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Pharmacogenetics and Pharmacokinetic of Azithromycin Eyedrops in Meibomian Gland Dysfunction Treatment

Syena Damara Riza Gustam[1*]

[1]Department of Opthalmology, Faculty of Medicine, Universitas Sriwijaya/Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia

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Corresponding author:
Syena Damara Riza Gustam

E-mail address:
damarasyena@gmail.com

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ABSTRACT

Meibomian gland dysfunction (MGD) is the leading cause of ocular surface disease throughout the world, which has a prevalence that varied widely from 3.5 to 70% according to age, sex, and ethnicity. Azithromycin (AZM) is the first azalidic antibiotic, a class of macrolide antibiotics, which has derived from erythromycin. It is widely used in clinical practice, not only for respiratory diseases and sexually transmitted infections but also for ocular diseases. azithromycin suppressed zymosan-induced mRNA expression and protein production of proinflammatory cytokines (tumor necrosis factor α and IL-1β), chemokines (IL-6 and RANTES), and MMPs (MMP-1, MMP-3, and MMP-9) by human corneal epithelial cells and suggested the potential for using azithromycin to treat ocular surface It controls the initiation and resolution of inflammatory responses through the regulation of chemotaxis, activation, and survival of lymphocytes. The anti-inflammatory role of TGF-β1 has been recognized in different cell types by inhibiting proinflammatory cytokines including tumor necrosis factor α, IL-1, and interferon γ.The combination of a topical AZM solution 1.0% with corticosteroid (DEX 0.1%) was found superior in the comprehensive treatment of MGD after 2 weeks. AZM is a one of the safest antibiotics, well tolerated, and has special pharmacokinetic properties. Moreover, it has a broad antimicrobial spectrum. AZM is efficacious for the treatment of a lot of ocular diseases and may be included as monotherapy or in combination therapy in new treatment protocols for more ocular infections.

1. Introduction

Meibomian gland dysfunction (MGD) is the leading cause of ocular surface disease throughout the world, which has a prevalence that varied widely from 3.5 to 70% according to age, sex, and ethnicity. MGD also has a major impact on patients' quality of life. The pathophysiology of MGD is due to meibomian gland obstruction and hyperkeratinization of meibomian ductal epithelium that leads to reduced availability of meibum over the aqueous layer of the tear film. The deplet- ed meibum results in increased tear evaporation, tear hyperosmolarity, tear film instability, and increased bacterial growth on the lid margin.[1-3]

Conventional therapy of MGD includes mechanical options of lid massage and lid expression as well as medicinal therapy of systemic tetracycline and doxycycline. Oral azithromycin therapy improved the signs and symptoms associated with dry eyes. The use of azithromycin in DuraSite for the treatment of MGD has recently been reviewed. Clinical trials have identified topical azithromycin as a potentially effective and well-tolerated therapy of lid margin disease and MGD. Azithromycin is antiinflammatory, inhibiting proinflammatory cytokines, and is potent against Gram-negative microorganisms. It is believed to penetrate into the ocular surface where it remains at therapeutic levels days after the therapy has stopped. It also demonstrated bacteriostatic activity at concentrations achieved by topical administration. This results in the control of bacterial growth on the lid margin.[4,5]

Pharmacogenetics and Pharmacokinetics of Azythromycin 1.5%

Azithromycin (AZM) is the first azalidic antibiotic, a class of macrolide antibiotics, which has derived from erythromycin. It is widely used in clinical practice, not only for respiratory diseases and sexually transmitted infections but also for ocular diseases.It has bacteriostatic properties against a wide spectrum of both gram-positive and gram-negative bacteria, atypical bacteria, and some protozoa.Although it was synthesized already in the early 1980s, it is still being investigated for the treatment of various diseases. In 2007, it was approved as the first ophthalmic solution (AZM 1.0%) to treat bacterial conjunctivitis.[4,5]

Previously, it was prescribed (mainly orally) for a number of very important and frequent eye infections, such as trachoma, as well as for diseases with ocular manifestations. In recent years, it has received increasing attention because of its supplementary effects on host defense reactions and chronic human diseases. Its immunomodulatory effects are under investigation and are considered of significant clinical importance.This review summarizes the newest information on AZM's clinical usefulness over ocular diseases.[5]

