



# **Azithromycin as an Adjunct to Non-Surgical Periodontal Therapy in Periodontitis: A Comprehensive Review**

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**Abstract:** *Periodontitis is associated with inflammation of periodontal apparatus, leading to destruction of connective attachment and loss of teeth. Chronic periodontitis is a multifactorial disease. Periodontal therapy including either surgical and/or non-surgical methods results in improvement of periodontal health. In some cases, scaling and root planing (SRP) is insufficient to treat periodontal infection. SRP in combination with local/systemic antibiotics has been shown to yield better results than SRP alone. Azithromycin is an acclaimed macrolide, among a broad antimicrobial spectrum, competent contending on periodontopathic microorganisms. This manuscript reviews the efficacy of azithromycin as an adjunct to non-surgical periodontal therapy in managing periodontitis. It centers around pharmacokinetics, immunomodulatory effects, and clinical efficacy based on several studies. Recent evidence suggests that azithromycin not only reduces microbial load, but it also enhances periodontal tissue healing by modulating inflammatory pathways and improves function of fibroblasts. The findings suggest that azithromycin helps in improving periodontal health, but its long-term effectiveness and resistance concerns necessitate further research.*

**Keywords:** *Azithromycin, Periodontitis, Non-Surgical Periodontal Therapy, Scaling and Root Planing, Immunomodulation, Periodontal tissue healing.*

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## **I. Introduction**

Periodontitis is a chronic inflammatory disease driven by bacterial pathogens and is one of the most common oral infections worldwide (WHO 2004)<sup>1</sup>. The host response to periodontal pathogens represents a crucial determinant of the individual's susceptibility to periodontitis. It results from an imbalance between the microorganisms in the plaque biofilm, the host response and modifying factors. The goals of treatment of periodontal disease are The primary goal of periodontal therapy is to halt disease progression, eliminate bacterial pathogens, and restore periodontal health. Though etiology of periodontitis is multi-factorial, but bacterial species are considered as primary etiologic agents. The importance of bacteria in the etiology of periodontal pockets has been clearly established, as a result, therapy is necessarily directed at controlling the bacterial flora associated with the periodontium. Periodontitis is commonly treated in a non-surgical way initially. Non-surgical periodontal therapy includes scaling and root planing (SRP) combined with oral hygiene instructions which helps to gain clinical

attachment and recession of the gingival margin by resolving the periodontal inflammation. However, residual periodontal pockets often persist which requires the treatment that involve adjunctive interventions<sup>2</sup>.

Azithromycin, a broad-spectrum macrolide antibiotic that acts by inhibiting protein synthesis by binding to 50S ribosomal subunits thereby inhibiting translocation of aminoacyl transfer RNA and inhibit polypeptide synthesis. Azithromycin is an antibiotic used extensively in medicine for the treatment of a wide range of infections<sup>2,3,4</sup>. Azithromycin is effective against most common periodontopathogens like *Actinobacillus actinomycetemcomitans*, *Porphyromonas gingivalis*. Azithromycin is concentrated in neutrophils, macrophages & fibroblasts which are considered as central players in periodontal pathogenesis. Its ability to persist in macrophages and fibroblasts allows for prolonged antimicrobial activity and modulation of the immune response, reducing inflammation and enhancing tissue repair. It has been explored that azithromycin has a triple role in treating & resolution of periodontal disease by suppressing pathogenic activity, anti-inflammatory activity & healing through persistence at low levels in macrophages & fibroblasts. This complex action makes azithromycin a promising therapeutic option beyond its antibacterial effects.

Azithromycin has significantly less bacterial resistance to the subgingival microflora of chronic periodontitis compared to other commonly prescribed antibiotics. It has been found to accumulate in the periodontal tissues and gingival crevicular fluid (GCF), making it a potential therapeutic agent in periodontitis management. This review evaluates the effectiveness of azithromycin in improving periodontal outcomes.

## II. Pharmacokinetics and Mechanism of Action

Azithromycin exhibits unique pharmacokinetic properties that make it favorable for periodontal therapy. It has a high affinity for tissues and is selectively taken up by phagocytic cells, enabling targeted drug delivery to inflamed sites. The key mechanisms of azithromycin include:

**2.1 Bacteriostatic Activity:** Inhibits bacterial protein synthesis by binding to the 50S ribosomal subunit, affecting periodontopathogens such as *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans*, and *Treponema denticola*.

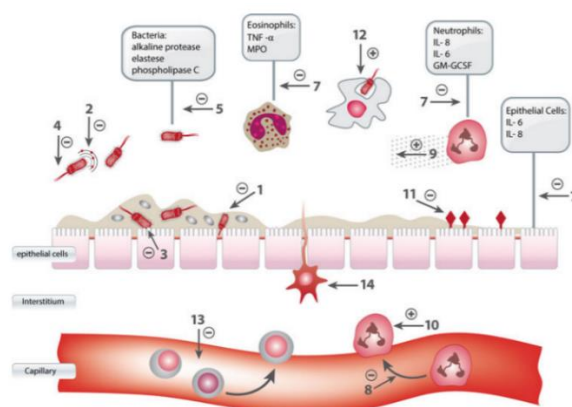
**2.2 Biofilm Penetration:** Biofilm present a major challenge to antimicrobial therapy as they protect bacteria from antibiotics via several mechanisms.

