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REVIEW

The place of azithromycin in the treatment of periodontal disease

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Abstract

The occurrence of periodontal disease in the population is on the increase and the therapeutic means combine conventional mechanic treatment with antibiotics and guided tissue regeneration and guided osseous regeneration. The most frequently used antibiotics are penicillins and tetracyclines and their derivatives. Unfortunately, the occurrence of allergic reactions especially to penicillins, as well as the steadily growing bacterial resistance require the choice of new alternative antibiotics active on the mainly Gram-negative anaerobic strains. Azithromycin is a new generation macrolide mainly used in respiratory tract infections and in urogenital infections, but it has pharmacokinetic properties such as tissular penetration and it is readily taken up by neutrophils, macrophages and fibroblasts and anti-inflammatory effects which recommend it for treatment of periodontal disease. Computerised research of PubMed-NCBI resources, EBSCO Dentistry & Oral Sciences Sources, EBSCO Discovery Service and Ovid MEDLINE(R) resources has shown that there are relatively few clinical and microbiological studies on azithromycin as compared to the number of studies on the other antibiotics used in the treatment of periodontal disease. However, they are relevant for the efficacy of including azithromycin in periodontal treatment.

Keywords: periodontal disease, azithromycin, antibiotics, periodontal bacterial species, periodontal treatment.

1. Introduction

Periodontal disease is an inflammatory disease produced as the result of the microbial aggression. Although microbial flora is permanently present in the oral cavity and in the gingival area, the beginning of periodontal disease is defined by the existence of periodontal pathogens and susceptibility of host organism. Gram-negative bacteria known as periodontal pathogens are present in small numbers at patients without periodontal disease. Their presence does not necessarily imply the development of periodontitis (G. LOOZEN & al. [1]). Unlike other diseases, the periodontal disease seems to be generated by the overgrowth of commensal organisms rather than by exogen pathogens (A. CEKICI & al. [2]). Tissular destruction in periodontal disease is due partly to bacterial virulence factors, and partly to the action of elements of (over)activated immune system, such as pro-inflammatory cytokins and prostaglandins. This is why periodontal disease treatment targets both pathogen flora and reconstruction of normal periodontal structure. Therefore, antimicrobial agents play an important part in periodontal treatment especially at advanced stages of the disease, at the rapidly progressing ones or in case of an immune system altered by associated diseases (diabetes, liver disesase, etc.). The main classes of antibiotics/ kemotherapic antibiotics are: beta-lactamins (penicillin and its derivatives), tetracycline, macrolides, nitroimidazole derivatives, lincosamides, fluoroquino-

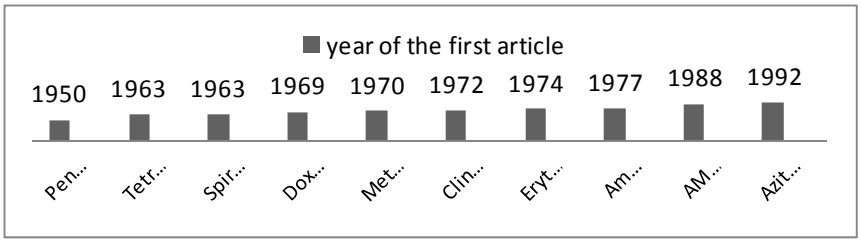
lones, aminoglycosides. Most of these are antibiotics with bactericidal effects, except for tetracycline and macrolides, which are bacteriostatic. Tetracyclines have additional characteristics that give them a special place in periodontal disease treatment: they concentrate in the subgingival area, they inhibit collagenase, they interfere with restorative and regenerative processes of the periodontium. (A.S. DUMITRIU [3]). The disadvantages of systemic antibiotics are their side effects, interaction with other medicines and the bacterial resistance they can develop. Therefore, research focuses on finding new antibiotics with efficiency in the treatment of periodontal pathogen flora and with good tissular penetration.

2. Material and Methods

An online search for the pharmacokinetic proprieties of azithromycin and its related with periodontal disease using PubMed-NCBI resources, EBSCO Dentistry&Oral Sciences Sources, EBSCO Discovery Service and Ovid MEDLINE(R) resources. All articles published were searched based on key words: „azithromycin periodontitis", „azithromycin pharmacokinetics", „azithromycin resistance", „azythromycin risk", „antibiotics periodontitis". A hand search of the following journals was applied: *Journal of Clinical Periodontology*, *Journal of Periodontology*, *Journal of Periodontal Research* and *Periodontology 2000*. The reviewers evaluated the titles and abstracts for selection and full-papers were evaluated for inclusion.

