

Effectiveness, tolerability and safety of azithromycin 1% in DuraSite[®] for acute bacterial conjunctivitis

Susannah McLean
Aziz Sheikh

Centre for Population Health Sciences: GP Section, Allergy and Respiratory Research Group, University of Edinburgh, Medical School, Edinburgh, United Kingdom

Purpose: Bacterial eye infections are commonly treated with topical antibiotics, despite limited evidence of effectiveness. Azithromycin 1% in DuraSite[®] is a new formulation of azithromycin in a gel polymer designed for use in acute bacterial conjunctivitis.

Methods: We conducted systematic searches of the Cochrane Database of Clinical Trials, PubMed and Google Scholar to find randomized controlled trials of “azithromycin DuraSite[®]”. These searches of published literature were supplemented with searches for unpublished trials and trials in progress.

Results: We found six reports of randomized controlled trials investigating the role of azithromycin 1% in DuraSite[®] for the management of acute bacterial conjunctivitis. The quality of these trials was judged to be moderate to high. These trials assessed effectiveness, tolerability and safety outcomes, but we found no trials looking at cost-effectiveness. DuraSite[®] is a relatively stable formulation and so azithromycin 1% in DuraSite[®] has a simpler dosing schedule than other available topical antibiotics. It appears to be similar to other topical antibiotics in its effectiveness, but minor side effects are quite common.

Conclusion: Acute bacterial conjunctivitis is a relatively mild, typically self-limiting, infection. Antibiotics should seldom be required. If, however, a decision to prescribe antibiotics is made, azithromycin 1% in DuraSite[®] is likely to be broadly comparable in its effectiveness to most other antibiotics used to treat acute bacterial conjunctivitis. Further research is needed to determine its cost-effectiveness.

Keywords: conjunctivitis, bacterial eye infection, azithromycin 1% in DuraSite[®]

Introduction

Bacterial eye infections are common, accounting for up to 1% of consultations in primary care.^{1,2} Patients typically experience unpleasant symptoms of a “gritty” eye, with blurred vision and increased lacrimation. On examination, crusted deposits can often be seen along the line of the eyelashes and the upper and lower conjunctivae appear infected, red, and irritated. Infection frequently spreads to involve both eyes.³ Infective conjunctivitis is either bacterial or viral and, in the latter case, mainly caused by adenovirus. Bacterial conjunctivitis is a relatively minor self-limiting illness without serious sequelae in those with an intact immune system.⁴⁻⁶ Conjunctivitis occurring early in the neonatal period is the main exception to this general rule. This should be investigated and treated aggressively as it may indicate the presence of sight-threatening trachoma.⁷ The main differential diagnoses of infective conjunctivitis include allergic conjunctivitis, chemical conjunctivitis and a foreign body. Although rare, the

Correspondence: Susannah McLean
Centre for Population Health Sciences: GP Section, Allergy and Respiratory Research Group, The University of Edinburgh, Medical School, Teviot Place, Edinburgh, EH8 9AG, United Kingdom
Tel +44 131 650 9242
Fax +44 131 650 9119
Email susannah.mclean@ed.ac.uk

major complication of bacterial conjunctivitis is the possible sight-threatening emergency of orbital cellulitis.

Patient considerations

It is difficult to distinguish bacterial from viral conjunctivitis on clinical grounds. Bacterial overgrowth may occur in the presence of viral conjunctivitis. Patients seek medical attention for symptom relief and this often results in the prescription of a topical antibiotic in the form of eye drops or ointment.⁸ Drops can be either soothing or irritating depending on their pH and viscosity.⁹ Ointments frequently blur vision and therefore tend to be prescribed for patient's use just prior to bed time. Many of these topical antibiotics have frequent dosing regimens of up to every two hours.¹⁰ Achieving good compliance with such preparations is, understandably, difficult.

