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Review Article

Azithromycin in periodontal treatment: more than an antibiotic

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Azithromycin is a macrolide antibiotic used extensively in medicine for the treatment of a wide range of infections such as upper respiratory tract infections, middle ear infections, sexually transmitted infections and trachoma. It is also effective against the most common periodontopathogens. The versatility of the macrolides extends beyond their antibiotic properties as a result of their well-documented immune-modulating/anti-inflammatory effects. Macrolides, including azithromycin, are therefore used to treat diseases not associated with bacteria, such as severe asthma, chronic obstructive pulmonary diseases and, more recently, cystic fibrosis. Azithromycin is concentrated in neutrophils, macrophages and particularly fibroblasts; all of these cells are central players in the pathogenesis of most periodontal diseases. This paper reviews the diverse properties of azithromycin and the clinical periodontal studies of its effects in both the treatment of periodontitis and in resolving drug-related gingival overgrowth. Evidence exists to support the use of a single course of azithromycin in the treatment of advanced periodontal diseases. 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.

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9-Deoxo-9a-aza-9a-methyl-9a-homoerythromycin (azithromycin) is an azalide, a subclass of macrolides (1), first synthesized in 1980 (2). Azithromycin has enhanced activity against gram-negative pathogens compared with its predecessors (e.g. erythromycin) and is therefore used to treat a wide range of infections (1). Azithromycin also has significant immunomodulatory properties and, for this reason, is used to treat diseases distinct from infections. Recently it has been used as an adjunctive agent in the treatment of a variety of periodontal diseases, including acute and chronic periodontitis and drug-induced gingival overgrowth.

Chemical structure, dosage and side effects

Azithromycin is a semisynthetic analogue of erythromycin in which an additional nitrogen atom has been inserted into the macrocyclic lactone ring. This 15-member macrolide is also known as an azalide (2). The extra nitrogen atom provides a higher degree of structural stability for azithromycin compared with erythromycin, resulting in excellent tissue penetration, low toxicity and a long half-life of approximately 68 h (3–5).

Azithromycin (500 mg) taken orally once a day for 3 d, 1 h before food, is the most common dosage regime. Patient compliance is good because of the short course of administration and the low incidence of side effects (6). Azithromycin should not be prescribed to patients with known hypersensitivity

to erythromycin. Adverse reactions associated with the use of a single course of azithromycin are relatively uncommon; the most frequent (in approximately 5%) are nausea, abdominal pain and diarrhoea. Rare, serious, allergic reactions, including angioedema and anaphylaxis (rarely fatal), have been reported in patients on azithromycin therapy. Drug interactions include antacids, warfarin (its effect may be potentiated; 7), digoxin and ergot derivatives. A full list of adverse reactions to azithromycin may be found in the Zithromax prescribing guide (8).

Antibiotic properties of azithromycin

Like all macrolide antibiotics, azithromycin reversibly inhibits bacterial protein synthesis by targeting the 23S ribosomal RNA of the 50S ribosomal subunit in susceptible organisms (9,10) while having a long half-life and good periodontal tissue penetration (11). Its long terminal half-life (12) enables azithromycin to combat bacterial infections at a lower dosage and shorter treatment regimes than other antibiotics. It is effective against a variety of bacterial infections, such as upper respiratory tract infections, middle ear infections, malaria, sexually transmitted infections and trachoma (3,12–19).

Azithromycin has bacteriostatic effects against a wide range of bacteria *in vitro*, including gram-positive bacteria such as *Staphylococcus aureus* and *Streptococcus pyogenes*, and has particularly strong antibacterial activity against gram-negative anaerobic bacteria in comparison with earlier macrolides such as erythromycin and clarithromycin (1,5,20–22). Common respiratory pathogens such as *Haemophilus influenzae*, *Moraxella catarrhalis* and *Bordetella pertussis* have all been shown to be susceptible to low doses of azithromycin; azithromycin was eight times more potent than erythromycin against *H. influenzae* (20). Enteric pathogens and gram-negative bacilli associated with endocarditis, such as *Escherichia coli*, *Salmonella enteritidis* and *Aggregatibacter actinomycetemcomitans* (also thought to be involved in aggressive periodontitis), which are resistant to high doses of erythromycin, clarithromycin and roxithromycin, have all shown susceptibility to low-dose azithromycin (23). Azithromycin is highly effective against *Porphyromonas gingivalis*: all strains tested were inhibited at $\leq$ 1.0 μg/mL of azithromycin. The minimal inhibitory concentrations (MICs) were 0.25 μg/mL for 50% of strains tested and 0.5 μg/mL for 90% of strains tested (24). *In vivo*, bacteria within biofilm are thought to be protected from antibiotics (25); however, unlike other macrolides and tetracyclines, azithromycin is capable of efficiently infiltrating this barrier (22,26), thus permitting more effective antimicrobial activity against microbes within the biofilm.

