Establishing Criteria for Assessment of Efficacy of Antimicrobial Agents in Acute Otitis Media

In a recent article, Dagan et al. (1) report on the comparative bacteriologic efficacies of oral azithromycin and oral cefaclor in children with acute otitis media. The authors assert that based on a double-tympanocentesis method of evaluating bacteriologic eradication in otitis media susceptibility breakpoints for antibiotics can be determined and previous clinical efficacy studies are inadequate compared to this method. We would like to point out some of the pitfalls inherent in the bacteriologic eradication trials and the particular bias introduced into the trial described by Dagan et al.

In order to determine bacteriologic efficacy, the authors use a methodology first utilized by Howie and Ploussard in 1969 (5). Despite 30 years of experience, the double-tympanocentesis method has yet to be validated in clinical trials conducted to the most rigorous scientific standards in which all possible measures to exclude bias are employed. The diagnosis of acute otitis media is subjective in nature; therefore, the “gold standard” methodology for evaluation of anti-infective agents is the double-blind, double-dummy clinical trial design used in reported data from a third, randomized, open-label study in azithromycin-treated group of patients. The open-label design or single-blinded studies allow bias to influence both assessment by the investigator and actions of the patient. For example, the apparent failure of azithromycin to eradicate Haemophilus influenzae in the study reported by Dagan et al. may be due to the timing of the tympanocentesis in relation to the time-dependent bactericidal activity of the drug. In an open-label study, children on the shorter azithromycin regimen may return to the physician earlier compared with children on the 10-day beta-lactam regimen.

This was, in fact, the case (Fig. 1). The median time to second tympanocentesis was 1 day earlier in the azithromycin arm compared with the cefaclor arm, and this trend, despite the small sample size, nearly reached statistical significance. A double-blind, double-dummy clinical trial design minimizes the potential for bias due to differences in length of therapy.

Dagan et al. cite their previous publication (2) as evidence that their model evaluating early bacteriologic eradication is a valid surrogate for eventual clinical response. The previous report uses the same data as the azithromycin-cefaclor study, combined with data from reported studies and randomized, amoxicillin-treated group of patients. The open-label design and the failure to follow the established randomization schedule preclude an unbiased assessment of drug-specific clinical response. Therefore, validation of a model in a three-arm study that uses the same data to report clinical and bacteriologic results from only two of the arms is a deviation from sound clinical-trial conduct and emphasizes how important it is to adhere to established methods in clinical-trial research in order to remove bias from scientific inference.

Dagan et al. also fail to provide a sound theoretical explanation for the observed results. The authors postulate that although azithromycin is highly concentrated in phagocytic leukocytes it is not available in the extracellular space to act against extracellular pathogens. This is inconsistent with previous clinical-trial experience and in vitro data demonstrating that 93.3% of the intracellular amount of azithromycin is released within 24 h under resting conditions (4) and immediately in bacteriologic stimulation (J. M. Hyatt, S. A. Mangione, and J. J. Schentag, Fifth Int. Conf. Macrolides Azalides Streptogramins Ketolides Oxazolidinones, abstr. 3.02, 2000).

It remains to be determined whether the timing of the tympano- centesises, investigator bias, and other factors can be removed from the evaluation of these double-tap trials. Given the potential pitfalls inherent in the methodology used in this study, as well as the lack of clinical validation, it would be premature to consider changes in susceptibility breakpoints or clinical-trial design based on these data as the authors have suggested. The peer review community must ask the difficult questions that might shed light on why a drug that has performed well in large, double-blinded clinical trials is perceived to be relatively inactive in children in a small bacteriologic study fraught with methodological problems. Until the double-tympanocentesis method is independently validated, clinical researchers should continue to use established designs for evaluating antimicrobials in otitis media by conducting large, double-blinded clinical trials in accordance with advice from experts in the field and the Food and Drug Administration (3).

REFERENCES


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Fig. 1. Median time to second tympanocentesis. For azithromycin (AZ) the median was 4 days (range, 3 to 6 days). For cefaclor (CFC) the median was 5 days (range, 4 to 6 days). P = 0.1044.
Authors’ Reply

We thank the authors of the letter for their comments. We agree that “the diagnosis of acute otitis media is subjective.” Erhardt et al. suggest that using a trained otosclist is best. However, even the best otosclist can, at best, provide indirect evidence for the presence of purulent acute otitis media. In contrast, the tympanocentesis method used in our study enabled us to enroll only patients with direct proof of purulent otitis as evidenced by the presence of culture-positive purulent exudate. This is in fact the gold standard for diagnosis of acute bacterial otitis media. Similarly, the mandatory second tympanocentesis on day 4 to 6 (3 to 5 days after initiation of therapy) not only allowed us to evaluate the pathogen eradication rate but also, in a direct way, the presence and nature of middle ear fluid. No other indirect method, such as pneumatic otoscopy, is as accurate.

