International Journal of Science and Research (IJSR)
ISSN: 2319-7064
Impact Factor 2024: 7.101

Azithromycin in Periodontal and Peri-Implant Therapy: A Comprehensive Literature Review

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Abstract: ***Azithromycin, a macrolide antibiotic with broad medical applications, has also found significant use in dentistry. It's established as a preventive measure against bacterial endocarditis in high-risk dental patients and is employed in treating pertussis and mycobacterial infections. Azithromycin is notably recognized for its minimal likelihood of interacting with other drugs. Its antimicrobial action works by anchoring to the 50S ribosomal subunit, which in turn prevents the synthesis of bacterial proteins. Beyond its antibiotic capabilities, azithromycin has demonstrated efficacy in managing cyclosporin-associated gingival hyperplasia, particularly when administered during the early stages of the condition. Furthermore, its anti-inflammatory and immunomodulatory properties have led some researchers to consider it a 'wonder drug' for periodontal disease management. In this review, the various attributes of azithromycin are analyzed, and clinical research is compiled regarding its role in periodontal treatments, both surgical and non-surgical. This encompasses the management of periodontitis and peri-implantitis, the facilitation of periodontal regeneration, and the treatment of gingival hyperplasia induced by drugs.***

Keywords: azithromycin, mechanism of action, periodontitis, peri implantitis, systemic antimicrobials

1. Introduction

Dr. Slobodan Đokić in 1980 was part of a group of scientists working at the Croatian drug company Pliva, and they made an important discovery of a medicine called azithromycin. The compound was officially patented in 1981. A decade later, in 1991, the pharmaceutical giant Pfizer acquired a license from Pliva, allowing them to sell azithromycin worldwide as Zithromax. Much later, the FDA gave its stamp of approval for AzaSite, an ophthalmic form of azithromycin designed to treat eye infections [1].

Azithromycin (AZM) is a modified version of erythromycin. It's designed with an extra methyl-substituted nitrogen atom in its lactone ring. This alteration makes it more resistant to acid, allows it to penetrate tissues better, and gives it a wider spectrum of antibacterial action. Their antibacterial action works by sticking to the 50S part of the bacterial ribosome, which stops the bacteria from making proteins they need to survive [2],[3]. AZM has the chemical name **9-deoxo-9a-methyl-9a-aza-9a-homoerythromycin A** and its formula is **C38H72N2O12**. It is made by changing the carbonyl group at the **9a** position in the aglycone ring to a methyl nitrogen atom. The structure of AZM is shown in **Figure 1**.

Unlike erythromycin (ERY), AZM exhibits enhanced durability and strength. This improvement arises from the prevention of internal hemiketal formation. Consequently, the primary method for AZM's degradation involves the acid-induced separation of the ether connection to the neutral sugar L-cladinose [4].

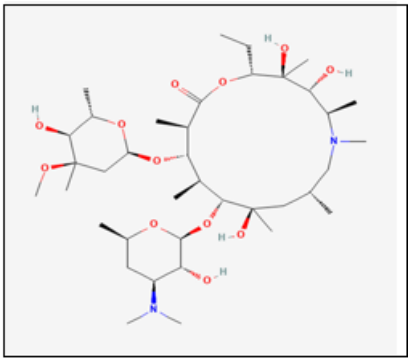

Figure 1 Chemical structure of azithromycin (https://pubchem.ncbi.nlm.nih.gov/compound/447043#section=Structures, accessed on June 25, 2025)

Understanding the multifaceted role of azithromycin in periodontal care contributes to evolving therapeutic strategies that integrate antimicrobial and host-modulating approaches, particularly amidst increasing antibiotic resistance. This review aims to explore the pharmacological properties and clinical utility of azithromycin in the management of periodontal and peri-implant diseases, evaluating its efficacy, mechanisms, and scope of application.

2. Mechanism of Action

The antimicrobial activity of AZM is attributed to its reversible interaction with the 23S rRNA of the 50S subunit, leading to bacterial protein synthesis disruption in susceptible organisms [5],[6]. This macrolide antibiotic exhibits a prolonged half-life and demonstrates favourable periodontal tissue penetration [7]. AZM's pharmacokinetic profile,

characterized by an extended half-life,8 permits efficient treatment of bacterial infections with lower drug concentrations and shorter treatment durations compared to alternative antibiotics. It works against various disease-causing bacteria, including the once causing middle ear and nasopharyngeal infections. Beyond this, it's also prescribed for conditions like malaria, sexually transmitted infections, and trachoma [8],[9]-[16].

