Macrolide Therapy of Group A Streptococcal Pharyngitis: 10 Days of Macrolide Therapy (Clarithromycin) Is More Effective in Streptococcal Eradication than 5 Days (Azithromycin)

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We compared recommended doses of 2 oral macrolide antibiotics (10 days of clarithromycin, 5 days of azithromycin) for eradicating group A streptococci from the throats of individuals aged ≥ 12 years with symptomatic pharyngitis and a positive throat culture. Patients received either clarithromycin (250 mg b.i.d. for 10 days [n = 260]) or azithromycin (500 mg on day 1, followed by 250 mg q.d. for 4 days [n = 265]). Follow-up throat cultures were obtained both at 13–19 days and at 28–38 days. We evaluated 392 patients (median age, 26 years; clarithromycin, 194 patients; azithromycin, 198 patients). Ten days of clarithromycin therapy was more effective than 5 days of azithromycin therapy in eradicating the organism (91% [176/194] vs. 82% [162/198]; P = .012). More than 97% of all streptococcal isolates were macrolide-sensitive. Whether these bacteriologic eradication rates were the result of the 2 macrolides compared or were due to differences in duration of therapy could not be determined, but the statistically significant difference in eradication of group A streptococci does raise additional questions about shortened courses of macrolide therapy for this common infection.

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The study protocol was approved by the local institutional review board of each of the participating centers. Informed consent was obtained from the patients or their guardians, and guidelines for human experimentation of the US Department of Health and Human Services were followed in the conduct of the clinical research.

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The major cause of bacterial pharyngitis and/or tonsillitis is the group A β-hemolytic streptococcus (Streptococcus pyogenes) [1]. Although streptococcal tonsillopharyngitis usually is a self-limited disease that may resolve clinically even without antibiotic treatment, antibiotic therapy can shorten the clinical course [2, 3]. However, the major objective of antibiotic therapy has been eradication of the organism from the upper respiratory tract, which has been shown to be necessary to prevent rheumatic fever [4–6].

Penicillin has been the “gold standard” for treatment, although other antibiotics have also been shown to be effective in eradicating the organism. These agents include penicillin congeners (e.g., ampicillin, amoxicillin, and semisynthetic penicillins), cephalosporins, macrolides, and clindamycin. Although most oral antibiotics classically have been administered for 10 days to maximize eradication of group A streptococci from the pharynx, it has been reported that selected newer agents may be equally effective when given for shorter periods of time [7–9]. Yet there has been reluctance to endorse shorter courses of antibiotic therapy in general because of a perceived need for additional confirmatory data [6].

This study was designed to examine and compare the bacteriologic eradication rates of group A streptococci in patients ≥ 12 years of age with acute-onset pharyngitis and with recovery of this organism from the upper respiratory tract, using currently recommended doses of 2 newer macrolides: either a 10-day course of oral clarithromycin or a 5-day course of oral azithromycin.

Patients. Male or nonpregnant female patients (≥ 12 years old) with signs and symptoms of pharyngitis from whom S. pyogenes was recovered by throat culture were randomly assigned to receive either of the 2 antibiotic regimens. To be eligible for enrollment, patients must have had a sore throat and at least 1 of the following signs or symptoms: pharyngeal or tonsillar erythema or exudate, anterior cervical lymph node tenderness, or fever. Those with a history of rheumatic fever or rheumatic valvular heart disease were not eligible to be enrolled; neither were patients who had taken a systemic antibiotic within 3 days before enrollment. Patients who had received a substrate inducer or inhibitor of the P450 CYP3A4 (e.g., phenytoin, terfenidine, astemizole, or cisapride) within 3 days before enrollment. Patients who had received a substrate inducer or inhibitor of the P450 CYP3A4 (e.g., phenytoin, terfenidine, astemizole, or cisapride) within the previous 4 weeks or would have required these drugs during the study period were also excluded.

Study design and protocol. This was an investigator-blinded parallel-group study in which patients were randomized in a 1:1 ratio at each study center (47 clinical centers...
Within the United States to receive either the recommended 10-day oral course of clarithromycin (250 mg b.i.d.) or the 5-day recommended oral course of azithromycin (500 mg on treatment day 1, followed by 250 mg q.d. for the next 4 days). At enrollment (visit 1), eligible patients with a sore throat who had a rapid antigen– detection test result positive for *S. pyogenes* from a pharyngeal swab (Abbott TestPack + Plus; Abbott Laboratories) were invited to participate. Before initiation of antibiotic therapy, a medical history was obtained and a physical examination was performed. A pharyngeal throat swab was obtained for culture to confirm the presence of *S. pyogenes*. The presence and severity of clinical signs and symptoms were recorded. These included sore throat, headache, or abdominal pain within the previous 24 h, malaise or fatigue, cough with or without production, cervical adenopathy, pharyngeal erythema or exudate, presence or absence of palatine tonsils, and fever (>37.8°C).