Microbiological considerations

Bacteria are responsible for an estimated 50%–70% of all infective conjunctivitis. The most common bacterial pathogens are *Staphylococcus aureus*, *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis*. The latter is often observed in children.¹¹

There is ongoing debate as to whether widespread prescribing of broad-spectrum antibiotics for minor illnesses, such as azithromycin for bacterial conjunctivitis, encourages the emergence of bacterial resistance. *In vitro* studies have, for example, found that azithromycin appears to be less active against *S. pneumoniae* and methicillin-susceptible *S. aureus* than erythromycin or clarithromycin. *H. influenzae* is, however, 2–8 times more susceptible to azithromycin than to clarithromycin or erythromycin. With increased beta-lactam resistance of *S. pneumoniae* the search continues for effective alternatives.^{12,13} Also of relevance, is work by Ohnsman and Ritterband,¹⁴ who compared *in vitro* resistance to azithromycin and moxifloxacin in bacterial conjunctivitis isolates and found no bacterial resistance to moxifloxacin, but a moderate to very high bacterial resistance to azithromycin for *S. epidermidis*, *S. pneumoniae*, and *S. aureus*.¹⁴

Management issues

The key management question is whether the prescription of an antibiotic is warranted. A recently updated Cochrane review⁴ of five trials,^{15–19} which included a total of 1034 participants, found evidence that the application of topical antibiotics overall improved early (days 2 to 5) clinical (relative risk [RR] = 1.24; 95% confidence interval [CI]: 1.05–1.45) and microbiological (RR = 1.77; 95% CI: 1.23–2.54) remission

rates. Later (days 6 to 10) data found that these early advantages in clinical (RR = 1.11; 95% CI: 1.02–1.21) and microbiological (RR = 1.56; 95% CI: 1.17–2.09) cure rates persisted, but were reduced. The majority of cases in the placebo arms of these trials resolved spontaneously with clinical remission being achieved in 65% (95% CI: 59–70) by days 2–5. No serious outcomes were reported in either the active or placebo arms of the five trials included in this review. Synthesis of these trials found that the prescription of topical antibiotics marginally accelerated remission of acute bacterial conjunctivitis. None of the trials reported on cost-effectiveness considerations.

Everitt et al¹⁹ conducted an innovative trial assessing the impact of delayed prescribing of antibiotics for conjunctivitis. Prescribing strategies did not affect the severity of symptoms, but the duration of moderate symptoms was reduced with antibiotics: ie, no antibiotics (control) mean of 4.8 days vs immediate antibiotics 3.3 days (RR = 0.7; 95% CI: 0.6–0.8); control vs delayed antibiotics 3.9 days (RR = 0.8; 95% CI: 0.7–0.9).²⁰

In this factorial trial, the researchers asked patients whether they thought they needed the antibiotics and also whether they would re-attend the surgery in future episodes of conjunctivitis. These questions were designed to assess the impact of medicalization on likely future health-seeking behavior.²⁰ Everitt et al concluded that delayed prescription of antibiotics was probably the most effective treatment strategy, particularly in that this approach was likely to also change patterns of health-seeking behavior for future episodes of suspected infective conjunctivitis. However, this conclusion needs to be re-examined since chloramphenicol eye drops recently became available in the UK from pharmacists without the need for a prescription.²¹

Another factor to be taken into account when prescribing for infective conjunctivitis is that children in nursery or school often infect one another and so institutions may ask parents to keep their children at home. The parents then may need to miss time from work to care for their children.^{21,22} Therefore, pressure from parents may result in more prescriptions for conjunctivitis so that children can return to childcare and parents can return to work as rapidly as possible.

The present review seeks to assess the place of azithromycin 1% in DuraSite® (Insite Vision, Alameda, CA, USA), a new preparation for the management of acute bacterial conjunctivitis.

