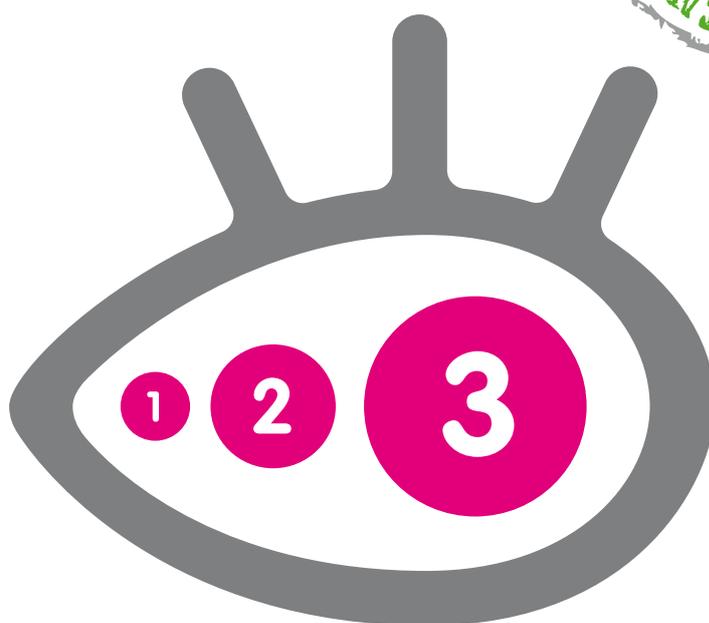


## AZITHROMYCIN IN OPHTHALMOLOGY

*A selection of abstracts and publications*



The purpose of this collection is to provide a synthesis of the studies and abstracts on azithromycin that had been published worldwide up until now and their corresponding references.

The document is divided into different parts to point out the specificity and the rational of azithromycin prescription and use in ophthalmology.

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## AZITHROMYCIN REVIEW



This symbol indicates that the article refers to Azytel®

# GENERAL CONSIDERATIONS

ANTI-INFLAMMATORY ACTION

PHARMACOKINETICS/PHARMACODYNAMICS

SPECTRUM & MICROBIOLOGICAL ACTIVITY

## Azithromycin. a review of its microbial activity, pharmacokinetic, properties and clinical efficacy

Peters DH, Friedel HA, McTavish D.

Drugs 1992; 44 (5): 750-799.

Azithromycin is an acid stable orally administered macrolide antimicrobial drug, structurally related to erythromycin, with a similar spectrum of antimicrobial activity. Azithromycin is marginally less active than erythromycin *in vitro* against Gram-positive organisms, although this is of doubtful clinical significance as susceptibility concentrations fall within the range of achievable tissue azithromycin concentrations. In contrast, azithromycin appears to be more active than erythromycin against many Gram-negative pathogens and several other pathogens, notably *Haemophilus influenzae*, *H. parainfluenzae*, *Moraxella catarrhalis*, *Neisseria gonorrhoeae*, *Urea-plasma urealyticum* and *Borrelia burgdorferi*. Like erythromycin and other macrolides, the activity of azithromycin is unaffected by the production of beta-lactamase. However, erythromycin-resistant organisms are also resistant to azithromycin. Following oral administration, serum concentrations of azithromycin are lower than those of erythromycin, but this reflects the rapid and extensive movement of the drug from the circulation into intracellular compartments resulting in tissue concentrations exceeding those commonly seen with erythromycin. Azithromycin is subsequently slowly released, reflecting its long terminal phase elimination half-life relative to that of erythromycin. These factors allow for a single dose or single daily dose regimen in most infections, with the potential for increased compliance among outpatients where a more frequent antimicrobial regimen might traditionally be indicated. The potential disadvantage of low azithromycin serum concentrations, however, is that breakthrough bacteraemia may occur in patients who are severely ill; nevertheless, animal studies suggest that tissue concentrations of azithromycin are more important than those in serum when treating respiratory and other infections.

The clinical efficacy of azithromycin has been confirmed in the treatment of infections of the lower and upper respiratory tracts (the latter including paediatric patients), skin and soft tissues (again including paediatric patients), in uncomplicated urethritis/cervicitis associated with *N. gonorrhoeae*, *Chlamydia trachomatis* or *U. urealyticum* and in the treatment of early Lyme disease. Azithromycin was as effective as erythromycin and other commonly used drugs including clarithromycin, beta-lactams (penicillins and cephalosporins), and quinolone and tetracycline antibiotics in some of the above infections. Some patients with acute exacerbations of chronic bronchitis due to *H. influenzae* may be refractory to therapy with azithromycin (as is the case with erythromycin) indicating the need for physician vigilance, although it should be noted that azithromycin is of equivalent efficacy to amoxicillin in the treatment of such patients. In the therapy of urethritis/cervicitis associated with *C. trachomatis*, *N. gonorrhoea* or *U. urealyticum*, a single dose azithromycin regimen offers a distinct advantage over currently available pharmacological options, while providing effective therapy. Furthermore, it is likely that azithromycin may supersede erythromycin in the treatment of early Lyme disease and become an alternative to therapy with penicillin or tetracycline antibiotics in this condition. Similarly, if the finding of clinical efficacy of azithromycin in a preliminary study of chancroid is sustained in further clinical trials, then the use of azithromycin might supplant the traditional use of a more frequent erythromycin regimen in this condition.

Small initial trials have shown azithromycin to be effective at least in the amelioration of *Mycobacterium avium* infection in AIDS patients.

Comparative clinical trials have shown azithromycin to be better tolerated than erythromycin principally through fewer gastrointestinal disturbances. Such studies have also shown the tolerated profile azithromycin to be superior to that of cefaclor, doxycycline or amoxicillin plus probenecid.

In conclusion, with its broad spectrum of antimicrobial activity, proven efficacy in a wide range of community-acquired infections, improved tissue pharmacokinetic and tolerability profiles, and suitability for once daily dosing, azithromycin provides a useful alternative to erythromycin and other macrolides with similar activity. In patients with uncomplicated urethritis or cervicitis associated with *C. trachomatis*, *N. gonorrhoeae* or *U. urealyticum*, azithromycin as a single dose regimen offers distinct advantages over current pharmacological options and should therefore be considered as a first-line therapy.

# Anti-inflammatory action

## Anti-Inflammatory Activity of Azithromycin as Measured by Its NF- $\kappa$ B Inhibitory Activity.

Cheung PS, Si EC, Hosseini K.

ARVO. Fort Lauderdale, USA, May 3-7, 2009. 2009; E-Abstract 839/A425.

### PURPOSE

Azithromycin has been reported to possess anti-inflammatory and immunosuppressive activities. This study used an activated NF- $\kappa$ B assay to assess azithromycin's anti-inflammatory potency, and compared that to a commonly used anti-inflammatory agent, hydrocortisone.

### METHODS

A reporter gene assay employing A549 cells was used to examine the effects of azithromycin and hydrocortisone on TNF- $\alpha$  stimulated NF- $\kappa$ B activity. By constructing the dose-response curves, the corresponding inhibitory potencies (IC50s) of azithromycin and hydrocortisone were estimated. Dexamethasone was also tested in the assay to compare its NF- $\kappa$ B inhibitory activity as related to the glucocorticoid activity.

### RESULTS

All three compounds dose-dependently inhibited TNF- $\alpha$  stimulated NF- $\kappa$ B activity. IC50 values of azithromycin, hydrocortisone and dexamethasone were 56  $\mu$ M, 2.6 nM and 0.18 nM, respectively. Hydrocortisone was approximately 4 orders of magnitude more potent than azithromycin while dexamethasone was approximately 14 times as potent as hydrocortisone. The latter approximates the reported glucocorticoid activity ratio between dexamethasone and hydrocortisone.

### CONCLUSIONS

In addition to its antibiotic activity, azithromycin also possesses a weak anti-inflammatory activity relative to the glucocorticoids. Since azithromycin can achieve much higher tissue concentration and has a long tissue half-life at clinical doses, this antibiotic might have utility for certain inflammatory ocular surface diseases.

## Azithromycin Alters ProMMP-2 and TIMP-1 Following Corneal Wounding in an Experimental Animal Model of Diabetic Ocular Complications.

Jacot JL, Jacot TA, Hahto S et al.

ARVO. Fort Lauderdale, USA, May 3-7, 2009. 2009; E-Abstract 2663/D895.

### PURPOSE

To determine the effect of topical azithromycin (AzaSite®) and its vehicle (DuraSite®) on MMP-2 and TIMP-1 in tears of control and galactosemic rats. Matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs), which modulate activity of certain MMPs, are involved in multiple processes in damaged and diseased eyes. MMP-2 is elevated after corneal wounding, ulceration, erosion, collagen remodeling and repair.

### METHODS

Male SD rats were randomized into 4 groups (n=6/group) and fed ad lib chow with either 50% starch (control) or 50% D-galactose. The dietary groups were treated bilaterally either with 3x/day 1% AzaSite® or DuraSite® for two months. Tears were collected 2 weeks after induction of a sterile 3 mm central corneal epithelial wound under anesthesia. Tears were placed in Tris (pH 7.4) w/ protease inhibitors. MMP-2 in tears was evaluated by gelatin sepharose affinity precipitation followed by gelatin zymography. Samples were normalized by equal protein load and semi-quantified using NIH-imageJ for integrated density units/per area. Microbead antibody immunoassay was used to determine tear levels of TIMP-1 (ng/ml).

### RESULTS

Tears from galactosemic rats exhibited elevated proMMP-2 relative to control group. Compared to DuraSite® treated galactosemic rats, the AzaSite® treatment suppressed proMMP-2 levels by 38%. Control group showed a 17% decrease in proMMP-2 with AzaSite® compared to DuraSite®. There was a trend towards elevation of TIMP-1 levels in the AzaSite® treated galactosemic rats compared to DuraSite®. No appreciable trend was observed in the control group.

### CONCLUSIONS

This study on modulation of tear levels of MMP-2 and TIMP-1 by the antibiotic, AzaSite®, provides preliminary mechanistic data for the use of AzaSite® therapy in the management of ocular surface tissue remodeling/injury, diabetic and neurotrophic keratopathies where corneal MMP levels can be elevated.

## Azithromycin Suppresses Pro-Inflammatory Mediators Stimulated by a TLR2 Ligand Zymosan in Human Corneal Epithelial Cells.

Zhou N, Ma P, Li DQ, Pflugfelder SC.

