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Double-Blind Randomized Study Comparing the Efficacies and Safeties of a Short (3-Day) Course of Azithromycin and a 5-Day Course of Amoxicillin in Patients with Acute Exacerbations of Chronic Bronchitis

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The efficacies and safeties of a three-dose regimen of azithromycin (500 mg once daily for 3 days) and a 15-dose regimen of amoxicillin (500 mg three times daily for 5 days) were compared in a double-blind manner in patients with an acute exacerbation of chronic bronchitis. A total of 92% of patients suffered a type 1 exacerbation. Treatment success, defined as cure or major improvement, was achieved in all patients in the azithromycin group by day 5, compared with 23 (92%) of 25 patients in the amoxicillin group. On day 12, these data were 24 of 25 (96%) in the azithromycin group and 20 of 25 (80%) in the amoxicillin group (results were not significantly different). Several pathogens were isolated (MIC ranges [micrograms per milliliter] in parentheses): *Haemophilus influenzae* or *Haemophilus parainfluenzae* was isolated 23 times (azithromycin, ≤0.06 to 32; amoxicillin, 0.12 to 2); *Streptococcus pneumoniae* was isolated from 11 patients (azithromcyin, ≤0.06 to >256; amoxicillin, ≤0.06 to 0.25); *Moraxella* (*Branhamella*) *catarrhalis* was isolated from eight patients (azithromycin, ≤0.06; amoxicillin, ≤0.06 to 16); and other members of the family *Enterobacteriaceae* were isolated from eight patients. One patient treated with azithromycin had *Legionella pneumophila* pneumonia, and another in that group had a significant rise in titer of antibody against influenza A virus. One patient treated with amoxicillin also had a significant rise in titer of antibody against influenza A virus. Microbiological response rates were comparable. One patient who received azithromycin developed abnormal liver function. Two patients treated with amoxicillin developed abnormal liver functions, one developed exanthema, and one treatment was stopped because of nausea. It is concluded that a three-dose (3-day) regimen of azithromycin is as effective clinically and microbiologically as a 15-dose (5-day) regimen of amoxicillin in the treatment of acute exacerbations of chronic bronchitis.

Azithromycin is a new azalide antibiotic (12) that differs from erythromycin by a methyl-substituted nitrogen at position 9a within the macrocyclic ring. This modification has resulted in improved stability at low pH and improved potency against *Haemophilus influenzae* and *Moraxella* (*Branhamella*) *catarrhalis* (10, 12). Although serum levels remain low after oral administration, the levels achieved in sputum, bronchial mucosa, and alveolar macrophages are sustained for 4 days well above the MICs for many respiratory pathogens (4). Moreover, azithromycin proved to be superior to erythromycin in a mouse pneumococcal pneumonia model, probably because of these improved pharmacokinetic parameters (2). Since the drug concentrates in macrophages as well, it is potentially active against intracellular pathogens such as *Legionella pneumophila* (4, 10). These properties suggested that a very short course (3 days) of treatment with once-daily administration of azithromycin could be useful in the treatment of respiratory infections. This paper reports the results of a double-blind comparison with a 5-day course of amoxicillin in patients with acute exacerbations of chronic bronchitis.

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MATERIALS AND METHODS

Fifty in- and outpatients with an acute exacerbation of chronic bronchitis were enrolled in this study. Patients were recruited from one location: Department of Pulmonary Medicine, Elisabeth's Gasthuis, Haarlem, The Netherlands. This study was part of an unpublished international multicenter study. In this double-blind study, patients were randomized to receive either azithromycin at a dosage of 500 mg (two 250-mg capsules) once daily for 3 days or amoxicillin at a dosage of 500 mg (two 250-mg capsules) three times daily for 5 days. Each patient received six capsules per day (six amoxicillin capsules or two azithromycin capsules plus four placebos). Patients were advised to take their medication either before or at least 2 h after a meal. Block randomization was done at Pfizer-Euroclin, Brussels, Belgium.