Methods

We used systematic review principles to search the Cochrane Central Database of Clinical Trials, PubMed and Google

Scholar with the keywords “azithromycin DuraSite®” for the period 1990–2009 in order to identify randomized controlled trials. Key data were extracted from studies and the data were narratively synthesized, together with a wider body of literature on azithromycin DuraSite® to provide a broader context within which to consider these trials. We searched for unpublished material by searching online trials databases (<http://clinicaltrials.gov> and <http://www.controlled-trials.com/>).

Results

We found reports of six randomized controlled trials^{23–28} enrolling a total of 2933 patients. Two of these were as yet unpublished in their full form.^{24,26} There were three reports^{23–25} focusing on clinical effectiveness: two^{23,24} comparing azithromycin 1% in DuraSite® with placebo (vehicle) and a randomized controlled trial²⁵ comparing azithromycin 1% in DuraSite® with tobramycin 0.3%, all in patients with clinically diagnosed conjunctivitis. The searches of the online trial databases listed details of one planned and one ongoing study of azithromycin 1% in DuraSite® and 0.1% dexamethasone for blepharo-conjunctivitis.

In total, three reports^{26–28} included details of safety and tolerability: one²⁶ comparing 1% azithromycin in DuraSite® with vehicle, another²⁷ comparing it with 0.3% tobramycin and finally a comparison with 0.5% moxifloxacin.²⁸

Formulation

The studies on formulations give insight into how this new preparation is thought to work.^{29,30} Azithromycin is hydrophobic and is sparingly soluble in water at neutral pH. Aqueous preparations of azithromycin for topical administration to the eye are therefore labile at room temperature and can degrade. The most stable pH for azithromycin in solution is 6.3 and a range of 6.3 ± 0.3 has therefore been set for the manufacture of the solution. This is within the range commonly used for ophthalmic solutions. Azithromycin 1% in DuraSite® has been shown to be stable in formulation for at least 24 months at refrigerated storage temperatures ($\sim 5^{\circ}\text{C}$). Stored at room temperature for six months, ocular formulation samples maintained 93%–98% of their azithromycin content.³⁰

DuraSite® is a polycarboxophil (polymer of polyacrylic acid) bio-adhesive support matrix, which facilitates topical delivery of azithromycin.²⁹ It binds neutral, cationic and anionic small molecules and then releases these over a period of time in a controlled fashion. The cross-linked polymer chains form hydrogen bonds with glycosaminoglycans in

mucus. Polycarboxophil is therefore sometimes described as being muco-adhesive. This delivery mechanism ensures that the azithromycin is “glued” to the eye conjunctiva, where it persists for longer than less “sticky” alternatives, which offers the benefit of a less-frequent dosing regimen.

Also relevant is that at high shear stress, such as when dispensed from a bottle tip, the azithromycin 1% in DuraSite® flows and spreads over the ocular surface. When the shear stress is removed the polymer returns to a gel state, which, in contrast with conventional aqueous drops, limits its loss through reflex tearing and naso-lacrimal drainage. This results in a sustained level of medication on the conjunctiva, which makes the formulation useful for treatment of ocular surface infections.²⁹

Azithromycin 1% in DuraSite®’s persistence on the eye’s surface means that it needs to be administered only twice daily for the first two days, and then only once a day for days 3–5 to complete the course. The full treatment course, comprising of a total of only seven doses, is thus potentially very convenient for patients. This is in contrast to drugs such as tobramycin which require dosing four times a day.

An azithromycin 2% in DuraSite® delivery system has been evaluated in rabbits and its pharmacokinetic/pharmacodynamic profile suggests that it may have efficacy against common bacteria with just one dose per day for three days. Again, it is hoped that such a dosing regimen will, when made available for humans, improve concordance.³⁰

Mode of action

Azithromycin is a macrolide antibiotic derived from erythromycin. It has better stability than erythromycin in acidic environments. Azithromycin works by binding the 50s subunit of the 70s bacterial ribosome, thereby inhibiting RNA-dependent protein synthesis and preventing bacterial growth.³¹