3. Unique abilities of azithromycin

AZM is readily taken up by various cell types, including fibroblasts and white blood cells [17]. It exhibits a range of biological effects, including **immunomodulatory**, **anti-inflammatory**, and **antibacterial properties**. AZM treatment is generally of short duration. For adults, the usual total dose is 1500 mg of immediate-release AZM. This can be taken as 500 mg OD for 3days, or as 500 mg on the first day followed by 250 mg each day for the next 4days [18].

4. Antibiotic properties of Azithromycin

AZM is effective against various gram-positive bacteria, including *Staphylococcus aureus* and *Streptococcus pyogenes*. It stands out for its markedly enhanced antibacterial activity against gram-negative anaerobic bacteria compared to older macrolides antibiotics like erythromycin and clarithromycin [19]-[23].

At low doses, AZM has shown effectiveness against common respiratory tract pathogens such as *Haemophilus influenzae, Moraxella catarrhalis*, and *Bordetella pertussis*. Notably, azithromycin's potency against *H. influenzae* has been found to be eight times higher than that of erythromycin [21]. Additionally, AZM demonstrates potential effectiveness against specific enteric pathogens and gram-negative bacilli associated with endocarditis. This includes bacteria such as *Escherichia coli, Salmonella enteritidis, and Aggregatibacter actinomycetemcomitans,* (which is a major contributor to aggressive periodontitis). These particular strains, often highly resistant to erythromycin (ERY), clarithromycin, and roxithromycin, are still susceptible to lower concentrations of AZM [24].

Against *Porphyromonas gingivalis*, AZM displays strong inhibitory action, with all tested strains suppressed at concentrations of ≤1.0 µg/mL. The minimal inhibitory concentrations (MICs) to inhibit 50% and 90% of the strains were 0.25 µg/mL and 0.5 µg/mL [25].

While bacteria within biofilms are generally considered more resistant to antibiotics [26], AZM uniquely possesses the ability to effectively penetrate these protective barriers, unlike other macrolide and tetracycline antibiotics [23],[27]. This characteristic allows for more effective antimicrobial activity against bacteria residing within biofilms.

5. Azithromycin anti inflammatory properties

AZM has been observed to lessen inflammatory cytokine and chemokine output from human gingival fibroblasts exposed to *P. gingivalis* LPS. Specifically, it reduced IL-6, IL-8, MCP-1, and GRO production. This decreased chemokine synthesis might, in turn, reduce the influx of polymorphonuclear leukocytes and monocytes to inflamed sites by inhibiting chemotaxis, though more research is needed to confirm its overall anti-inflammatory significance.

Additionally, the potential effects of AZM on fibroblast functions related to matrix synthesis and turnover, including the regulation of matrix metalloproteinases and their inhibitors, need to be explored further. These investigations are crucial to understand the underlying mechanisms of the clinically observed pro-resolution effects of AZM in periodontitis treatment [28].

6. Azithromycin administration in periodontal therapy

Prophylactic oral AZM, taken once daily for three days preceding periodontal therapy, demonstrated a substantial decrease in bacteremia after scaling and root planning (SRP). The observed bacteremia rates were 20% in the AZM group, 90% in SRP group, and 70% in the group receiving SRP followed by essential oil antiseptic subgingival irrigation [29]. The bacterial species *Porphyromonas gingivalis, Prevotella intermedia*, and *Tannerella forsythia* was monitored.

When healthy subjects received AZM at 500 mg (day 1) and 250 mg (days 2 & 3), their gingival crevicular fluid contained over 40 times more antibiotic than their blood serum. Significantly, these GCF levels persisted above the MIC for key periodontopathogens (*A. actinomycetemcomitans*, *P. gingivalis*, *P. intermedia*) for a full week after the final dose [30].

7. Azithromycin effect on biofilm production

In *Pseudomonas aeruginosa*, AZM has been observed to potentially disrupt quorum sensing, a bacterial communication mechanism. This interference can result in diminished virulence factor production [31], [32], reduced biofilm formation, and decreased oxidative stress resistance [33]. Research indicates that even sub-MICs of AZM significantly impede quorum-sensing signal production and biofilm development in *P. aeruginosa* under laboratory conditions [34].

Research implies that sub-MIC AZM can reduce *P. gingivalis* host cell adhesion by inhibiting fimbriae and hemagglutinin production. This highlights AZM's potential as a strong therapeutic option for *P. gingivalis*-mediated periodontal disease, by targeting biofilm and adhesion [35].

