Drug Class Review
on
Macrolides

Preliminary Scan Report 5

July 2014

Last Report: Original August 2006

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OBJECTIVE:

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant to assist with Participating Organizations' consideration of allocating resources toward a full report update, a single drug addendum, or a summary review. Comprehensive review, quality assessment, and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, comparative effectiveness reviews, and actions taken by the U.S. Food and Drug Administration (FDA) since the last report. Other important studies could exist.

Date of original report:

August 2006 (searches through 1st quarter 2006)

Date of Last Preliminary Update Scan:

September 2013

Scope and Key Questions

The purpose of this review is to compare the benefits and harms of different macrolide antibiotics used for treatment of specific infectious diseases. The Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These were reviewed and revised by representatives of the Washington state Medicaid agency, with input from the public. These representatives are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. Representatives of the Washington state Medicaid agency approved the following key questions to guide this review:

1. For adults and children with community-acquired pneumonia, acute bacterial sinusitis, acute exacerbations of chronic bronchitis, otitis media, pharyngitis, and Mycobacterium Avium Complex, do macrolide antibiotics differ in efficacy?

2. For adults and children with community-acquired pneumonia, acute bacterial sinusitis, acute exacerbations of chronic bronchitis, otitis media, pharyngitis, and Mycobacterium Avium Complex, do macrolide antibiotics differ in safety or adverse events?

3. Are there subgroups of patients based on demographics (age, racial groups, gender), other medications, or co-morbidities, or in pregnancy for which one macrolide is more efficacious or associated with fewer adverse events?

Inclusion Criteria

Populations

Adult patients and children (under age 18) in outpatient settings with the following diagnosis:

- Community-acquired pneumonia
- Acute bacterial sinusitis
- Acute exacerbations of chronic bronchitis
- Otitis Media
- Pharyngitis
- Mycobacterium Avium Complex

Table 1: Interventions

Generic Name	Trade Name	Forms
Azithromycin	Zithromax, ZMAX	Oral tablets and suspension
Erythromycin	E.E.S., Eryc, Eryped, Ery-tab, PCE, Pediamycin, others	Oral tablets, suspension, and capsules
Clarithromycin	Biaxin, Biaxin XL	Oral tablets and suspension

Efficacy Outcomes

- Clinical cure rate (to be further specified)
- Bacteriological cure rate
- Percent switch to different antibiotic
- Hospitalization rates
- Mortality

Harms

- Overall adverse effect reports
- Withdrawals due to adverse effects
- Serious adverse events reported
- Specific adverse events (nausea, vomiting, diarrhea, prolongation of QT interval, torsades de pointes, ventricular arrhythmias)

Study Designs

- Head-to-head randomized controlled trials and good-quality systematic reviews

METHODS

Literature Search

To identify relevant citations, we searched MEDLINE (2006-June 25, 2014). We used terms for included drugs and clinical indications and limits for humans, English and controlled clinical trials. We also searched for relevant systematic reviews produced since the original report was prepared by AHRQ, CADTH, the VA's Evidence-based Synthesis Program, and the University of York's Centre for Reviews and Dissemination**. For some earlier scans, we searched the Cochrane Library as well.** We searched the FDA website for identification of new drugs, indications, and boxed warnings.

Study Selection

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

New Drugs

Identified in this Preliminary Update Scan
None

Identified in previous Preliminary Update Scans
None

New Indications

Identified in this Preliminary Update Scan
None

Identified in previous Preliminary Update Scans
None

New Safety Alerts

Identified in this Preliminary Update Scan
None

Identified in previous Preliminary Update Scans
On March 12, 2013, FDA notified public that azithromycin (Zithromax or Zmax) can cause abnormal changes in the electrical activity of the heart that may lead to a potentially fatal irregular heart rhythm. Patients at risk for developing this condition include those with known risk factors such as existing QT interval prolongation, low blood levels of potassium or magnesium, a slower than normal heart rate, or use of certain drugs used to treat abnormal heart rhythms, or arrhythmias. Detailed FDA notification is included in Appendix A.

Comparative Effectiveness Reviews

Identified in this Preliminary Update Scan
None

Identified in previous Preliminary Update Scans

Searches for Cochrane reviews for previous scans produced 3 reviews (one since updated), listed in Table 2 with citations in Appendix B.