3. Results and Discussions

According to the PubMed-NCBI, the first article about the usage of antibiotics in the periodontal disease dating from 1950, "*Penicillin and streptomycin in the treatment of periodontitis and paradentitis"* was published by E. VAN DEN MOLEN [4]. It was followed by *Aureomycin therapy of marginal periodontitis,* published by S.A. MARTENSEN [5] in 1953. In 1963 J.C.A SILVEIRA [6] writes *Spiramycin as auxiliary drug in the treatment of inflammatory periodontal diseases,* the first article to make reference to the usage of a macrolide, spiramycin, in periodontal treatment (fig. 1).



(AMOX+ ac. clav = amoxicillin and acid clavulanic)

Fig.1. The year of the first publication related to used of an antibiotics in periodontal disease.

Macrolides, especially erythromycin, have been less used in periodontal pathology due to the reduced action on periodontal pathogens. They are effective against gram-positive bacteria and spirochetes, but not against most Gram-negative organisms (G.M.S. SOARES & al. [7]). They are recommended to patients who are allergic to penicillin and its derivatives. The macrolide's mechanism of action against susceptible microorgamisms is to inhibit protein synthesis at the ribosomal level by binding to the 50S subunit like tetracyclines and lincosamides (H.T. DUMITRIU [8], T.P. DUMITRESCU & al. [9]).

Azithromycin is a second generation macrolide, a member of a subclass called azalide, which was first synthesized in 1980 (R. HIRSCH & al. [10], M.J. PARNHAM & al. [11]). It is a semi-synthetic derivative of erythromycin with a 15-membered aglycone ring possessing

an additional nitrogen which leads to the increase of the molecule basicity and improves the drug activity against Gram-negative bacteria (G.P. DINOS & al. [12]).

It has a long half-life and an excellent periodontal tissue penetrability into both normal and pathological periodontal tissues, where it can reach higher levels than in non-infected similar tissues or than in plasma. (G. FOULDS & al. [13], Academy Report [14], R.P. GLADUE & al [15], M.J. PARNHAM & al. [11]). In contrast to other macrolide agents, azithromycin distributes and accumulates extensively in a number of cells such as epithelial cells, hepatocytes, peripheral blood mononuclear cells, polymorphonuclear leukocytes and fibroblasts, and also in tubules of kidneys and in spleen (PARNHAM & al. [11], T.P. DUMITRESCU &al. [9], R. P. GLADUE & M. E. SNIDER [16], M. MATIJASIC & al. [17]). Due to its basic character azithromicyn is stored in lysosomes, especially in white blood cells, with little or no accumulation in erythrocytes (T.P. DUMITRESCU & al. [9]).

Fibroblasts are a key element in periodontal regeneration processes. Fibroblasts have a wide distribution and are most numerous in periodontium structure with a role in the synthesis and degradation of collagen, a basic substance in the structure of periodontal ligament, and also in the synthesis of proteoglycans and glycoproteins in the chorion structure. Thus, they are considered a potential reservoir for azithromycin in tissue, slowly releasing or passing it to nearby phagocytes for transport to the site of infection (PARNHAM & al. [11], R. P. GLADUE & M. E. SNIDER [16]). On the other hand, by secreting and binding fibronectine which can fix microorganisms they may also contribute to microbial virulence. Fibroblasts may also serve an immune regulatory role by responding to endotoxin-induced monokines to produce factors which can increase the function and recruitment of phagocytes (R. P. GLADUE & M. E. SNIDER [16]).

The studies showed the azithromycin concentration in the tissues lining the periodontal pockets and its detectability in inflamed periodontal tissues is possible ≥ 14 days after 500 mg /q.d / 3 days systemic administration and decreases from 50% after 7 days to 20% after 14 days (K. GOMI & al. [17]). Furthermore, a study made by P.C. LAI & J. D. WALTERS [18] in 2013 demonstrates that human oral epithelial cell lines possess an active transport system that concentrates azithromycin and facilitates the killing of *A. actinomycetemcomitans* inside infected gingival epithelium.

Azithromicyn has also anti-inflammatory effects by inhibiting nuclear factor kappa B (NF-$_K$B) in oral epithelium, by reducing levels of pro-inflammatory cytokines in gingival crevicular fluid (P.C. LAI & J. D. WALTERS [18]), inhibit IL-6 and PGE_2 (M. MATIJASIC & al. [19] and inhibits LPS-induced IL-8 production in an oral epithelial cell line (Y. MATSUMURA & al. [20]).