Azithromycin administered orally once daily for 3 d before periodontal treatment significantly reduced the incidence of bacteraemia after scaling and root planing (20% incidence) compared with scaling and root planing alone (90%) and with adjunctive subgingival irrigation with an essential oil containing antiseptic (70%; 27). The bacterial species tested included *P. gingivalis*, *Prevotella intermedia* and *Tannerella forsythia*. When azithromycin (500 mg followed by 250-mg doses on each of the next 2 d) was given to healthy volunteers, the levels of azithromycin in the gingival crevicular fluid were more than 40-fold higher than the levels of azithromycin in serum. After 7 d, the levels of azithromycin in gingival crevicular fluid were above the MIC for *A. actinomycetemcomitans*, *P. gingivalis* and *P. intermedia* (28). The authors attributed this to active accumulation of azithromycin by cells of the peripheral tissues.

Furthermore, azithromycin may interfere with quorum-sensing in *Pseudomonas aeruginosa*, leading to reduced production of virulence factors (29,30), reduced biofilm formation and oxidative stress resistance (31). Sub-MIC concentrations of azithromycin significantly inhibited the production of quorum-sensing signals and biofilm formation of *P. aeruginosa in vitro* (32).

As the use of antibiotics increases, there is concern regarding the emergence of macrolide-resistant bacteria (33). In one study, *Viridans* group oropharyngeal streptococcal resistance to macrolides was found in 71% of adults, with 32% having more than one unique macrolide-resistant isolate (34). Oral streptococci were sampled from the tonsils and posterior pharyngeal wall in subjects before and after taking a single course of azithromycin (500 mg once daily for 3 d), clarithromycin (500 mg twice daily for 7 d) or a placebo (35). Approximately 28% of all subjects harboured macrolide-resistant streptococci at the beginning of the study. The proportion of macrolide-resistant streptococci was significantly higher in the azithromycin group (compared with the clarithromycin group) at days 14, 28 and 42 after treatment, but not after 180 d. Azithromycin was thought to persist for at least 3–4 wk after treatment and therefore may heighten the threat of increased dissemination of resistant organisms (35). The resistance of five periodontal pathogens to a battery of antibiotics, including azithromycin, was compared in Spain and the Netherlands (36). All strains of *P. gingivalis* from both countries were susceptible to azithromycin, whereas 33% of *A. actinomycetemcomitans* strains were resistant to azithromycin in the Spanish isolates but all were susceptible in the Dutch sample.

A study of the microbiological effects of azithromycin, metronidazole and subantimicrobial doxycycline showed that a similar percentage of resistant isolates and the percentage of sites harbouring resistant species (predominantly streptococcal species and *Veillonella parvula*) were present before and 12 mo after administration of these agents (25). Periodontal pathogens generally had little resistance to azithromycin.

Immunomodulatory properties of azithromycin

The immunomodulatory properties of macrolides are applied in the treatment of diseases that are not associated with bacteria, such as severe asthma, diffuse panbronchiolitis, chronic obstructive pulmonary diseases and, more recently, cystic fibrosis and bronchiectasis

(10,13,37,38). The spectrum of action of macrolides extends from the reduction of inflammation, regulation of neutrophil and macrophage activity and production of cytokines, to altering fibroblast activity and host immunity. The effective anti-inflammatory properties have mainly been studied in chronic inflammatory airway diseases; however, the exact mechanisms are still not fully understood (39,40).

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 (13). It is rapidly taken up by neutrophils, macrophages and fibroblasts (41–43) with a high degree of retention (44).

Azithromycin is carried efficiently into inflamed tissues by neutrophils through chemotaxis (45), while maintaining its activity. When azithromycin (500 mg once daily for 3 d) was taken by healthy volunteers, it persisted in neutrophils for 28 d after the last dose, presumably as a result of accumulation in neutrophil precursor cells (46). 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, noninfective inflammatory responses (46). A 10-fold internal to external concentration-gradient differential between azithromycin and erythromycin in human neutrophils, and a 26-fold difference for murine macrophages, was found after 24 h of incubation (41). Following removal of the extracellular drugs from the culture medium, only 19% of intracellular azithromycin was found to be released within the first hour compared with 85% for erythromycin. Similar uptake differentials (21-fold of erythromycin after 72 h) have been found in human fibroblasts cultured in 10 μg/mL of each drug, indicating that fibroblasts may act as a reservoir for sustained release of azithromycin and for transfer of azithromycin to neutrophils migrating through inflamed tissue.