Kinetic properties

Pharmacokinetics (ie, absorption, distribution, metabolism, and elimination) are predictive of the concentration and time-course of the drug in the body, but do not necessarily correlate with expected antibacterial effect. The regimen of once-a-day dosing for five days demonstrated that peak concentrations of 150–200 $\mu\text{g/g}$ and trough concentrations of 40 $\mu\text{g/g}$ were sustained during a 24 hour period. These concentrations are higher than the minimum inhibitory concentrations (MICs) needed to combat eye surface infections.³¹ *In vitro* studies have confirmed that once-a-day dosing is adequate to provide antibiotics at a level high enough to counter typical conjunctival pathogens.

There are some caveats to this advantage to consider, however. As azithromycin is used less frequently than other topical antibiotic preparations, each dose represents a greater percentage of the total dose and this means that missing a dose has greater significance. When doses are missed, the infection can take longer to resolve and there is the theoretical possibility that resistance is more likely to arise when trough concentrations fall below the MIC for prolonged periods.

Clinical effectiveness

Table 1 summarizes key data from trials assessing the effectiveness of azithromycin 1% in DuraSite®. There are two studies^{23,24} comparing azithromycin 1% in DuraSite® with vehicle, both of which have used an appropriate randomization technique. The patients and clinicians who were rating the clinical and bacterial cure levels were blinded to the allocation of the patients. Overall, these studies appear to have been of moderate to good quality. The Abelson-controlled Phase III clinical trial²⁷ for bacterial conjunctivitis was performed with 316 randomized participants aged 1–96 years. A five-day regimen of 1% azithromycin in DuraSite® was compared with a five-day regimen of 0.3% tobramycin eye drops administered four times a day. Twenty drops of masked study medication were given to all participants. In the azithromycin in DuraSite® arm, subjects received active drug in a twice-daily loading dose on days 1 and 2 and once daily on days 3–5 and vehicle drops were administered at other times. On day 6, clinical resolution rates of 1% azithromycin in DuraSite® were found to be equivalent to 0.3% tobramycin (79.9% vs 78.3%; $P = 0.78$). Bacterial eradication was defined as the absence of detectable levels of new pathogens in cultures taken at study exit. Bacterial eradication with azithromycin 1% in DuraSite® was reported as being as effective as with 0.3% tobramycin (88.1% vs 94.3%; $P = 0.07$).

Lichtenstein and Granet^{28,32} have, however, been critical of this study. They argue that the addition of twice daily vehicle drops to the azithromycin 1% in DuraSite® drops constituted a possible additional therapeutic effect. That is, that the vehicle drops possibly diluted the infection and washed it out of the eye giving the azithromycin 1% in DuraSite® arm of the trial an artificially enhanced appearance of effectiveness. They argue that the azithromycin 1% in DuraSite® arm does not represent a true once daily regimen due to this “washout” effect of the vehicle drops. When Lichtenstein and Granet considered all factors related to therapy (ie, bacterial resistance, blurriness, dosing compliance, and comfort) they recommend

ophthalmic fourth-generation fluoroquinolones, such as moxifloxacin, as better options for the treatment of conjunctivitis.³³

We found no studies assessing the cost-effectiveness of azithromycin 1% in DuraSite®.

Safety and tolerability

Three reports^{26–28} (Table 2) pertain to the safety and tolerability of azithromycin 1% eye drops in DuraSite®. Heller et al conducted a large trial with 685 participants and found the rate of adverse events to be approximately 12% in both the azithromycin 1% in DuraSite® arm and the vehicle arm in patients with bacterial conjunctivitis. Protzko et al²⁷ randomized 743 patients and compared azithromycin 1% in DuraSite® with tobramycin 0.3%. Adverse events observed in the azithromycin group in the Protzko trial, included eye irritation (1.9%), conjunctival hyperemia (1.1%) and worsening bacterial conjunctivitis (1.1%). Finally, the third study,²⁸ which was conducted in healthy volunteers, tested azithromycin 1% in DuraSite® in comparison with moxifloxacin 0.5%. A much higher rate of ocular adverse events was found in the azithromycin 1% in DuraSite® arm: 17.3% of patients' eyes experienced ocular adverse events including redness, irritation, stinging, burning, dryness, itching or chemosis; whereas only 1% of eyes receiving moxifloxacin experienced similar adverse events. This is a considerable difference and has implications when considering whether a prescription of azithromycin 1% in DuraSite® should be continued for its full course by any patient who experiences these effects.