ARVO. Fort Lauderdale, USA, May 3-7, 2009. 2009; E-Abstract 5545/A516.

### PURPOSE

In addition to antibiotic effects, azithromycin (AZM) has been noted to have anti-inflammatory effects, particularly in the context of bacterial infections. The goal of this study was to explore the suppressive effects of AZM on pro-inflammatory mediators stimulated by toll like receptor (TLR) ligands, in human corneal epithelial cells.

### METHODS

Primary human corneal epithelial cells were cultured from donor corneal limbal explants and grown to sub-confluence in SHEM. The cells were treated with extracted or synthetic microbial components, ligands for TLRs 2-6, respectively for 6-48 hours, with or without pre-incubation with azithromycin (1-50 µg/ml) or TLR antibodies. The cells were subjected to total RNA extraction, reverse transcription (RT) and real-time PCR using Taqman gene expression assays (Applied Biosystems). The medium supernatants of cells treated for 48 hours were collected for protein quantitation using Luminex immunobead assays.

### RESULTS

The expression of pro-inflammatory cytokines (TNF- $\alpha$  and IL-1 $\beta$ ), chemokines (IL-8, RANTES), and matrix metalloproteinases (MMP-1 and -9) by human corneal epithelial cells was dramatically stimulated by zymosan, poly I:C (dsRNA) and flagellin, ligands for TLRs 2, 3 and 5 respectively, with peak stimulation at 16 hours. AZM, added 1 hour pre-stimulation, suppressed expression of these pro-inflammatory mediators stimulated by zymosan, but not by flagellin or poly I:C. TLR2 antibody or AZM each partially blocked the expression of TNF- $\alpha$ , IL-1 $\beta$ , IL-8, RANTES, MMP-1 and MMP-9 induced by zymosan in human corneal epithelial cells.

### CONCLUSIONS

These findings indicate that AZM has a potential to suppress inflammatory responses stimulated by zymosan through a TLR2 pathway in human corneal epithelial cells.

## Modification of Meibomian Gland Lipids by Topical Azithromycin

Foulks GN, Borchman D, Yappert M.

ARVO 2009. Fort Lauderdale, USA, May 3-7, 2009. 2009; E-Abstract 2676/D908

### PURPOSE

To determine abnormalities of the Meibomian gland lipids in lid margin disease and measure the effects of topical azithromycin on lipid function.

### METHODS

Mechanical expression of the Meibomian glands of subjects with Meibomian gland dysfunction (MGD) before and after therapy with topical azithromycin provided samples of secretions that were analyzed by Fourier transform infrared (FTIR), MALDI-TOF, and nuclear magnetic resonance spectroscopies. Measurement of lipid structure and function was determined for each subject.

### RESULTS

All MGD subjects were found to have abnormal lipid structure and function prior to therapy with evidence of increased lipid ordering (49% versus 34% trans rotamer) and higher phase transition temperature (32.8oC versus 28oC) than normals. Fifteen subjects were treated with topical azithromycin solution with reduction of the abnormal lipid behavior measured at 2 and 4 weeks of treatment. Azithromycin was identifiable in the lipid samples at 2 and 4 weeks.

### CONCLUSIONS

The structure and behavior of lipids of the Meibomian glands is altered in subjects with MGD with evidence of increased phase transition temperature that correlates with a more ordered (greater % trans rotamer) lipid structure. This pattern correlates with clinical features of thickened and turbid Meibomian gland secretions. Therapy with daily topical azithromycin solution for one month reduces the phase transition temperature and % trans rotamer pattern of the lipids to that of normal secretions.

# Pharmacokinetics/Pharmacodynamics



## Ocular pharmacokinetic study following single and multiple azithromycin administrations in pigmented rabbits.

Amar T, Caillaud T, Elena PP.

Curr Eye Res 2008; 33 (2): 149-158.

### PURPOSE

The aim of this study was to investigate whether the ocular pharmacokinetic parameters observed following systemic administration are also seen following topical administration.

### METHODS

Azithromycin concentrations were measured by HPLC-MS in pigmented rabbits' tears, cornea, bulbar conjunctiva, and aqueous humor following single instillation and twice-daily instillations for three consecutive days of topical 1.50% azithromycin dehydrate solution.

### RESULTS

Following a single administration, azithromycin levels were higher than the MIC 4 µg/g breakpoint for susceptible germs for at least 4 hr in tears, 1 hr in conjunctiva, and 1 hr in cornea after instillation. Following multiple administrations, azithromycin levels were higher than the MIC 4 µg/g for at least 16 hr in tears, 24 hr in conjunctivae, and 1 week in cornea after the last instillation.

### CONCLUSIONS

Both dosage regimens resulted in adequate and long-lasting azithromycin levels in the conjunctiva, the ocular target tissue relative to the expected therapeutic indication in man (bacterial conjunctivitis), and also in the cornea and tears.



### Effects of dehydration on corneal tissue absorption of topical azithromycin in rabbits.

Tabbara KF, Kotb AA, Hammouda EF, Elkum N.

Curr Eye Res 2005; 30 (10): 915-8.

#### PURPOSE

to assess the corneal tissue absorption of azithromycin in desiccated and normal eyes of rabbits.

#### METHODS

A total of 25 New Zealand Albino rabbits weighing 2-3 kg each were included. One eye of each rabbit was desiccated. The other eye was left as control. Azithromycin 1.5% topical eyedrops were instilled in both eyes. Five rabbits were sacrificed at each of the following time points: 30 min, 3 hr, 6 hr, and 12 hr. Corneal tissues specimens were subjected to high-performance liquid chromatography mass spectrometry. A paired t test was used to evaluate the statistical difference in corneal tissue absorptions of azithromycin at each time point.

#### RESULTS

The mean corneal tissue levels of azithromycin in dry eyes were 66.3 microg/ml, 92.6 microg/ml, 117.5 microg/ml, and 179.9 microg/ml, and the mean corneal tissue levels of azithromycin in normal eyes were 42.0 microg/ml, 43.4 microg/ml, 43.3 microg/ml, and 80.0 microg/ml at 30 min, 3 hr, 6 hr, and 12 hr respectively. Both groups showed increase in corneal tissue absorption overtime ( $p < 0.0001$ ). Significantly higher levels of azithromycin were noted in dry eyes at each time point except at the 30-min time point.

#### CONCLUSIONS

This study demonstrated that corneas exposed to desiccation showed statistically significant increase in azithromycin level compared to normal eyes.

## The pharmacodynamic properties of azithromycin in a kinetics-of-kill model and implications for bacterial conjunctivitis treatment.

Dorfman MS, Wagner RS, Jamison T, Bell B, Stroman DW. *Adv Ther* 2008; 25 (3): 208-17.

### INTRODUCTION

Antibiotics have traditionally been classified as bactericidal or bacteriostatic. Azithromycin belongs to the parent class of macrolides that are characteristically bacteriostatic. Some evidence suggests that this molecule demonstrates bactericidal kill and has concentration-dependent effects. This study tests the hypothesis that azithromycin demonstrates a bactericidal, concentration-dependent antibiotic effect at concentrations corresponding to and exceeding published tear and conjunctival levels.

### METHODS

The antibacterial activity of different concentrations of azithromycin 1% in DuraSite(R) (AzaSite(R); Inspire Pharmaceuticals Inc, Durham, NC, USA) was evaluated using a kinetics-of-kill model. Recent conjunctivitis isolates of *Staphylococcus aureus*, *Streptococcus pneumoniae* or *Haemophilus influenzae* were exposed to four concentrations of azithromycin (100, 250, 500 and 750 microg/ml). Starting concentrations were similar to the maximum concentrations (C<sub>max</sub>) that have been demonstrated in conjunctiva (83 microg/g) and tears (288 microg/ml) following topical ocular administration. The percentage of surviving bacteria at 30 and 60 minutes following exposure to each concentration were determined.

### RESULTS

Azithromycin failed to demonstrate bactericidal activity (i.e. a 3-log reduction in surviving bacteria) against *S. aureus*, *S. pneumoniae* or *H. influenzae*. Furthermore, the rate and extent of antibacterial activity with azithromycin did not change with higher concentrations, even at the highest tested concentration of 750 microg/ml.

### CONCLUSIONS

Similar to the parent macrolide class, azithromycin demonstrates bacteriostatic activity against common conjunctival pathogens up to the maximum tested concentration of 750 microg/ml (i.e. 2.6-times and 9-times published C<sub>max</sub> tear and conjunctival concentration, respectively). Azithromycin's bacteriostatic effects and prolonged elimination half-life will likely lead to a corresponding increase in the emergence of macrolide-resistant isolates

## Azithromycin Suppresses Bacterial Lipases Expressed by *Staphylococcus*

Guogas LM, Boyer JL. ARVO. Fort Lauderdale, USA, May 3-7, 2009. 2009; E-Abstract 5943/A549.

### PURPOSE

Bacteria produce virulence factors, including lipases, which lead to tear film instability and contribute to lid margin disease. We investigated the efficacy of azithromycin to inhibit the expression of bacterial lipases as compared to other antibiotics.

### METHODS

Saturated cultures of *S. epidermidis* (ATCC 14990) and *S. aureus* (ATCC 12600) were incubated at 37°C in the presence of a range of concentrations of azithromycin, erythromycin, ofloxacin, doxycycline or left untreated for two hours. Following the drug incubation period, bacterial lipase levels were estimated from activity measurements in the culture media using a fluorogenic substrate. Viability of the cultures following incubation with drug compounds was assessed by colony count.

### RESULTS

Azithromycin exhibited a  $\geq 75\%$  reduction of bacterial lipase activity in the culture media for *S. aureus* and *S. epidermidis* at concentrations above 2 and 4  $\mu\text{g}/\text{mL}$  respectively, as compared to the untreated control. A  $>90\%$  reduction in lipase activity was observed at the highest treatment dose, 16  $\mu\text{g}/\text{mL}$ . The inhibition of lipase activity observed with erythromycin treatment was lower than with azithromycin at the same dose. Treatment with doxycycline showed a greater reduction in measured lipase activity than azithromycin; however, doxycycline treatment caused a significant reduction of bacterial viability in *S. aureus*. Ofloxacin was bactericidal in both *Staphylococcus* species and its effect on lipases could not be dissociated from its antibacterial effect. Azithromycin did not inhibit the enzymatic cleavage of the lipid substrate, suggesting that the effects of the drug are produced by inhibition of expression or secretion of lipases.