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)-1β, IL-6, IL-8 and tumour necrosis factor (TNF)-α] and growth factors such as granulocyte–macrophage colony-stimulating factor (19,47). Similar anti-inflammatory effects were found in cystic fibrosis airway epithelial cells; azithromycin *in vitro* reduced the expression of IL-8 and of the proinflammatory transcription factors nuclear factor kappaB (NF-κB) and activator protein 1 (AP-1) (48). Azithromycin changes the macrophage phenotype, shifting macrophage polarization towards the alternatively activated phenotype, thus suppressing the production of proinflammatory cytokines and increasing the production of anti-inflammatory cytokines (49,50).

The inhibitory effects on TNF-α-induced NF-κB *in vitro* appeared to be significantly lower than the inhibitory effects of hydrocortisone and dexamethasone, both of which are potent anti-inflammatory agents (i.e. corticosteroids) (51). A study of human gingival fibroblasts stimulated with lipopolysaccharide (LPS) derived from *P. gingivalis* and treated with azithromycin showed a dose-dependent increase in the production of IL-8 (52), whereas azithromycin was found to reduce LPS-induced IL-8 production in an oral epithelial cell line, thereby modifying innate immunity and exerting an anti-inflammatory effect on human oral epithelial cells (53). 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.

When azithromycin (500 mg followed by 250 mg per day for the next 2 d) was given to periodontally healthy subjects, a marked decrease in the volume of gingival crevicular fluid was observed on the day of the last dose; a return to baseline levels of gingival crevicular fluid had occurred after 14 d. The amounts of the proinflammatory cytokines IL-8, TNF-α and vascular endothelial growth factor decreased significantly on day 4 of the study (54).

Clinical periodontal studies of azithromycin

Azithromycin concentrations in plasma, saliva, normal gingiva and pathological periodontal tissues were measured for up to 6.5 d in 32 subjects (smoking status not reported) after a single 3-d course of azithromycin (500 mg; 55). The concentration of azithromycin peaked 12 h after the last dose but the drug was still present after 6.5 d; azithromycin levels in pathological periodontal tissues were significantly higher than in normal gingiva up to 4.5 d after the last dose. The longevity of azithromycin in gingiva, alveolar bone and saliva has been confirmed previously (56), but the study only extended for 6.5 d.

Clinical periodontal microbiological studies of azithromycin

The first reported periodontal clinical study of azithromycin was performed in 1996 (57). Forty-six patients with periodontitis were given either azithromycin (500 mg once daily for 3 d) or placebo as an adjunct to periodontal therapy. Microbiological assessment was made of the same periodontal pocket in each patient for up to 22 wk; pigmented anaerobes were significantly reduced at weeks 3 and 6 by azithromycin, and spirochaetes were suppressed throughout the study.

Clinical and microbiological improvements were reported in 34 patients with periodontitis who took azithromycin 500 mg once daily for 3 d (5). There was no control group; this limited the value of the study, which extended for only 14 d. The study measured the azithromycin concentration in the tissues lining the periodontal pockets by agar-diffusion bioassay. At day 14, azithromycin was still detectable in inflamed periodontal tissues at a concentration that was effective against *P. intermedia* and

A. actinomycetemcomitans. Sustained reduction in the numbers of six different species of periodontally pathogenic bacteria did not occur until day 14.

The microbiological effects of scaling and root planing alone vs. scaling and root planing with adjunctive azithromycin, metronidazole or subantimicrobial doses of doxycycline were compared in a 92-subject randomized, controlled, single-blinded trial over 12 mo (25). All treatment modalities significantly reduced the mean counts of *P. gingivalis*, *T. forsythia*, *P. intermedia* and other bacteria (red- and orange-complex bacteria). A significant decrease in the numbers of red and orange-complex bacteria was observed in both azithromycin and metronidazole groups within the first 2 wk of treatment, but only *T. forsythia* in the azithromycin group was significantly reduced at 12 mo. This study hints at the long-term effects of a single course of azithromycin on bacteria in periodontal pockets.

Clinical trials of azithromycin

There are relatively few clinical studies of the effects of azithromycin on the outcomes of periodontal therapy. The studies have been summarized in Table 1, which highlights the small number of subjects included in many of them, the lack of adequate treatment controls and the failure to control for smoking in some studies. The studies also vary with respect to the periodontal treatment protocol that accompanies the use of azithromycin. With these limitations in mind, a consistent outcome of the studies is that azithromycin used in conjunction with periodontal therapy improves the clinical periodontal and microbiological outcome compared with periodontal therapy alone. There is a need for definitive, properly controlled clinical periodontal studies that investigate the effects of azithromycin as a monotherapy and as an adjunct to nonsurgical periodontal treatment.

