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Article

Randomized, Multicentre Study of the Efficacy and Tolerance of Azithromycin versus Clarithromycin in the Treatment of Adults with Mild to Moderate Community-Acquired Pneumonia

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Abstract Adults with mild to moderate community-acquired pneumonia were treated with azithromycin (500 mg once daily for 3 days) or clarithromycin (250 mg twice daily for 10 days) and clinically assessed between days 3 and 7 and days 12 and 16. Patients classified as improved at the day 12–16 visit were also evaluated between days 19 and 23. Two hundred three patients were treated (101 with azithromycin, 102 with clarithromycin). A satisfactory clinical response was recorded at the end of therapy in 83 of 88 (94%) evaluable azithromycin-treated and 84 of 88 (95%) evaluable clarithromycin-treated patients ($P=0.518$). At day 19–23, only one patient in each treatment group had relapsed. Thirty-one of 32 (97%) pathogens isolated from patients in the azithromycin group were eradicated, compared with 32 of 35 (91%) isolated from clarithromycin patients. In all patients with atypical pneumonia, the clinical response was satisfactory at follow-up. Incidences of treatment-related adverse events were similar for the two groups ($P=0.815$). Two (2%) clarithromycin patients discontinued therapy due to severe treatment-related adverse events; none in the azithromycin group did. This study shows that a 3-day, once-daily course of azithromycin is as clinically effective and well tolerated as a 10-day, twice-daily course of clarithromycin in the treatment of mild to moderate community-acquired pneumonia.

Introduction

Azithromycin and clarithromycin are macrolide antibiotics that are structurally related to erythromycin [1]. Both antibiotics retain the established macrolide spectrum of activity against gram-positive pathogens and those causing atypical pneumonia while demonstrating improved activity against some gram-negative bacteria, especially in the case of azithromycin [2–4]. Compared with clarithromycin, azithromycin has particularly good in vitro activity against *Haemophilus influenzae* [5–7] and the atypical organisms *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella pneumophila* [8, 9], which are some of the most common causes of community-acquired pneumonia. Clarithromycin has a minimum inhibitory concentration (MIC) of ≤ 0.25 mg/l against most respiratory pathogens except *Haemophilus influenzae* [3, 10]. In contrast, the mean MIC90 of clarithromycin for *Haemophilus influenzae* is 9 mg/l and that of its 14-hydroxy metabolite 3 mg/l [11]. Significantly ($P<0.001$) more isolates of *Haemophilus influenzae* have been found susceptible to azithromycin than to clarithromycin (95.7% vs. 63.1%) [12].

Azithromycin is also noted for its pharmacokinetic profile, which is characterized by favorable penetration into sputum, bronchial mucosa, and alveolar macrophages. Baldwin et al. [13] demonstrated that, after a single 500 mg dose of azithromycin, levels in pulmonary tissue remained well above the MICs for the most important respiratory pathogens for 4 days.

The efficacy of a 3-day, once-daily course of azithromycin (500 mg/day) in the treatment of community-

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acquired pneumonia has been described previously in an open, noncomparative pilot study [14]. The aim of the present study was to evaluate this regimen with regard to clinical and microbiological efficacy and tolerance and compare it with a 10-day clarithromycin regimen (250 mg twice daily) in the oral treatment of mild to moderate community-acquired pneumonia.

Materials and Methods

Patient Selection. Male and female outpatients with clinically diagnosed community-acquired pneumonia were eligible for enrollment in the study. Patients were considered to have pneumonia if, in addition to a chest radiograph showing a new pulmonary infiltrate or consolidation, they had at least three of the following: nonproductive cough, new onset of purulent sputum (productive cough), or change in the character of their sputum; sputum culture positive for gram-positive diplococci; body temperature of 38 °C or more at least twice within a 24 h period; and/or elevated leukocyte count ($\geq 10 \times 10^9$/l). Patients were not admitted to the study if they were outside the age range of 12–75 years.