### CONCLUSIONS

All antibiotics tested except ofloxacin reduced the level of lipase activity of *S. epidermidis* and *S. aureus*. However, azithromycin treatment resulted in the greatest reduction of lipase activity at concentrations below antibacterial activity in both *Staphylococcus* species. It is likely that azithromycin is acting to reduce the expression and/or secretion of lipases. Reduced production of bacterial lipases may be beneficial for alleviating the inflammation associated with lid margin disease.

## Pharmacokinetic Modeling of Azithromycin in Rabbit Eyelids Following Topical Ocular Administration of AzaSite®.

Vittitow JL, Parham AJ, Bodnar WM, Crean CS.

ARVO. Fort Lauderdale, USA, May 3-7, 2009. 2009; E-Abstract 2672/D904.

### PURPOSE

To evaluate and mathematically model the pharmacokinetics (PK) of a proprietary, polycarbophil-containing formulation of azithromycin (AZM) in rabbit eyelids following topical administration.

### METHODS

Dutch-belted rabbits were instilled with 30 µL of AZM ophthalmic solution 1% to the right cornea. Drug was administered BID (0800 and 1700) on days 1 and 2 and QD (0800) on days 3-7. Eyelids were collected preinstillation, 0.5 and 1 h following the 0800 instillation on days 1-6 and at multiple time points for 16 days after the last instillation on day 7 (144 h after 1st administration). AZM levels were measured by LC/MS/MS and PK analysis was conducted with Winnonlin v5.2. A mathematical PK model was developed based on the above data and validated with a second study involving a different administration paradigm, where drug was instilled QD (0800) on days 1-7 and 15-21 and eyelids collected Qam (0800) on days 15, 22 and 30.

### RESULTS

In the first dosing paradigm, peak eyelid concentrations increased over the course of administration with  $C_{max}$  of 180.3 µg/g on Day 7. The AUC<sub>0-144h</sub> prior to the last administration was 8,926 µg\*h/g, whereas the total observed AUC<sub>0-504h</sub> was 21,813 µg\*h/g. AZM exhibited a terminal elimination half-life of 193 h. A 3-compartment model with 15 minute constant order drug input after each instillation was developed that demonstrated a 94.3% correlation between predicted and observed concentrations from the model development study. Predicted eyelid concentrations from the validation study were within the 90% confidence interval (CI) of the experimental data on Days 15 [28.4 µg/g, CI (28.4-40.6)], 22 [88.8 µg/g, CI (49.2-91.1)] and 30 [23.8 µg/g, CI (21.0-39.1)].

### CONCLUSION

The rapid absorption and distribution associated with the polycarbophil-containing formulation of AZM ophthalmic solution 1% (AzaSite®) resulted in high and sustained exposure of drug in rabbit eyelids (half life of 8 days). A 3-compartment PK model was developed to model AZM levels in eyelid following dosing with drug. This PK model can be used to predict AZM eyelid exposure following different topical administration paradigms of AzaSite®.

### Cell-Associated Azithromycin Confers Protection to Human Corneal Epithelial Cells From Staphylococcus aureus Infection.

Boyer JL, Bodnar W, Crean CS, Guogas LM.

ARVO. Fort Lauderdale, USA, May 3-7, 2009. 2009; E-Abstract 2659/D891.

#### PURPOSE

Topical administration of azithromycin (AZM) results in its high deposition and sustained levels in human ocular tissues. Using a cell-associated model of antibiotic efficacy developed by the Charles T. Campbell Laboratory (UPMC), this study evaluated the cytoprotective effects of AZM and other antibiotics against *S. aureus* infection.

#### METHODS

Human corneal epithelial cells (HCE, ATCC CRL11516) were treated for 24 h with concentrations ranging from 4 to 512 µg/mL of AZM, erythromycin (ERY), moxifloxacin (MOX), ofloxacin (OFX), or doxycycline (DOX). Untreated cells were included as controls. Free antibiotic was subsequently removed and cells were washed twice prior to challenge with *S. aureus* (ATCC 12600, 5 × 10<sup>5</sup> cfu/mL). Challenged cells and uninfected controls were incubated for 24 h. An aliquot of media was plated for colony counting to assess bacterial number. Plates were washed and the destruction of the cell monolayer as evidence of bacterial infection (or drug toxicity) was assessed by staining with gentian violet. Cells receiving drug treatment but not bacterial challenge served as controls for antibiotic-induced toxicity. Parallel experiments were conducted to study the drug disposition in HCE cells.

#### RESULTS

Protection of HCE cells was observed for pre-treatment concentrations ≥16 µg/ml for AZM and ≥64 µg/mL for MOX and ERY. OFX was not protective in the assay. Protection by DOX could not be determined because DOX was not protective at <16 µg /mL and was cytotoxic at ≥16 µg/mL. Cell protective effects of AZM correlated with bacterial cell count since cytoprotective concentrations of AZM reduced bacterial load and infection while non-protective concentrations permitted bacterial growth and HCE cell death. Bioanalytical measurements of AZM suggest that a time-dependent release of cell-associated AZM may contribute to the cytoprotective effect against infection.

#### CONCLUSIONS

Azithromycin protected HCE cells from *S. aureus* challenge at a dose at least 4X lower than that of MOX, ERY and OFX. The cell-associated nature of AZM observed previously in ocular tissues likely contributes to its protective effect against bacterial infection of corneal epithelial cells.

## Pharmacokinetics of Azithromycin and Moxifloxacin in Human Conjunctiva and Aqueous Humor During and After the Approved Dosing Regimens.

Stewart WC, Crean CS, Zink RC, Haque R, Hwang DG.

ARVO. Fort Lauderdale, USA, May 3-7, 2009. 2009; E-Abstract 2670/D902.

### PURPOSE

To evaluate the pharmacokinetics (PK) of azithromycin and moxifloxacin in human conjunctiva and aqueous humor throughout and following the labeled dosing regimens of azithromycin 1% ophthalmic solution (AzaSite®) and moxifloxacin HCl 0.5% ophthalmic solution (Vigamox®).

### METHODS

This study was a multi-center, randomized, open-label clinical trial in subjects undergoing routine cataract surgery. Conjunctival biopsy and aqueous humor samples were obtained from subjects immediately prior to cataract surgery at one of ten time points ranging from 1 to 14 days (1-312 hours) during or following an approved dosing regimen of either azithromycin 1% ophthalmic solution (twice daily on days 1 and 2; once daily on days 3-7) or moxifloxacin 0.5% ophthalmic solution (three times daily on days 1-7). Drug concentrations were determined using liquid chromatography-mass spectrometry (LC/MS/MS).

### RESULTS

The mean concentration of azithromycin in the conjunctiva was 40.4 µg/g after the first dose and was 269.46 µg/g one hour after the final dose on Day 7. By contrast, the mean concentration of moxifloxacin in the conjunctiva was 5.7 µg/g one hour after the first dose and 5.4 µg/g one hour after the final dose on Day 7. Mean azithromycin concentration in the aqueous humor was 0.022 µg/g one hour after the first dose and 0.052 µg/g one hour after the last dose. Mean concentrations of moxifloxacin in the aqueous humor were 0.58 µg/g one hour after the first dose, and 0.67 µg/g one hour after the final dose.

### CONCLUSION

Per label dosing of azithromycin 1% provided high and prolonged concentrations in human conjunctiva that were 1 to 2 orders of magnitude higher than moxifloxacin 0.5% at equivalent time points. By contrast, aqueous concentrations of moxifloxacin were ~1 log higher than azithromycin at equivalent time points. Azithromycin and moxifloxacin appear to differ in their PK profiles, indicating differential characteristics in partitioning and retention within the conjunctival and aqueous humor compartments. The potential clinical implications of these findings require further study.

## Conjunctival tissue pharmacokinetic properties of topical azithromycin 1% and moxifloxacin 0.5% ophthalmic solutions: a single-dose, randomized, open-label, active-controlled trial in healthy adult volunteers.

Torkildsen G, O'Brien TP.

Clin Ther 2008; 30 (11): 2005-2014.

### BACKGROUND

Effective ocular tissue concentrations and prolonged residence times of antibacterial agents are important in treating both acute and chronic diseases. Conjunctival biopsy allows the determination of specific tissue concentration data for topical ophthalmic agents. Drug concentration analysis at various time points following instillation allows interpretation of the residence time and a rationale for dosing frequency.

### OBJECTIVE

This study compared the pharmacokinetic parameters of 2 currently available topical ocular antibiotics—azithromycin ophthalmic solution 1% and moxifloxacin ophthalmic solution 0.5%—in the conjunctiva of healthy volunteers after a single topical administration.

### METHODS

This single-dose, randomized, open-label, active-controlled clinical trial was conducted at ORA Clinical Research and Development, North Andover, Massachusetts. Subjects were randomly assigned to receive a single dose of azithromycin or moxifloxacin and to undergo biopsy sampling at 30 minutes or 2, 12, or 24 hours after administration. Concentrations of azithromycin and moxifloxacin were determined using liquid chromatography tandem mass spectrometry. Adverse events (AEs) were assessed at all visits using visual acuity measurements, slit-lamp biomicroscopy, and direct questioning.

### RESULTS

Forty-eight subjects (mean age, 40.0 years; 48% female; 96% white, 2% black, and 2% Asian) underwent conjunctival biopsy. Mean (SD) concentrations of azithromycin in conjunctival tissue (lower limit of quantitation [LLOQ], 1 microg/g for 1-mg biopsy specimen) were 131 (89), 59 (19), 48 (24), and 32 (20) microg/g at 30 minutes and 2, 12, and 24 hours, respectively (median values, 117, 69, 46, and 30 microg/g). Mean concentrations of moxifloxacin in conjunctival tissue (LLOQ, 0.05 microg/g for 1-mg biopsy sample) were 1.92 (2.03), 3.77 (8.98), 0.02 (0.04), and 0.01 (0.02) microg/g at 30 minutes and 2, 12, and 24 hours, respectively (median values, 1.12, 0.12, <0.05, and <0.05 microg/g). Thirteen subjects (6 in the azithromycin group and 7 in the moxifloxacin group) experienced 20 AEs, 11 of which were considered possibly related to study treatment, and 15 of which were ocular (most commonly conjunctival hemorrhage).

### CONCLUSIONS

In this single-dose study of 2 currently available topical ocular antibiotics in healthy volunteers, therapeutic concentrations were achieved with both agents. Both treatments were well tolerated in the population studied.