Patients were excluded by the following conditions: terminal illness; pregnancy or lactation; known allergy to macrolides or penicillin; concomitant use of antibiotics, ergotamine, or carbamazepine or the use of antibiotics within 48 h prior to treatment; infectious mononucleosis; cystic fibrosis; or past or present gastrointestinal abnormal-

ity affecting absorption. The study protocol was approved by the hospital's Medical Ethics Committee for Human Studies. Informed consent was obtained from all patients.

Chronic bronchitis was defined according to the American Thoracic Society statement as a chronic or recurrent productive cough present on most days for a minimum of 3 months a year and for at least 2 successive years. An acute exacerbation was defined in terms of symptoms described by Anthonisen et al. (1). Three levels of severity of exacerbation were recognized. Type 1 exacerbation (the most severe grade) was defined as increased dyspnea and increased sputum volume and purulence. Type 2 exacerbation (a less severe grade) was defined as occurring when two of these three symptoms were present, and type 3 exacerbation (the least severe grade) was defined as occurring when one of the three symptoms was present in addition to at least one of the following findings: fever of 37.5 to 38.5°C, sore throat or nasal discharge within 5 days, increased wheezing, or increased cough. Medication (bronchodilators, adrenergic stimulators, or corticosteroids) in addition to the study drug was given to 20 patients (80%) treated with azithromycin, who received a mean of 2.9 drugs. In the control group, 25 patients (100%) were treated with a mean of 2.8 drugs (numbers were not significantly different).

Each patient was clinically examined before treatment and on days 5 to 7 and 12 to 15. Before treatment and on days 5 to 7 (that is, within 48 h after the end of amoxicillin treatment or 48 to 96 h after the end of azithromycin therapy), serum chemistry and hematology tests were performed. A chest X ray was made for patients with a temperature of more than 38°C or with signs of pneumonia. The second visit included monitoring for possible side effects of the drug. Compliance was confirmed by counting remaining capsules which were returned on the second visit (after therapy). If a patient had not fully recovered by the third visit, he or she was rejudged 1 week later to assess the definite outcome 21 to 24 days from the start of treatment.

Sputum cultures were performed before and after therapy. Microorganisms were isolated and identified according to standard bacteriological methods. Antimicrobial susceptibility to the study drugs was assessed by determining MICs by a standard agar dilution method. A Gram stain from each sputum sample was examined to determine the number of leukocytes. A sputum sample was considered reliable for culture if it contained fewer than 10 epithelial cells and 25 or more polymorphonuclear leukocytes per low-power microscopic field (×100). On the first and third visits, blood samples were obtained for serologic determination. The presence of antibodies against respiratory pathogens such as influenza A and B viruses, parainfluenza virus, respiratory syncytial virus, adenovirus, *Chlamydia psittaci*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *L. pneumophila*, and *Coxiella burnetii* was determined. A viral infection or infection with one of these other pathogens was considered a possible diagnosis for patients with at least a fourfold rise in antibody (immunoglobulin G) titers.

Clinical response to therapy was classified as follows: cure was defined as the complete remission of all baseline symptoms of acute infection; improvement was defined as the amelioration of symptoms but not their complete disappearance; and failure was defined as the persistence or deterioration of symptoms of infection, death from the primary diagnosis, or the presence of side effects of the study drug leading to discontinuation of therapy. Treatment success was defined as the cure or major improvement of symptoms. The patient had to take the study medication for a minimum of 3 full days, unless there was clear evidence of therapeutic failure or the presence of side effects, to be eligible for evaluation. Bacteriological response was graded as follows: eradication of the causative microorganism was when the second culture became negative; persistence was when the second culture remained positive, yielding the same organism; colonization was when the second culture showed growth of a new pathogen; and an indeterminate response was when the prestudy culture was negative.

The two treatment groups were compared for efficacy by using the chi-square test. For comparison of means ± standard deviations of demographic and medical patient characteristics before study entry, Student's *t* test was used.