8. Azithromycine immunomudatory properties

Azithromycin (AZM) stands out among macrolides due to its remarkable pharmacokinetic profile, which makes it an excellent immune modulator [36].

After oral intake, AZM spreads widely throughout the body, penetrating various tissues and maintaining high concentrations even after serum levels decline. Immune cells,

including neutrophils, macrophages, and fibroblasts, readily absorb and retain AZM [37]-[40].

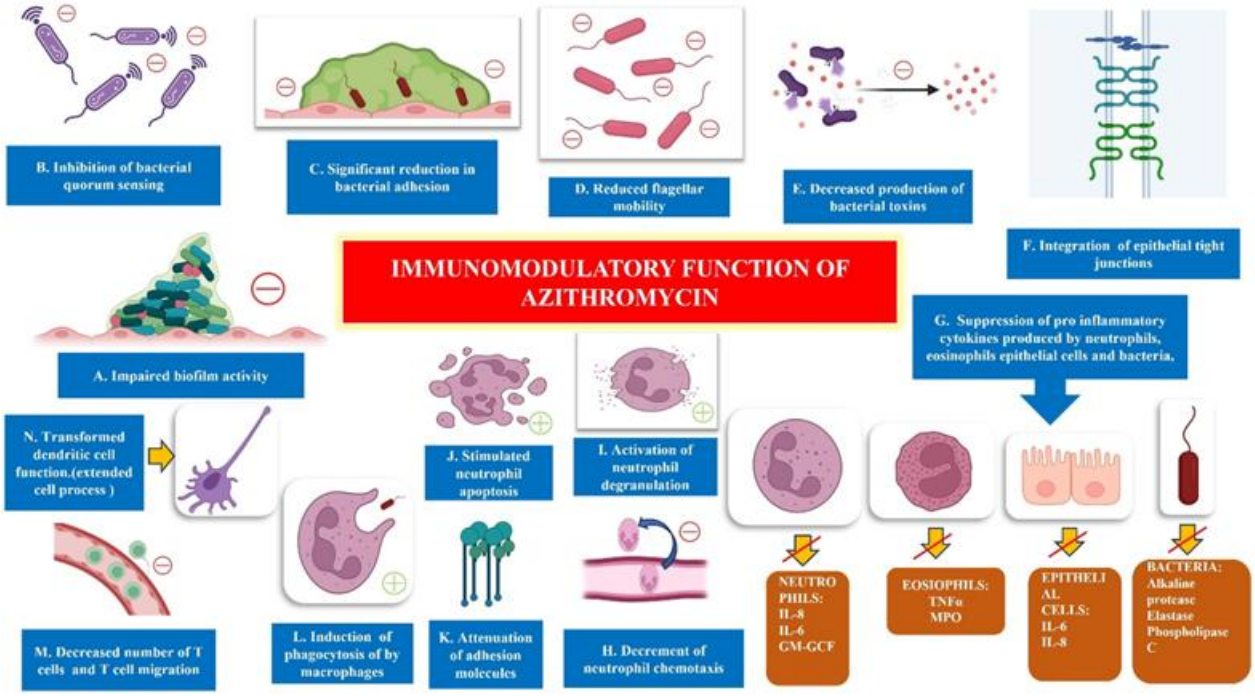

Figure 2: Schematic representation of immunomodulatory function of AZM [51]

Neutrophils play a crucial role in transporting AZM to inflamed tissues via chemotaxis [41], all while the drug retains its antibacterial properties. Notably, a short three-day course of 500 mg daily AZM in healthy individuals resulted in the antibiotic remaining detectable in neutrophils for an astonishing 28 days post-treatment. This prolonged presence is likely due to AZM's accumulation within neutrophil precursor cells [42].

Beyond its sustained presence, AZM acutely influences neutrophil function. It alters the secretion of granular enzymes, impacts oxidative burst responses, and boosts oxidative defence mechanisms. The extended degranulation of circulating neutrophils observed may play a key role in AZM's anti-inflammatory properties in subacute, non-infectious inflammatory conditions [42].

Comparative studies highlight substantial differences in intracellular accumulation between AZM and erythromycin (ERY). After 24 hours, human neutrophils showed a 10-fold higher intracellular concentration of AZM than ERY, while murine macrophages exhibited a 26-fold difference. 37 Once extracellular drug was removed, AZM showed a remarkably slower efflux rate, with only 19% released in the first hour compared to ERY's 85%. Similar accumulation patterns were seen in human fibroblasts, where AZM reached 21-fold higher concentrations than ERY at 72 hours. This suggests fibroblasts could act as a reservoir for sustained AZM release, potentially aiding its transfer to neutrophils migrating into inflamed areas.

