Study Design Questions in Treatment of Children with Acute Otitis Media

Comment Letter 1

In comparing high-dose azithromycin with high-dose amoxicillin-clavulanate for children with recurrent or persistent acute otitis media (AOM), Arrieta and colleagues reported that, at days 12 to 16, clinical success rates for the two regimens were comparable and that, at days 28 to 32, clinical success rates for azithromycin were superior (1). The study incorporated many favorable features, including a double-dummy design, stringent criteria for the diagnosis of AOM, and baseline tympanocentesis with culture of middle-ear contents. Unfortunately, the number of children whose baseline cultures were positive for pathogens was insufficient for the results of the study to be considered conclusive.

Of 296 children studied, baseline middle-ear cultures were positive in only 163 (55%). Among children whose baseline pathogen was *Streptococcus pneumoniae*, clinical success rates at days 12 to 16 were 85% (22 of 26) in those receiving azithromycin versus 80% (31 of 39) in those receiving amoxicillin-clavulanate (95% confidence interval [CI] of the difference in proportions, −13.7 to 23.9%). Corresponding values at days 28 to 32 were 65% (17 of 26) versus 67% (26 of 39) (95% CI of the difference, −24.8 to 22.2%). Among children whose baseline pathogen was *Haemophilus influenzae*, success rates at days 12 to 16 were 67% (24 of 36) for azithromycin versus 81% (25 of 31) for amoxicillin-clavulanate (95% CI of the difference, −34.7 to 6.8%). Corresponding values at days 28 to 32 were 47% (17 of 36) versus 52% (26 of 39) (95% CI of the difference, −28.4 to 19.6%). Given these CIs, the findings permit no inference either that the two regimens were equivalent or that either of the two regimens was superior to the other. However, the 95% CI of the difference in proportions at days 12 to 16 suggests that the efficacy of azithromycin for AOM caused by *H. influenzae* was less than that of amoxicillin-clavulanate, a circumstance that, as Arrieta et al. noted, has been reported previously (2). It was only with inclusion of the initially culture-negative children that the difference overall became statistically significant: 72% (107 of 148) for azithromycin versus 61% (88 to 144) for amoxicillin-clavulanate (P = 0.047). Yet the superiority of any antimicrobial drug over another in treating culture-negative children would seem difficult to account for except on the basis of chance. For the subgroup of initially culture-positive children ≤2 years of age—the most therapeutically problematic subgroup—outcome data were not provided.

The authors speculated that their relatively low culture positivity rate may have been attributable to suppression of bacterial growth by prior therapy or site-to-site variability in processing specimens. An alternative explanation would have been the possibility that some children had otitis media with effusion rather than AOM: a result would have been blurring of any differences in efficacy between the two regimens. In our limited experience, culture positivity rates in children with bona fide AOM have been as high in those already receiving antimicrobials as in those who have not been treated.

In summary, the study by Arrieta et al., while incorporating many favorable features, cannot, in our judgment, be viewed as having answered the question it set out to address.

Comment Letter 2

Arrieta et al. reported a difference in clinical outcome favoring high-dose azithromycin versus high-dose amoxicillin-clavulanate at days 28 to 32 (1). The authors’ conclusion that the two drugs are comparable must be interpreted in the context of the study design. First, the study was powered to only be able to detect a >15% difference in overall clinical outcome, so very large numbers of patients are needed to show this difference. Second, 45% of patients had no pathogens. Third, high rates of spontaneous resolution of bacterial infection in AOM mask underlying differences in drug efficacy (12, 14). As expected with small, noninferiority studies (2, 12, 15), this study showed no differences in clinical outcome at days 12 to 16. There was a difference overall at days 28 to 32 (P = 0.047), but no difference in the key group—culture-positive patients—which is consistent with other studies (14). Furthermore, high-dose amoxicillin-clavulanate was achieved by giving two medications: amoxicillin at 45 and clavulanate at 6.4 mg/kg/day plus amoxicillin at 45 mg/kg/day. High-dose amoxicillin-clavulanate (amoxicillin at 90 and clavulanate at 6.4 mg/kg/day) is now available as a single formulation, and recalibration of the results taking compliance into consideration results in the difference no longer being statistically significant (P = 0.19 instead of 0.047).