The special pharmacokinetic properties of AZM are the main reason for the continued interested in the drug. In short, these are as follows: a wide antimicrobial spectrum, long half-life, excellent tissue penetration and extensive tissue distribution, high drug concentrations within cells (including phagocytes), and considerable immunomodulatory effects. In comparison with earlier macrolides, it shows enhanced stability in acidic media while it expresses increased antimicrobial activity at alkaline pH. Moreover, because AZM is metabolized slowly and produces inactive metabolites, does not affect the P450 cytochromes, so it does not interact with medications being metabolized by P450.Its absolute oral bioavailability extends to 35– 42% in healthy individuals and people suffering from cystic fibrosis and its extensive uptake in tissues (10- to 100-fold higher than mean serum concentrations) principally contribute to its extended half-life. The widespread location of fibroblasts renders them to be considered as a reservoir for AZM, which also accumulates to other cells such as epithelial cells, hepatocytes, and phagocytic cells (polymorphonuclear leukocytes and macrophages). Intracellularly, it is localized in lysosomes.Phagocytes accumulate high amounts of AZM, up to 200 times higher intracellular than extracellular concentrations. This the main reason of high AZM's accumulation in the site of inflammation. There are two mechanisms of AZM's delivery to the site of infection.[4-6]

In the first mechanism, AZM is directly uptaken by tissues, mainly by fibroblasts and phagocytic cells, while in the second, the drug is released during phagocytosis to achieve high concentrations in the exact site of inflammation.AZM penetrates poorly cerebrospinal fluid and peritoneal fluid but crosses the placenta After topical installation of an ophthalmic solution of AZM (1.0% or 1.5%), the drug is not detectable in the blood of patients at the applauded dose (detection limit: 0.0002 μg/mL of plasma). It achieved persistent concentration in tissues above MIC90 in ocular surface and eyelids. Half-life of topical administration is equivalent to its systemic administration (approximately 65.7 h). But a sole dose of AZM 1.5% ophthalmic solution in healthy volunteers had a mean elimination half-life of 15.67 h. The pharmacokinetics of AZM ophthalmic solution appear to be dose dependent. Interestingly, polycarbophil asan excipient raises the higher AZM's concentrations in the lacrimal functional unit. This was attributed partly to the longer contact time.Topical administration achieved far less lower concentrations than the MIC90 in the aqueous humor, similar to the systemic administration of the drug.[5-7]

The genes relevance to pharmacogenetics of Azythromycin 15%

Azithromycin has also been used topically to treat ocular surface infections including bacterial conjunctivitis. In addition to its antibiotic effects, azithromycin has been shown to have a variety of anti-inflammatory effects, particularly in the context of microbial infections. Our previous study showed that azithromycin suppressed zymosan-induced mRNA expression and protein production of

proinflammatory cytokines (tumor necrosis factor α and IL-1β), chemokines (IL-6 and RANTES), and MMPs (MMP-1, MMP-3, and MMP-9) by human corneal epithelial cells and suggested the potential for using azithromycin to treat ocular surface inflammation.11 Clinical trials have reported that azithromycin improved the signs and symptoms of MGD, including tear break-up time, corneal staining, conjunctival staining, Schirmer scores with anesthetic, meibomian gland score, and patients' symptom scores expression levels of major proinflammatory mediators IL-1β, IL-8, and MMP-9 were much higher in patients with MGD blepharoconjunctivitis than in healthy controls ($P < .001$). The elevated levels of those mediators gradually decreased ($P < .001$) during 4 weeks of azithromycin treatment.[6-8]