Case reports

Four case reports of the effects of azithromycin taken in conjunction with scaling and root planing in patients who had periodontal abscesses showed radiographic evidence of significant bone growth in severe localized periodontal defects (58). Three patients were given three courses of azithromycin (500 mg, once daily for 3 d), up to 5 years apart; one patient had two courses 32 mo apart. One patient had no follow-up care, and three patients had intermittent visits for periodontal maintenance, but none had periodontal surgery. This was the first report of the bone-regenerative potential of azithromycin in cases of bone destruction related to periodontal abscesses. The authors also reported the long-term beneficial effects of two to three courses of azithromycin in 15 patients on regular periodontal maintenance, with significant reduction in bleeding observed both clinically and reported by patients. Time between maintenance visits has been prolonged. The authors suggested that clinical trials should study more than a single course of azithromycin.

Three cases have recently been reported of significant periodontal healing, bone regeneration and resolution of medication-induced gingival overgrowth following a single course of azithromycin in patients with severe localized and generalized periodontitis (59). One of these patients had no periodontal treatment, and another had minimal debridement. Healing was observed to occur progressively over a period of 6–8 mo with resolution of inflammation, improved gingival tissue contours and bone regeneration. This report gives a glimpse of the clinical possibilities of azithromycin and supports the need for further clinical and laboratory studies of its periodontal potential.

Azithromycin and gingival overgrowth

Insights into the long-term periodontal immune-modulating properties of azithromycin come from reports of its effect in reducing gingival overgrowth induced by cyclosporine A. This was first reported in a letter to the *New England Journal of Medicine* in 1995 (60). Two patients with substantial inflammatory gingival overgrowth related to cyclosporine A had been prescribed azithromycin to treat chest infections. The patients reported that gingival bleeding had resolved over a period of 3–4 mo and gingival overgrowth had resolved in one patient and regressed in the other, without periodontal intervention or reduction in the dose of cyclosporine A. Partial regression of severe gingival overgrowth occurred over 3 mo subsequent to azithromycin treatment (500 mg once daily for 3 d) in a 19-year-old woman taking cyclosporine A (61). There is a single report of the resolution of cyclosporine A-induced gingival overgrowth after the administration of metronidazole (62).

The resolution of gingival overgrowth related to medication with a calcium-channel blocker was first reported in 1997 (63) in subjects who were also taking cyclosporine A and was subsequently found to be one of the long-term beneficial effects of azithromycin observed on the periodontal tissues over 8 mo (59).

Table 2 summarizes clinical studies of the effects of azithromycin on cyclosporine A-induced gingival overgrowth; generally the studies were carried out in a medical setting rather than in a dental or periodontal setting. Although many of these studies lack proper controls and scientific rigour, their consistent findings were that azithromycin reduced gingival inflammation and gingival overgrowth in the absence of periodontal therapy.

Animal and *in vitro* studies of azithromycin and gingival overgrowth

Gingival overgrowth was induced in rats by treatment with cyclosporine A for 6 wk; this was followed by 1 week of treatment with oral azithromycin in mineral oil (64). Mineral oil without azithromycin was used as control. Histological analysis and culture of gingival fibroblasts was performed at 7 wk. Cyclosporine A caused gingival overgrowth and decreased fibroblast phagocytic activity. Azithromycin reduced the amount of gingival

Table 1. Summary of clinical periodontal studies of azithromycin used as an adjunct to periodontal therapy