Any patient with a terminal illness or any condition that could interfere with the attendance schedule was excluded from the study. Also excluded were patients with (i) a condition likely to affect gastrointestinal absorption of the antimicrobial agent or (ii) significant hepatic disease with a serum transaminase level more than three times the upper limit of the normal range [serum glutamic oxalacetic transaminase (SGOT) 0.02–0.90 μM/s/l; serum glutamic pryruvic transaminase (SGPT) 0.15–0.95 μM/s/l]. Patients hypersensitive to azithromycin, clarithromycin, or other macrolides were excluded. Concurrent medication with ergotamine, cyclosporine, theophylline, astemizole, terfenadine, or antacids (except H_2-antagonists) was not permitted. Women were not enrolled if they were pregnant, breast-feeding, or of childbearing age and not using adequate contraceptive precautions (oral contraceptives or a barrier method). Other reasons for exclusion were concurrent infections requiring additional antimicrobial therapy, a Gram stain that suggested the presence of an organism against which the study antibiotics would be ineffective (e.g. *Enterobacteriaceae*, *Pseudomonas, Klebsiella*), and evidence of drug or alcohol abuse. Patients were also excluded if they had received another antimicrobial agent in the 2 weeks preceding the start of the study unless treatment was a microbiologically documented failure, if they were treated with another investigational drug in the previous month, or if they had already participated in the current study.

Study Design. The study was conducted at 28 centers in four countries. Patients were randomized to receive either an oral once-daily dose of 500 mg azithromycin tablets for 3 consecutive days or a twice-daily administration of one 250 mg clarithromycin tablet for 10 consecutive days. The study, which was not blinded, included at least 80 patients who were evaluable for bacteriological response.

Evaluation of Clinical Response. Patients were evaluated before the start of therapy (day 1) and between days 3 and 7 and days 12 and 16. Patients who were considered clinically improved only at the day 12–16 visit were evaluated further between days 19 and 23.

Clinical symptoms were recorded before treatment on day 1; changes were monitored between days 12 and 16 and, when necessary, between days 19 and 23. Clinical cure was defined as the disappearance of all acute pretreatment clinical signs and symptoms. Improvement was defined as the partial disappearance or improvement of pretreatment clinical signs and symptoms. A failure was recorded if there was no change or a worsening of the signs and symptoms of infection present before treatment. A patient was considered to have relapsed if pretreatment clinical signs and symptoms had initially improved or disappeared but subsequently returned or worsened, requiring additional antibiotic therapy.

Evaluation of Bacteriological Response. If possible, sputum samples were obtained at each clinic visit. In addition, paired acute and convalescent sera were obtained at baseline and at the day 12–16 visit, respectively, for serological testing by an enzyme-linked immunosorbent assay for *Mycoplasma*, *Chlamydia*, and *Legionella* and for use in a viral screening test (urine was also collected for *Legionella* antigen assay). Organisms were isolated and identified using standard microbiological methods. Susceptibility testing was carried out by the disk diffusion technique according to guidelines established by the National Committee for Clinical Laboratory Standards [15].

Bacterial response to therapy was assessed from candescent specimens obtained after treatment at the day 12–16 visit and at the day 19–23 visit and was classified according to the following definitions: eradication, the elimination of baseline pathogens or the absence of culturable material; persistence, the presence of a baseline pathogen at the end of treatment; recurrence, the reappearance of a baseline pathogen after its eradication; and reinfection, the eradication of the baseline pathogen followed by the appearance of a new organism in sputum that was thought to cause symptoms requiring treatment.

Laboratory Tests. Blood and urine were collected for laboratory analysis at baseline, at the day 12–16 visit, and at the day 19–23 visit. The following tests were conducted by the hematology laboratory: determination of hemoglobin, hematocrit, erythrocyte count, platelet count, leukocyte count with differential, total bilirubin, SGOT, SGPT, alkaline phosphatase, and blood urea nitrogen (or equivalent). Urine was analyzed for hemoglobin, protein, and glucose.

Safety. Adverse events, either reported by the patient or observed by the investigator, were recorded at each clinic visit and classified according to severity, time of onset, relationship to treatment, duration, treatment required, and outcome.