## Ocular Distribution of a DuraSite Formulation Containing 2% Azithromycin in Rabbit Eyes.

Si EC, Cheung PS, Bowman LM, Hosseini K.

ARVO. Fort Lauderdale, USA, May 3-7, 2009. 2009; E-Abstract 2662/D892.

### PURPOSE

The ocular bioavailability of a 2% ophthalmic solution of azithromycin in DuraSite was evaluated in pigmented rabbits.

### METHOD

Forty-two pigmented rabbits were divided into 7 dose groups, one for each of 7 time points, at 0.5, 1, 2, 4, 8, 13, and 24 hours post-dosing. At the zero hour time point, 25  $\mu$ L of 2% azithromycin in DuraSite was instilled into both the right and left eyes of each animal. At the designated time points, animals were sacrificed, and tears, bulbar conjunctiva, cornea, and plasma were harvested. The level of azithromycin in these tissues were determined using an HPLC/MS/MS method.

### RESULTS

High concentrations of azithromycin were detected in the cornea, bulbar conjunctiva, and tears. Peak tissue concentrations ( $C_{max}$ ) ranged from 50  $\mu$ g/g in the cornea to 195  $\mu$ g/g in tears between 0.5 and 4 hours post dosing. The  $t_{1/2}$  in these tissues were 20, 12, and 5 hours, respectively. At the end of 24 hours, ocular tissue concentrations exceeded the MIC breakpoint for the most common causative pathogens of bacterial conjunctivitis by at least 7-fold. In contrast, plasma azithromycin levels were generally 4 to 5 orders of magnitude lower than those in the ocular tissues.

### CONCLUSIONS

The long half-lives and high tissue concentrations attained by topical application of the 2% azithromycin formulation in DuraSite suggest the possibility for a shorter dosing regimen against ocular infections.

### Lipid emulsions as a potential delivery system for ocular use of azithromycin. *Drug Dev Ind Pharm* (2009)

Liu Y, Lin X, Tang X.

*Drug Dev Ind Pharm* 2009; 35 (7):887-96.

#### OBJECTIVE

To obtain stable positively charged Azithromycin (AZI) emulsions with a mean droplet size of 120 nm for the treatment of eye diseases.

#### METHODS

The emulsions were obtained by using a suitable homogenization process. The physical stability was monitored by measuring the particle size, zeta potential, and visible appearance. The drug entrapment efficiency was measured by both ultracentrifugation and ultrafiltration methods. Compared with a phosphate solution of AZI, the stability profiles of AZI in lipid emulsions at various pH values were monitored by high-performance liquid chromatography. A pharmacokinetic study was performed to determine the drug levels in rabbit tear fluid using Ultra-performance liquid Chromatography-mass spectrometry.

#### RESULTS

Almost all the AZI in the lipid emulsion was distributed in the oil phase and small unilamellar liposomes without contact with water, thereby avoiding hydrolysis. The elimination of the AZI lipid emulsions in tear fluid was consistent with the basic linear pharmacokinetic characteristics. The AUC(0-t) of the AZI lipid emulsion (1%, w/v) and aqueous solution drops (1%, w/v) was 1873.58 +/- 156.87 and 1082.46 +/- 179.06 mug/ml respectively.

#### CONCLUSIONS

This study clearly describes a new formulation of AZI lipid emulsion for ocular administration, and lipid emulsions are promising vehicles for ophthalmic drug delivery.



## Tear Concentrations of Azithromycin following Topical Administration of a Single Dose of Azithromycin 0.5%, 1.0% and 1.5% Eye-drops (T1225) in Healthy Volunteers.

Chiambaretta F, Garraffo R, Elena PP, Pouliquen P, Delval L, Rigal D, Dubray C, Goldschmidt P, Tabbara K, Cochereau I.

Eur J Ophthalmol 2008;18 (1): 13-20

### PURPOSE

To evaluate azithromycin tear concentrations after one drop of T1225 0.5%, 1.0%, and 1.5% eyedrops.

### METHODS

In this randomized, double-masked study, 91 healthy volunteers received one drop into each eye of T1225 0.5% (n=23), T1225 1.0% (n=38), or T1225 1.5% (n=38). Azithromycin tear concentrations were measured by HPLC-MS at seven time points for 24 hours. Tolerability was evaluated.

### RESULTS

T1225 1.0% and 1.5% had similar pharmacokinetic profiles. After a post-instillation peak (167 to 178 mg/L after 10 minutes), mean concentrations remained above 7 mg/L for 24 hours (except for T1225 1% at H24). A delayed increase of the azithromycin mean tear concentration might be explained by the known late azithromycin release from tissues after storage in cells. Areas under inhibitory curve (AUCs) of T1225 1.0% and 1.5% were higher than AUCs of T1225 0.5% and ranged between 47 and 90. The three T1225 concentrations were safe for the ocular surface.

### CONCLUSIONS

Once daily instillation of T1225 1.0% and 1.5% was shown to reach an AUC markedly above the required threshold for an antibacterial activity against Gram-positive bacteria (25-35). These results suggest that a BID instillation is more likely to ensure antimicrobial activity against Gram-negative bacteria (threshold >100).



### Evaluation Of Topical Administration T1225 (azithromycin Oil Based Eye Drops) In Corneal Wound Healing After Refractive Surgery In An Experimental Model.

Merayo-Lloves JM., Blanco-Mezquita T, Ibares-Frias L, Cantalapiedra R, Alvarez-Barcia A.

ARVO. Fort Lauderdale, USA, May 5-10, 2007. 2007; E-Abstract 783/B686.

#### PURPOSE

The expected benefit of topical application of T1225 eye drops (Laboratories Thee, France) in corneal refractive surgery is antimicrobial prophylaxis of the ocular surface. Therefore it makes sense to evaluate the tolerance of this topical drug in various models of surgically-induced corneal injuries like surface ablation model (PRK) and LASIK. As these eye drops are oil-based we wonder whether this slippery characteristic might negatively interfere with the good achievement of the cornea stromal and epithelial flap and corneal wound healing after injury.

The purpose of this project is to evaluate the effect of the antibiotic eye drops T1225 in corneal wound healing after refractive surgery in hens

#### METHODS

60 adult Lothmann Braun hens were divided in 6 groups of 10 animals. Group 1 (unmanipulated), group 2 (PRK) and group 3 (Lasik) were given 20 Microliters of saline eye drops 3 days prior to surgery and 3 days after surgery bid. Groups 4, 5, and 6 underwent the same surgery as 1, 2, and 3 and were treated with T1225 (1.5% azithromycin) in the same fashion.

Outcome was measured by clinical parameters on days 1 to 6 (corneal epithelial closure, clinical grade of haze and corneal thickness). Cell biology parameters were evaluated on day 6 post operative: light histology, apoptosis (Tunnel) cell proliferation (BrdU Staining), migration and differentiation (myofibroblast formation).

#### RESULTS

T 1225 was well tolerated with no clinical differences (time of closure, haze and pachymetry) for PRK and Laic groups compared with the saline treated animals. Animals that underwent corneal surgery developed apoptosis, proliferation and myofibroblast formation (more in the PRK groups with statistical significant differences) but there were no differences among the groups treated with saline or T1225 for the same type of corneal surgery

#### CONCLUSIONS

Topical administration of T1225 oil based azithromycin eye drops is well tolerated in the non manipulated animals and hens treated with corneal refractive surgery (PRK and Lasik). There were no differences in wound healing and flap adherence.



## Microbiological Efficacy Of 3-Day Treatment With Azithromycin 1.5% Eye-Drops for Purulent Bacterial Conjunctivitis. (2008).

Denis F, Chaumeil C, Goldschmidt P, Delval L., Pouliquen P, Cochereau I; Chainier D, de Barbeyrac B.

Eur J Ophthalmol 2008; 18 (6): 858-68.

### PURPOSE

Antibacterial efficacy of topically applied azithromycin 1.5% was compared with tobramycin 0.3% in a multicenter, randomized, investigator-masked study for the treatment of purulent bacterial conjunctivitis.

### METHOD

A total of 1043 adults and children received either azithromycin twice daily for 3 days (n=524) or tobramycin every 2 hours while awake for 2 days, then four times daily for 5 days (n=519). Conjunctival swabbing was taken at days 0, 3, and 9, using alginate swabs re-suspended in a dissolution-transport medium, providing rapid and reproducible results. Cagle's criteria were used to define the pathogenicity level for each isolated bacterium.

### RESULTS

In the per-protocol set, the rate of bacteriologic resolution was 85.2% for Azithromycin versus 83.8% for tobramycin on day 3, and 92.8% for azithromycin versus 94.6% for tobramycin on day 9. Azithromycin was demonstrated to be noninferior to tobramycin according to the 10% noninferiority margin. Although some bacteria were categorized as resistant to tested antibiotics, eradication was observed (for azithromycin: Acinetobacter, Enterobacteriaceae, Pseudomonas), highlighting the specific pharmacokinetics/pharmacodynamics of the ocular route.

### CONCLUSIONS

In total, topical therapy with azithromycin 1.5% administered only twice daily for 3 days effectively eradicates most pathogenic bacteria associated with bacterial conjunctivitis. These microbiologic results are in accordance with the observed clinical outcome. This new anti-infective product has the advantage of a short treatment course which could lead to an improvement in patient compliance. (Eur J Ophthalmol 2008; 18: 858-68)

## Comparison of in vitro Susceptibility Rates of Moxifloxacin and Azithromycin Against Representative Ocular Isolates From 1997-2007.

Ovodenko B, Ritterband DC, Shah MK, Seedor JA., Koplin RS.

ARVO. Fort Lauderdale, USA, Apr 26-May 1, 2008. 2008; E-Abstract 5531/A142.

### PURPOSE

To study the in-vitro susceptibility profiles of moxifloxacin and azithromycin against representative conjunctiva strains of *S. aureus*, *S. epidermidis*, *S. pneumoniae*, *S. viridans*, and *H. influenzae* over the past decade.

### METHODS

66 ocular isolates archived at the New York Eye and Ear Infirmary (NYEEI) from 1997-2007 from cases of bacterial conjunctivitis were tested for in vitro susceptibility against moxifloxacin and azithromycin. Etest® antimicrobial gradient strips were used for the quantitative determination of Minimum Inhibitory Concentration (MIC) for each organism. The MIC90 was calculated and reported below. The MIC90 represents the antibiotic concentration that would inhibit the growth of 90% of the tested bacterial isolates. All data was analyzed according to CLSI criteria based on serum concentrations. The archived organisms were subcultured on 5% sheep blood agar. A bacterial suspension was prepared from the subcultures and this suspension was swabbed on a Mueller-Hinton agar plate and incubated for 18-24 hours at 36°C. To facilitate growth, the streptococcus isolates were inoculated on the Mueller Hinton agar plate with 5% sheep blood. Etest® strips were applied and the MIC was read where the inhibition ellipse intersected the scale on the strip.