Because the durations of the 2 macrolide treatments are based on a difference in their pharmacokinetic properties [10, 11], streptococcal eradication was assessed at 2 follow-up visits, once between days 13 and 19 after the initial visit (visit 2) and again between days 28 and 38 after the initial visit (visit 3). Compliance with the assigned treatment regimen was assessed at visit 2; the number of dispensed doses of macrolide was compared with the returned tablet count to determine compliance. Bacteriologic treatment failure was defined as recovery of group A streptococci of the same serotype (concordance) at any follow-up visit. Recovery of a different serotype at a convalescent visit was counted as an initial bacteriologic cure followed by a second group A streptococcal acquisition. No subjects developed suppurrative or nonsuppurrative complications of group A streptococcal infection.

**Microbiological evaluation.** Pharyngeal swabs were placed in transport medium and sent by overnight courier to a central laboratory (World Health Organization Collaborating Center for Reference and Research on Streptococci, University of Minnesota) for culture, characterization of group A streptococci, and antibiotic susceptibility testing. Single-colony isolates of *S. pyogenes* from all positive culture plates were frozen in blood broth and stored at −20°C until they were characterized. Acute visit and follow-up visit isolates of group A streptococci were serologically characterized by T-agglutination pattern and by M/OF serotyping using conventional techniques [12].

In vitro antibiotic susceptibility of the group A streptococcal isolates was determined by means of the disk diffusion method and standards recommended by the National Committee for Clinical Laboratory Standards [13].

**Statistical analysis.** These analyses included only those subjects who had an initial throat culture positive for group A streptococci, who had clinical observations and throat samples obtained at all 3 visits, and who were compliant in taking the assigned antibiotic. Complete compliance with the assigned regimen was documented in 92% and 98% of patients in the clarithromycin and azithromycin groups, respectively.

The comparability of the treatment groups was assessed with respect to sex and race, using Fisher’s exact test; for age and weight, using one-way analysis of variance; for the number of streptococcal pharyngitis or tonsillitis episodes in the previous year (including the current infection), using the Wilcoxon 2-sample test; and for pretreatment clinical findings, using the Cochran-Mantel-Haenszel test. Group A streptococcal eradication rates and clinical cure rates were compared by Fisher’s exact test.

This study was designed to enroll ~500 subjects (~250 in each treatment group) to obtain 350 evaluable patients (175 per treatment group), assuming a 70% rate of evalubility. This sample size provides ~80% power to detect significant differences of 11% in eradication at the .05 (2-tailed) significance level.

**Results.** A total of 525 patients originally were randomized, were enrolled, and received the assigned antibiotic (260 and 265 patients to the clarithromycin and azithromycin groups, respectively). Of these, 392 (75%) were evaluable by previously stated criteria for the bacteriologic and clinical analyses (194 and 198 patients in the clarithromycin and azithromycin groups, respectively). A total of 133 patients were excluded from the present analyses for the following reasons: being culture-negative for group A streptococci at initial visit (80 patients), no follow-up sample taken for culture at either visit 2 or 3 (31 patients), and noncompliance with the assigned antibiotic (22 patients).

The treatment groups were comparable at enrollment with respect to demographic characteristics, number of streptococcal pharyngitis or tonsillitis episodes in the previous year (including the current infection) (table 1), and pretreatment signs and symptoms of infection. At enrollment into the study, the vast majority of patients (79%, 311/392) were experiencing their first episode of streptococcal pharyngitis or tonsillitis within a year. The mean age for each treatment group was ~26 years; the median ages also were 26 years.

The most common presenting symptoms included sore throat (100% of patients, as required by the inclusion criteria), erythematous pharynx with or without exudate (97%), erythematous tonsils with or without exudate (89% of those with tonsils), and anterior cervical node tenderness (86%). The percentages were similar for the 2 treatment groups (data not shown).

Ten days of macrolide therapy (oral clarithromycin) proved more effective than a 5-day course (oral azithromycin) in eradicating *S. pyogenes* from the pharynx at visit 2 (95% [184/194] vs. 88% [174/198], respectively; \( P = .019 \)) as well as at visit 3 (91% [176/194] vs. 82% [162/198], respectively; \( P = .012 \)) (fig-
Table 1. Demographic characteristics and presenting conditions of evaluable patients with group A streptococcal pharyngitis, at baseline, by treatment group.

<table>
<thead>
<tr>
<th>Demographic characteristic</th>
<th>Clarithromycin (n = 194)</th>
<th>Azithromycin (n = 198)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>71 (37)</td>
<td>82 (41)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>123 (63)</td>
<td>116 (59)</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>26.8 ± 11.5</td>
<td>26.1 ± 10.9</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>26</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>12–61</td>
<td>12–59</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>176 (91)</td>
<td>183 (92)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>7 (4)</td>
<td>6 (3)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>11 (6)</td>
<td>9 (5)</td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>72.1 ± 19.4</td>
<td>71.7 ± 21.2</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>34–168</td>
<td>28–130</td>
<td></td>
</tr>
<tr>
<td>Infections during past year, no. b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>1.27 ± 0.64</td>
<td>1.27 ± 0.56</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. Data are no. (%) of patients, unless otherwise indicated.
* By use of Fisher’s exact test (for sex and race), 1-way analysis of variance (for age and weight), and Wilcoxon 2-sample test (for no. of infections that occurred during the previous year).
* No. of streptococcal pharyngitis or tonsillitis infections that occurred during the past year, including current infection.