Statistical Analysis. The analysis of safety and efficacy was based on pooled data from the 28 centers that enrolled patients. The distribution of clinical response for the two treatment groups was compared using the Mantel-Haenszel chi-square test. Safety data for the two groups were compared using chi-square or Fisher's exact test as appropriate. All statistical tests were performed as two-tailed tests, and differences between treatment groups were considered significant if $P \leq 0.05$.

Results

Patients. A total of 203 patients were enrolled, 101 in the azithromycin group and 102 in the clarithromycin group. All patients were diagnosed as having either bronchopneumonia (59% of azithromycin group, 48% of clarithromycin group) or lobar pneumonia (41% of azithromycin group, 52% of clarithromycin group). The diagnosis had been confirmed by a chest radiograph. Patients in the two treatment groups were not significantly different with respect to their baseline demographic characteristics (Table 1).

All patients enrolled in the study received oral treatment with either 500 mg azithromycin once daily for

Table 1 Patient characteristics at baseline

Characteristic	Azithromycin group	Clarithromycin group
No. (gender) of patients	101 (60 M/41 F)	102 (59 M/43 F)
Mean age in years (range)	50.1 (14.1–75.2)	51.5 (12.5–78.9)
Mean weight in kg (range)	74.4 (49.0–120.0)	72.0 (41.5–138.0)
Diagnosis at baseline		
No. (%) with bronchopneumonia	60 (59%)	49 (48%)
No. (%) with lobar pneumonia	41 (41%)	53 (52%)

3 days (101 patients) or 250 mg clarithromycin twice daily for 10 days (102 patients). Five patients (4 in the clarithromycin group and 1 in the azithromycin group) discontinued treatment during the study. In two patients in the clarithromycin group, treatment was stopped due to severe treatment-related adverse events.

Thirteen patients in the azithromycin group and 14 in the clarithromycin group were excluded from the analysis of clinical response. The majority of these (7 azithromycin-treated, 8 clarithromycin-treated) did not meet entry criteria; in particular, there was no confirmation of the diagnosis of pneumonia at baseline. Three azithromycin and five clarithromycin patients deviated from the study protocol. Additional anti-infective agents were administered to 15 azithromycin-treated and 11 clarithromycin-treated patients; seven of these (3 azithromycin, 4 clarithromycin) were excluded from the evaluation of clinical response.

There were 111 patients (57 azithromycin-, 54 clarithromycin-treated) excluded from the analysis of bacterial response; in 45 azithromycin- and 39 clarithromycin-treated patients, no pathogen was isolated from their pretreatment sputum specimens.

Clinical Response. Clinical response was evaluable in 88 azithromycin and 88 clarithromycin-treated patients at the end-of-therapy visit (day 12–16). A satisfactory clinical response (cure plus improvement) was recorded in 83 of 88 (94%) azithromycin-treated patients and in 84 of 88 (95%) patients who had received clarithromycin (Table 2); this difference was not statistically significant ($P = 0.518$).

Of the 26 azithromycin- and 23 clarithromycin-treated patients classified as having improved at the day 12–16 visit, two in the azithromycin and one in the clarithromycin group were not followed up between days 19 and 23. The distribution of clinical response for the remaining 46 patients was similar ($P = 0.486$) for the two treatment groups (Table 3). A satisfactory clinical response was attained in 23 of 24 (96%) azithromycin-treated patients and in 21 of 22 (95%) patients who had received clarithromycin. Only one patient in each treatment group experienced a relapse.

Bacteriological Response. At baseline, 32 pathogens were isolated from 31 evaluable patients with a positive sputum sample who were treated with azithromycin (Table 4). At the end of therapy, 31 (97%) of these pathogens were eradicated. In the clarithromycin group, 35 pathogens were isolated at baseline from the sputum samples of patients who were evaluable for bacteriological response. Following clarithromycin treatment, 32 (91%) of these pathogens were eradicated.