### RESULTS

Of the 66 organisms tested 7 were resistant to both antibiotics. 59 organisms were sensitive to moxifloxacin and 57 organisms were sensitive to azithromycin. The MIC90 against *S. aureus* was 0.094 µg/ml for moxifloxacin and >256 µg/ml for azithromycin. The MIC90 against *Strep viridans* was 0.125 µg/ml for moxifloxacin and 4 µg/ml for azithromycin. The MIC90 against *H. Influenzae* was 0.47 µg/ml for moxifloxacin and 4 µg/ml for azithromycin. There were too few organisms to calculate MIC90 for *Strep pneumoniae*.

### CONCLUSIONS

Despite the preferential use of the fluoroquinolone class of antibiotics in ophthalmology over the past decade, moxifloxacin maintains a superior in vitro susceptibility profile with far lower MIC90 values as compared to azithromycin in representative conjunctival strains of *S. aureus*, *S. epidermidis*, *S. viridans*, and *H. influenzae*.

## Comparison Of Azithromycin And Moxifloxacin Against Bacterial Isolates Causing Conjunctivitis (2007)

Ohnsman C, Ritterband D, O'Brien T, Girgis D, Kabat A.

Curr Med Res Opin 2007; 23 (9): 2241-2249.

### OBJECTIVE

To examine in vitro resistance to azithromycin and moxifloxacin in bacterial conjunctivitis isolates.

### METHODS

MIC90s (Minimum Inhibitory Concentration) and resistance rates to azithromycin and moxifloxacin were determined based upon micro-titer broth dilution and/or antimicrobial gradient test strips in a multi-center phase III study and confirmed externally.

### RESULTS

The most common isolates collected from bacterial conjunctivitis patients in the phase III study were *Haemophilus influenzae* (40.6%), followed by *Staphylococcus epidermidis* (19.3%), *Propionibacterium acnes* (17.3%), *Streptococcus pneumoniae* (16.8%), and *Staphylococcus aureus* (0.06%). MIC90s for all of these organisms were well below established resistance breakpoints for moxifloxacin, indicating no bacterial resistance. On the other hand, the MIC90 for *H. influenzae* was 3-fold higher than the resistance breakpoint for azithromycin, > or = 128-fold higher for *S. epidermidis*, 16-fold higher for *S. pneumoniae* and > or = 128-fold higher for *S. aureus*, indicating moderate to very high bacterial resistance to azithromycin.

### CONCLUSIONS

Resistance to azithromycin is more common than resistance to moxifloxacin in clinical isolates causing bacterial conjunctivitis

## Evaluation of Azithromycin Topical Ophthalmic Formulations Using Time-Kill Studies.

Kowalski RP, Romanowski EG, Mah FS et al.

ARVO. Fort Lauderdale, USA, May 3-7, 2009. 2009; E-Abstract 2666/D898.

### PURPOSE

We compared the antibacterial efficacy of AzaSite (1.0% azithromycin formulated in DuraSite containing 0.01% benzalkonium chloride) to Azyter (1.5% azithromycin formulated in a non-preserved oil) using in vitro time-kill studies.

### METHODS

Time-kill studies were processed to test *Proteus mirabilis*, *Staphylococcus epidermidis*, *S aureus*, *S aureus* [MRSA] azithromycin-resistant, *Streptococcus viridans*, *St pneumoniae*, *Pseudomonas aeruginosa*, *P putida*, *Branhamella catarrhalis*, *Bacillus cereus*, *Enterococcus faecalis*, *Serratia marcescens*, *Enterobacter aerogenes*, *Klebsiella pneumoniae*, *E coli*, and *Haemophilus influenzae* to AzaSite and Azyter at time points 0, 15 min, 30 min, 1 hr, 2 hrs, 4 hrs, 6 hrs, 8 hrs, and 24 hrs, using the standard colony count method.

### RESULTS

AzaSite (94%, 15/16) significantly ( $p=0.00017$ , Fisher's exact test) killed more bacterial isolates by 15 min than Azyter (25%, 4/16). The colony counts for *Proteus mirabilis* at each time point (15 min to 8 hrs) were more reduced for AzaSite than Azyter.

### CONCLUSIONS

In vitro time-kill studies demonstrated that AzaSite was more effective in eradicating bacterial isolates than Azyter. Clinical trials are recommended to determine if these in vitro results parallel in vivo efficacy.

## The Development of a Novel *in vitro* Efficacy Testing Method for a Cell-Associated Antibiotic

Romanowski EG, Kowalski RP, Mah FS, Yates KA, Gordon YJ, Shanks RMQ  
ARVO. Fort Lauderdale, USA, May 3-7, 2009. 2009; E-Abstract 2678/D910.

### PURPOSE

Some antibiotics are cell-associated and their efficacy may not be optimally evaluated using standard MIC methods. We developed and evaluated a novel *in vitro* method of antibiotic efficacy testing for cell-associated antibiotics. Specifically we determined the ability of cell-associated azithromycin (AZ) and ofloxacin (OFX) to protect conjunctival cells from infection with *Staphylococcus aureus* (SA).

### METHODS

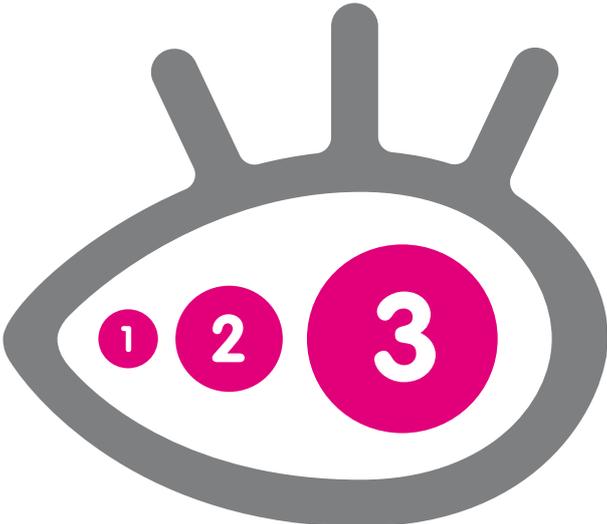
Chang conjunctival epithelial cells were grown to confluence in 96 well plates. Triplicate wells were incubated with medium containing a range of concentrations (4-512 µg/ml) of AZ, OFX, or no-antibiotics. After 24 hrs, the antibiotic and control medium-treated cells were washed to remove non-cell-associated antibiotics. The cells were then challenged with 4 isolates of AZ-, OFX-susceptible (AZ MICs <1.5 µg/ml; OFX MICs <0.75 µg/ml) SA (5 x 10<sup>5</sup> CFU/ml) for 24 hrs. Subsequently, the cells were stained with gentian violet. Positive deep-blue staining indicated that the cell monolayer was intact and was deemed protected from bacterial challenge and free of any antibiotic toxicity. Unstained wells were deemed unprotected from bacterial challenge and/or demonstrated antibiotic toxicity. Microscopy verified the presence or lack of cells.

### RESULTS

Incubation of conjunctival epithelial cells with >32 µg/ml of AZ fully protected all cells from challenge with all 4 SA isolates, while incubation with 256 µg/ml of OFX was required for comparable protection for some isolates but was inadequate for others. Toxicity was observed for OFX at 512 µg/ml whereas AZ exhibited no toxicity.

### CONCLUSIONS

AZ protected conjunctival cells from SA challenge at a dose at least 8-fold lower than OFX, suggesting that AZ is more cell associated than OFX. The susceptibility of bacteria to an antibiotic *in vivo* may be, in part, a function of the affinity of the antibiotic to host cellular components. Antibacterial activity and cell protection may not be accurately measured by standard susceptibility testing alone, and further study is warranted.



# INDICATION AND PRESCRIPTION IN OPHTHALMOLOGY

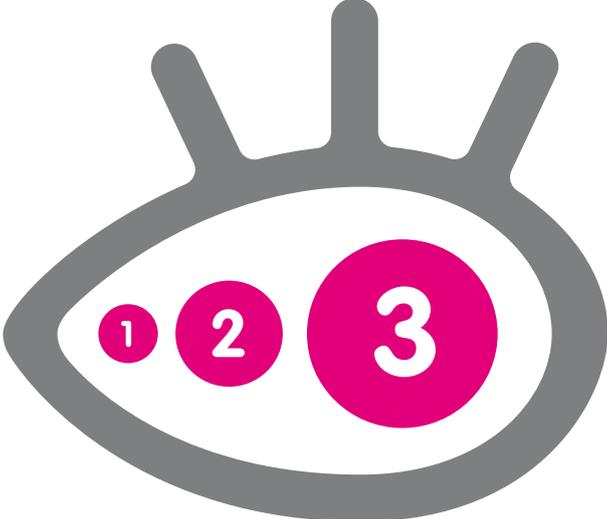
**BACTERIAL CONJUNCTIVITIS**

**BLEPHARITIS**

**KERATITIS**

**TRACHOMA**

**SAFETY**



# BACTERIAL CONJUNCTIVITIS



## 3-day treatment with azithromycin 1.5% eye drops versus 7-day treatment with tobramycin 0.3% for purulent bacterial conjunctivitis: multicentre, randomised and controlled trial in adults and children.

Cochereau I, Meddeb-Ouertani A, Khairallah M, Amraoui A, Zaghloul K, Pop M, Delval L, Pouliquen P, Tandon R, Garg P, Goldschmidt P, Bourcier T. *Br J Ophthalmol* 2007; 91 (4): 465-469

### AIM

to compare the efficacy and safety of Azyter, azithromycin 1.5% eye drops, for 3 days with tobramycin 0.3% for 7 days to treat purulent bacterial conjunctivitis.

### METHODS

This was a multicentre, randomised, investigator-masked study including 1043 children and adults with purulent bacterial conjunctivitis. Patients received either azithromycin 1.5% twice-daily for 3 days or tobramycin 0.3%, 1 drop every two hours for 2 days, then four times daily for 5 days. Clinical signs were evaluated and cultures obtained at D0, D3 and D9 (where D refers to "day"). Primary variable was the clinical cure at the Test-of-Cure (TOC)-visit (D9+/-1), for patients with D0-positive cultures. The cure was defined as: bulbar conjunctival injection and discharge scores of 0.