Azithromycin is usually indicated for adult and pediatric respiratory tract infections, urogenital infection, including sexually transmitted diseases, dermal and other bacterial infections, and also has beneficial effects in chronic inflammatory diseases due to their additional anti-inflammatory and immunosuppressive properties (M.J. PARNHAM & al. [11] P. MATZNELLER & al. [21]). But in the latest years the studies have focused on the efficacy of azithromycin in periodontal disease.

The search for “azithromycin periodontitis” in the PubMed data base reported 71 articles (one third of the articles on macrolides in periodontitis), 61 studies on humans; 14 articles have been excluded since not directly related to periodontitis or not written in English. Twenty-three of the remaining articles were on clinical trials, 27 on microbiology and pharmacokinetics, 9 reviews and 2 case reports. At first sight the number of articles on azithromycin is significantly small as compared to 990 articles on “tetracycline periodontitis”, 595 on „metronidazole periodontitis”, 381 on „doxycycline periodontitis”, 335 on „amoxi-

cillin periodontitis", 138 on „clindamycin periodontitis", and 103 on „amoxicillin clavulanic acid periodontitis". One explanation could be that azithromycin is a new antibiotic and studies cover a short period of time (fig. 1). Doing the search again over the interval 1992 – 2014 figures are still unfavourable to azithromycin (71/755/490/355/307/107/95 respectively), tetracycline and metronidazole still being the most studied.

The first article about azithromycin related to periodontal disease was issued in 1992 and it was a microbiological study which tested in vitro susceptibility of *Actinobacillus actinomycetemcomitans* to azithromycin compared to erythromycin. The conclusion of the study was that all 82 isolated strains were inhibited at 2.0 μg/ml azithromycin, the best in vitro activity was against the serotype a of *A. actinomycetemcomitans*, at 1.0 μg/ml, the lowest MICs were recorded by serotype b strains, while erythromycin showed poor in vitro activity against *A. actinomycetemcomitans* (R. PAJUKANTA & al. [22]). The same author published next year another microbiological study about in vitro antimicrobial susceptibility of *Porphyromonas gingivalis* to azithromycin and concluded that azithromycin was highly effective against *P. gingivalis*, all 82 strains were inhibited at 1.0 μg /ml of azithromycin or less, the MICs 0.25 μg/ml for 50% and 0.5 μg /ml for 90% and indicated azithromycin for refractory periodontitis (R. PAJUKANTA [23]). The results are still sustained by the study published in 2011 by A. JAPONI & al. [24] who tested 50 strains of *P. gingivalis* and revealed also a sensitivity of 100% of *P. gingivalis* strains to azithromycin and also to doxycycline and amoxicillin/clavulanic acid.

The in vitro results of a comparative study of macrolides activity published by J.D. WILLIAMS & al. [25] in 1992 suggest that azithromycin and clarithromycin may be valuable in the treatment of dental sepsis and the prophylaxis of endocarditis. For the authors azithromycin was, in general, the most active antibiotic tested against the Gram-negative anaerobes: *Fusobacterium spp*., *Bacteroides spp*., *Wolinella spp*., *Actinobacillus actinomycetemcomitans*, *Selenomonas spp*. and *Mitsuokella multiacida*, including those isolates which were insusceptible to erythromycin.

Despite this, in 2002 a study made by Muller on 60 isolated strains of *A. actinomycetemcomitans* showed a moderate susceptibility for azithromycin (MIC90 of 3*m*g/mL) besides good susceptibilities for ampicillin/sulbactam and doxycycline (MIC90 of 0.75*m*g/mL and 1*m*g/mL, respectively) and resistance of the most strains to metronidazole and roxithromycin (H.P. MULLER & al. [26]).

Some *Enterococcus, Staphylococcus, Eikenella corrodens, Fusobacterium nucleatum* and *Peptostreptococcus* strains may also exhibit resistance to azithromycin according to the American Academy Report [14].