Clinical study	Study type/ no. of subjects/ age/time	Periodontal diagnosis/ smoking	AZM regimen/ control	Summary	Comments
Smith *et al.* (75)	RCT 23/21 (control) Median age 42.7 years 22 wk	Moderate periodontitis Smoking status not reported	AZM: 500 mg × 3 d after SRP Control: SRP + placebo	Pockets with depths initially 4–5 mm or 6–9 mm showed significantly more depth reduction in patients on AZM, at weeks 6, 10 and 22, even when plaque control was poor. No differences in plaque index, bleeding on probing, and calculus index	Short study, uncertain whether controlled for smoking
Fujii *et al.* (76)	Case–control 5/6 control Age: 16–34 years 4.7 mo/ 11.2 mo control	Aggressive periodontitis Smoking status not reported	AZM: 500 mg × 3 d after SRP 2 mo Control: SRP only	Study was terminated when gingival in dex = 1. AZM reduced time of initial treatment and was more effective than SRP in treating aggressive periodontitis	Few subjects. Length of study 2.4 times longer in control group vs. test group; unknown smoking status
Mascarenhas *et al.* (77)	Case–control 15/15 (control) Age: 45.3–47 years 6 mo	Moderate periodontitis Heavy smokers	AZM: 2 × 250 mg day 1; 250 mg × 4 d after SRP Control: SRP; no placebo	AZM group showed enhanced reductions in pocket depth and gains in CAL at moderate (4–6 mm) and deep (> 6 mm) sites. Favourable changes in microflora in AZM group	Beneficial effect of AZM shown in smokers
Gomi *et al.* (11)	Case–control 17/17 control Median age: 48.2 years 25 wk	Severe chronic periodontitis. Smoking status not reported	AZM: 500 mg × 3 d. Full-mouth debridement 3 d after AZM Control: SRP was completed in 5 wk	Significantly greater reductions in mean pocket depth, number of bleeding on probing sites and GCF levels at 13 and 25 wk. Not possible to compare test and control as they had different periodontal treatments over different time periods	Short study, not properly controlled
Dastoor *et al.* (78)	RCT 15/15 control Median age: 49.4 years 6 mo	Moderate to advanced chronic periodontitis Heavy smokers	All patients had periodontal surgery with osseous contouring after initial SRP; all subjects were given 600 mg of ibuprofen after surgery. AZM: 500 mg x 3 d Placebo control: AZM and placebo given after surgery	Sustained reduction in periodontal pathogens in AZM group. No significant difference was found for bleeding on probing, pocket depths or clinical attachment gain between both groups	Only study of effects of AZM after periodontal surgery; cannot compare with other studies
Haffajee *et al.* (6)	Case–control AZM 25/ MET 24/ SDD 20/ control 23 Age: 43–47 years 12 mo	Chronic periodontitis (mean pocket depth 3.11 mm); nine subjects were smokers, they were unevenly distributed among groups	AZM: 500 mg × 3 d; MET: 250 mg × 14 d; SDD: 20 mg × 3 mo. All medications were started at the first of four SRP visits. Control: SRP only (no placebo)	Significantly greater pocket-depth reduction and greater clinical attachment gain in sites with pockets > 6 mm initially for AZM and MET groups for up to 12 mo. AZM reduced levels of *Tannerella forsythia* for up to 12 mo, whereas metronidazole and doxycycline did not	Study not controlled for smoking. Severity/ diagnosis of periodontitis at baseline difficult to assess. Study was not placebo controlled

Table 1. (Continued)

Clinical study	Study type/ no. of subjects/ age/time	Periodontal diagnosis/ smoking	AZM regimen/ control	Summary	Comments
Pradeep *et al.* (79)	RCT 40/40 control Age: 25–50 years 12 wk	Chronic periodontitis Nonsmokers	0.2 mL of 0.5% controlled-release AZM gel injected into periodontal pocket after SRP Control: SRP only	Significantly greater pocket depth reductions, clinical attachment gains with AZM gel. AZM gel resulted in a shift towards healthier microflora with decreased spirochetes and motile rods, and increased numbers of cocci, straight rods, filamentous and fusiform bacteria noted in the test group for up to 3 mo	AZM gel was injected once into periodontal pockets; this study cannot be compared with the others in this table which used systemically administered azithromycin
Haas *et al.* (80)	RCT 12/12 control Age: 13–26 yrs 12 mo	Aggressive periodontitis Three smokers AZM; two smokers control	AZM: 500 mg × 3 d at start of SRP Control: SRP + placebo	Significantly greater pocket-depth reductions and clinical attachment gains in AZM group for up to 12 mo. No differences in plaque index, bleeding on probing and supragingival calculus	Five smokers out of 24 subjects. Study not properly controlled for smoking status
Yashima *et al.* (81)	Case–control 10 FM-SRP 10 SRP 10 Control Median age: 51 years 12 mo	Chronic periodontitis Nonsmokers	AZM: 500 mg × 3 d before periodontal therapy FM-SRP: three visits in 7 d Control: SRP, six visits over 6 wk, no placebo	Significantly greater pocket-depth reductions, clinical attachment gain, number of bleeding on probing sites, gingival index in AZM group for up to 12 mo. Not possible to compare test and control as they had different periodontal treatments over different time periods	Different treatments for test and control groups make results difficult to compare
Oteo *et al.* (82)	RCT 15/13 control Median age: 46.9 years 6 mo	Moderate *P. gingivalis*-associated periodontitis Eight smokers test, six control	AZM 500 mg × 3 d after SRP (two visits in 7 d) Control SRP (two visits in 7 d) + placebo	Significantly greater pocket-depth reductions, clinical attachment gains, decreased *A. actinomycetemcomitans, P. intermedia, T. forsythia* and *P. micra* after 1, 3 and 6 mo in AZM group. No differences in plaque index and number of bleeding on probing sites	Small number of subjects further compromised by including both smokers and nonsmokers

AZM, azithromycin; CAL, clinical attachment loss; FM-SRP, full mouth SRP single visit; GCF, gingival crevicular fluid; MET, metronidazole; RCT, randomized controlled trial; SDD, subantimicrobial doxycycline; SRP, scaling and root planing.

overgrowth and significantly increased the phagocytic activity of gingival fibroblasts in culture.