### RESULTS

Among 471 patients with D0-positivity in the per protocol set, 87.8% of the azithromycin 1.5% group and 89.4% of the tobramycin group were clinically cured at the TOC-visit. Azithromycin was non-inferior to tobramycin for clinical and bacteriological cure. Clinical cure was significantly higher with azithromycin 1.5% at D3. The safety profile of azithromycin was satisfactory with a good patient and investigator's acceptability.

### CONCLUSIONS

Azithromycin 1.5% for 3 days was as effective and as safe as tobramycin for 7 days. Furthermore, more azithromycin than tobramycin patients presented an early clinical cure at Day 3. Due to its twice daily dosing regimen for 3 days, azithromycin represents a step forward in the management of purulent bacterial conjunctivitis, especially in children.



## Efficacy assessment of azithromycin 1.5% eye drops versus tobramycin 0.3% on clinical signs of Purulent Bacterial Conjunctivitis

Robert PY, Bourcier T, Meddeb-Ouertani A, Khairallah M, Zaghloul K, Amraoui A, Bhagat Y, Pop M, Cochereau I.

J. Fr Ophthalmol 2010. Article in press ;

### INTRODUCTION

Bacterial conjunctivitis are characterised by hyperaemia and discharge of one or two eyes. Those clinical signs appear quickly and are contagious. This study compares the clinical efficacy (signs and symptoms) and safety of azithromycin 1.5% eye drops with tobramycin 0.3%.

### PATIENTS AND METHODS

This was a multicentre, randomised, investigator-masked study including 1,043 patients with purulent bacterial conjunctivitis. Patients received either azithromycin twice-daily for 3 days or tobramycin, 1 drop every two hours for 2 days, then four times daily for 5 days. Primary variable was the clinical cure at the Test-of-Cure (TOC)-visit (D9) on the worse eye. The cure was defined as: bulbar conjunctival injection and discharge scores of 0. Clinical signs were evaluated at D0, D3 and D9.

### RESULTS

87.8% of patients in azithromycin group and 89.4% in the tobramycin group were clinically cured at D9. Clinical cure with azithromycin was non-inferior to tobramycin at D9: discharge was absent in 96.3% of patients treated with azithromycin and 95.1% with tobramycin. Azithromycin was well tolerated.

### CONCLUSIONS

Azithromycin 1.5% for 3 days (6 drops) was as effective as tobramycin for 7 days (36 drops). Furthermore, patients under azithromycin presented an early clinical cure at Day 3 than patients under tobramycin. Azyter<sup>®</sup>, with its convenient dosing (BID during 3 days) represents a step forward in the management of purulent bacterial conjunctivitis.



## Efficacy and Safety of Azithromycin 1.5% Eye Drops for Purulent Bacterial Conjunctivitis in Pediatric Patients.

Bremond-Gignac D, Mariani-Kurkdjian P, Beresniak A, El Fekih L, Bhagat Y, Pouliquen P, Delval L, Goldschmidt P, Bingen E, Cochereau I.

*Pediatr Infect Dis J* 2009 Nov 20. [Epub ahead of print]

### BACKGROUND

Purulent bacterial conjunctivitis affects all ages with high frequency in newborns and children. In a subset of 150 children included in a large study having enrolled 1043 patients, our aim was to analyze in children, the efficacy and safety of azithromycin 1.5% eye-drops in the treatment of this disease.

### METHODS

This multicenter, randomized, investigator-masked, parallel-group study, included 150 children and adolescents to study safety and compare azithromycin 1.5% eye drops twice daily for 3 days and tobramycin 0.3% 1 drop every 2 hours for 2 days then 4 times daily for 5 days. Out of 150 patients included, 58 had positive cultures and were studied for efficacy. Signs and symptoms were evaluated and cultures obtained at baseline, Days 3 and 9. Primary efficacy variable was the clinical cure (score 0 for bulbar conjunctival injection and purulent discharge) at the test of cure visit (day 9).

### RESULTS

Both treatments were effective with a clinical and microbiologic cure of more than 80% of children on day 9. Azithromycin therapy provided a greater bacteriologic cure on day 3 than did tobramycin ( $P < 0.001$ ) and eradicated bacteria that were defined as resistant, using classical antibiogram. No adverse effects were noted on the ocular surface.

### CONCLUSIONS

Azithromycin 1.5% eye drops leads to a rapid clinical and microbiological cure.



## Ocena skuteczności i tolerancji 1,5% kropli ocznych azytromycyny w leczeniu bakteryjnego zapalenia spojówek

### [Evaluation of effectiveness and tolerance of treatment with azithromycin 1.5% eye drops in bacterial conjunctivitis]

Ambroziak AM, Szaflik JP, Hapunik A.

Z Katedry i Kliniki Okulistyki II Wydziału Lekarskiego Warszawskiego Uniwersytetu Medycznego. spkso@spkso.waw.pl. Klin Oczna 2009; 111 (1-3): 46-9.

#### INTRODUCTION

Azithromycin is a macrolide class antibiotic, recently adapted for topical use in ophthalmology. It is effective against the most frequent pathogens found in bacterial conjunctivitis, Gram positive and Gram negative bacteria. Azithromycin has the specificity to have sustained high tissue levels: after repeated instillation, it has been shown to reach sustained concentrations above the MICs of susceptible bacteria for 4 days in tears and for 7 days in conjunctiva.

#### THE AIM OF STUDY

To investigate the effectiveness and tolerance of treatment with Azithromycin 1.5% eye drops in bacterial conjunctivitis.

#### MATERIALS AND METHODS

The prospective study included 40 patients (69 eyes) with purulent bacterial conjunctivitis; aged 21-70 years; average: 38.05. Patients were treated with 1.5% azithromycin eye drops topically twice-daily for 3 days. Conjunctival swabbings were taken at the 1st and the 7th +/- 1 day of the treatment. Effectiveness and tolerance of eye drops were assessed in 7th +/- 1 day from the beginning of the treatment.

#### RESULTS

Bacteriological cultures were positive before treatment in 34 eyes (49.28%), negative--35 eyes (50.72%). In 69 eyes with bacterial conjunctivitis the following microorganisms were identified (34 eyes): *Streptococcus pneumoniae* 23.53% (8 eyes), *Staphylococcus aureus* 23.53% (8 eyes), *Staphylococcus epidermidis* 20.59% (7 eyes), *Haemophilus influenzae* 17.65% (6 eyes), *Morganella Morgani* 2.94% (1 eye), *Proteus mirabilis* 2.94% (1 eye), *Enterococcus* species 2.94% (1 eye), *Streptococcus viridians* 2.94% (1 eye), *Moraxella (Branhamella) catarrhalis* 2.94% (1 eye). Positive bacteriological culture at the 7th day of treatment--2 eyes (1 eye--*Staphylococcus epidermidis* MSC-NS, 1 eye--*Morganella Morgani*). Clinical recovery or significant improvement were observed in 68 of 69 evaluated eyes.

#### CONCLUSIONS

Three-day topical therapy with azithromycin 1.5% eye drops is an effective and well tolerated therapy for purulent bacterial conjunctivitis.

## A randomized trial assessing the clinical efficacy and microbial eradication of 1% azithromycin ophthalmic solution vs tobramycin in adult and pediatric subjects with bacterial conjunctivitis

Abelson M, Protzko E, Shapiro A, Garces-Soldana A, Bowman L.

Clin Ophthalmol 2007;1 (2): 177-82.

### OBJECTIVE

The study was designed to evaluate the efficacy of an ophthalmic formulation of 1% azithromycin in DuraSite(R) (AzaSite, InSite Vision, Alameda CA, USA) and demonstrate equivalence with 0.3% tobramycin ophthalmic solution, USP, for the treatment of bacterial conjunctivitis as defined by the resolution of clinical signs and the eradication of pathogens.

### DESIGN

Prospective, randomized, active-controlled, double-masked, phase 3 trial conducted at 47 US sites between 6 August 2004 and 6 October 2005.

### PARTICIPANTS

Subjects aged 1 year or older with diagnosis of acute bacterial conjunctivitis.

### METHODS

Bacteriologically confirmed participants received either 1% azithromycin in Dura-Site (n = 159) or tobramycin (n = 157). Masked study medications were dosed 4 times a day for 5 days. Participants in the 1% azithromycin in DuraSite group were dosed twice a day with active drug on days 1 and 2 and once daily on days 3 through 5. The other doses were vehicle. Clinical signs and bacterial cultures were evaluated at visit 3 (day 6 + 1).

### RESULTS

Clinical resolution was observed in 79.9% of participants in the 1% azithromycin in DuraSite group, as compared with 78.3% of those in the tobramycin group (95% CI: -7.4-10.5). Bacterial eradication was 88.1% in the 1% azithromycin in DuraSite group vs 94.3% in the tobramycin group (95% CI: -12.4-0.0). Analyses of resistance confirmed that 1% azithromycin in DuraSite eradicated Staphylococci and Streptococci strains that are commonly resistant to azithromycin, erythromycin, and fluoroquinolones.

### CONCLUSIONS

The efficacy of 1% azithromycin in DuraSite and tobramycin are equivalent; however, this formulation of azithromycin also permits effective dosing intervals of twice a day on days 1 and 2 followed by once daily on the last 3 days of therapy, for a total of 65% fewer doses. In vitro, the killing spectrum of 1% azithromycin in DuraSite appears to be enhanced relative to 1% azithromycin without DuraSite.

## Clinical Cure of Bacterial Conjunctivitis With Azithromycin 1%: Vehicle-Controlled, Double-Masked Clinical Trial

Abelson MB, Heller W, Shapiro AM, SI E, Hsu P, Bowman LM.

AzaSite Clinical Study Group. *Am J Ophthalmol* 2008; 145 (6): 959-65.

### PURPOSE

To analyze the effect of azithromycin 1% ophthalmic solution in DuraSite (InSite Vision, Inc, Alameda, California, USA) on bacterial conjunctivitis. DESIGN: Prospective, randomized, vehicle-controlled, parallel-group, double-masked multicenter clinical study.