Expression of IL-1β, IL-8, and MMP-9 remained suppressed at the 4-week follow-up after drug withdrawal, although there was a slight rebound from their lowest point after 4 weeks of azithromycin treatment. The tear MMP-9 activity assay further confirmed higher MMP-9 activity in patients with MGD and the suppressive effects of topical azithromycin on this activity. These findings suggest that patients with MGD-associated eyelid and conjunctival inflammation may need intermittent pulse therapy with a topical anti-inflammatory agent such as azithromycin. We found that TGF-β1 expression was much lower in patients with MGD than in healthy controls and that it increased in the eyelid margin and conjunctiva during treatment with azithromycin. The TGF-β1 expression was still higher than in healthy controls 4 weeks after azithromycin withdrawal. Transforming growth factor β1 is a polypeptide member of the TGF-β cytokine superfamily. It was first identified in human platelets with a potential role in wound healing. Many types of cells secrete TGF-β1, including human corneal and conjunctival epithelia as well as lacrimal gland acinar cells. The pivotal function of TGF-β in the immune system is to maintain tolerance via the regulation of lymphocyte proliferation, differentiation, and survival. It controls the initiation and resolution of inflammatory responses through the regulation of chemotaxis, activation, and survival of lymphocytes. The anti-inflammatory role of TGF-β1 has been recognized in different cell types by inhibiting proinflammatory cytokines including tumor necrosis factor α, IL-1, and interferon γ.[8-10]

2. Results

Meibum quality grades at baseline and 4 weeks later in each group. Both groups showed a significant improvement in meibum quality ($P < 0.001$). Fifty participants (58.82%) in the azithromycin group showed improvement in meibum quality score. Azithromycin showed significant improvements in meibum expression ($P < 0.001$), TBUT ($P < 0.001$), ocular surface staining ($P < 0.001$), and MGD-related symptoms ($P < 0.02$). There was no statistically significant difference in meibum expression, ocular surface staining, and MGD-related symptoms after treatment. TBUT after treatment in the azithromycin group and the doxycycline group were 4.99 ± 2.86 and 5.35 ± 2.92 s, respectively. No significant difference between groups was detected ($P = 0.36$, mean difference − 0.36, 95% CI − 1.13 to 0.41). Drug side effects were found in 45 (54.88%) of 82 participants in the azithromycin group and 16 (19.75%) of 81 participants in the doxycycline group ($P < 0.001$). The common side effects in the azithromycin group were eye irritation (45.12%) and blurred vision (13.41%) while the common side effect in the doxycycline group was gastrointestinal disturbance (11.11%) The number of participants who discontinued medications due to side effects was comparable.[11]

Efficacy of Azithromycin 1.5% Eyedrops as a Therapy

The efficacy of AZM in has been tested in different treatment protocols. Treatment which lasted for 1 month seemed to be superior to shorter treatments. The treatment of chronic MGD with topical AZM 1.5% ocular suspension b.i.d. for the first 2 days followed by single administration each day for 28 days (Group A) versus for 12 days (Group B) demonstrated improved and more sustained outcomes in favor of Group A. Both groups were monitored before the

beginning of their eyedrops administration, at the end of the accomplishment of each treatment protocol and 4 weeks later. In addition, Tear Break-Up Time (TBUT) values and Schirmer test were performed.Similarly, Fadlallah and colleagues conducted a clinical study between two groups of patients suffering from moderate to severe MGD. Both groups were administered topical 1.5% AZM b.i.d. for 3 days and were instructed to perform lid hygiene twice daily (warm compresses and lid cleaning with soap), although Group II continued topical installation of AZM 1.5% only once every night for 27 more days. Patients' signs and symptoms were documented and then sorted in accordance with severity. In conclusion, Group II showed better improvement than Group I. No safety issues were reported. Moreover, after a month-long treatment with azithromycin 1.0% ophthalmic solution, MGD signs and symptoms were significantly improved, which persisted 4 weeks posttreatment. Eyelid margin culture exhibited significant decreases in microbial load but no changes were observed in tear cytokine concentrations. As far as the AZM ophthalmic solution efficacy compared with other treatments for MGD/ blepharoconjunctivitis is concerned, recent research finds the combination of antibiotic plus a steroid in ophthalmic solution superior to the AZM drops alone, without severe adverse events.[12-13]

