A Comparison of Two Macrolide Antibiotics in the Treatment of Community-Acquired Infections

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ABSTRACT

From 1993 to 1999, resistance to new macrolide antibiotics used for pneumococcal infections increased by 9.8%. We conducted a retrospective study in an effort to detect a difference in failure rates and performed a cost-minimization analysis for azithromycin (Zithromax®, Pfizer) and clarithromycin (Biaxin®, Abbott). We assessed 465 prescriptions for azithromycin and 168 prescriptions for clarithromycin from the year 2000 and noted no significant difference in failure rates between the two agents. After performing a cost-minimization analysis, however, we found that there was a cost difference between clarithromycin and azithromycin.

BACKGROUND

Azithromycin (Zithromax®, Pfizer), classified as an azalide, a subclass of macrolides, and clarithromycin (Biaxin®, Abbott), a semisynthetic macrolide, have been available in the U.S. for about a decade. Even though they are chemically related to erythromycin and share a common mechanism of action, their pharmacokinetic properties are better than those of erythromycin. Azithromycin and clarithromycin are resistant to degradation by acid catalysis, thereby allowing dosing once or twice per day.

These two drugs are commonly prescribed for the treatment of upper and lower respiratory tract infections because of their enhanced activity, convenient dosing, and improved tolerability. In 1993, 17.7 million macrolide prescriptions were filled; by the year 1999, the number of prescriptions increased by 20%. During that time period, resistance to macrolides for pneumococcal infections also increased by 9.8%.

Researchers have speculated that a major route of macrolide resistance is via an efflux mechanism expressed on mef genes. In this process, the antibiotic is actively pumped out of the microbe. An alternative mechanism of resistance is via methylation of the ribosomal binding site. Because of the documented increase in resistance, these antibiotics should be prescribed appropriately in an attempt to decrease resistance.

Nine clinical trials comparing the efficacy and safety of azithromycin and clarithromycin have been published. Two of the nine were performed in children with acute otitis media (middle-ear infection) or pharyngitis. One trial was published in Japanese, and these results were not incorporated.

On the basis of six out of nine studies, we observed no significant differences in the efficacy and safety of azithromycin and clarithromycin, but patients who received azithromycin experienced more adverse drug events (ADEs) than those taking clarithromycin. Therefore, the goal of this retrospective study was to determine whether there was a difference in effectiveness, defined as therapeutic failure, between the two drugs for the outpatient treatment of community-acquired infections.

For our study, we defined therapeutic failure as the need for a subsequent antibiotic prescription within 21 days after the initiation of azithromycin or clarithromycin treatment for a given subject. Our primary objective was to compare the failure rates of azithromycin versus clarithromycin in subjects new to antibiotic therapy (i.e., patients who had received no antibiotic prescriptions within 21 days before taking the study drug).

Our secondary objectives included (1) an assessment of failure rates with the two antibacterials in subjects who did not respond to any antibiotics 21 days before receiving either study drug and (2) a cost-minimization analysis of the two drugs.

METHOD

For a one-year period, we collected data from a managed care database for all prescriptions filled for a three- to five-day course of azithromycin therapy or a five- to 14-day course of clarithromycin therapy. The following groups of people were excluded from the study:

- patients younger than 18 years of age
- patients who were receiving concurrent antibiotic therapy
- patients taking immunosuppressive medications, such as cyclosporine, tacrolimus, or chronic corticosteroid therapy (i.e., a prednisone equivalent of 20 mg/day or more)
- patients taking medications for human immunodeficiency virus (HIV) infection
- patients receiving chronic antibiotic therapy, including those taking azithromycin 1,200 mg/week or a single dose of azithromycin
- patients receiving treatment for Helicobacter pylori

Even though we gathered data from December 1999 to January 2001, we compiled azithromycin and clarithromycin prescriptions from January 2000 through December 2000 for this retrospective study. The months of December 1999 and January 2001 were used to gather additional data.