### METHODS

Eligible male or female participants with a clinical diagnosis of acute bacterial conjunctivitis were randomized to either 1% azithromycin in DuraSite or vehicle for five days. Infected eyes were dosed twice daily on days 1 and 2 and once daily on days 3 through 5. Conjunctival cultures were obtained at baseline, visit 2 (day 3 or 4), and visit 3 (day 6 or 7). The primary end point was clinical resolution of signs and symptoms (rating of zero on ocular discharge, bulbar and palpebral injection) at visit 3. Efficacy measures were clinical resolution and bacterial eradication as evaluated in the per-protocol population. Safety was assessed by adverse events, slit-lamp findings, and ophthalmoscopy.

### RESULTS

Two hundred and seventy-nine participants (n = 130, 1% azithromycin in DuraSite; n = 149, vehicle), age one to 96 years, were evaluated for efficacy. Clinical resolution with azithromycin ophthalmic solution was statistically significant compared with that of vehicle (P = .030) at visit 3. Bacterial eradication rates with azithromycin ophthalmic solution reached 88.5% at visit 3 (P < .001) and included some pathogens resistant to azithromycin in vitro. Overall, adverse event rates were similar in both treatment groups.

### CONCLUSIONS

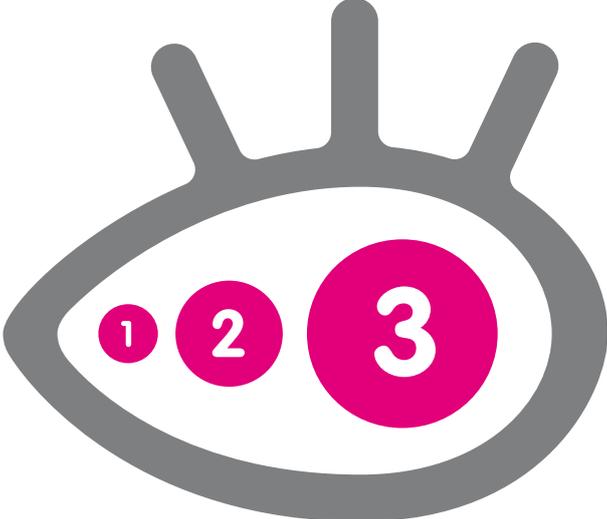
Azithromycin 1% ophthalmic solution in DuraSite showed statistically significant differences in clinical resolution and bacterial eradication rates when compared with vehicle. Because it was well tolerated in this population, it may be a viable treatment option for children and adults with bacterial conjunctivitis.

### **Clinical development of 1% azithromycin in DuraSite, a topical azalide anti-infective for ocular surface therapy.**

**Friedlaender MH, Protzko E.**

Clin Ophthalmol 2007; 1 (1): 3-10.

Conjunctivitis, or inflammation of the conjunctiva, refers to a diverse group of ocular surface diseases of viral or bacterial origin that primarily affect the conjunctiva. In developed countries, the most common causative bacterial pathogens are *Staphylococcus aureus*, *Haemophilus influenzae*, and *Streptococcus pneumoniae*. Most varieties of conjunctivitis are self-limiting; however, some cases can be extremely contagious or cause serious complications if left unchecked. New ocular antibiotics are needed to keep pace with the increasing incidence of bacterial resistance and provide options that decrease the overall treatment burden and encourage patient compliance. Azithromycin is a well known systemic anti-infective with broad spectrum activity against gram positive-, gram negative-, and atypical bacteria species. Ocular use has been limited because its solubility and stability profiles in aqueous media were not favorable for delivery to the eye. An eyedrop of 1% azithromycin in DuraSite(R) (AzaSite, InSite Vision, Alameda, CA, USA), a bioadhesive ocular drug delivery system, was recently developed and evaluated in clinical trials. This formulation is well tolerated, delivers a high concentration of azithromycin to the conjunctiva, has a broader eradication profile than aqueous azithromycin, and can be effectively dosed with 7 drops, a 65% reduction in the amount of drops required by the most popular antibiotics currently used for conjunctivitis.



## Efficacy of topical azithromycin ophthalmic solution 1% in the treatment of posterior blepharitis

Luchs J.

Adv Ther 2008; 25 (9): 858-70

### INTRODUCTION

Azithromycin, a broad-spectrum antibiotic with potent anti-inflammatory activities, has the potential to effectively treat blepharitis, an inflammatory disease of the eyelid with abnormal eyelid flora as an etiologic determinant. The present study compared the efficacy of topical azithromycin ophthalmic solution 1% (AzaSite; Inspire Pharmaceuticals, Inc, NC, USA) combined with warm compresses (azithromycin group) to warm compresses alone (compress group) in patients with posterior blepharitis.

### METHODS

Twenty-one patients diagnosed with posterior blepharitis were randomized in an open-label study to receive either azithromycin plus warm compresses (10 patients), or compresses alone (11 patients). All patients were instructed to apply compresses to each eye for 5-10 minutes twice daily for 14 days. Each eye in the azithromycin group also received azithromycin solution (1 drop) twice daily for the first 2 days followed by once daily for the next 12 days. Patients were evaluated at study initiation (visit 1) and at end of treatment (visit 2) for the severity of five clinical signs: eyelid debris, eyelid redness, eyelid swelling, meibomian gland (MG) plugging, and the quality of MG secretion. At visit 2, patients also rated their degree of overall symptomatic relief.

### RESULTS

Twenty patients completed the study. At visit 2, patients in the azithromycin group demonstrated significant improvements in MG plugging, MG secretions, and eyelid redness as compared with the compress group. In the azithromycin group, MG plugging resolved completely in three patients and MG secretion returned to normal in two patients; no such results were seen in the compress group. Furthermore, a higher percentage of patients in the azithromycin group rated overall symptomatic relief as excellent or good. Visual acuity measurements and biomicroscopic evaluation revealed no ocular safety issues.

### CONCLUSION

Azithromycin ophthalmic solution in combination with warm compresses provided a significantly greater clinical benefit than warm compresses alone in treating the signs and symptoms of posterior blepharitis.

### **Use Of Azithromycin Ophthalmic Solution In The Treatment Of Chronic Mixed Anterior Blepharitis**

**John T., Shah AA.**

*Ann Ophthalmol (Skokie) 2008; 40 (2): 68-74*

We tested the efficacy of azithromycin ophthalmic solution for the treatment of chronic mixed anterior blepharitis. The findings suggest that patients with chronic mixed anterior blepharitis can be more effectively treated with azithromycin ophthalmic solution than erythromycin ophthalmic ointment. Patients treated with azithromycin ophthalmic solution show an extraordinary clinical response with shorter treatment duration.

## New Considerations In The Treatment Of Anterior And Posterior Blepharitis

**Donnenfeld ED, Mah FS, McDonald MB, O'Brien TP, Kerry D. Solomon B.**

A Continuing Medical Education Supplement to Refractive Eyecare 2008; 12 (4).

The AIM of this article is a discussion about blepharitis and how it can be treated. Indeed, there are a lot of treatment options for this disease but there is no simple and effective means to treat it. However, one class of antibiotics, the macrolides, could be solution. They possess both anti-inflammatory and anti-infective properties. Within this call, azithromycin is an attractive candidate for treating a chronic condition within a solid tissue such as eyelid.

Blepharitis may be the most common medical condition that is encountered. The management of Blepharitis is a vital aspect of preventing complications and obtaining optimal outcomes in the cataract and refractive surgery. If not treated prior to surgery, blepharitis can negatively affect surgical outcomes; anterior blepharitis may contribute to disastrous postoperative complications such as endophthalmitis.

Topical azithromycin can have high and sustained anti-inflammatory levels without steroid side effects and produces high levels of antibiotic to combat the overgrowth of flora that characterizes anterior blepharitis. Eventually, the discussion concludes by suggesting that azithromycin can provide effective treatment for both anterior and posterior blepharitis.

### **Efficacy of Topical Azithromycin Ophthalmic Solution 1.0% in the Treatment of Chronic Blepharitis Patients.**

**Touhey D, Shapiro A, Torkildsen G, Haque R, Zink RC, Kowalski RP, Mah FS, Pflugfelder SC.**

ARVO. Fort Lauderdale, USA, May 3-7, 2009. 2009; E-Abstract 2661/D893.

#### **PURPOSE**

To evaluate the efficacy of 4-week treatment with azithromycin ophthalmic solution 1.0% in reducing the eyelid margin bacterial load, tear cytokines, and the signs and symptoms of blepharitis in patients with moderate to severe chronic blepharitis.

#### **METHODS**

Eight-week multi-center, open-label clinical study in chronic blepharitis patients. The use of eyelid scrubs or mechanical therapy was not permitted during the study. Patients instilled azithromycin ophthalmic solution 1% BID on days 1 and 2 and QD on days 3-28. Tear samples for cytokine analysis and eyelid margin bacterial cultures were collected at baseline and after 4 weeks of treatment. Bacteria were identified by genus and species when possible and colony counts were graded on a 0-4 scale. Tear samples were evaluated for cytokine concentrations using Luminex multiplex immunobead assay. The severity of the blepharitis signs and symptoms was assessed on a 0-3 or 0-4 ORA blepharitis scale.

#### **RESULTS**

Twenty-six patients were enrolled and twenty-three completed the study. Eyelid margin cultures exhibited significant decreases in coagulase-negative staphylococci ( $p=0.037$ ) and *Corynebacterium xerosis* ( $p<0.001$ ) bacteria. Complete bacterial results for all species will be provided in the poster. Tear cytokine concentrations did not appear to be affected by azithromycin treatment. Median scores for all symptoms (eyelid itching, foreign body sensation/sandiness/grittiness, ocular dryness, ocular burning/pain and swollen eyelids) were significantly decreased from baseline upon treatment completion after 4 weeks of treatment ( $p<0.001$ ). Median scores for the clinical signs of blepharitis including: eyelid margin redness, palpebral conjunctival redness and meibomian gland plugging were significantly reduced after 4 weeks of treatment ( $p<0.001$  to  $p=0.008$ ).

#### **CONCLUSIONS**

Treatment with topical azithromycin ophthalmic solution 1% resulted in a significant reduction in the most common eyelid bacterial flora and provided significant improvement in both signs and symptoms of blepharitis.

## **In vitro transcorneal diffusion of the antimicrobial macrolides azithromycin and clarithromycin and the impact on microbial keratitis**

Van Eyk AD, Seifart HI, Meyer D, van der Bijl P.  
*Cornea* 2009; 28 (4): 441-446.

### **PURPOSE**

To compare the in vitro penetration of azithromycin and clarithromycin across both human and rabbit corneas.