Fusobacterium nucleatum is one of the most studied bacteria implicated in periodontal disease and has an important role in biofilm colonization by *P. gingivalis*, *P. intermedia, Tannerella forsythia* but it is also one of the most common oral species isolated from many extra-oral infections, including blood, brain, lung, liver, joint, abdominal, obstetrical and gynecological infections and abscesses (B. SIGNAT & al. [27]). Its products are involved in reactivation of latent HIV infection (K. NAGAOKA & al. [28]) and in pregnancy complication such as delivery of premature low weight infants (B. SIGNAT & al. [27]). *F. nucleatum* was detected in association with species such as *Tannerella forsythia, Campylobacter rectus* in periodontal sites that had the most attachment loss and the deepest pockets and in sites refractory to treatment (B. SIGNAT & al. [27]). In a study made by F.S. ALECU & al. [29], the most frequent bacteria isolated from periodontal pockets belonged to *Prevotella*, followed by *Fusobacterium*, *Bacteroides* and *Porphyromonas*, and a few isolates of *Peptostreptococcus*. Sensibility of isolates was 83.3% at azithromycin compared with 100% at ampicillin/sulbactam, 91.7 % at doxycycline and erithromicyne and 66.6 % at

tetracycline. The resistant isolates belonging to *Peptostreptococci* and *Fusobacteria* and shown resistance to tetracycline and azithromycin.

In most clinical studies azithromycin is administered systemically, only in 5 studies placebo-controlled clinical trials (1 for smokers and one with type 2 diabetes) all made by Indian researchers used local delivery of prepared 0,5% azithromycin gel in association with scaling and root planing and results showed a significant improvement in clinical parameters such as gingival index, probing pocket depth, clinical attachment level, bleeding index and plaque index compared with scaling and root planning alone (A.R. PRADEEP & al. [30], A.R. PRADEEP & al. [31], M.P. VENKATESH & al. [32], E. AGARWAL & al. [33], P. TYAGI& al. [34]). But the products were extemporaneously prepared as it did not exist as trade mark product.

In most studies azithromycin was sistemically administered 500 mg per day for 3 days except for Sampaio's study who administered it for 5 days (E. SAMPAIO & al. [35]) and Mascharenas who administered 250 mg/day on the first day, followed by 250 mg x 4 days (P. MASCARENHAS & al. [36]).

The position of the American Academy of Periodontology in 2004 was to recommend the common Azithromycin therapies in the treatment of periodontitis is 500 mg/q.d./4-7 days and antibiotic regimens for adult patients with acute periodontal abscesses is Azithromycin loading dose of 1.0 g on day 1, followed by 500 mg/q.d. for days 2 and 3 (ACADEMY REPORT [14]).

Although it has been shown that bacterial species residing in biofilms are much more resistant to antibiotics than the same species in a planktonic state, the biofilm acting like a protective barrier for bacteria, the macrolides have a high permeability into biofilm, inhibit polysaccharide production and dissolve the biofilm (A.D. HAFFAJEE & al. [37], P.L. WANG [38]). The study of H. MAEZONO & al. [39] publised in 2011 demonstrated the efficacy of azithromycin at subinhibitory concentrations and it's capacity to inhibiting *P. gingivalis* biofilm even at a sub-MIC level comparativelly with erytromycin.

Thus, clinical studies are divided as regards the moment of azithromycin administration: in some studies it was administered after scaling and root planing (B. HAN & al. [40], E. SAMPAIO & al. [35], A. OTEO & al. [41], S.F. DASTOOR & al. [42], S.R. SMITH & al. [43]), in others at the same time as scaling and root planning (A.N. HAAS & al. [44], G. EMINGIL & al. [45], A.N. HAAS & al. [46], A.N. HAAS & al. [47], P. MASCARENHAS & al. [36]), 1 study before scaling and root planning (K. GOMI & al. [17]). In one study azithromycin and debridement were used in the retreatment of the patients with residual pockets (≥6 mm) at 6 months after surgery or scaling and root planning (S.R. MIREMADI & al. [49]). In 6 studies a microbiological analysis was also made (A.N. HAAS & al. [46], B. HAN & al. [40], E. SAMPAIO & al. [35], A. OTEO & al. [41], S.F. DASTOOR & al. [42], P. MASCARENHAS & al. [36]). Two studies in which azithromycin was administered after scaling and root planning also used a different medication: a 0.12% chlorhexidine rinse twice a day for 2 weeks plus 600 mg ibuprofen every 6 hours for 2 days after apically positioned flap with osseous recontouring (S.F. DASTOOR & al. [42]) and paracetamol 500 mg for group with open flap debridment (S.R. MIREMADI & al. [49]). Six studies used azithromycin in the treatment of aggresive periodontitis, 4 were clinical trials (A.N. HAAS & al. [44], G. EMINGIL & al. [45], A.N. HAAS & al. [46], A.N. HAAS & al. [47]) and 2 case reports (R. HIRSCH [50], P.L. WANG [38]).