The authors further conclude that clinical outcomes with both agents are comparable for both *H. influenzae* and *Streptococcus pneumoniae*. In fact, a difference of 14% was found with *H. influenzae* at days 12 to 16, a large difference that is quite noteworthy in light of the particularly high rates of spontaneous resolution in this organism (10, 11). AOM studies have shown azithromycin to have similar bacteriologic and clinical efficacy to placebo (5, 9, 13; A. Hoberman, R. Dagan, A. Rosenblut, E. Leibowitz, A. Huff, and B. Wynne, Abstr. 43rd Intersci. Conf. Antimicrob. Agents Chemother., abstr. G-459, p. 279, 2003). A conclusion of comparability is clearly unwarranted. As for *S. pneumoniae*, clinical success with azithromycin at days 12 to 16 was 21 of 22 (95%) for macrolide-susceptible organisms versus 5 of 8 (63%) for macrolide-resistant organisms. This is similar to the results of a much larger study of regular-dose azithromycin in which the difference was statistically significant (Hoberman et al., 43rd ICAAC).

While a bacteriologic diagnosis and outcome study requires...
only 30 patients per arm to differentiate a highly active agent from a placebo and 100 per arm from an agent with 60% bacteriologic efficacy, 234 and 780 patients per arm, respectively, are needed in bacteriologic diagnosis and clinical outcome studies (12). The study by Arietta et al. included <85 microbiologically evaluable patients per arm, which is far short of the 234 per arm needed to even distinguish an active agent from placebo based on clinical outcome. Bacteriologic outcome or considerably larger clinical outcome studies are clearly needed to determine if high-dose azithromycin offers any advantage (8).

Given all that has been learned in recent years about the need for bacterial eradication and its relationship to clinical outcome (3–8, 11, 12; Hoberman et al., 43rd ICAAC), the continued overprescribing of antibiotics for this condition, and the ease of obtaining bacterial outcome data (8), it is disappointing that AOM studies are still being designed based only on clinical outcomes with small sample sizes. We therefore believe that the conclusion of these investigators that their data support consideration of high-dose azithromycin as an option for treating AOM in children who have failed first-line therapy or who experience recurrent episodes of AOM is not supported by the data presented.

REFERENCES


Authors’ Reply

We appreciate the comments of Drs. Hoberman and Paradise on our recent paper comparing high-dose azithromycin with high-dose amoxicillin-clavulanate for treatment of children with recurrent or persistent acute otitis media (AOM) (2). The study was a randomized, double-blind, double-dummy design, consistent with current Food and Drug Administration (FDA) guidance (4), with stringent criteria for diagnosis and carried out with high evaluability and compliance rates. Of all children randomized, 55% had positive cultures, a finding consistent with the 58 and 56% rates reported in two recent studies of children with recurrent or nonresponsive AOM (1, 9). Drs. Hoberman and Paradise express concern that the number of children with positive cultures was insufficient for the results to be considered conclusive. Among these 160 culture-positive children, we note that the 95% confidence interval for the difference in the success rates at days 12 to 16 was −14.3 to 10.4 and that for day 28 was −9.7 to 20.7, the lower bounds of both intervals within the prespecified value of −15. We suggest that these findings allow definitive conclusions to be drawn about noninferiority of the primary endpoint in comparing high-dose azithromycin 3-day therapy to 10-day amoxicillin-clavulanate antibiotic treatment and in the culture-positive children.

We appreciate Dr. Dagan et al.’s comments on the value of double tympanocentesis studies employing a bacteriologic endpoint evaluated on days 4 to 6, and we would like to make the following points.