### **METHODS**

In vitro diffusion studies were performed on frozen-thawed (liquid nitrogen, -80 degrees C) corneas using a flow-through diffusion apparatus (24 hours, 20 degrees C, 1.5 mL/h). Either phosphate-buffered saline (PBS) or 2 mg/g polyacrylic acid (Teargel) formulations of clarithromycin and azithromycin (1 or 4 mg/mL) were used in the donor chambers. Effluent samples collected (2 hours) were analyzed using binary high-performance liquid chromatography in conjunction with either UV/VIS or tandem mass spectrometry detection.

### **RESULTS**

The flux values of azithromycin (PBS and polyacrylic acid) across both types of corneas showed concentration dependence. Polyacrylic acid formulations showed a decrease in flux values of azithromycin across both types of corneas. For clarithromycin, flux values across both types of corneas were approximately 2.3-2.4 times higher than azithromycin. The flux values of azithromycin at 4 mg/mL (PBS and polyacrylic acid) across human cornea were higher than those across rabbit cornea, whereas the inverse was true at 1 mg/mL PBS for both drugs.

### **CONCLUSIONS**

Both macrolides penetrated the corneas, and the flux values were found to be concentration dependent (azithromycin). Clarithromycin had a higher diffusion rate across corneas than azithromycin. Although the human cornea had a higher permeability to azithromycin at a higher concentration, the inverse was found at lower concentrations for both drugs. Rabbit cornea can be used in general as an in vitro permeability model for human cornea; however, care must be taken with the extrapolation of results.

## Effect of Topical Azithromycin on Innate Immune Responses in Experimental Keratitis.

Sadrai Z, Hajrasouliha AR, Chauhan SK, Saban DR, Dastjerdi MH, Dana R. ARVO 2009. Fort Lauderdale, USA, May 3-7, 2009. 2009; E-Abstract 5536/A507.

### PURPOSE

Azithromycin (AZM) is a broad-spectrum macrolide antibiotic which may have endogenous anti-inflammatory properties similar to other macrolides via suppression of NF- $\kappa$ B signal transduction pathway. This study aimed to determine the potential immunomodulatory effects of AZM on corneal inflammation.

### METHODS

6-8 week old BALB/c mice underwent thermal cautery to the corneal surface to induce inflammation and leukocyte influx. Corneas were treated topically either with AZM ophthalmic solution 1% (AzaSite®; Inspire Pharmaceuticals, Inc, NC, USA) or the relevant vehicle, twice per day. Corneas were harvested at various time-points (day 1, 3, 7, 10, and 14) to characterize the inflammatory infiltrates via FACS analysis, and to quantitate relevant chemokines/cytokines via real time PCR.

### RESULTS

AZM treatment significantly decreased the overall influx of total bone marrow-derived (CD45+) cells on day 7 by nearly 40%. The majority of the reduction in the CD45+ cells appeared to be found among the CD11b+ (macrophage) and CD11c+ (dendritic cell) subsets, but not among Gr-1+ cells (neutrophils). Moreover, pro-inflammatory chemokines CXCL10 and CCL5, and IL-1 $\beta$  levels were significantly reduced ( $p < 0.05$ ) on day 7 with AZM treatment.

### CONCLUSIONS

Topical AZM reduces infiltration of macrophages and dendritic cells considerably in inflamed corneas. This was further supported by an associated reduction in CXCL10 and CCL5, as well as IL-1 $\beta$ . In addition to its anti-microbial properties, topical AZM holds anti-inflammatory properties in a mouse model of keratitis.



## Trachoma mass treatment with azithromycin 1.5% eye drops in Cameroon: feasibility, tolerance and effectiveness.

Huguet P, Bella L, Einterz E, Goldschmidt P, Bensaid P.

Br J Ophthalmol. 2009 Aug 26. Epub ahead of print

### BACKGROUND/AIMS

An epidemiological study carried out in 2006 indicated the existence of a high prevalence of blinding trachoma in the Kolofata Health District, Far North Region, Cameroon. As a result, the national blindness control program of Cameroon instituted a trachoma elimination programme using the SAFE strategy.

### METHODS

A campaign to treat the entire district population with azithromycin 1.5% eye drops was undertaken in February, 2008. To measure the effectiveness of treatment on the prevalence of active trachoma, two epidemiological studies were conducted on a representative sample of children aged between 1 and 10 years. The first study was performed just prior to the treatment campaign and the second study was performed one year later.

### RESULTS

The prevalence of active forms of trachoma (TF + TF/TI) dropped from 31.5% (95%CI 26.4-37.5) before treatment to 6.3% (95%CI 4.1-9.6) one year after treatment; a reduction of nearly 80%. There were no reports of serious or systemic side effects. Tolerance was excellent. No treatment was interrupted.

### CONCLUSION

Mass treatment with azithromycin 1.5% eye drops is therefore feasible, well tolerated, and effective.



**Efficacy and safety of short duration azithromycin eye drops versus azithromycin single oral dose for the treatment of trachoma in children: a randomised, controlled, double-masked clinical trial.**

Cochereau I, Goldschmidt P, Goepogui A, Afghani T, Delval L, Pouliquen P, Bourcier T, Robert PY.

Br J Ophthalmol 2007; 91 (5): 566-567.

**AIMS**

Efficacy and safety of a short-duration treatment of azithromycin 1.5% eye drops versus oral azithromycin to treat active trachoma.

**METHODS**

Randomised, controlled, double-masked, double-dummy, non-inferiority explanatory study including 670 children from Guinea Conakry and Pakistan if: 1-10 years old; active trachoma (TF+TI0 or TF+TI+ on simplified World Health Organisation (WHO) scale). Three groups received either: azithromycin 1.5% eye drops twice daily for 2 days, for 3 days or azithromycin single 20 mg/kg oral dose. Patients' contacts were treated whenever possible. Clinical evaluation was performed using a binocular loupe. Primary efficacy variable was the cure (no active trachoma (TF0)) at day 60. Non-inferiority margin for difference between cure rates was 10%.

**RESULTS**

Cure rate in per protocol set was as follows: 93.0%, 96.3% and 96.6% in 2-day group 3-day group, and oral treatment group, respectively. Azithromycin 1.5% groups were non-inferior to oral azithromycin. The intend to treat (ITT) analysis supported the results. Clinical re-emergence rate was low: 4.2%. Ocular tolerance was similar for all groups. No treatment related adverse events were reported. Logistic regression analyses found prognostic factors such as: country ( $p < 0.001$ ) and trachoma severity ( $p = 0.003$ ).

**CONCLUSIONS**

In active trachoma, azithromycin eye drops twice daily for 2 or 3 days are as efficient as the WHO's reference treatment and represent an innovative alternative to oral azithromycin.

## Phase 3 safety comparisons for 1.0% azithromycin in polymeric mucoadhesive eye drops versus 0.3% tobramycin eye drops for bacterial conjunctivitis

Protzko E, Bowman L, Abelson M, Shapiro A

Invest Ophthalmol Vis Sci 2007; 48 (8): 3425-3429.

### PURPOSE

To compare the safety and tolerability of 1.0% azithromycin in a polymeric mucoadhesive delivery system with 0.3% tobramycin ophthalmic solution for the treatment of bacterial conjunctivitis.

### METHODS

This study was a prospective, randomized, active-controlled, double-masked, phase 3 trial conducted from August 6, 2004, to October 6, 2005, at 47 sites. Subjects with a clinical diagnosis of bacterial conjunctivitis were randomly assigned to receive either 1% azithromycin in DuraSite (AzaSite; InSite Vision, Alameda, CA) (n = 365) or 0.3% tobramycin (n = 378). Both groups received masked medication four times daily for 5 days, but participants received an active dose of 1% azithromycin in DuraSite only twice a day on days 1 and 2 and daily on days 3 to 5. Conjunctival cultures were taken, and ocular signs and symptoms were evaluated at baseline and at two follow-up visits.

### RESULTS

A total of 743 patients were randomized, and 710 (96%) completed the trial. Both study medications were well tolerated. The most frequently observed ocular adverse events in the azithromycin group were eye irritation (1.9%), conjunctival hyperemia (1.1%), and worsening bacterial conjunctivitis (1.1%). These rates compared favorably with those obtained with tobramycin. Rates of microbial eradication (an efficacy parameter) and bacterial infection recurrence (a safety parameter) were the same in both groups.

### CONCLUSIONS

This is the first report of the safety and tolerability of a commercially manufactured preparation of azithromycin for ophthalmic use. Azithromycin 1% in DuraSite is safe and can be administered in a regimen of less frequent doses than can tobramycin, while producing an equivalent clinical outcome. The formulation is well tolerated in patients over the age of 1 year for the eradication of bacteria commonly associated with conjunctivitis.



### An assessment of the tolerability of moxifloxacin 0.5% compared to azithromycin 1.0% in DuraSite

Granet D., Lichtenstein S J., Onofre B., Katz J A.

Clin Ophthalmol 2007; 1 (4): 519-525.

#### ABSTRACT

This subject-masked, randomized, active and placebo-controlled study compared subjects' perceptions of two antibiotic ophthalmic drops. One hundred and twenty-five healthy volunteers received two of the following solutions: moxifloxacin 0.5% ophthalmic solution (Vigamox<sup>®</sup>, Alcon Laboratories, Inc., Ft Worth, TX, USA), azithromycin 1% in DuraSite<sup>®</sup> (AzaSite<sup>™</sup>, Inspire Pharmaceuticals, Inc., Durham, NC, USA), or Tears Naturale II<sup>®</sup> (Alcon Laboratories, Inc., Ft. Worth, TX, USA) in contralateral eyes. Immediately following instillation and at 1, 3, 5, and 10 minutes thereafter, subjects rated comfort, acceptability, and blurring on 0–10 point analog scales stating their preference of treatment. Among subjects receiving moxifloxacin and azithromycin in contralateral eyes, 84% preferred moxifloxacin. Moxifloxacin was rated more comfortable and acceptable with less blurring than azithromycin ( $p < 0.0001$ ). These differences were observed in both the adult and pediatric populations. Ocular adverse events (redness, irritation, stinging, burning, dryness, itching and chemosis) were observed in 18 (17.3%) eyes receiving azithromycin and 1 (1%) eye receiving moxifloxacin. Moxifloxacin was significantly more tolerable than azithromycin in healthy adult and pediatric eyes. Tolerability and patient acceptance affect compliance; thus these data should be of significance to the clinician.



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