As regards the results of clinical and microbiological studies, figures are slightly in favour of associating azithromycin in periodontal treatment with clear benefits in deeper periodontal pockets treatment and wound healing. Subjects administering azithromycin showed a higher percentage of teeth with attachment gain ≥1mm (A.N. HAAS & al. [47]).

The microbiological study made by Oteo et al. in 2010 showed the reductions in the

frequency of detection of *P. gingivalis*, *A. actinomycetemcomitans* and *T. forsythia* after the adjunctive use of systemic azithromycin in the periodontal treatment (A. OTEO & al. [41]), for *T. forsythia* the same notice was confirmed also by Haffajee in 2008, but with few significant differences in the subgingival microbiota at 12 months among treatment group (A.D. HAFFAJEE & al. [37]). Haffajee compared the microbiological changes associate with azithromycin, doxycycline, metronidazole and scaling and root planning alone and the data indicated that subjects receiving systemically administered azithromycin or metronidazole had significant reductions in red and many orange complex species at 2 weeks.

Regarding the bacterial resitance to azithromycin Haffajee found that before therapy the percentage of species was about 22% in both the test and control samples (46 and 37% were resistant to metronidazole and 8 and 9% were resistant to doxycycline in the test and control samples, respectively), a large percentage of sites harbored strains of *V. parvula* that were resistant to azithromycin and doxycycline, both before and after antibiotic administration and a greater percentage of sites harbored azithromycin-resistant orange and red complex species compared to metronidazole. Instead of this, H. MAEZONO & al. [39] did not find any evidence of acquisition of resistance of *P. gingivalis* strains after exposure to sub-MICs of azithromycin or erytromycin. Moreover, species like *Fusobacterium spp*., *P. intermedia/nigrescens*, *P. gingivalis* and *A. actinomycetemcomitans* isolated from periodontal abcesses by A. JARAMILLO & al. [51] were not find resistant to azithromycin, despite some of this showed antimicrobial resistance to tetracycline, metronidazole and amoxicillin. A.J. VAN WINKELHOFF & al.[52] noticed differences in the susceptibility profiles of periodontal pathogens isolated from periodontitis patients in Spain and in the Netherlands and were found a number of *A. actinomycetemcomitans* strains resistant for azithromycin in Spain.

Regarding the sides effects after treatment with azithromycin the most common adverse reaction is diarrhea 5% (ACADEMY REPORT [14]), but among the reports of the clinical study the majority of authors reported no side effects, except Sampaio who reported 4 adverse reaction (2 cases with diarrhea, 1 with headache and dizziness, and 1 with metallic taste) (E. SAMPAIO & al. [35]), OTEO et al. [41] reported 1 case of diarrhea and A.D. HAFFAJEE & al. [48] reported 1 allergic reaction. Instead of this, US Food and Drug Administration warning in 2013 that azithromycin may increase the risc of sudden cardiac death especially to patients with arrhytmias and QT interval prolongation and the recommendation was to avoid polypharmacy with multiple QT-prolonging drug, a good monitoring of the patient until the treatment has been completed (J.R. GIUDICESSI & M.J. ACKERMAN [53]) or even prescribing other antibiotic medication for older patients (G.A. RAO & al [54]).

The Academy Report [14] in 2004 noticed that the interactions of erythromycins, azithromicin, clarithromycin with other medication lead to the increases of serum level of carbamazepine, cisapride, methylprednisolone, antihistamines like terfenadine, astemizole and probable of cyclosporin and oral anticoagulants and with risk of side effects. Azithromycin is categorized as a class B drug during pregnancy (A. ER [55]). Regarding interaction with ciclosporine there was a contradiction with HIRSCH & al. [10] who reviewed 12 articles about the effects of azithromycin on cyclosporine A-induced gingival overgrowth and found that azithromycin improved 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.

4. Conclusions

There is a small number of clinical and microbiological studies on the usage of azithromycin in the periodontal treatment and they targeted a small number of patients, they used

different methods and microbiological tests were made on few species of periodontal pathogens. Taking into account the pharmacokinetic properties of azithromycin with respect to both its antibacterial action, anti-inflammatory effect, and the reduced side-effects the use of azithromycin might provide possible benefits in periodontal therapy, but more clinical and microbiological studies are necessary.

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The authors declare that there is no conflict of interest in this study.

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