Haemophilus influenzae and *Streptococcus pneumoniae* were the most commonly isolated pathogens at baseline. In the azithromycin group, all 18 (100%) *Haemophilus influenzae* isolates (91% sensitive, 9% intermediately sensitive pretreatment) and five of six (83%) *Streptococcus pneumoniae* isolates (100% sensitive pretreatment) were eradicated. In the clarithromycin group, 14 of 16 (88%) *Haemophilus influenzae* isolates (94% sensitive, 6% intermediately sensitive pretreatment) were eradicated. The one patient in the clarithromycin group who was considered a clinical failure had a persistent baseline pathogen (*Haemophilus*

Table 2 Assessment of clinical outcome of patients at days 12–16

Clinical response	No. (%) of patients	
	Azithromycin group	Clarithromycin group
Cure	57 (65%)	61 (69%)
Improvement	26 (30%)	23 (26%)
Failure	5 (6%)	4 (5%)
Total evaluable	88 (100%)	88 (100%)

Table 3 Assessment of clinical outcome at days 19–23 of those patients who had improved by days 12–16

Clinical response	No. (%) of patients	
	Azithromycin group	Clarithromycin group
Cure	19 (79%)	15 (68%)
Improvement	4 (17%)	6 (27%)
Failure	1 (4%)	1 (5%)
Total evaluable	24 (100%)	22 (100%)

Table 4 Correlation of clinical and bacteriological responses

Pathogen	Clinical response	Bacteriological response			
		Total no.	Eradication	Reinfection	Persistence
Azithromycin group					
Haemophilus influenzae	cure	17	17	1	0
	improvement	1	0	0	0
	failure	0	0	0	0
	relapse	0	0	0	0
Moraxella catarrhalis	cure	6	6	0	0
	improvement	0	0	0	0
	failure	0	0	0	0
	relapse	0	0	0	0
Staphylococcus aureus	cure	2	2	0	0
	improvement	0	0	0	0
	failure	0	0	0	0
	relapse	0	0	0	0
Streptococcus pneumoniae	cure	4	4	0	0
	improvement	2	1	0	1[a]
	failure	0	0	0	0
	relapse	0	0	0	0
Clarithromycin group					
Haemophilus influenzae	cure	12	12	0	0
	improvement	3	2	0	1[b]
	failure	1	0	0	1[c]
	relapse	0	0	0	0
Moraxella catarrhalis	cure	2	2	0	0
	improvement	1	1	0	0
	failure	0	0	0	0
	relapse	0	0	0	0
Streptococcus pneumoniae	cure	12	12	0	0
	improvement	4	3	1	0
	failure	0	0	0	0
	relapse	0	0	0	0

[a] Isolate became resistant after in vitro treatment
[b] Isolate became intermediately resistant in vitro after treatment
[c] Isolate remained sensitive in vitro after treatment

influenzae) that continued to be susceptible to clarithromycin in vitro after treatment.

Seven clinically evaluable patients had serologically confirmed atypical pneumonia caused by *Mycoplasma pneumoniae* (3 in the azithromycin group, 1 in the clarithromycin group), *Chlamydia pneumoniae* (1 in the azithromycin group), or *Legionella pneumophila* (2 in the clarithromycin group). At the end of the study, all seven were clinically cured (5 by the day 12–16 visit, the remaining 2 by the day 19–23 visit).

Adverse Events. Treatment-related adverse events were monitored in all 203 patients enrolled in the study who received at least one dose of a study drug. Adverse events thought by the investigators to be related to treatment were experienced by 14 (14%) patients treated with azithromycin and by 13 (13%) treated with clarithromycin ($P = 0.815$). Gastrointestinal events were the most frequently reported class of event in both treatment groups and were experienced by seven azithromycin- and eight clarithromycin-treated patients. Two patients in the clarithromycin group experienced severe adverse events: one had pruritus, and the second had asthenia, depression, and taste perversion, all thought to be treatment-related. In contrast, none of the patients treated with azithromycin experienced a severe adverse event. Two of the clarithromycin-treated patients discontinued treatment because of treatment-related adverse events. One patient discontinued therapy after 4 days because of asthenia, depression, nausea, and taste perversion, and a second patient withdrew from the study 6 days after developing a rash. None of the patients in the azithromycin group discontinued therapy as a result of adverse events.

