Mouth – SRP (FMSRP) + AZM 2. FMSRP without AZM	SRP+AZM showed more success in removing the disease-causing pathogens and AZM effectively reduced the FM-SRP induced bacteremia
Oliveira *et al.*[25]	RCT	34	6 months	Severe periodontitis	1. Quadrant wise SRP (4 weeks) + AZM 500 mg x 3 days 2. FMSRP+AZM 50 mg x 3 days	Both groups showed almost similar results. FMSRP group showed superior outcome with regard to antibacterial effects in 6 months
Morales *et al.*[29]	RCT	47	12 months	Severe periodontitis	1. Placebo (SRP+AZM placebo+probiotic placebo) 2. Probiotic (SRP+probiotic+AZM placebo) 3. Antibiotic (SRP+AZM+probiotic placebo)	All groups showed reduction in PPD, PI. Placebo and antibiotic group exhibited reduction in BOP. Placebo showed reduction in CAL
Čuk *et al.*[26]	RCT	40	6 months	Severe periodontitis	4. SRP+Placebo 5. SRP+AZM (500 mg x 3 days)	Group 3 exhibited reduction in *A.A., P.G., C. rectus*. Improvements in periodontal parameters seen in both groups

CAL: Clinical attachment level

the properties which make azithromycin a practical alternative to be used as an adjunct as well as a viable substitute to the typically used antibiotics in periodontology. Confirming to the presented evidence indicating beneficial results in non-surgical, surgical as well as anti-biofilm outcomes, the drug can become an exceptional agent in rectifying advanced periodontal diseases.

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