Patient perspectives

As nonadherence is an important consideration in bacterial resistance, we now consider the patients' perspectives. This includes what affects their decision to consult and their expectations of the treatment.

There are a variety of possible reasons for patient nonadherence with eye drops including: poor motivation (stemming from lack of understanding of the function of the medication); inability to use eye drops properly (eg, difficulty aiming the drop, inability to squeeze the container well enough, blinking, inability to see the tip of the container, physical difficulties such as arthritis); and patients' reluctance to admit that they have problems with the process.^{9,33}

Indirect evidence on the importance of patient preferences comes from a study by Jampel et al³⁴ who performed a willingness-to-pay analysis on subjects taking eye drops

Table I Randomized controlled trials assessing the clinical effectiveness of azithromycin 1% in DuraSite®

Author, references	Number of patients/ patient age	Azithromycin	Comparator	Result	Quality
Abelson ²⁶	N = 279 Age 1–96	1% in DuraSite® dosed twice daily on days 1–2 and once daily on days 3–5	Vehicle with same dosing schedule; vehicle was identically supplied and formulated except that it contained no azithromycin.	Clinical resolution with azithromycin in DuraSite® was statistically improved compared with that of vehicle $P = 0.03$	Prospective randomized vehicle-controlled, double-masked study. Randomization protocol not explained in study. Allocation concealment appears to be adequate during enrolment. Possible problem as “data monitoring committee” was not blinded, although these team members did not have any contact with study participants.
Abelson ²⁷ Unpublished	N = 685 Age not available	1% in DuraSite® dosed twice daily for days 1–2 and four times a day for days 3–5	Vehicle with same dosing schedule.	Clinical resolution and bacterial eradication significantly better in the azithromycin group than in the vehicle group $P < 0.05$.	Unpublished study, double-masked and randomized, but insufficient information to determine quality.
Abelson ²⁹	N = 316 Age 1–83	1% in DuraSite® dosed twice a day with active drug on days 1–2 and once daily days 3–5, other doses were vehicle.	Tobramycin 0.3% four times a day	Clinical resolution was 79.9% in azithromycin group and 78.3% in the tobramycin group. The difference in clinical resolution between the two groups was not statistically significant ($P = 0.78$).	Although the study states that it was randomized there is no explanation of sequence generation or allocation concealment during enrolment. Patients could not have been blinded to their treatment as the viscosity of the drops would be different. The results may also be affected by incomplete outcome data (ie, 17 patient withdrawals due to adverse events, 16 patients lost to follow-up, withdrawn consent or lack of efficacy).

for glaucoma. They found that patients preferred drops that did not produce blurring, drowsiness or inhibit sexual performance. If such drops were available, then patients would be willing to pay more for them than for drops with

such side effects. Willingness-to-pay analysis may be useful when adapted for investigating the preferred characteristics of antibiotic eye drops in a population of subjects with conjunctivitis.³⁴

Table 2 Randomized controlled trials assessing safety and tolerability of azithromycin 1% in DuraSite®