Correspondingly, the combination of a topical AZM solution 1.0% with corticosteroid (DEX 0.1%) was found superior in the comprehensive treatment of MGD after 2 weeks. The combination was also found well tolerated. In addition, the combination of another topical antibiotic solution (tobramycin, TOB) with corticosteroid was also found superior in the treatment of MGD/blepharoconjunctivitis. Namely, TOB/DEX ocular solution 0.3%/0.05% proved to be more efficacious at day 8 and reached quicker inflammatory relief than AZM 1.0% alone. Yet, the dosage scheme of eyedrops administration would be a worthwhile element to further evaluation of the above results as TOB/DEX was administered higher than the usual treatment dose (q.i.d. for 2 weeks) and AZM b.i.d. for 2 days and then once daily for 12 days.Likewise, other two clinical studies proved the efficacy of AZM in the remedy of posterior MGD, while a third compared the clinical effects of oral doxycycline (DOX) to topical AZM and finds them similar. The administration of oral AZM 500 mg once a day for three subsequent days in three turns with a week gap between two successive turns and the administration of AZM 1.0% ophthalmic suspension b.i.d. for 2 days, then once a day in the evening a month long, were found to be effective for the treatment of posterior MGD. Moreover, in the first half of patients treated with warm eyelid compress and massage three times a day for 3 weeks was administered AZM 1.0% ophthalmic solution b.i.d. for 1 week and then once a day for 2 weeks, and in the other half orally DOX 100 mg for 3 weeks. Even though both treatments relieved signs and symptoms after 3 weeks, topical AZM was found more efficacious in alleviating eye redness, while oral DOX proved to be more potent in decreasing corneal staining and in the cure of meibomian glands plugging. AZM is widely prescribed for MGD although it remains off-label, presumably to suppress the MGD-associated posterior MGD, the associated conjunctival inflammation, and growth of lid bacteria. Indeed, recent data widely support the use of AZM in MGD ± dry eye disease. AZM was found to have a direct effect on meibomian gland epithelial cells [human meibomian gland epithelial cell (HMGECs)] to incite their function,while the MGD treatment of choice, which is oral tetracyclines do not exhibit similar properties. Topical AZM has been found effective in treating MGD and slightly more effective to DOX in improving foreign body discomfort and the signs of plugging and secretion. In addition, it may represent a synergistic treatment to oral DOX for ocular rosacea, and their combination may severely enhance the efficacy in treating MGD, as their mechanism of action may differ signifficantly.[13,18]

Oral AZM has been found preferable to the use of oral tetracyclines. More in detail, a retrospective case note audit in 11 patients (9 diagnosed with MGD/rosacea and 4 with dry eye syndrome) showed an important improvement in their symptoms (73%)

and signs (82%) and no compliance issues. Because of our current poor comprehension of the fundamental mechanism of MGD, the previous percentages show a reasonable response in the treatment of MGD ± dry eye. Moreover, almost two thirds (73%) of these 11 patients had been administered oral tetracyclines in the past. With poor overall satisfaction because of the common reasons referring to tetracycline administration, such as severe side effects and compliance issues partly provoked by side effects and partly by long treatment's duration. The 11 patients were administered 500 mg AZM per os once a day every day for only 3 days. For reasons of comparison, we shall notice the rather extended treatment period of tetracyclines (2–3 months). Another study, a randomized double masked open label trial, proposed favorably a 5-day oral AZM (500 mg on the first day and then 250 mg each following day) in contrast to a month treatment with oral DOX, 200 mg per day. It was found that oral AZM had considerably fewer adverse effects and was more advantageous in improving the signs of the illness. As far as the symptoms were concerned, oral AZM also proved relatively better, as there was no statistical significance between the corresponding results. Besides, the total cost of remedy with oral AZM is notably decreased, as well as treatment's duration, compared to oral DOX. Finally, AZM has been proven effective against ocular rosacea, which is a comorbid condition of both MGD and MGD. Topical administration of AZM 1.5% eyedrops b.i.d. for 6 days was compared with the prescription of oral DOX 100 mg/day for 1 month and was found effective in the management of patients with ocular involvement in acne rosacea also providing less side effects (no gastrointestinal disturbances were reported).[15-19]

3. Discussion

Meibum quality grade significantly improved during the course of the treatment in both groups. However, there was no significant difference in term of improvement in meibum quality between groups. For secondary analysis, despite the slightly higher number of participants with improvement in doxycycline group, there was no significant difference in the percentages of the participants with improvement in respect to.

4. Conclusion

AZM is a one of the safest antibiotics, well tolerated, and has special pharmacokinetic properties. Moreover, it has a broad antimicrobial spectrum. AZM is efficacious for the treatment of a lot of ocular diseases and may be included as monotherapy or in combination therapy in new treatment protocols for more ocular infections. However, more research is needed to determine this.

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