An *in vitro* study investigated the effects of azithromycin on human gingival fibroblasts cultured either from healthy gingival tissues or from gingival tissues harvested from people with cyclosporine A-induced gingival overgrowth (65). Azithromycin inhibited cyclosporine A-induced proliferation of the fibroblasts and activated MMP2 in both healthy and gingival overgrowth fibroblasts. Furthermore, azithromycin inhibited cyclosporine A-induced accumulation of collagen. Azithromycin was thought to improve the symptoms of cyclosporine A-induced gingival overgrowth by blocking the ability of cyclosporine A to induce cell proliferation and collagen production, and by activating MMP2 rather than MMP1 in cyclosporine A-affected fibroblasts.

It is perplexing that, in spite of existing evidence about azithromycin and drug-related gingival overgrowth,

Table 2. Summary of clinical studies of the effects of azithromycin on cyclosporine A-induced gingival overgrowth

Clinical study	Study type/no. subjects/age/time	AZM regimen/ control	Summary	Comments
Gomez *et al.* (63)	Noncontrolled trial 31 Median age: 48 years Up to 6 mo	AZM 500 mg × 3 d No periodontal treatment	GO improved in all subjects; bleeding on brushing stopped in all but one subject after 7 d. Cyclosporine A, creatinine and ALT levels were unaltered. AZM was effective in subjects taking calcium-channel blockers as well as cyclosporine A	First trial of AZM and first report of efficacy in reducing GO related to both cyclosporine A and calcium-channel blockers
Puig *et al.* (83)	Noncontrolled trial 15 Age not specified 3 mo	AZM 500 mg day 1, 250 mg next 4 d No periodontal treatment	Less gingival bleeding 2–7 d after AZM; GO regressed over 3 mo in all patients. The authors speculated that the gingival response resulted from the antibacterial action of AZM and down-regulated responsiveness of fibroblasts to cyclosporine A stimulation	
Jucgla *et al.* (84)	Noncontrolled trial 15 Age range: 23-61 years Up to 6 mo	AZM 500 mg day 1, 250 mg next 4 d Professional tooth cleaning in 10 subjects who had 50% reduction in GO at 3 mo	At 3 mo, there were five complete responders, seven partial responders and three nonresponders. At this time-point 10 patients with 50% reduction in GO had tooth cleaning. At 6 mo there was complete resolution of GO in seven patients: six had partial response and one showed no response	Impressive clinical reduction in GO at 6 mo, shown in clinical photographs of one subject
Nash and Zaltzman (85)	Randomized crossover trial 17 Median age 42.2 years 12 wk	AZM 500 mg day 1, 250 mg next 4 d All patients took a placebo for 5 d, 2-wk washout period after AZM No periodontal treatment	Significant reduction in sulcus depth and decreased length of interdental papillae. Patients reported less gingival bleeding. One patient had reduction in palatal tissue overgrowth. The authors concluded that AZM should be considered as a first line of therapy in managing cyclosporine A GO	Short study, 2-week washout probably too short for AZM, but placebo was the alternative. Unclear why crossover study design was chosen
Wirnsberger *et al.* (86)	Controlled trial Group A: 9 Group B: 15 Median age: 43.6 years 12 mo	AZM: 500 mg × 3 d Group A: no gingivectomy prior to study Group B: had gingivectomy prior to study	The 15 patients in Group B previously had 27 gingivectomies which had not significantly suppressed GO. Gingival bleeding stopped within the first week and a significant improvement in GO occurred 1 mo after AZM. At 12 mo, 17 subjects had no gingival overgrowth and six had slight overgrowth. Subjects in Group B (previous gingivectomies) had less reduction of GO than Group A. The authors attributed the results to the anti-inflammatory effect of AZM and its concentration in fibroblasts leading to interactions "with endogenous growth factors and inflammatory mediators."	Confusing presentation of results, no discussion about role of prior gingivectomy relative to AZM treatment
Citterio *et al.* (87)	Controlled trial 29/6 control Age not specified 17 ± 4 mo	AZM: 500 mg day 1, 250 mg next 4 d No periodontal treatment Control: no placebo	After 1 mo, GO was successfully treated in 86% of patients, with bleeding eliminated in all but one. After 17 mo, 69% had no overgrowth and 83% no gingival bleeding. AZM was found to be highly effective in treating cyclosporine A GO. A control group of six subjects had no change in degree of overgrowth or bleeding tendency. No change in blood levels of cyclosporine A occurred after AZM treatment	AZM did not alter blood levels of cyclosporine A

Table 2. (Continued)

