Randomized, double-blind study of the clinical efficacy of 3 days of azithromycin compared with co-amoxiclav for the treatment of acute otitis media

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Background: Compared with 5 days of dosing, a 3 day dosing regimen of azithromycin for treatment of acute otitis media (AOM) may improve compliance, will simplify therapy for the caregiver and, by giving the same total dose as the 5 day regimen, provide more drug when the bacterial burden is highest.

Methods: Children of 6 months–12 years were enrolled if they had had symptoms and signs of AOM for <4 weeks and tympanic membrane effusion by acoustic reflectometry. Eligible children were randomized to azithromycin 10 mg/kg/day × 3 days or co-amoxiclav 45 mg/kg/day × 10 days. The primary endpoint was clinical response at day 28.

Results: One hundred and eighty-eight children (mean age 3.5 years) were randomized to azithromycin and 185 to co-amoxiclav. At day 10, the clinical success rate was 153/185 (83%) in children treated with azithromycin and 159/181 (88%) in children treated with co-amoxiclav. At day 28, 134/182 (74%) of the children were cured on azithromycin compared with 124/180 (69%) on co-amoxiclav. Also at day 28, signs of AOM, such as abnormal reflectometry (45% versus 59%; P = 0.017), bulging of the eardrum (10% versus 16%; P = 0.059) and loss of tympanic membrane landmarks (11% versus 22%; P = 0.010) were seen less frequently in azithromycin- than co-amoxiclav-treated children, respectively. Adverse events related to therapy were seen in 11% of azithromycin patients compared with 20% on co-amoxiclav (P = 0.014).

Conclusions: Azithromycin given over 3 days is as effective as co-amoxiclav for treatment of AOM, may result in more complete resolution of tympanic membrane disease, and is better tolerated.

Keywords: tympanic membrane disease, children, AOM

Introduction

Antibiotic treatment of acute otitis media (AOM) hastens symptomatic relief and potentially prevents the development of more serious invasive disease.1–3 Because this is a disease of young children, treatment is provided by the caregiver, extending the socio-economic burden of this disease beyond the child alone. Safe and effective therapies that are easy to deliver and optimize compliance offer important advantages over existing treatment.

Azithromycin has been provided as a 3 day regimen for upper respiratory tract infections in Europe for a number of years, but studies have not been performed with this regimen in the USA. As
ketonuric, had been treated with antibiotics in the prior 30 days, had had more of the following: bulging or marked erythema of the tympanic membrane, loss of the normal light reflex or tympanic membrane landmarks, or impaired tympanic mobility on biphasic pneumatic otoscopy. This was also to be documented by acoustic reflectometry (Ear Check PRO, Becton Dickinson, Franklin Lakes, NJ, USA) with an acoustic spectral gradient angle of less than 70° (i.e. level 3, 4 or 5).4 The majority of primary investigators (23/28) were general paediatricians experienced in the physical diagnosis of otitis media and the use of the acoustic reflectometer. Patients were excluded if they had a history of hypersensitivity to β-lactams, macrolides or azithromycin, were phenylketonuric, had been treated with antibiotics in the prior 30 days, had had more of the following: bulging or marked erythema of the tympanic membrane, loss of the normal light reflex or tympanic membrane landmarks, or impaired tympanic mobility on biphasic pneumatic otoscopy. The effusion was also to be documented by acoustic reflectometry (Ear Check PRO, Becton Dickinson, Franklin Lakes, NJ, USA) with an acoustic spectral gradient angle of less than 70° (i.e. level 3, 4 or 5).4 The majority of primary investigators (23/28) were general paediatricians experienced in the physical diagnosis of otitis media and the use of the acoustic reflectometer. Patients were excluded if they had a history of hypersensitivity to β-lactams, macrolides or azithromycin, were phenylketonuric, had been treated with antibiotics in the prior 30 days, had had symptoms of otitis media for >4 weeks or had been receiving antimicrobial prophylaxis.

The institutional review board of each participating centre reviewed and approved the final protocol and the informed consent documentation. After written informed consent was obtained from the parent or guardian, patients underwent a history and physical examination including pneumatic otoscopy and acoustic reflectometry. Patients then received two suspension formulations containing either azithromycin 10 mg/kg once daily for 3 days and a matching co-amoxiclav placebo suspension, or co-amoxiclav 45 mg/kg/day in divided doses twice daily for 10 days and a matching azithromycin placebo suspension. Assignment to drug was performed from a computer-generated randomization list in which the two drugs were allocated randomly in a 1:1 ratio.

On day 5, patients were contacted by phone for an assessment of adverse events, concomitant medications, and compliance with study drug therapy. A clinical assessment was not obtained at that time. At day 10 and at days 24–28, assessments made at the baseline visit were repeated, in addition to an assessment of response to therapy. Definitions included: clinical cure (complete resolution of all signs and symptoms of AOM); improvement (partial resolution of signs and symptoms); or failure (no change or worsening of signs and symptoms, or requirement for additional antibiotic therapy for AOM). Based on guidance from the FDA, the primary endpoint was clinical outcome at day 28. Compliance with study treatment was assessed by measuring the amount of unused study drug returned to the investigator.