We also agree that the blinded way to evaluate drug efficacy is the best one, at least for judging clinical improvement, since the symptoms of otitis are extremely subjective. For these exact reasons we clearly stated that “all otologic evaluations were done by an otolaryngologist who was unaware of the culture results and drug allocation.” In addition, we performed a second comparative study (azithromycin versus amoxicillin-clavulanate) in the United States, Israel, and the Dominican Republic (3). In that study, also performed using the double-tympanocentesis method, the clinical outcome was assessed in such a way that the treatment regimen was blinded not only to the otolaryngologist but to the study physician as well, thus avoiding the potential biases mentioned by Erhardt et al. The results showed the same poor bacteriologic outcome in the azithromycin arm in patients with *H. influenzae* infections. Furthermore, we are not aware of any studies that evaluated the bacteriologic efficacy of azithromycin in otitis media other than the two studies performed by our group, and therefore the results published in these studies are unique. However, documentation of the failure of azithromycin and related agents to eradicate *H. influenzae* is not unique, as this has been shown in other diseases. Two comparative studies looking at both bacteriologic and clinical efficacies in acute exacerbations of chronic bronchitis treated with either azithromycin or clarithromycin made essentially the same point. In the first study Beghi et al. (1) compared azithromycin and amoxicillin-clavulanate for bacteriologic and clinical outcomes. The bacteriologic efficacies of azithromycin and amoxicillin-clavulanate were 70 and 100%, respectively, for *Streptococcus pneumoniae* and 50 and 100%, respectively, for *H. influenzae*. In the second study Chodosh et al. (2) compared clarithromycin and ciprofloxacin. The respective values for *S. pneumoniae* were 93 and 63%, and for *H. influenzae* they were 65 and 100%. The clinical efficacies in the two studies were 68% for azithromycin versus 97% for amoxicillin-clavulanate and 75% for clarithromycin versus 89% for ciprofloxacin.

Another important point made by Erhardt et al. concerns the timing of the second tympanocentesis. One of the main reasons for the importance of timing is the high spontaneous rate of bacteriologic clearance. In fact, 52% of *H. influenzae* organisms were spontaneously eradicated at second tympanocentesis, performed 2 to 7 days after the first one, without antibiotic treatment (4). Erhardt et al. point out that a “nearly statistically significant” difference in the timing of the second tympanocentesis between the cefaclor and the azithromycin groups was present in our study. In fact, *H. influenzae* eradication rates on day 4 and day 5 in the azithromycin group were not significantly different: of the 30 children positive for *H. influenzae* at enrollment, the second tympanocentesis was done on day 4 for 13 children and on day 5 or 6 for 17 children (16 on day 5 and 1 on day 6). The respective bacteriologic failure rates were 7 of 13 (54%) and 9 of 17 (53%), demonstrating that there was no difference in bacteriologic outcome between day 3 second tympanocentesis and day 4 second tympanocentesis. Thus, the theoretical criticism raised by Erhardt et al. was not an issue.

Erhardt et al. raise concerns regarding our 1998 study looking at the correlation between bacteriologic and clinical outcomes, stating that it was performed with an “open-label” design. In fact, the otolaryngologist was blinded to the drug regimen and to the culture results. Furthermore, the otolaryngologist’s evaluation was done on day 4 or 5, at the time of the second tympanocentesis, when the sample was sent for culture, thus making it a blinded observation with respect to the results of the culture, which became known only 1 to 3 days later. The second point in the same paragraph is absolutely not valid, since our main comparison was between bacteriologically positive and bacteriologically negative patients at the time of the second tap.

Our response to the comment regarding the theoretical explanation for the failure of azithromycin to eradicate pathogens is as follows. Even if we fail to provide a good theoretical explanation, one cannot deny the facts that the eradication rates of *H. influenzae* and macrolide-resistant *S. pneumoniae* treated with azithromycin were poor and not different from those expected if a placebo had been administered in two different studies and in more than one country (1, 2). Erhardt et al. argue that within 24 h, 93.3% of the intracellular amount of azithromycin is released under resting conditions. They do not take into account the fact that there is a continued influx of polymorphonuclear leukocytes (PMNs) to the middle ear cavity in acute otitis media and the drug can immediately enter fresh PMNs (this occurs in vivo, when a continuous supply of cells exists). The in vitro models or even specific animal models may therefore not be appropriate. We would welcome any alternative theory that could explain the poor results of azithromycin with macrolide-resistant *S. pneumoniae* and with *H. influenzae* but cannot accept denial of the same finding in two studies.

In the last paragraph, Erhardt et al. summarize the letter and try to provide guidelines. In light of all of the above, it is clear that this summary is incorrect and contains several presumptuous statements which have no factual basis. We still believe in the validity of the peer review process.

Our last comment is that the study was planned in collaboration with Pfizer International, Pfizer Inc., and was sponsored and monitored by them as well. It is only after the unfavorable outcome became obvious, that the present criticisms were expressed. We find no scientifically sound reasons in the letter of Erhardt et al. to consider our work invalid in any way and are confident that our findings will be validated further if additional studies are undertaken.

REFERENCES


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