Clinical study	Study type/no. subjects/age/time	AZM regimen/ control	Summary	Comments
Nafar *et al.* (88)	RCT Group 1: 9 Group 2: 9 Group 3: 4 Group 4: 3 Median age: 40 years 6 wk	All subjects had 2 g of amoxicillin and SRP before entering the study. Group 1: AZM for 5 d (dose unspecified) Group 2: placebo tablet Group 3: azithromycin gel (25%) for 1 week Group 4: placebo gel	Gingival bleeding improved significantly after 2 wk in the AZM group, but otherwise no differences were noted between the groups	Low subject numbers, confusing design, confounder for all subjects is 2 g dose of amoxicillin at start of study
Mesa *et al.* (89)	RCT AZM: 14 MET: 13 Placebo: 13 Median age: 41.4 years 30 d	AZM: 500 mg twice daily for 7 d MET: 250 mg three times daily for 7 d Placebo: no periodontal treatment	GO was reduced in 62% of the subjects who had taken AZM and in 54% of subjects given MET; in no patients had the overgrowth completely resolved, but the study was short	Very short study. There is a single report of the resolution of cyclosporine A GO after the administration of MET (62)
Tokgoz *et al.* (90)	Noncontrolled 18 Median age: 35 years 6 mo	AZM 500 mg × 3 d No periodontal treatment	GO was reduced in all subjects, with the degree of improvement being more significant between days 0–7 and 7–30 than at other time-periods up to 180 d. Histologically there was a significant reduction in chronic inflammation in the gingival tissues between days 0 and 30; this correlated with the reduction in GO	
Chand *et al.* (91)	Case–control study AZM: 11 MET: 14 Median age: 17.5 years 6 mo	AZM: 10 mg/kg for 1 d with 500 mg maximum, then 5 mg/kg for 4 d with 250 mg maximum per day. MET: 45 mg/kg divided into three doses for 7 d No periodontal treatment	AZM was more effective in reducing GO than MET, resulting in its sustained reduction across all time intervals. Patients who had taken AZM reported decreased gingival bleeding	
Argani *et al.* (92)	Controlled trial AZM toothpaste: 10 Control toothpaste: 10 Median age: 36.5 years 3 mo	All subjects had SRP at least 4 wk prior to the study. AZM toothpaste (85 mg/g) used twice daily for 4 wk. Placebo: toothpaste without AZM	No adverse reactions to the AZM-containing toothpaste. Both GO and bleeding was significantly reduced in the group using the AZM-containing toothpaste after 3 mo	Topical, rather than systemic, application of AZM
Ramalho *et al.* (93)	Controlled trial 10/10 control Median age: 32.1 years 30 d	All subjects had oral hygiene instruction. AZM: 500 mg × 3 d No placebo tablet	AZM plus oral hygiene (but not oral hygiene alone) resulted in a striking reduction in GO after 30 d	Very short study

ALT, alanine transaminase; AZM, azithromycin; GO, gingival overgrowth; MET, metronidazole; RCT, randomized controlled trial; SRP, scaling and root planing.

this property of azithromycin remains largely unknown in periodontal theory and clinical practice. Definitive clinical studies are required to determine whether azithromycin alone, or as an adjunct to periodontal therapy, can enhance the management of gingival overgrowth related to cyclosporine A, calcium-channel blockers and phenytoin.

Discussion

Antibiotics have a long history of being used as adjuncts to the therapy of chronic and aggressive periodontitis, with variable outcomes (66,67). With the rising incidence of bacteria resistant to many antibiotics, there is a justified concern about their profligate use in both humans and animals. There is a clear link between increased use of antibiotics in a population and the occurrence of resistant bacteria (35). These issues have been covered relative to the use of antibiotics in periodontal therapy (6,36,67).

The most extensively studied periodontal antibiotic regimen is the combination of amoxicillin (375 mg) and metronidazole (500 mg), both taken