A biofilm is defined as a microbially derived sessile community characterized by cells that are irreversibly attached to a substratum or interface or to each other, which are embedded in a matrix of extracellular polymeric substances that they have produced and exhibit an altered phenotype with respect to growth rate and gene transcription. Microbial resistance in the biofilm is due to 3 factors: decreased growth, protection by the matrix or changes in phenotype.

Macrolides can inhibit biofilm formation<sup>5</sup> although they do not seem to be able to destroy the microbial film entirely<sup>6</sup>. In the context of periodontitis, azithromycin has been shown to be effective against *P.gingivalis*. Azithromycin can penetrate bacterial biofilms, which protect periodontal pathogens from conventional antibiotics.

**2.3 Immunomodulation:** Azithromycin is carried efficiently into inflamed tissues by neutrophils through chemotaxis<sup>7</sup>, 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 because of accumulation in neutrophil precursor cells<sup>8</sup>. This prolonged retention in immune cells enhances its immunomodulatory effects, reducing tissue destruction and promoting periodontal healing. Azithromycin modulates host immune response by reducing pro-inflammatory cytokines, enhancing neutrophil function, and suppressing tissue destruction.

**2.4 Prolonged Tissue Retention:** Due to its extended half-life, azithromycin maintains therapeutic concentrations in periodontal tissues for several days post-administration. This prolonged action improves patient compliance as there will be no need for frequent dosing.



### Schematic representation of immunomodulatory function of azithromycin [9]

1. Attenuation of biofilm function
2. Suppression of bacterial quorum sensing
3. Decrease in bacterial adherence.
4. Loss of flagellar mobility
5. Reduced production of bacterial toxins
6. Consolidation of epithelial tight junctions
7. Inhibition of proinflammatory cytokines produced by bacteria, neutrophils, eosinophils and epithelial cells.
8. Reduction of neutrophil chemotaxis
9. Stimulation of neutrophil degranulation
10. Accelerated neutrophil chemotaxis.
11. Down regulation of adhesion molecules
12. Stimulation of phagocytosis by macrophages
13. Reduction of T cells and T cell migration
14. Modulation of dendritic cell function

### III. Clinical Evidence Supporting Azithromycin Use in Periodontitis

Several randomized clinical trials (RCTs) and studies have assessed the adjunctive use of azithromycin in periodontal therapy. Key findings include:

- 3.1. Pocket Depth Reduction:** Studies indicate that adjunctive azithromycin significantly improves probing depth reduction compared to SRP alone, particularly in deep periodontal pockets.
- 3.2. Clinical Attachment Level (CAL) Gain:** Patients receiving azithromycin adjunctively demonstrate greater attachment level gains, indicating improved periodontal stability.
- 3.3. Reduction in Inflammatory Markers:** Azithromycin has been shown to decrease levels of interleukin-1 $\beta$ , tumor necrosis factor-alpha (TNF- $\alpha$ ), and matrix metalloproteinases (MMPs) in GCF.
- 3.4. Enhanced Microbial Clearance:** Azithromycin effectively reduces subgingival pathogenic bacterial load and delays recolonization.
- 3.5. Impact on Smokers and Aggressive Periodontitis Patients:** Smokers and individuals with aggressive periodontitis may benefit more from azithromycin adjunctive therapy due to its anti-inflammatory effects.

Following administration of azithromycin its concentration in gingival crevicular fluid is higher and more stable compared to serum levels and this makes a potential potent bioactive agent for the use in treatment of periodontitis<sup>10,11</sup>.

#### IV. Comparison with Other Antibiotics

Azithromycin has been compared with other antibiotics used in periodontal therapy, such as doxycycline and metronidazole-amoxicillin combination. Findings suggest:

- 4.1. **Azithromycin vs. Doxycycline:** While both exhibit antibacterial effects, azithromycin provides additional immunomodulatory benefits and better patient compliance due to its short-duration regimen.
- 4.2. **Azithromycin vs. Metronidazole-Amoxicillin:** The combination of metronidazole and amoxicillin shows higher efficacy in aggressive periodontitis cases; however, azithromycin is better tolerated with fewer gastrointestinal side effects.

#### V. Potential Concerns and Limitations

Despite its benefits, the use of azithromycin in periodontal therapy presents certain challenges:

- 5.1. **Antimicrobial Resistance:** Overuse of antibiotics can contribute to microbial resistance, necessitating careful prescription.
- 5.2. **Short-Term vs. Long-Term Benefits:** While short-term improvements are evident, long-term benefits remain inconclusive.
- 5.3. **Adverse Effects:** Although generally well-tolerated, some patients may experience gastrointestinal disturbances, liver toxicity, and rare cardiovascular risks.
- 5.4. **Patient-Specific Considerations:** Individual patient response varies, and factors such as systemic health, compliance, and severity of periodontitis influence treatment outcomes.