8.1 In Vitro Immunomodulatory Effects

In laboratory studies, AZM exhibits significant immunomodulatory effects that vary with concentration. It has been shown to enhance the population of actively phagocytic alveolar macrophages and to suppress the production of pro-inflammatory cytokines, including IL-1β, IL-6, IL-8, and TNF-α, along with growth factors such as granulocyte-macrophage colony-stimulating factor [16], [43]. Comparable anti-inflammatory effects were observed in airway epithelial cells from cystic fibrosis patients, where AZM reduced IL-8 expression and the activity of pro-inflammatory transcription factors NF-κB and AP-1 [44]. Additionally, AZM shifts macrophages toward an alternatively activated phenotype, promoting decreased production of pro-inflammatory cytokines and increased synthesis of anti-inflammatory ones [45], [46].

Nevertheless, AZM's ability to inhibit TNF-α-induced NF-κB activity in vitro were found to be less potent than those of strong anti-inflammatory corticosteroids like hydrocortisone and dexamethasone [47]. Interestingly, research involving human gingival fibroblasts exposed to *Porphyromonas gingivalis* lipopolysaccharide (LPS) revealed a dose-dependent increase in IL-8 production [48], following AZM treatment. In contrast, AZM was shown to lower LPS-induced IL-8 levels in an oral epithelial cell line, highlighting its capacity to regulate innate immunity and provide anti-inflammatory effects in human oral epithelial cells [49]. Given these contrasting outcomes, researchers have proposed that initiating AZM treatment early in periodontal therapy could help decrease IL-8 levels.

8.2. Clinical Observations in Periodontal Health

Subjects without periodontal disease who received AZM (500 mg on day one followed by 250 mg daily for the next two days), exhibited a marked decrease in gingival crevicular fluid (GCF) volume by the end of treatment. These GCF volumes, however, rebounded to baseline levels within 14 days. Notably, pro-inflammatory cytokines such as IL-8,

TNF-α, and vascular endothelial growth factor were significantly reduced by day 4 of the study.

When subjects without periodontal disease received AZM (500 mg initially, followed by 250 mg daily for two days), a significant reduction in gingival crevicular fluid (GCF) volume was observed by the final day of treatment. However, these levels returned to baseline within 14 days. Importantly, levels of pro-inflammatory cytokines such as IL-8, TNF-α, and vascular endothelial growth factor showed a significant decline by day 4 of the study [50]. **Figure 2** represents the immunomodulatory function of AZM.