therapy [16–18]. Because of this, newer macrolides have been among antibiotics mentioned as alternatives for the treatment of streptococcal tonsilopharyngitis [7–9, 19, 20]); this is especially true for individuals who are allergic to penicillin. Two newer macrolides, azithromycin (strictly speaking, an azalide) and clarithromycin, each have been reported to be comparable or superior to penicillin in eradicating group A streptococci from patients with pharyngitis [7, 19, 21]. Equal or better eradication rates have been reported with shortened courses of macrolide therapy; the shorter course has the additional advantage of increasing patient compliance [22]. In fact, O’Dougherty [8] has even reported successful eradication of group A streptococci from the throat after only 3 days of macrolide (azithromycin) therapy. Furthermore, the study by Hooton [7] described essentially equal success with 5 days of macrolide therapy (azithromycin) compared with 10 days of oral penicillin V therapy (91% vs. 96%). However, in the latter study, patients were evaluated and culture samples taken at 11 days only; there was no long-term assessment to determine the true rate of eradication.

A number of published studies, however, have reported decreased microbiological efficacy after a shortened course of macrolide therapy for group A streptococcal sore throat. Although not involving a direct comparison of these two macrolides, other published evidence to support concern about the relative efficacy of 5-day macrolide therapy is available. For example, in 2 studies in which 5-day therapy was compared with 10-day therapy with oral penicillin V, Schaad and Heynen [23] showed

Figure 1. Positive throat cultures before and after therapy with oral azithromycin (5 days) or oral clarithromycin (10 days). Visit 1 = initial visit, enrollment; visit 2 = 13–19 days; visit 3 = 28–38 days. There were statistically significantly fewer failures to eradicate group A streptococci after 10 days of therapy with clarithromycin. Statistical comparisons were made with Fisher’s exact test.
only a 55% microbiological cure, which was 20% less than resulted from 10 days of oral penicillin V therapy. Additionally, Tarlow [24] found that, 14 days after completion of therapy, 95% of patients who had completed a 5-day course of azithromycin had throat cultures negative for group A streptococci. When culture samples from these patients were obtained again 2 weeks later (30 days after the final dose), the eradication rate due to azithromycin had fallen to 79%, a change of 16%. Thus, once again, although the 5-day course of azithromycin resulted in a high initial “eradication” rate, the documented increased recovery of the concordant serotype at 30 days likely represented temporary suppression of the group A streptococci in the throat, followed by regrowth with time [24]. This also was the case in the report by Hamill [25]; there were more positive cultures at 30 days in the short-course macrolide group than in the 10-day penicillin group [25].

Because of such conflicting reports, the efficacy of abbreviated courses of macrolide therapy for eradication of group A streptococci remains controversial. It is important to recognize that short-course and conventional 10-day macrolide therapy continue to be selected by primary care physicians. Because an important objective of antibiotic treatment of group A streptococcal pharyngitis is prevention of sequelae, which has been convincingly shown to be dependent on eradication of the organism, a direct comparison of microbiological efficacy between the 2 therapies is warranted [4].

To our knowledge, there are no published data describing such a direct comparison; this was the purpose of the present study. The data reveal that the streptococcal eradication rate following 10 days of macrolide therapy (oral clarithromycin) was statistically superior (P<.002) to a 5-day regimen of the other tested macrolide (oral azithromycin). This direct comparison has important practical implications for practitioners, not only for reasons previously mentioned but also for public health reasons.

One obvious factor that may influence the microbiological effectiveness of any antibiotic is its pharmacokinetic profile. Although we acknowledge this potential influence, the purpose of this evaluation was to compare microbiological efficacy, not the pharmacokinetic properties of these 2 macrolides. Both of these macrolides are approved and are used for treatment of streptococcal pharyngitis in the doses and for the lengths of administration used in this study.

Our data from patients from multiple geographic regions of the United States showed a low (2%) prevalence of macrolide resistance among the 444 tested S. pyogenes strains. This fact offers additional evidence that macrolide resistance has not been a clinically significant problem in the United States during the 1990s [26].

In summary, a 10-day course of oral macrolide therapy (clarithromycin) proved to be superior to a 5-day course of another macrolide (azithromycin) for eradication of group A streptococci from the pharynx of patients ≥12 years old with acute pharyngitis. The difference in efficacy could not be attributed to compliance or to antibiotic resistance rates. Whether the outcome was the result of the specific macrolides used or the duration of therapy could not be ascertained in this study. Additional carefully conducted comparative studies of shortened courses of macrolide and other antibiotic therapy for treatment of group A streptococcal pharyngitis are warranted.

Acknowledgments


References