Table 2. Systematic Reviews

Systematic Review	Title	Comparison
Cochrane: Bjerre, 2009	Antibiotics for community acquired pneumonia in adult outpatients	RCTs in which one or more antibiotics were tested for the treatment of CAP in ambulatory adolescents or adults
Cochrane: Lodha, 2013	Antibiotics for community-acquired pneumonia in children	RCTs comparing at least two antibiotics for CAP
Cochrane: Kozyrskyj, 2010	Short-course antibiotics for acute otitis media	RCTs of children randomize to antimicrobial therapy for less than 7 days vs 7 or more days

New studies

Medline searches resulted in 40 citations for this July 2014 scan. None met eligibility criteria. Cumulatively, 3 potentially relevant head-to head trials have been published since the 2006 report, all obtained from previous scans (Table 3). Appendix C lists the abstracts for these publications.

Table 3. Head-to head trials

Study	Population	Comparison
Lee, 2008	Children with community acquired pneumonia	Erythromycin vs clarithromycin
Block, 2006	Pediatric and adolescent patients with group A streptococcal pharyngitis, sinusitis, ambulatory pneumonia	Twice-daily clarithromycin vs once-daily ER clarithromycin
Jorgensen, 2009	Adults and adolescents with group A streptococcal pharyngitis	Single-dose ER azithromycin vs 3-day IR azithromycin

Abbreviations: ER = extended release; IR = immediate release

Appendix A

Azithromycin (Zithromax or Zmax): Drug Safety Communication - Risk of Potentially Fatal Heart Rhythms

[Posted 03/12/2013]

AUDIENCE: Family Practice, Patient, Pharmacy, Health Professional

ISSUE: FDA is warning the public that azithromycin (Zithromax or Zmax) can cause abnormal changes in the electrical activity of the heart that may lead to a potentially fatal irregular heart rhythm. Patients at particular risk for developing this condition include those with known risk factors such as existing QT interval prolongation, low blood levels of potassium or magnesium, a slower than normal heart rate, or use of certain drugs used to treat abnormal heart rhythms, or arrhythmias. FDA has issued a Drug Safety Communication today as a result of our review of a study by medical researchers as well as another study by a manufacturer of the drug that assessed the potential for azithromycin to cause abnormal changes in the electrical activity of the heart.

FDA previously released a Statement on May 17, 2012, about a study that compared the risks of cardiovascular death in patients treated with the antibacterial drugs azithromycin, amoxicillin, ciprofloxacin (Cipro), and levofloxacin (Levaquin), or no antibacterial drug. The study reported an increase in cardiovascular deaths, and in the risk of death from any cause, in persons treated with a 5-day course of azithromycin (Zithromax) compared to persons treated with amoxicillin, ciprofloxacin, or no drug. The risks of cardiovascular death associated with levofloxacin treatment were similar to those associated with azithromycin treatment.

BACKGROUND: Azithromycin is marketed under the brand names Zithromax and Zmax. FDA-approved indications for azithromycin include: acute bacterial exacerbations of chronic obstructive pulmonary disease, acute bacterial sinusitis, community-acquired pneumonia, pharyngitis/tonsillitis, uncomplicated skin and skin structure infections, urethritis and cervicitis, genital ulcer disease.

RECOMMENDATION: Health care professionals should consider the risk of torsades de pointes and fatal heart rhythms with azithromycin when considering treatment options for patients who are already at risk for cardiovascular events. FDA notes that the potential risk of QT prolongation with azithromycin should be placed in appropriate context when choosing an antibacterial drug: Alternative drugs in the macrolide class, or non-macrolides such as the fluoroquinolones, also have the potential for QT prolongation or other significant side effects that should be considered when choosing an antibacterial drug.

Appendix B. Citations for comparative effectiveness reviews identified in previous preliminary update scans

Bjerre LM, Verheij TJM, Kochen MM. Antibiotics for community acquired pneumonia in adult outpatients. Cochrane Database of Systematic Reviews 2009, Issue 4. Art. No.: D002109. DOI: 10.1002/14651858.C D002109.pub3.

Lodha R, Kabra SK, Pandey RM. Antibiotics for community-acquired pneumonia in children. Cochrane Database of Systematic Reviews 2013, Issue 6. Art. No.: CD004874. DOI: 10.1002/14651858.C D004874.pub4.

Kozyrskyj AL, Klassen TP, Moffatt M, Harvey K. Short-course antibiotics for acute otitis media. Cochrane Database of Systematic Reviews 2010, Issue 9. Art. No.: CD001095. DOI: 0.1002/14651858.C D001095.pub2.