9. Azithromycin and periodontal disease: Classical Studies

1) **Smith *et al.* (2002)** conducted a randomized control trail with test group- AZM 500mg for 3 days after SRP and control group- SRP with placebo in moderate periodontitis patients. They concluded that there is significant reduction in probing pocket depth (PPD) in case of use of AZM for 3 days after SRP. The study was short and smoking status of patient was not reported [52].
2) **Fuji *et al.* (2004)** assessed the impact of adjunctive AZM in patients with aggressive periodontitis (Agp) in a case-control design. Subjects in the experimental arm received 500 mg AZM for three days following two months of SRP, while the control arm received SRP alone. The study's primary endpoint was a gingival index of 1. The data suggested a potential benefit of AZM in reducing the time required to reach the endpoint. However, the study's conclusions are constrained by methodological limitations. Specifically, a small sample size, a 2.4-fold difference in treatment duration between groups, and the absence of smoking status data introduce significant uncertainties into the interpretation of the findings [53].
3) **Mascarenhas *et al.* (2005)** designed a case-control study for patients with moderate periodontitis condition and heavy smoking. Here the test group had AZM 250 mg twice on 1st day and continued 250 mg for 4 days following SRP. Control group had only SRP with no placebo. In smokers with moderate periodontitis, azithromycin adjunctive to SRP resulted in greater PPD reduction and CAL gain, along with improved microflora, indicating a beneficial effect [54].
4) **Gomi *et al.* (2007)** conducted a case-control study in patients with severe chronic periodontitis. Test group consist of AZM 500mg for 3 days and full mouth debridement for 3 days after azithromycin course. Control group consist of SRP which was completed in 5 weeks. There was significant greater reduction in mean PPD, number of BOP sited and GCF levels at 13 and 25 weeks. This study was short and not properly controlled along with that smoking status of patient was not reported [7].
5) **Dastoor *et al.* (2007)** conducted randomized study involving heavy smokers with moderate to advanced chronic periodontitis, patients who received AZM (500mg for three days) following periodontal surgery, osseous contouring, and ibuprofen (600mg) administration exhibited a sustained reduction in periodontal pathogens compared to a control group receiving a placebo. This suggests that AZM can enhance the microbiological outcomes of periodontal surgery in this patient population [55].
6) **Haffajee *et al.* (2007)** conducted a case-control which included patients suffering from chronic periodontitis. Test group patients were prescribed following medication:-
   AZM: 500mg for 3 days
   Metronidazole: 250 mg for 3 days
   Sub antimicrobial doxycycline: 20mg for 3 days
   This 12-month clinical investigation examined the impact of adjunctive systemic antibiotics on periodontal treatment. Participants underwent four SRP sessions, with above mentioned antibiotic administration commencing at the initial visit. Compared to SRP alone, AZM and metronidazole significantly enhanced PPD reduction and CAL gain in deep pockets (≥6mm) over the study period. AZM uniquely demonstrated a sustained reduction in *T. forsythia* levels. Methodological limitations, including the absence of a placebo control, lack of smoking control, and challenges in baseline periodontitis assessment, warrant cautious interpretation of these findings [56].
7) **Pradeep *et al.* (2008)** performed a randomized controlled trial involving non-smoking patients with chronic periodontitis, a single application of 0.5% controlled-release AZM gel(0.2ml) into deep periodontal pockets after SRP yielded improved clinical outcomes, including greater PPD reduction and CAL gain. Microbiological analysis revealed a positive shift in periodontal microflora, with an increase in cocci, straight rods, filamentous, and fusiform bacteria and decrease in spirochetes and motile rods, in AZM gel study group, observed for up to three months. The study's limitation is the single localized application of the AZM gel, making direct comparisons with systemic AZM studies difficult [57].
8) **Haas *et al.* (2008)** conducted randomized control trial in aggressive periodontitis patients. Test group with AZM 500mg for 3 days at start of SRP and control group with SRP and placebo. This study concluded that AZM up to 12 months showed significant reduction in PPD with gain in CAL. This study is not properly controlled for smoking status [58].
9) **Yashima *et al.* (2009)** designed a case-control study for nonsmoker chronic periodontitis patients. Test group had AZM 500mg for 3 days before periodontal therapy full mouth SRP which should be done in 3 visits in 7 days. Control group will have SRP done in 6 visits over a period of 6 weeks, no placebo. This study concluded that AZM group for up to 12 months had greater reduction in PPD, gain in CAL. The results of this study were difficult to compare as the treatments were different for test and control group [59].
10) **Osteo *et al.* (2010)** conducted a randomized controlled trial investigating the efficacy of adjunctive systemic AZM in the treatment of moderate *Porphyromonas gingivalis*-associated periodontitis. Participants underwent two sessions of SRP within a seven-day period. The experimental group received AZM (500mg for three days) following SRP, while the control group received SRP alone. Clinical parameters, including PPD and CAL, were measured at 1, 3, and 6-month follow-up intervals. Microbiological analysis quantified levels of *A.*

actinomycetemcomitans, P. intermedia, T. forsythia, and *P. micra*.

Results from the study showed that the AZM group experienced statistically significant reductions in PPD and gain in CAL compared to the control group across all follow-up visits. Furthermore, the AZM group displayed lower levels of the specific periodontal pathogens mentioned earlier. However, the study had its limitations. These include a small sample size and the inclusion of both smokers and non-smokers, which could have introduced confounding variables and limited how broadly the findings can be applied. To confirm these results, larger and more uniform studies are needed [60].

10. Azithromycine effect on cyclosporine induced gingival hyperplasia

Cyclosporine, a potent immunosuppressant frequently prescribed to prevent organ rejection after transplants and manage autoimmune diseases, is known to cause several side effects. Among these, nephrotoxicity, hepatotoxicity, hypertension, and gingival overgrowth are common. Gingival enlargement is a particularly frequent adverse reaction in patients on long-term cyclosporine therapy, provided other contributing factors are ruled out. A systematic review and meta-analysis examining the impact of azithromycin on cyclosporine-induced gingival enlargement found that azithromycin significantly reduced both the enlargement and bleeding on probing [61].