### Statistical analyses

The study was powered to demonstrate equivalence between the cure rates of the two treatment groups, requiring that the two-sided 95% CI of the difference between the success rates be contained within ±15%. Assuming 10%–15% of patients are non-evaluable, 320 subjects were required to meet these criteria. The efficacy analysis was carried out based on a modified intent-to-treat population that included all subjects who had at least one dose of study medication and a diagnosis of AOM. An assessment of failure at the end-of-therapy visit (day 10) was carried forward to the test-of-cure visit (days 24–28). The primary measure of efficacy was the investigator assessment of the clinical outcome at the visits on days 24–28. The normal approximation to the binomial distribution was used in computing the 95% CIs. P values were calculated using Fisher’s Exact Test. A Kaplan–Meier plot was constructed to assess time to additional antibiotic use.

### Results

Three hundred and seventy-three patients were randomized between 4 January 2000 and 31 March 2000 and all received study drugs. Eleven subjects (3%) did not have a visit on days 24–28 and were excluded from the efficacy analysis at that time point; all of these subjects had been either cured or had improved by the visit on day 10. The mean age of the children was 3.5 years (s.d. ± 2.5 years). Sixty-one children receiving azithromycin and 53 receiving co-amoxiclav were ≤2 years. The mean age of the children ≤2 years was 9.6 months and 8.4 months on azithromycin and co-amoxiclav, respectively. Seventy-four percent of these children ≤2 years randomized to azithromycin and 72% receiving co-amoxiclav had a prior history of AOM. (Table 1). Of a sample of 196 children overall, 40% were in day care and 29% had been exposed to passive smoking.

Overall success rates at day 10 (Table 2) and cure rates at days 24–28 (Table 3) demonstrated statistical equivalence between the two drugs. Abnormal acoustic reflectometry scores indicating a persistent middle ear effusion were similar at day 10, although were observed more frequently in children treated with co-amoxiclav at days 24–28. Abnormalities of the tympanic membrane, such as bulging and loss of landmarks, were also observed more frequently at days 24–28 in children treated with co-amoxiclav; however, these signs were observed more frequently in the azithromycin group at
day 10. To evaluate additional time points, especially those early in the study, we looked at ‘time to additional antibiotic use’ as a surrogate for failure (Figure 1). During the first 10 days of the study, the proportion of children administered an additional antibiotic was similar regardless of study drug: azithromycin group [11/185 (5.9%); co-amoxiclav group [7/181 (3.9%); P = 0.343].

Adverse events considered related to study drug were seen more frequently in children treated with co-amoxiclav compared with those who received azithromycin (20% versus 11%, respectively; P = 0.014). Commonly observed events were diarrhoea (14.6% for co-amoxiclav and 5.9% for azithromycin; P = 0.006), rash (4.3% and 0%, respectively; P = 0.003) and vomiting (1.1% and 2.1%, respectively; P = 0.685). Complete compliance with active therapy was observed in 99% of children taking azithromycin and 89% of those receiving co-amoxiclav.

**Discussion**

The results of this trial demonstrate that azithromycin given over 3 days is as effective by clinical criteria as a 10 day course of co-amoxiclav for the treatment of AOM. Whereas this azithromycin regimen is used commonly in Europe, it has not been tested in the USA. The clinical outcome from the 3 day dosing regimen observed in this study is similar to that of other published 3 day dosing studies. A 5 day course of therapy has been shown previously to be equivalent to 10 days of co-amoxiclav. The data presented here provide evidence that 3 days of treatment with a similar total dose of 30 mg/kg is as effective as co-amoxiclav given at 45 mg/kg/day. This finding provides further support for the claim that, given the pharmacokinetic characteristics of azithromycin, it is the total dose that is most likely to correlate with clinical outcome rather than the number of days in the treatment regimen. Although the 3 day regimen was not compared directly to a 5 day regimen of azithromycin, the safety profile of this shorter course does not appear to indicate a significant increase in the rate of adverse events.

The totality of the data suggests some differentiating characteristics between the two therapies. While the overall assessment of clinical efficacy was equivalent at each observation point, treatment with co-amoxiclav may have led to a quicker resolution of disease of the tympanic membrane, such as bulging and loss of landmarks, although...
The emergence of antimicrobial resistance.12 Repeat courses of antibiotic treatment and, hence, a driving force for the emergence of antimicrobial resistance.12

There are limitations to these data. In this trial, a tympanocentesis was not required at baseline. As a consequence it is not possible to associate a response to treatment with a bacterial aetiology of infection. The double-blind nature of this trial, however, allowed for a statistically valid comparison of the two treatment groups based on clinical grounds. In addition, while co-amoxiclav 45 mg/kg/day was the preferred dosing regimen at the time this study was performed, infection due to more resistant S. pneumoniae may no longer be clinically responsive to these exposures of amoxicillin. As the susceptibility profile of offending pathogens changes, new studies will be required to establish clinical effectiveness. The data from this study, however, establish a benchmark of clinical parity against which future studies may be compared.

In conclusion, azithromycin given over 3 days is as effective as co-amoxiclav for treatment of AOM, may result in more complete resolution of tympanic membrane disease, and is better tolerated.

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References