Laboratory Abnormalities. All 203 patients enrolled were included in the analyses of laboratory test abnormalities. One (1%) patient in the azithromycin group and three (3%) in the clarithromycin group developed clinically significant, treatment-related liver function test abnormalities ($P = 0.621$). None of the events was severe, and no patient was withdrawn from the study as a result of a laboratory test abnormality.

Discussion

The in vitro microbiological activity of azithromycin against *Streptococcus pneumoniae*, *Haemophilus influenzae*, and atypical pathogens such as *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella pneumophila* suggests that this agent may demonstrate good clinical and bacteriological efficacy in the treatment of community-acquired pneumonia [2–4]. This conclusion is supported by the current study, in which a satisfactory clinical response was recorded in the majority of patients treated with azithromycin.

There is some concern about macrolide resistance among *Streptococcus pneumoniae* isolates. Levels of 10% have been reported [16]. However, the results of the ARTEMIS Project (an international microbial susceptibility surveillance project) show that over 90% of the penicillin-susceptible strains tested were macrolide-susceptible, and approximately 80% and 70% of the penicillin-resistant strains were susceptible to azithromycin and clarithromycin, respectively [17].

Azithromycin is distinguished from clarithromycin by its superior in vitro activity against *Haemophilus influenzae* [5, 7]. The results of the present study confirm this distinction. Azithromycin eradicated all the baseline *Haemophilus influenzae* infections, but among patients treated with clarithromycin, the pathogen persisted in two cases, one of which was classified as a clinical failure. Macrolides, unlike the β-lactam agents, demonstrate good in vitro activity against atypical respiratory pathogens [8, 9]. In this study all patients infected with *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, or *Legionella pneumophila* at baseline were clinically cured at the end of the study.

Long-term evaluation of the safety of azithromycin shows that azithromycin is well tolerated [18]. The present study confirmed the good tolerability of azithromycin. No significant difference between the treatment groups was noted in the frequency of gastrointestinal side effects. However, clarithromycin treatment resulted in two serious treatment-related adverse events, and two clarithromycin-treated patients discontinued treatment prematurely because these events were considered treatment-related. In addition, laboratory abnormalities were detected more frequently in the clarithromycin treatment group.

Our efficacy data are comparable with those previously reported in a noncomparative pilot study of once-daily 500 mg azithromycin administered for 3 days [14] and a pooled comparison of 222 patients treated with a similar dosage of azithromycin administered over 5 days for the treatment of community-acquired pneumonia [19]. The present results also compare with those reported for other studies evaluating azithromycin in the treatment of adults with lower respiratory tract infections. Azithromycin (500 mg once daily for 3 days) and clarithromycin (250 mg twice daily for 10 days) have been compared previously in an open multicentre study of 510 adult patients with lower respiratory tract infections that included acute bronchitis, acute exacerbations of chronic bronchitis, and pneumonia [20]. Clinical and bacteriological efficacy was similar in both groups and both treatments were equally well tolerated. In addition, the results of a study of 206 patients with acute infectious exacerbations of chronic bronchitis showed that bacteriological eradication on day 4 was better in azithromycin-treated patients (500 mg once daily for 3 days) than in those treated with 250 mg clarithromycin twice daily for 7 days [21].

A problem commonly experienced by physicians is poor patient compliance, as patients frequently fail to complete a course of therapy [22]. Studies have shown that patient compliance can be improved with the use of short-course antibiotic therapy [23], which may lead to faster resolution of symptoms [24, 25]. Three-day, once-daily azithromycin is a convenient and effective therapy for the treatment of community-acquired pneumonia that may offer practical advantages over antibiotics with longer or more frequent dosing schedules.

In the present study, once-daily administration of 500 mg azithromycin for 3 days was as clinically and bacteriologically effective as a twice-daily course of 250 mg clarithromycin for 10 days in the treatment of mild to moderate community-acquired pneumonia.

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