First, use of a fixed bacteriologic endpoint at days 4 to 6 fails to address fundamental differences among antibiotic classes with regard to mechanism of action and bactericidal activity. For instance, protein synthesis inhibitors, such as macrolides, kill more slowly than do cell-wall-active β-lactams (5). Thus, for macrolides—as noted by Babl et al. (3)—if follow-up tympanocentesis were to be performed at a later time point, eradication might be observed.

Second, when using a fairly insensitive, nonquantitative, “growth/no growth” bacteriologic endpoint, patients in whom a drug has achieved a significant reduction in bacterial load at days 4 to 6 would be erroneously classified as bacteriologic failures.

Third, Johann-Liang et al. (8) recently discussed the low specificity of bacteriologic failure predicting clinical failure. Low values for Kappa coefficients from three double-tap studies demonstrated the lack of substantial correlation between bacteriologic and clinical outcomes. While a bacteriologic endpoint has value in evaluating rapid clearance of organisms,
bacterial persistence in the setting of clinical symptom resolution is too complex to simply equate an antibiotic with placebo.

Dagan et al. note that the response rates for azithromycin among children with *H. influenzae* are similar to rates of spontaneous resolution of infections caused by this pathogen, as reported by Howie and coworkers (6, 7). Our study compared two drugs under rigorous controls employing randomization and doubleblinding. It is difficult to make direct comparisons of these results with data from uncontrolled historical studies. In Howie’s studies, patient risk factors and inclusion criteria were not strictly defined; thus, his high spontaneous resolution rates may not be applicable to children with a history of recurrent or persistent disease. Similarly, the conclusions of Marchant and colleagues (10), which Dagan et al. cite in discussing sample size, are not applicable to the statistics employed prospectively in the present study. Marchant et al. derived a model from data on 293 patients treated with six different antimicrobials at various times over 9 years. The children were enrolled in several different arms of a treatment algorithm to derive a model for outlining criteria for detecting statistical differences in superiority studies. The comparator in our study (high-dose amoxicillin-clavulanate) is recommended for the treatment of children with recurrent or persistent AOM; thus, a noninferiority trial with a highly active comparator agent rather than a superiority trial is entirely appropriate. This trial design is supported by one of the recommendations of a recent FDA Advisory Committee reviewing issues in studies of AOM (11).

Moreover, the hypothetical sample sizes given by Dagan et al. (234 or 780 for bacteriologic diagnosis or clinical outcome studies) are for total sample sizes, not sample sizes per arm, as stated (10). In Fig. 1, data are plotted from the a priori defined primary endpoint at days 28 to 32, as well as several relevant subsets. A drug regimen would be considered noninferior to its comparator only if the lower bound of the 95% CI surrounding the difference between the two regimens remains within −15%. The results of the study in all patients, in patients with a positive baseline pathogen, and in children less than 2 years of age provide robust evidence that the trends in this study were independent of subset. Indeed, significant differences were observed in this double-blinded trial for overall clinical outcome at the day 28-to-32 visit and notably in children ≤2 years of age. This finding is consistent with reports from a recent international congress where superiority of azithromycin to amoxicillin-clavulanate was reported when time points beyond on-therapy assessments were measured and reported (A. Arguedas, D. Jorgensen, C. Soleyn, and M. W. Dunne, Abstr. 43rd Intersci. Conf. Antimicrob. Agents Chemother., abstr. G-1852, 2003; C. Quach, D. L. Moore, J. P. Collett, and J. Lelorier, Abstr. 43rd Intersci. Conf. Antimicrob. Agents Chemother., abstr. G-460, 2003).

FIG. 1. Difference in efficacy rates between azithromycin (AZ) and amoxicillin-clavulanate (A/C) with a 95% CI for primary clinical endpoint (CE). Results are shown for children <2 years of age (<2 y/o), all children with a baseline pathogen (ME), and children <2 years of age with a baseline pathogen.

### REFERENCES