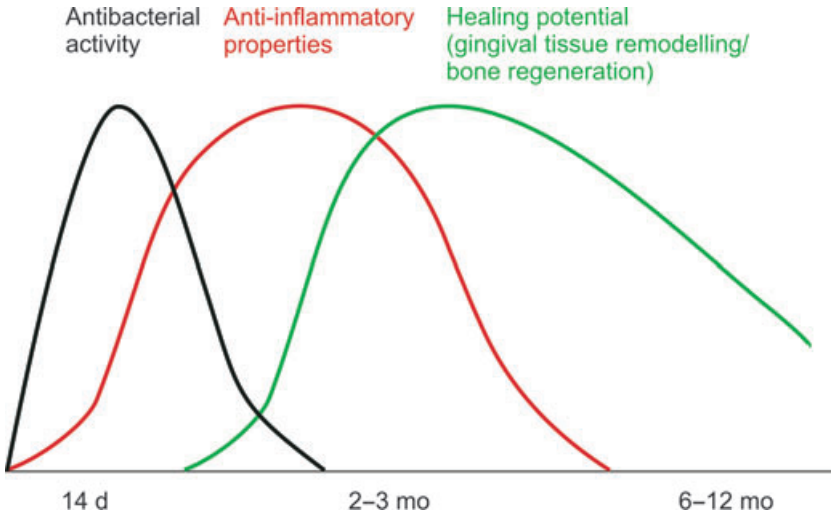

Fig. 1. Temporal model of the three overlapping phases of periodontal activity after a single course of azithromycin in the treatment of periodontitis. The antibacterial phase is the drug's most studied and understood activity; it is known to be active against periodontopathogens for at least 14 d. The anti-inflammatory properties of azithromycin and its concentration in neutrophils, macrophages and fibroblasts are well documented, but it is not known how long these effects persist after a single course and what intracellular concentration of the drug is required to exert its immunomodulatory effects. Finally, there is evidence of the ability of azithromycin to cause regression of cyclosporine A-induced gingival overgrowth over time as well as case reports of periodontal healing and bone regeneration for up to 12 mo after a single course of azithromycin.

three times a day for 7 d (67), in conjunction with periodontal therapy. To date, no comparative trial has shown the superiority of any other antibiotic regimen over amoxicillin/metronidazole in any clinically or microbiologically defined variant of periodontal disease (67). However, a recent study found that mechanical therapy with topical chlorhexidine was as effective as the same treatment with adjunctive amoxicillin (500 mg) and metronidazole (250 mg) after 6 mo and that any early effects were short lived (68,69).

Relative to azithromycin (1.5 g of antibiotic), the regimen used by Mombelli *et al.* (67) loads patients with a significantly greater antibiotic burden (18.4 g of antibiotic) over 7 d rather than 3 d, thus increasing the potential risk of development of resistant bacterial species. Short-course antibiotics may reduce the development of resistant bacterial species (70). Side effects are very common with the amoxicillin/metronidazole regimen (42%; 71) and compliance is therefore compromised. Amoxicillin is not noted for immunomodulatory or anti-inflammatory properties that are distinct from its antibiotic effects. Metronidazole suppressed the production of proinflammatory cytokines by human periodontal ligament cells (72), but there is sparse evidence of specific immunomodulatory action.

First, azithromycin, when given as a single course of three, 500-mg tablets, could well play a triple role in the treatment of moderate to advanced periodontitis. Its effectiveness against gram-negative bacteria, the ability to penetrate biofilm, and a long antibacterial half-life and short course make it an attractive antibiotic option as an adjunct to the management of advanced inflammatory periodontitis. Second, the uptake of azithromycin by neutrophils and macrophages allows it to target and be concentrated at sites of periodontal inflammation and exert its anti-inflammatory properties. 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 (49). Third, 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 (to M2), thus increasing the production of anti-inflammatory cytokines (49) and favouring healing. If an agent was being specifically designed to treat inflammatory forms of periodontitis, it would have these distinct and temporally overlapping activities (Fig. 1). 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 immunemodulating action (53).

Long after the tissue concentrations of azithromycin fall below antibacterial levels, prolonged retention of biological (immunomodulatory) activity in long-lived cells of the periodontium, such as macrophages and fibroblasts (44), and perhaps periodontal stem cells, has the potential to exert the drug's anti-inflammatory and healing properties. The resolution of cyclosporine-induced gingival overgrowth over time is a pointer to the drug's long-term host-modulatory/healing properties. The property of azithromycin to reduce drug-related gingival overgrowth is generally unknown in the periodontal literature as it has not translated to clinical

practice, texts or significant periodontal research.

Azithromycin may prove to be a more effective host modulator in the treatment of periodontitis than low-dose doxycycline [which requires patients to take two tablets a day for 3 mo or longer and is accompanied by side effects (73)]. It may be possible to develop a subantimicrobial azithromycin dosing regimen that avoids potential bacterial resistance. Of interest, the development of a nonantibiotic macrolide derived from azithromycin has recently been reported; it had immunomodulatory effects in animal models of inflammatory bowel diseases and arthritis (74).

Conclusion

Some evidence exists to support the use of azithromycin in the treatment of periodontal diseases. Its potent activity against periodontal pathogens, short treatment regimen ensuring good patient compliance, low incidence of side effects, persisting antibiotic effects and even longer lasting immunomodulatory effects after a single course, are all favourable characteristics. If future periodontal research confirms these properties, it could become a unique agent to enhance the treatment of advanced or resistant forms of inflammatory periodontitis and severe gingival overgrowth by antibacterial activity and host modulation.

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