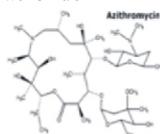


Azithromycin In Cyclosporine Induced Gum Overgrowth : An Amazing Fact!Gharote M A¹, Panchal H P², Anand A S³**ABSTRACT**

Ever since, its discovery, macrolides have amazed clinicians, not only for their agility, but also by their hidden mechanism of action. For instance, macrolides have been used as an immunomodulator! Isn't it amazing! Tacrolimus, a macrolide antibiotic is used in renal transplantation, as an immunomodulator. Here we have, yet another amazing fact about azithromycin.

Azithromycin :

Class : Macrolide

**Structure :****Mechanism of action (Macrolide) :**

1. It acts by binding to the 50S ribosomal subunit of susceptible microorganisms and, thus, interfering with microbial protein synthesis. Nucleic acid synthesis is not affected.
2. Decrease mucus secretion, both in vitro, and in vivo.
3. Macrolides may have an effect on airway chloride ion transport; this seems to be an acute and dose-related effect and is probably not of clinical relevance.
4. Macrolides are able to modulate mucin gene expression, most likely at the level of mitogen-activated protein kinase (MAPK) pathways or transcription factors, suggesting that this effect is part of a general modulation of immunity and inflammation.
5. Macrolides initially increase the production of pro-inflammatory cytokines but that this then rapidly normalizes via immunomodulation.
6. Macrolides have been shown to decrease stimulated expression of adhesion molecules, which may contribute to resolution of airway neutrophilic inflammation.
7. Macrolides may modulate the lipoygenase pathway of arachidonic acid metabolism.

8. Immunomodulatory effects of macrolides on transcription factors such as NF- κ B. Interactions between MAPK signaling and transcription factor expression and function explains most of the immunomodulatory effects observed.

Uses as antibiotic :

1. Respiratory, skin, soft tissue, sexually transmitted, H. pylori and atypical mycobacterial infections.
2. Alternative therapy for the prophylaxis of recurrent acute rheumatic fever and of infective endocarditis after dental treatment.

Uses as Immunomodulator :

1. Bronchitis, Asthma, cystic fibrosis, diffuse panbronchiolitis (DPB), chronic obstructive pulmonary disease (COPD) and bronchiectasis.
2. Post transplant bronchiolitis obliterans syndrome.
3. Tacrolimus is used in renal transplant.
4. Remission of cyclosporine A-induced gingival overgrowth (CIGO).

Ever since, its discovery, macrolides have amazed clinicians, not only for their agility, but also by their hidden mechanism of action. For instance, macrolides have been used as an immunomodulator! Isn't it amazing! Tacrolimus, a macrolide antibiotic is used in renal transplantation, as an immunomodulator. Here we have, yet another amazing update about azithromycin.

Erythromycin, the first macrolide antibiotic discovered, has been used since the early 1950s for the treatment of upper respiratory tract and skin and soft tissue infections caused by susceptible organisms, especially in the penicillin-allergic patient.¹

In order to, increase, pharmacodynamic profile, less frequent dosing and henceforth improving

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tolerability. In 1991 and 1992, the US Food and Drug Administration (FDA) approved two of these agents, clarithromycin and azithromycin, for clinical use.

Since their introduction, these advanced macrolides have been used extensively for the treatment of respiratory tract infections, sexually transmitted diseases, and infections caused by *Helicobacter* or *Mycobacterium avium* complex.

Azithromycin (AZI) (9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin) is formed by inserting a methyl-substituted nitrogen in place of the carbonyl group at the 9a position of the aglycone ring. The resulting dibasic 15-membered ring macrolide derivative is more appropriately referred to as an “azalide.”