Author, references	Number of patients/ patient age	Azithromycin	Comparator	Result	Quality
Heller ²⁷	N = 685 Age 1–96	1% in DuraSite® twice daily for 2 days then four times a day for days 3–5 in adults and children.	Vehicle with same dosing schedule.	12% of patients experienced at least one adverse event in both the Azasite (azithromycin 1% in DuraSite®) and vehicle groups. No drug-related serious adverse events.	Unpublished study from Cochrane register of trials. Double-masked and randomized. No summary statistics reported.
Protzko ²⁸	N = 743 Age 1–93	1% in DuraSite® dosed twice a day with active drug on days 1 and 2 and once daily days 3–5; other doses were vehicle.	0.3% Tobramycin four times a day for 5 days.	Both medications well-tolerated. A reported 3% of azithromycin group and 5.6% of tobramycin group had treatment-related adverse events. Rates of microbial eradication and bacterial infection recurrence were the same in both groups.	Prospective randomized active-controlled double masked study, but no details of randomization protocol given in study. The medication was masked. No odds ratios reported.
Granet ²⁸	N = 125 34 adults and 50 children received moxifloxacin and contralateral azithromycin; 11 adults and 10 children received moxifloxacin and contralateral placebo	1% azithromycin in DuraSite®	Tears Natural II® or moxifloxacin 0.5% in contralateral eyes.	Ocular adverse events were observed in 17% of participants receiving azithromycin 1% in DuraSite® and 1% receiving moxifloxacin. Moxifloxacin was significantly more tolerable in healthy eyes.	This study was supported by Alcon and used Alcon's preparation of moxifloxacin. No summary statistics were reported.

Further research

The willingness-to-pay study design discussed above could be used to determine whether patients would be prepared to pay more for the convenient dosing schedule of azithromycin 1% in DuraSite®.

We did not find studies comparing azithromycin 1% in DuraSite® to chloramphenicol ointment/drops or to fusidic acid drops. Since these are the two antibiotics most commonly prescribed in the UK, a comparison of their effectiveness and costs would be particularly useful. This is also relevant because chloramphenicol has an inconvenient dosing schedule (ie, every two hours), which can result in doses being missed or delayed. Fusidic acid drops are administered twice a day and so are more comparable with azithromycin 1% in DuraSite®. Research needs to be carried out before a recommendation of the place of azithromycin in the UK can be made. Studies comparing azithromycin 1% in DuraSite® with the topical

treatments most commonly used in other parts of the world are also needed to inform local prescribing decisions. Such trials should focus on patient-reported outcome measures and should also assess cost-effectiveness considerations.

Conclusion

Based on the evidence of the Cochrane review and Everitt et al's randomized controlled trial incorporating a delayed treatment arm, we believe there is a strong argument for not prescribing antibiotics for the treatment of acute bacterial conjunctivitis as this is, in the majority of cases, a relatively minor self-limiting illness. Furthermore, treatment may also increase the risk of development of antibiotic resistance in the community and also runs the risk of unnecessary medicalization of this problem.

If, however, a decision to prescribe antibiotics is made, the available evidence suggests that azithromycin 1% in

DuraSite® (Box 1³⁵) is likely to be as effective as other topical antibiotics. Its main advantage is a convenient once-a-day dosing schedule, which may aid concordance. This benefit may be offset however by a relatively high risk (compared with tobramycin and moxifloxacin) of minor side effects. We did not find data formally assessing cost-effectiveness considerations.

In summary, we suggest that the preferred course of action is not to prescribe antibiotics for the management of acute bacterial conjunctivitis, with the delayed prescription strategy being a proven alternative approach. In the minority of patients who may need to be given an antibiotic, this needs to be prescribed by the physician after considering the patient's preferences regarding convenience, side effects, safety, effectiveness, and cost.

Acknowledgments

We are grateful to Vicky Hammersley, Dr Allison Worth and James McLean for their helpful comments on an earlier draft of this paper.

Box 1 Key considerations for prescribing azithromycin 1% in DuraSite

- Licensed for use in those aged over 1 year
- Use in pregnancy only if clearly needed, as some animal data have shown maternal toxicity
- Exercise caution in breast-feeding mothers as it is not known whether it is excreted in breast milk
- Dosing twice a day for 2 days then once a day for 3 days
- The most common adverse reaction reported in patients is eye irritation (in 1%–2% of patients).