Research by Kim and colleagues revealed azithromycin's (AZM) significant influence on the fibroblast elements contributing to gingival overgrowth (GO). Their study showed that AZM boosted the activity of matrix metalloproteinases (MMP)-1 and MMP-2, not just in healthy fibroblasts but also in those from kidney transplant patients treated with cyclosporine. More precisely, within cyclosporine-treated cells, AZM acted on several fronts: it stopped collagen from clumping in the culture, prevented the rise in type I collagen mRNA, and brought MMP-2 mRNA levels back to normal. These findings hint that AZM might alleviate Cyclosporine A-induced GO by curbing the cell proliferation and collagen synthesis that Cyclosporine A encourages, while simultaneously activating MMP-2 in gingival fibroblasts. It is also important to remember that scaling helps manage the inflammatory aspects of gingival overgrowth [62], [63].

11. Regenerative effect of Azithromycin

Azithromycin has demonstrated potential for both tissue regeneration and antimicrobial activity in treating periodontitis, regardless of the severity of gingival inflammation. Adding azithromycin to standard SRP has proven effective in promoting periodontal tissue regeneration, even when there is initial signs of gingival inflammation are present at baseline [64].

This drug works by encouraging periodontal ligament stem cells (PDLSCs) to undergo osteogenic differentiation, even when inflammation is present. It achieves this by suppressing the WNT and NF-κB signalling pathways and by preventing TNF-α-induced cell death. These findings indicate that AZM holds promise as a potential treatment for periodontitis [65].

Azithromycin reduces the activity of over-responsive macrophages, which are believed to drive periodontal destruction by releasing pro-inflammatory cytokines. It may also benefit fibroblast function within periodontal tissues, contributing to gingival tissue remodelling and reducing gingival overgrowth. A recent in vitro study demonstrated that azithromycin inhibits fibroblast proliferation and collagen synthesis induced by cyclosporine, while simultaneously boosting fibroblast MMP-2 activity [66]. The observed bone regeneration suggests that azithromycin may promote bone formation once inflammation in the tissue has reduced [67].

12. Peri-implantitis and Azithromycin

A persistent and irreversible condition affecting the hard and soft tissues around implants, peri-implantitis is linked to purulence, increased pocket development, impaired osseointegration, increasing bone loss, and bone resorption [68], [69]. Peri-implant mucositis is a condition where the soft tissues and connective tissues around a dental implant become reversibly inflamed [70].

There was a study which found that a combination of *Lactobacillus reuteri* probiotics and azithromycin reduced inflammation in peri-implantitis patients. This effect was due to changes in host response, rather than improvements in the microbial flora in peri-implant sulci in patients with peri-implantitis [71]. A randomized clinical trial investigated how well azithromycin works to treat peri-implantitis. The study concluded that adding a single course of systemic azithromycin can help manage peri-implant mucositis when treating peri-implantitis [72]. One of the systematic reviews examining the use of local or topical antimicrobials to treat peri-implantitis found that several antibiotics, including **azithromycin**, minocycline, tetracycline, doxycycline, amoxicillin & metronidazole, showed positive results in treating the condition [73].

13. Conclusion

Research indicates that azithromycin possesses a unique trifecta of pharmacological actions, exhibiting antibacterial, anti-inflammatory, and immunomodulatory effects. A critical aspect of its efficacy lies in its ability to disrupt biofilm formation, a key factor in periodontal disease pathogenesis. Azithromycin achieves this by significantly impeding quorum sensing (QS), the communication system within bacterial communities, through the suppression of QS-related genes. The sustained release of azithromycin from neutrophils, macrophages, and particularly fibroblasts, cells pivotal in periodontal disease progression, suggests a potential to effectively prevent further periodontal breakdown. This drug demonstrates an affinity for these cells, allowing for prolonged therapeutic concentrations at the site of inflammation. Furthermore, azithromycin impacts both innate and adaptive immune responses, influencing the host's immune system in multifaceted ways.

A substantial body of literature supports the use of azithromycin in treating advanced and progressive periodontitis, facilitating periodontal regeneration, managing peri-implantitis, and addressing drug-induced gingival overgrowth. These studies highlight the drug's versatility in various periodontal conditions. However, further more research is essential to clarify the complete range of azithromycin's immunomodulation and the sustained nature of its anti-inflammatory activity. This deeper understanding will be crucial for establishing azithromycin as a reliable and routinely utilized therapeutic agent in daily dental clinical practice.

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