Appendix C. Abstracts of head-to head trials identified in previous preliminary update scans

Community Acquired Pneumonia

Lee, P.-I., et al., An open, randomized, comparative study of clarithromycin and erythromycin in the treatment of children with community-acquired pneumonia. Journal of Microbiology, Immunology & Infection, 2008. 41(1): p. 54-61.
BACKGROUND AND PURPOSE: This study aimed to evaluate the efficacy and safety of clarithromycin and erythromycin in the treatment of community-acquired pneumonia in children. METHODS: Children with community-acquired pneumonia were randomly assigned to receive 10-day regimens of either clarithromycin 15 mg/kg/day, twice a day, or erythromycin 30-50 mg/kg/day, four times daily. RESULTS: A total of 97 children entered this study, including 26 with Mycoplasma pneumoniae infection, 15 with Chlamydia pneumoniae infection, and 6 with mixed mycoplasma and chlamydia infections. Fifty and 47 children received clarithromycin and erythromycin treatment, respectively. Three children withdrew from the study because the identified pathogens were resistant to the study drugs. All 47 children with mycoplasma or chlamydia infection were cured clinically. Delayed defervescence, defined as a fever lasting for more than 72 h after treatment, was observed in 4 of 22 clarithromycin-treated children (18%) and in 3 of 15 erythromycin-treated children (20%) [p>0.05]. Gastrointestinal side effects, including vomiting, abdominal pain and diarrhea, were observed in 3 of 50 children (6%) receiving clarithromycin and in 11 of 49 children (22%) receiving erythromycin (p=0.039). Excluding children with abnormal pretreatment liver function, abnormal liver function after treatment was observed in only one child, treated with erythromycin. Post-treatment eosinophil and platelet counts were significantly elevated after treatment in both groups. CONCLUSIONS: Clarithromycin showed efficacy equivalent to erythromycin for the treatment of mycoplasma or chlamydia pneumonia in children. However, the tolerability of clarithromycin was superior to that of erythromycin.

Pharyngitis and/or Sinusitis

Block, S.L., Comparative tolerability, safety and efficacy of tablet formulations of twice-daily clarithromycin 250 mg versus once-daily extended-release clarithromycin 500 mg in pediatric and adolescent patients. Clinical Pediatrics, 2006. 45(7): p. 641-8.
Clarithromycin is widely used to treat respiratory tract and superficial skin infections in pediatric and adult populations. Using clinical endpoints and 7-day therapy, we compared the efficacy of clarithromycin 250 mg tablets given twice daily versus clarithromycin 500 mg extendedrelease tablets given once daily in ambulatory children and adolescents 6 to 16 years old. Of the 199 evaluable patients, 124 were infected with group A streptococcal pharyngitis, 39 with sinusitis, 21 with ambulatory pneumonia, and 15 with superficial skin infections. The overall cure rate exceeded 90% for each treatment group. Discontinuation rates and adverse events were 4.5% and 24.6%, respectively.

Jorgensen, D. M. (2009). "Single-dose extended-release oral azithromycin vs. 3-day azithromycin for the treatment of group A beta-haemolytic streptococcal pharyngitis/tonsillitis in adults and adolescents: a double-blind, double-dummy study." Clinical Microbiology &

Infection **15**(12): 1103-10.
The azithromycin immediate-release formulation (AZ-IR) provides effective treatment for group A beta-haemolytic streptococcal pharyngitis in adults. Single-dose therapy with a novel azithromycin extended-release (AZ-ER) formulation could reduce treatment failure and eliminate non-compliance contributing to antimicrobial resistance. A randomized, double-blind, double-dummy, multicentre trial was conducted comparing AZ-ER (single oral 2-g dose) with AZ-IR (3 days, 500 mg once daily) for the treatment of group A beta-haemolytic streptococcal pharyngitis/tonsillitis in adults and adolescents (n = 598). The primary endpoint was bacteriological eradication at test -of-cure (TOC; day 24-28) in the bacteriological per-protocol population (n = 420). Bacteriological eradication was achieved in 85.4% (175/205) and 81.4% (175/215) of subjects in the AZ-ER and AZ-IR groups, respectively (95% CI -3.1-11.1). Clinical cure at TOC occurred in 99.0% of subjects in the AZ-ER group and in 96.7% in the AZ-IR group. At long-term follow-up, bacteriological recurrence was observed in 5.5% (9/163) and 7.7% (12/156), respectively. Both treatments were well tolerated; and most adverse events (AEs) were mild to moderate in intensity. The most frequent treatment-related AE was diarrhoea, or loose stools, in 11% of both treatment groups. AZ-ER-treated and AZ-IR-treated subjects had AE burdens (AE days/patient-year) of 7.6 days and 9.2 days, respectively. A similar trend in favour of AZ-ER was noted for treatment-related diarrhoea burden (1.9 days vs. 2.5 days). A single 2-g dose of AZ-ER is as effective and well tolerated as 3 days of AZ-IR (500 mg once daily) for treating group A beta-haemolytic streptococcal pharyngitis/tonsillitis in adults and adolescents.