Disclosures

The authors report no conflicts of interest in this work.

References

1. Dart J. Eye disease at a community health centre. *BMJ*. 1986;293:1477–1480.
2. McDonnell P. How do general practitioners manage eye disease in the community? *Br J Ophthalmol*. 1998;72:733–376.
3. Sheikh A, Hurwitz B. Topical antibiotics for acute bacterial conjunctivitis: a systematic review. *Br J Gen Pract*. 2001;51:473–477.
4. Sheikh A, Hurwitz B. Antibiotics versus placebo for acute bacterial conjunctivitis. *Cochrane Database Syst Rev*. 2006;2:CD001211.
5. Sheikh A, Hurwitz B. Topical antibiotics for acute bacterial conjunctivitis: Cochrane systematic review and meta-analysis update. *Br J Gen Pract*. 2005;55:962–964.
6. Rose P, Harnden A, Brueggemann A, Perera, Sheikh A, Crook D, et al. Chloramphenicol treatment for acute infective conjunctivitis in children in primary care: a randomized double-blind placebo-controlled trial. *Lancet*. 2005;366:37–43.
7. West S. Azithromycin for control of trachoma. *Community Eye Health*. 1999;12:55–56.
8. Everitt H, Little P. How do GPs diagnose and manage acute infective conjunctivitis? A GP survey. *Fam Pract*. 1999;12:55–56.
9. Perry H, Donnenfeld D. Issues in the use of preservative-free topicals *Manag Care*. 2003;12 Suppl:39–42.
10. Friedlaender MH, Protzko E. Clinical development of 1% azithromycin in DuraSite, a topical azalide anti-infective for ocular surface therapy. *Clin Ophthalmol*. 2007;1(1):3–10.
11. Buznach N, Dagan R, Greenberg D. Clinical and bacterial characteristics of acute bacterial conjunctivitis in children in the antibiotic resistance era. *Pediatr Infect Dis J*. 2005;24:823–828.
12. Friedlaender MH, Protzko E. Response to correspondence from Lichtenstein and Granet Re: Fluoroquinolones compared to 1% azithromycin in DuraSite for bacterial conjunctivitis. *Clin Ophthalmol*. 2008;2(1):242–244.
13. McCracken G. Microbiologic activity of the newer macrolide antibiotics. *Pediatr Infect Dis J*. 1997;16:432–437.
14. Ohnsman C, Ritterband D, O'Brien T, Gargis D, Kabat A. Comparison of azithromycin and moxifloxacin against bacterial isolates causing conjunctivitis. *Curr Med Res Opin*. 2007;23:2241–2249.
15. Gigliotti F, Hendley J, Morgan J, Michaels R, Dickens M, Lohr J. Efficacy of topical antibiotic therapy in acute conjunctivitis in children. *J Pediatr*. 1984;104:623–626.
16. Leibowitz H. Antibacterial effectiveness of ciprofloxacin 0.3% ophthalmic solution in the treatment of bacterial conjunctivitis. *Am J Ophthalmol*. 1991;112:295–335.
17. Miller I, Wittreich H, Vogel R, Cook T. The safety and efficacy of topical norfloxacin compared with placebo in the treatment of acute bacterial conjunctivitis. *Eur J Ophthalmol*. 1992;258–266.
18. Rietveld R, Tiet Gd, Bindels P, Bink D, Sloos J, Weert HV. The treatment of acute infectious conjunctivitis with fusidic acid: a randomized controlled trial. *Br J Gen Pract*. 2005;55(924–930).
19. Everitt H, Little P, Smith P. A randomized controlled trial of management strategies for acute infective conjunctivitis in general practice. *BMJ*. 2006;333:321.
20. Leibovici L, Lieve M. Medicalization: peering from the inside. *BMJ*. 2002;324:866.
21. Sheikh A. Delayed prescribing of antibiotics is an effective strategy in managing acute conjunctivitis. *J Pediatr*. 2007;150:114–115.
22. Little P, Gould C, Williamson I, Warner G, Ganley M, Kinmonth A. Reattendance and complications in a randomized trial of prescribing strategies for sore throat: the medicalizing effect of prescribing antibiotics. *BMJ*. 1997;314:177–182.
23. Abelson M, Heller W, Shapiero A, et al. clinical cure of bacterial conjunctivitis with azithromycin 1%: vehicle-controlled double-masked clinical trial. *Am J Ophthalmol*. 2008;145:959–965.
24. Abelson M, Heller W. Efficacy of azithromycin 1% eye drops vs vehicle as first line therapy for bacterial conjunctivitis. *Unpublished study the Cochrane Register of Controlled Trials (CENTRAL)*. 2006;ID CN00634804.
25. Abelson M, Protzko E, Shapiero A, Garces-Soldana A, Bowman L. 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 *Clin Ophthalmol*. 2007;1:177–182.
26. Heller W, Abelson M, Group TAS. Safety and tolerability of azithromycin 1% eye drops as anti-infective therapy for bacterial conjunctivitis. *Unpublished study for the Cochrane Register of Controlled Trials (CENTRAL)*. Study ID CN 00634521.
27. Protzko E, Bowman L, Abelson M, Shapiero A, Group TACS. Phase 3 safety comparisons for 1% azithromycin in polymeric muco-adhesive eye drops versus 0.3% tobramycin eye drops for bacterial conjunctivitis. *Invest Ophthalmol Vis Sci*. 2007;48(3425–3429).
28. Granet D, Lichtenstein SJ, Onofrey B, Katz JA. An assessment of the tolerability of moxifloxacin 0.5% compared to azithromycin 1.0% in durasite. *Clin Ophthalmol*. 2007;1:133–139.
29. Bowman L, Si E, Pang J, Archibad R, Friedlaender M. Development of a topical polymeric mucoadhesive ocular delivery system for azithromycin. *J Ocul Pharmacol Ther*. 2009;2:133–139.
30. Si PC, Bowman L, Hosseini K. Ocular pharmacokinetics of Azasite Xtra – 2% azithromycin formulated in a Durasite delivery system. *Curr Eye Res*. 2009;34:485–491.