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For each subject, we collected the following information (Figure 1):

- member identification number
- personal information (date of birth/age/sex)
- the treatment drug and pre-study and post-study antibiotics, with date of prescription, quantity, days of supply, and cost
- concurrent medications with date of prescriptions

For statistical analyses, we used Student’s t-test to measure failure rates of the two study drugs.

With the cost-minimization analysis for subjects who met the primary objective, we calculated the total cost of antibiotics for each patient, then summed total antibiotic costs in the azithromycin and clarithromycin study arms. We incorporated the cost of doctor visits and laboratory tests if therapy with two or more antibiotics was unsuccessful. We estimated the costs of $50 per doctor visit and $60 per laboratory test.

RESULTS

From January through December 2000, we assessed 633 prescriptions: 465 for azithromycin and 168 for clarithromycin. Of the 465 azithromycin prescriptions, 427 (92%) met the primary objective and 38 (8%) met the secondary objective. Of 168 clarithromycin prescriptions, 150 (89.3%) met the primary objective and 18 prescriptions (10.7%) met the secondary objective. Figure 2 illustrates the stratification of azithromycin and clarithromycin prescriptions.

The failure rates of azithromycin and clarithromycin were similar for both primary and secondary objectives. For the primary objective, the failure rate for azithromycin was 14.8%; for clarithromycin, it was 16% ($P = .7137$). For the secondary objective, the failure rates for azithromycin and clarithromycin were 34.2% and 22.2%, respectively ($P = .3621$).

We conducted a cost-minimization analysis for the prescriptions that met the primary criteria. After summing the cost of the study drugs, other antibiotics, doctor visits, and laboratory tests, we divided this value by the number of prescriptions. Table 1 (see page 659) clearly illustrates that clarithromycin was twice as expensive as azithromycin.

DISCUSSION

As with previous studies, this retrospective study also showed no difference in failure rates between azithromycin and clarithromycin, although clarithromycin therapy cost twice as much as azithromycin therapy. We could attribute no difference in failure rates to the small number of prescriptions assessed; 465 azithromycin prescriptions and 168 clarithromycin prescriptions were evaluated.
Figure 2  Stratification of azithromycin and clarithromycin prescriptions.  
AB = antibiotic; AZI = azithromycin; CLAR = clarithromycin; Rx = prescription.
Unfortunately, because of the limited amount of information extractable from a managed care database, we were unable to determine the cause of treatment failure. Failure rates could be attributed to any of the following:

- antibiotic resistance.
- lack of sufficient duration of treatment.
- inappropriate drug selection.
- nonadherence to regimens as a result of ADEs.

Another limitation of this study was the definition of therapeutic failure as 21 days, which was an arbitrary number. No published studies have defined the number of days to assess a failure rate. Clarithromycin prescriptions are usually intended to be taken for seven to 14 days, and we therefore estimated how long a patient might be able to tolerate an infection before receiving a new antibiotic prescription. Twenty-eight days might have been a long time for this, whereas 14 days might not be sufficient to detect a failure rate.

A major limitation of this study was the fact that the indications for all of the antibiotics were unknown. Some patients might have been prescribed an antibiotic for a viral or a parasitic infection.

Even though this study had many limitations, we noted a marked difference in costs between the two drugs. It is possible that this difference might be attributable to the duration of clarithromycin therapy, even though the average wholesale price (AWP) for a unit of clarithromycin is less expensive than the AWP for a unit of azithromycin.

CONCLUSION

The cost of health care, including prescription medications, has steadily increased over the years in the U.S. As health care professionals, we should aim to minimize costs while offering optimal therapy to our patients. Some possible strategies for reducing the costs of excessive antibiotic prescriptions might include:

- prescribing antimicrobials only for suspected bacterial infections.
- providing prescriptions only after an office visit.
- taking a specimen culture after unsuccessful therapy with two antimicrobial agents.

This approach can help to reduce health care costs while minimizing antibiotic resistance.

REFERENCES


### Table 1: Cost-Minimization Analysis

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<tr>
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<th>Azithromycin</th>
<th>Clarithromycin</th>
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<td>Drug cost</td>
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<td>Cost of other antibiotics</td>
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<td>Total cost/number of prescriptions</td>
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<td>$81.53</td>
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