This structural change makes the compound more stable in acid, significantly increases the serum half-life and tissue penetration, and results in increased activity against gram-negative organisms and decreased activity against some gram-positive organisms when compared with erythromycin.² Azithromycin is available as 250-, 500-, or 600-mg tablets; oral suspension (100/200 mg per 5 mL); and intravenous preparation (lyophilized 500 mg per 10 mL vial).¹

AZI is approved for use worldwide as a broad-spectrum antibiotic to treat a variety of community-acquired infections. It acts by binding to the 50S ribosomal subunit of susceptible organisms and interfering with protein synthesis.³ In addition, AZI and other macrolides are investigational products with anti-inflammatory/immunomodulatory actions that may be beneficial for those suffering from chronic pulmonary inflammatory syndromes, such as cystic fibrosis (CF), bronchiolitis obliterans syndrome (BOS), chronic obstructive pulmonary disease (COPD), asthma, and bronchiectasis.⁴

The nonantimicrobial properties of macrolides were suspected as far back as the 1960s, but their dramatic clinical effectiveness in treating diffuse panbronchiolitis (DPB) has served to extend their use to a number of chronic inflammatory diseases. The effects of macrolides in patients with chronic inflammatory airway disease appear to be

independent of antimicrobial properties. Immunomodulation, which differs from immunosuppression or anti-inflammation, is a nonlinear resetting of the inflammatory response by modifying or regulating one or more functions of the immune system.⁵

“Immunomodulation” is a term used to describe the downregulation of a hyperimmunity or hyperinflammation without impairing the normal immune or inflammatory response to defend against infection.⁵

Modulation of host defense by azithromycin and other macrolide antibiotics occurs through interaction with structural cells, such as epithelial or endothelial cells, smooth muscle cells or fibroblasts, as well as with leukocytes (macrophages, polymorphonuclear leukocytes or neutrophils, mononuclear leukocytes or monocytes, T cells and dendritic cells).⁵

Mechanism of Gingival hypertrophy.

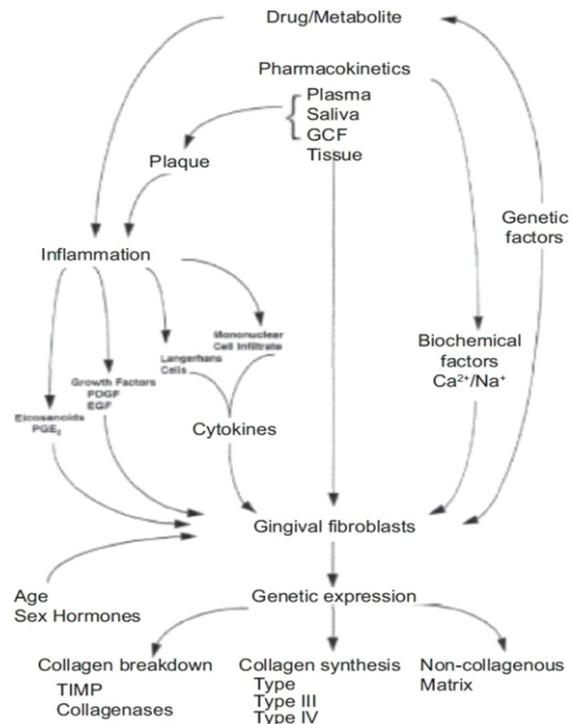


Fig. 1 : Schematic diagram to illustrate the potential multifactorial features and interactions involved in the pathogenesis of drug-induced gingival overgrowth⁶

Mechanism of action in cyclosporine induced gum overgrowth. (CIGO)

Gingival hyperplasia is a well-known complication of cyclosporine therapy, affecting 21% to 35% of renal transplant patients. Metronidazole, clarithromycin, and azithromycin, all azalid antimicrobial agents derived from the macrolide antibiotic erythromycin, have been used for treatment. Marked improvements in gingival hyperplasia have been recorded in particular with azithromycin.⁷

The first reported periodontal clinical study of azithromycin was performed in 1996. A study was conducted in which concentration of azithromycin in plasma, saliva, normal gingival and pathological tissues were assessed after administration of azithromycin 500 mg/day orally for three consecutive days. Azithromycin levels were measured by microbiological plate assay using *Micrococcus luteus* and it was found that azithromycin levels were higher than minimum inhibitory concentration in pathological tissues than those in normal gingiva suggesting that azithromycin represents a promising option in both adjunctive and prophylactic treatment of chronic periodontal disease.⁸

Azithromycin is carried efficiently into inflamed tissues by neutrophils through chemotaxis while maintaining its activity. 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, non-infective inflammatory responses.⁹

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)1b, IL-6, IL-8 and tumor necrosis factor (TNF)-a] and growth factors such as granulocyte-macrophage colony stimulating factor.