TABLE 1. Patient characteristics

Characteristic	Value for group	
	Azithromycin	Amoxicillin
Total no. of patients	25	25
Mean age (yr) (SD)	65 (12)	58 (15)
Male/female ratio	14/11	16/9
No. of patients with:		
Type 1 exacerbation	22	24
Type 2 exacerbation	3	1
Type 3 exacerbation	0	0

RESULTS

All 50 patients enrolled were evaluable for clinical efficacy. The two treatment groups were comparable with respect to age, male/female ratio, and underlying diseases (data not shown), and the majority of patients suffered a type 1 exacerbation (Table 1). Clinical response is presented in Table 2. Treatment success (cure or improvement) occurred by day 5 in all patients receiving azithromycin compared with 23 patients (92%) in the amoxicillin group (results were not significantly different). One of the two other patients in the amoxicillin group was infected with *H. influenzae* and a β-lactamase-producing *M. catarrhalis*; this patient's condition had deteriorated by day 5, and the patient recovered after a switch to co-trimoxazole and the addition of prednisone. The other was infected with *Streptococcus pneumoniae*; prednisone was added on day 5, therapy was continued, and the patient's response was classified as improvement on day 12. Both patients experienced a type 1 exacerbation. Treatment failures occurred by day 12 in four additional patients (20%) in the amoxicillin group versus 1 (4%) in the azithromycin group. Two of them were infected with *H. influenzae* (MICs of amoxicillin were 0.5 μg/ml before and after therapy); for another patient also infected with *H. influenzae* (the MIC of amoxicillin was 2 μg/ml), a significant rise in titer of antibody against influenza A virus was documented; for the last patient, no bacteria were

TABLE 2. Clinical response

Response	No. of patients in group			
	Day 5		Day 12	
	Azithromycin	Amoxicillin	Azithromycin	Amoxicillin
Cure	6	4	16	13
Improvement	19	19	8	7
Failure	0	2	1	5

TABLE 3. Microbiological response

Response	No. (%) of patients in group[a]	
	Azithromycin	Amoxicillin
Eradication	13 (52)	10 (40)
Persistence	5 (20)	6 (24)
Indeterminate[b]	7 (28)	9 (36)
Colonization[c]/reinfection	7 (28)	5 (20)

[a] Each treatment group had a total of 25 patients.
[b] Eleven patients had negative prestudy cultures, and five had indeterminate poststudy cultures.
[c] Patients could become colonized with another pathogen, although the original pathogen persisted or was eradicated.

cultured. All had a type 1 exacerbation. On day 12, one patient with a type 2 exacerbation, treated with azithromycin and infected with *H. influenzae* (the MIC of azithromycin was 0.5 μg/ml), experienced a reinfection with a resistant *Haemophilus haemoglobinophilus* strain (the MIC of azithromycin was 4 μg/ml).

For nine patients, two pathogens were cultured; for one patient, three were cultured; and for 11 patients, no pathogens were found. These pathogens and the MIC ranges for them (micrograms per milliliter) were as follows: *H. influenzae* or *Haemophilus parainfluenzae* was isolated 23 times (azithromycin, ≤0.06 to 32; amoxicillin, 0.12 to 2); *S. pneumoniae* was isolated from 11 patients (azithromycin, ≤0.06 to >256; amoxicillin, ≤0.06 to 0.25); *M. catarrhalis* was isolated from eight patients (azithromycin, ≤0.06; amoxicillin, ≤0.06 to 16); and members of the *Enterobacteriaceae* were isolated from eight patients. One patient treated with azithromycin had a right-upper-lobe infiltrate and a significant rise in titer of antibody against *L. pneumophila*, and another had a significant rise in titer of antibody against influenza A virus. In addition, one patient treated with amoxicillin also had a significant rise in titer of antibody against influenza A virus. Data on the microbiological responses are presented in Table 3. Eradication occurred in 52% of patients in the azithromycin group versus 40% of those in the amoxicillin group (results were not significantly different). Persistence of the causative organism was seen in 20% of patients in the azithromycin group versus 24% of those in the amoxicillin group. Seven (28%) of the patients treated with azithromycin became colonized with other bacteria after therapy, compared with five (25%) of the patients treated with amoxicillin. Table 4 lists the pathogens isolated from patient sputum which were cultured before and after therapy. No significant difference between the eradication rates of the two drugs for any of the pathogens was seen. The MICs did not change significantly.