31. Dorfman M, Wagner R, Jamison T, Bell B, Stroman DW. The pharmacodynamic properties of azithromycin in a kinetics of kill model and implications for bacterial conjunctivitis treatment. *Adv Ther.* 2008;25:208–217.
32. Lichtenstein S, Granet D. Fluoroquinolones compared to 1% azithromycin in durasite for bacterial conjunctivitis *Clin Ophthalmol.* 2007;1:519–525.
33. Winfield A, Jessiman D, Silliams A. A study of the causes of non-compliance by patients prescribed eyedrops. *Br J Ophthalmol.* 1990;74:477–480.
34. Jampel H, Schwartz G, Robin A. Patient preference for eye drop characteristics: a willingness to pay analysis. *Arch Ophthalmol.* 2003;121:540–546.
35. FDA. Patient information leaflet NDA 50-810. Revised 5/2007. Available from: <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search>. [Label Approval History] Accessed December 7, 2009.

Patient Preference and Adherence

Dovepress

Publish your work in this journal

Patient Preference and Adherence is an international, peer-reviewed, open access journal that focusing on the growing importance of patient preference and adherence throughout the therapeutic continuum. Patient satisfaction, acceptability, quality of life, compliance, persistence and their role in developing new therapeutic modalities and compounds to

optimize clinical outcomes for existing disease states are major areas of interest. This journal has been accepted for indexing on PubMed Central. The manuscript management system is completely online and includes a very quick and fair peer-review system. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <http://www.dovepress.com/patient-preference-and-adherence-journal>