Azithromycin changes the macrophage phenotype, shifting macrophage polarization towards alternatively activated phenotype, thus suppressing the production of proinflammatory cytokines and increasing the production of anti-inflammatory cytokines.⁹

In a study of human gingival fibroblasts stimulated with lipo-polysaccharides (LPS) derived from *P. gingivalis* and treated with azithromycin showed a dose dependent increase in the production of IL-8, whereas azithromycin was found to reduce LPS induces IL-8 production in oral epithelial cells.⁹

Azithromycin is effective for the remission of cyclosporine A-induced gingival overgrowth (CIGO) in persons who have undergone renal transplant. Cyclosporin A-induced proliferation of renal transplant fibroblasts and normal fibroblasts is inhibited by azithromycin. Azithromycin elevated the reduced metalloproteinase (MMP)-1 and MMP-2 activities in cyclosporine A-treated renal transplant fibroblasts and normal fibroblasts. In cyclosporine A-treated renal transplant fibroblasts, azithromycin blocked the accumulation of total collagen in culture media and the increase in type I collagen mRNA level, but recovered the reduced MMP-2 mRNA level to the control¹⁰.

Pharmacological properties of AZI that makes it a desirable agent in the management of dental infections include:

1. Stable in acid pH.
2. Well absorbed, absorption not affected by food
3. Sustained high tissue concentrations
4. Extensive penetration of cells
5. Rapid uptake by phagocytes
6. Delivery in high concentrations to site of infection
7. Once daily delivery
8. Short duration of treatment.¹¹

AZI extensively penetrates cells, including tissue fibroblasts. It is also rapidly and extensively taken up by phagocytic cells (polymorphonuclear leukocytes and macrophages). This produces intracellular concentrations far greater than those in

the extracellular medium.¹²

CyclosporinA-induced proliferation of renal transplant fibroblasts and normal fibroblasts is inhibited by azithromycin. Azithromycin elevates the reduced metalloproteinase (MMP)-1 and MMP-2 activities in cyclosporine A-treated renal transplant fibroblasts and normal fibroblasts. In cyclosporine A-treated renal transplant fibroblasts, azithromycin blocks the accumulation of total collagen in culture media and the increase in type I collagen mRNA level, but recovers the reduced MMP-2 mRNA level to the control.¹³

These results suggest that azithromycin may improve CIGO by blocking cyclosporine A-induced cell proliferation and collagen synthesis, and by activating MMP-2 in gingival fibroblasts of persons with cyclosporine A-induced gingival overgrowth.¹³

Dosage and response : Dose used to treat CIGO, in different study was **500-mg AZI for 5-days**. 72% showed complete healing.¹³ Nowicki et al documented partial resolution of severe CsA-induced gingival enlargement after 3 days of azithromycin administration, although recurrent gingival enlargement was evident 6 months posttreatment.¹⁵

Recently, **Azithromycin toothpaste** was used to treat gum hyperplasia. Azithromycin-containing toothpaste had 85 mg azithromycin per gram of toothpaste. Both toothpastes were prescribed b.i.d., each time using 1.5 cm, for 1 month. After following for 3 months, gingival overgrowth index decreased significantly in the azithromycin-containing toothpaste group. Bleeding on probing also decreased significantly in patients in the azithromycin-containing toothpaste group compared with controls (P=.001).¹⁶

FDA Approval : FDA-approved indications for azithromycin include :

- Acute bacterial exacerbations of chronic obstructive pulmonary disease
- Acute bacterial sinusitis
- Community-acquired pneumonia
- Pharyngitis/tonsillitis

- Uncomplicated skin and skin structure infections
- Urethritis and cervicitis
- Genital ulcer disease.¹⁷

Black box warning : Azithromycin belongs to a class of antibacterial drugs called macrolides, which have been associated with cardiovascular effects; specifically, prolongation of the QT interval. Prolongation of the QT interval can lead to torsades de pointes (TdP), an abnormal heart rhythm, which can be fatal. Azithromycin was the only macrolide examined in the published study; the study did not address other macrolide antibacterial drugs, such as clarithromycin (Biaxin) and erythromycin, regarding the potential for cardiovascular death.¹⁷

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