#### VI. Discussion

Periodontal disease is primarily caused by plaque biofilm, which harbors specific pathogenic bacteria that trigger chronic inflammation and tissue destruction. While SRP is the standard treatment, its effectiveness can be limited in deeper pockets, complex root anatomy, and inaccessible areas. Residual pathogens can lead to continued bone loss and disease progression. Macrolide antibiotics, such as erythromycin and clarithromycin, have been used for periodontal infections due to their tissue penetration and antibacterial properties. However, their efficacy varies, necessitating the search for better alternatives like azithromycin.

Azithromycin stands out among macrolides due to its superior pharmacokinetic properties, including prolonged tissue retention, high bioavailability, and ability to modulate the immune response. It accumulates in neutrophils, macrophages, and fibroblasts, allowing targeted delivery to inflamed periodontal tissues. Studies indicate that azithromycin reduces bacterial loads, suppresses pro-inflammatory cytokines, and promotes tissue healing<sup>12,13</sup>. Additionally, it enhances fibroblast function, potentially contributing to periodontal regeneration, which is unique of its nature. While dentists generally view the role of antibiotics in controlling infections, azithromycin has significantly wider properties which potentially account for the improvement in periodontal health reported here. It is more than an antibiotic. While azithromycin shows promise as an adjunct to SRP, concerns over antimicrobial resistance and long-term efficacy warrant further clinical research.

#### VII. Conclusion

Azithromycin serves as a valuable adjunct to non-surgical periodontal therapy, offering antimicrobial, biofilm-penetrative, and immunomodulatory benefits. Its unique ability to persist in immune cells and enhance fibroblast function adds regenerative potential in periodontal therapy. Its effectiveness in reducing pocket depth, enhancing

attachment gain, and improving inflammatory response makes it a promising therapeutic agent. However, concerns regarding antimicrobial resistance and long-term efficacy warrant further research. Future studies should focus on optimizing dosage protocols, evaluating long-term outcomes, and exploring combination therapies to maximize periodontal health benefits. Combining azithromycin with regenerative periodontal approaches, such as guided tissue regeneration and host modulation therapies, may strengthen treatment outcomes.

## References

- [1] Borrell LN, Burt BA, Taylor GW. Prevalence and trends in periodontitis in the USA: from the NHANES III to the NHANES, 1988 to 2000. *Journal of dental research*. 2005 Oct;84(10):924-30.
- [2] Retsema JA, Bergeron JM, Girard D, Milisen WB, Girard AE. Preferential concentration of azithromycin in an infected mouse thigh model. *Journal of Antimicrobial Chemotherapy* 31 Suppl E:5-16. 92.
- [3] Baldwin DR, Wise R, Andrews JM, Ashby JP, Honeybourne D. Azithromycin concentrations at the sites of pulmonary infection. *European Respiratory Journal* 3:886-890. 93.
- [4] Girard D, Regan PA, Milisen WB, Retsema JA, Swindell AC. Influence of immunosuppression on the pharmacokinetics and pharmacodynamics of azithromycin in infected mouse tissues. *Journal of Antimicrobial Chemotherapy* 1996;37 Suppl C:21-35. Heitz -mayfield 2009
- [5] Starner TD, Shrout JD, Parsek MR, Appelbaum PC, Kim G. Subinhibitory concentrations of azithromycin decrease nontypeable Haemophilus influenzae biofilm formation and diminish established biofilms. *Antimicrobial agents and chemotherapy*, 2008 Jan 1;52(1):137-45.
- [6] Norrington DW, Ruby J, Beck P, Eleazer PD. Observations of biofilm growth on human dentin and potential destruction after exposure to antibiotics. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology*, 2008 Apr 1;105(4):526-9.
- [7] Gladue RP, Snider ME. Intracellular accumulation of azithromycin by cultured human fibroblasts. *Antimicrob Agents Chemother* 1990;34:1056-1060.
- [8] McDonald PJ, Pruul H. Phagocyte uptake and transport of azithromycin. *Eur J Clin Microbiol Infect Dis* 1991;10:828-833.
- [9] Altenburg J, De Graaff CS, Van Der Werf TS, Boersma WG. Immunomodulatory effects of macrolide antibiotics—part 1: biological mechanisms. *Respiration*. 2011;81(1):67-74.
- [10] Lai PC, Ho W, Jain N, Walters JD. Azithromycin concentrations in blood and gingival crevicular fluid after systemic administration. *Journal of periodontology*. 2011 Nov;82(11):1582-6.
- [11] Jain N, Lai PC, Walters JD. Effect of gingivitis on azithromycin concentrations in gingival crevicular fluid. *Journal of periodontology*. 2012 Sep;83(9):1122-8.
- [12] McDonald PJ, Pruul H. Phagocyte uptake and transport of azithromycin. *Eur J Clin Microbiol Infect Dis* 1991;10:828-833.
- [13] Bosnar M, Bosnjak B, Cuzic S et al. Azithromycin and clarithromycin inhibit lipopolysaccharide-induced murine pulmonary neutrophilia mainly through effects on macrophage-derived granulocyte-macrophage colony-stimulating factor and interleukin-1beta. *J Pharmacol Exp Ther* 2009;331:104-113.