Twelve patients in the azithromycin group had initial cultures with *H. influenzae*, versus 11 patients in the amoxicillin group. These pathogens were eradicated equally. *S. pneumoniae* was isolated before therapy from four patients in the azithromycin group versus seven in the amoxicillin group. After treatment, pneumococcal strains persisted in one patient in each group. *M. catarrhalis* was eradicated in all patients who did not switch antibiotics.

One patient in the amoxicillin group stopped therapy on day 3 because of unacceptable nausea and vomiting. Although he was treated for only 3 days, his response was considered a cure; later, he was found to have a concomitant hepatitis B virus infection. Tests showed abnormal liver function developing in two other patients treated with amoxicillin and exanthema developing in one. Abnormal liver function developed in one patient treated with azithromycin.

TABLE 4. Pathogens isolated from sputum before and after therapy

Organism	No. of pathogens isolated from group			
	Azithromycin		Amoxicillin	
	Before therapy	After therapy	Before therapy	After therapy
H. influenzae group[a]	12	4	11	4
S. pneumoniae	4	1	7	1
M. catarrhalis	6		2	

[a] *H. influenzae* and *H. parainfluenzae*.

DISCUSSION

Most physicians include an antibiotic in their treatment regimen for acute exacerbations of chronic bronchitis. However, the question of the need for antibiotics in the management of patients with these diseases is still unanswered (9). Anthonisen et al. (1) reported a large community-based study in which exacerbations in 173 patients with chronic bronchitis were monitored over a 3.5-year period. Treatment consisted of antibiotics or placebos administered in a randomized double-blind crossover fashion. Anthonisen et al. defined three levels of severity of exacerbation (we recognized the same types in our study) and demonstrated that there was a significant benefit associated with antibiotic treatment in the most severe exacerbations, those classified as type 1 at onset and consisting of worsening dyspnea with increased sputum volume and purulence. Of our patients, 92% (46 of 50) experienced a type 1 exacerbation. The clinical outcome of a three-dose course of azithromycin (500 mg) was satisfactory compared with amoxicillin at a dosage of 500 mg three times daily for 5 days. Our data are comparable to those reported by others who compared a 5-day course of azithromycin with one of amoxicillin-clavulanic acid (Augmentin) and cefaclor prescribed for 10 days (5, 6). They are also comparable to data generated in a multicenter study comparing the macrolide clarithromycin with ampicillin prescribed for 7 to 14 days (3). Moreover, although this was a small study with the possibility of a large β error, the data are comparable to those previously reported for low-dose ofloxacin and amoxicillin-clavulanic acid prescribed for 10 days (11).

Also, no differences were found in the microbiological response (Tables 3 and 4), although one might have expected a difference in the elimination of bacteria due to the presence of β-lactamase-producing strains, as has been documented for *H. influenzae* in a comparative study of azithromycin and cefaclor (6). Moreover, when all data from the European centers are pooled, 85% of baseline pathogens were eradicated after azithromycin treatment, compared with 77% after amoxicillin (results were not significantly different). For *H. influenzae*, these data are 76 and 68%, respectively (10a).

To assess the value of antibiotics, it is necessary to know the likely frequency of a bacterial cause of the infection versus that of a viral cause. In contrast to other studies (7, 8), only 4% of exacerbations in this study could be related to viral infections. This is even lower than the 12% reported previously (11), making the current data even more valid.

In conclusion, a three-dose (3-day) regimen of azithromycin is as effective clinically and microbiologically as a

15-dose (5-day) regimen of amoxicillin in the treatment of acute exacerbations of chronic bronchitis.

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