

Randomized Double-Blind Study Comparing 3- and 6-Day Regimens of Azithromycin with a 10-Day Amoxicillin-Clavulanate Regimen for Treatment of Acute Bacterial Sinusitis

Dan C. Henry,¹ Ernie Riffer,² William N. Sokol,³ Naumann I. Chaudry,⁴ and Robert N. Swanson^{4*}

Foothill Family Clinic, Salt Lake City, Utah¹; Central Phoenix Medical Center, Phoenix, Arizona²; Health Research Institute, Newport Beach, California³; and Pfizer Inc, New York, New York⁴

Received 25 November 2002/Returned for modification 14 February 2003/Accepted 11 April 2003

A randomized, double-blind, multicenter study of adults with acute bacterial sinusitis (ABS) compared the efficacy and safety of two azithromycin (AZM) regimens, 500 mg/day once daily for 3 days (AZM-3) or 6 days (AZM-6) to the efficacy and safety of an amoxicillin-clavulanate (AMC) regimen of 500-125 mg three times daily for 10 days. A total of 936 subjects with clinically and radiologically documented ABS were treated (AZM-3, 312; AZM-6, 311; AMC, 313). Clinical success rates were equivalent among per-protocol subjects at the end of therapy (AZM-3, 88.8%; AZM-6, 89.3%; AMC, 84.9%) and at the end of the study (AZM-3, 71.7%; AZM-6, 73.4%; AMC, 71.3%). Subjects treated with AMC reported a higher incidence of treatment-related adverse events (AE) (51.1%) than AZM-3 (31.1%, $P < 0.001$) or AZM-6 (37.6%, $P < 0.001$). More AMC subjects discontinued the study ($n = 28$) than AZM-3 ($n = 7$) and AZM-6 ($n = 11$) subjects. Diarrhea was the most frequent treatment-related AE. AZM-3 and AZM-6 were each equivalent in efficacy and better tolerated than AMC for ABS.

Acute bacterial sinusitis (ABS) is an acute infection of the paranasal sinuses and nose most commonly caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* (2, 8). Accumulation of sinus mucus secondary to obstruction and inflammation facilitates pathogen growth. Approximately 30 million Americans develop acute bacterial sinusitis annually, resulting in an estimated 25 million physician visits and healthcare costs of U.S. \$2 to 6 billion (1, 12).

Clinical symptoms include mucopurulent nasal discharge, nasal congestion, fever, and facial pain or tenderness lasting 7 to 28 days. Culturing is the most definitive means of diagnosis; however, it is invasive, requires up to 72 h for identification, and does not always yield causative pathogens (13). Diagnosis is therefore often presumptive, being based on clinical presentation and diagnostic interpretation, and may include culturing. Diagnostic techniques include sinus radiography, sinus transillumination, sonography, fiber-optic endoscopy, and computerized tomography, although all but sinus radiographs may be cost prohibitive.

Treatment, which may also include adjunctive therapy for symptom relief, has consisted of empirical use of systemic antimicrobial agents, although their use for patients with ABS has been widely debated. Opponents to prescribing have cited cost effectiveness, development of antimicrobial-resistant pathogens, and adverse events associated with antimicrobials (8). Several studies, including a meta-analysis by the Agency for Healthcare Research and Quality, have demonstrated that at least half of the subjects with ABS symptoms improved or resolved without the need for antimicrobial therapy. However, they also concluded that antimicrobial therapy shortens dis-

ease duration, targeting the pathogens that cause sinusitis (12, 13, 16). A second meta-analysis separately determined that subjects with clinical and radiological evidence of ABS gained the greatest benefit from antimicrobial therapy compared with placebo (7).

Initial therapy may include antimicrobials, although its optimal duration for ABS treatment has not been established. A meta-analysis of several studies performed within the last decade demonstrated that shorter courses of antimicrobial therapy (3 to 5 days versus 7 to 10 days) tend to increase patient compliance, decrease adverse events by reducing drug exposure, decrease the emergence of resistant strains, and reduce cost (14). Both macrolides and quinolones offer shorter dosing schedules.

Azithromycin (AZM), like other macrolides, achieves its antimicrobial effect by binding to the 50S ribosomal subunit of susceptible microorganisms and interfering with bacterial protein synthesis. However, AZM is chemically and structurally different from all other macrolides, resulting in an expanded antimicrobial spectrum and a novel pharmacokinetic profile. The *in vitro* antimicrobial spectrum of AZM includes the gram-positive organisms susceptible to erythromycin and gram-negative bacteria, including the previously mentioned pathogens associated with sinusitis. Its pharmacokinetic profile supports once-daily oral dosing and a treatment course shorter than that of first-line antimicrobials.

AZM is approved in Europe and other areas as monotherapy for upper respiratory tract infections, including acute bacterial sinusitis. The recommended dosing regimen for sinusitis is 500 mg once daily for 3 days. In the United States, AZM is approved for the treatment of upper respiratory tract conditions caused by susceptible microorganisms, including *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, and of nonrespira-

* Corresponding author. Mailing address: Pfizer Inc, 235 East 42nd St., New York, NY 10017-5755. Phone: (212) 573-2975. Fax: (212) 808-6341. E-mail: Swansr1@pfizer.com.

tory infections (Zithromax (azithromycin) package insert, May 2002. Pfizer Inc., New York, N.Y.) in adults.

Amoxicillin-clavulanate (AMC) is a combination of a β -lactam antimicrobial, amoxicillin, and a β -lactamase inhibitor, clavulanate. β -Lactam antimicrobials are bactericidal through inhibition of bacterial cell wall biosynthesis during reproduction. Amoxicillin itself has a broad spectrum of activity that includes many gram-positive and gram-negative organisms. Amoxicillin is, however, ineffective against gram-negative bacteria that produce the enzyme β -lactamase. Up to 40% of *H. influenzae* isolates and 95% of *M. catarrhalis* isolates produce this enzyme. Clavulanate is structurally related to the penicillins but inhibits β -lactamase. Thus, the coadministration of clavulanate extends the antimicrobial spectrum of amoxicillin to include β -lactamase-producing gram-negative microorganisms.

In the United States, AMC is approved for the treatment of upper and lower respiratory, including sinusitis, and nonrespiratory infections caused by susceptible bacteria. The recommended dose regimen is 500 mg three times daily or 875 mg twice daily of the amoxicillin component (Augmentin [amoxicillin/clavulanate] package insert, May 2002. GlaxoSmithKline, Research Triangle Park, N.C.).

This study compared two novel dose regimens of AZM, i.e., 500 mg once daily for 3 days (AZM-3) or 6 days (AZM-6), to an approved regimen of AMC, i.e., 500-125 mg three times daily for 10 days, for efficacy and safety in the treatment of subjects with ABS. Three- and 6-day dosing regimens of AZM were studied to determine the optimal dosing schedule and explore flexible schedules, as indicated for use of other antimicrobials for ABS (i.e., levofloxacin, indicated for 10 to 14 days for ABS).

MATERIALS AND METHODS

Study design. This was a randomized, double-blind, double-dummy, comparative, multicenter trial performed in the United States, designed to comply with current Food and Drug Administration (FDA) guidance for demonstrating clinical efficacy in the treatment of ABS (5). All investigators and institutions obtained approval from the relevant institutional review boards in accordance with local legislation and good clinical practices. All screened and enrolled subjects or their legal representatives provided written informed consent prior to any study-related procedures performed.

Eligibility and accrual. Inclusion criteria included outpatient male and female subjects 18 years of age or older with clinical diagnosis of ABS of the maxillary sinuses upon entry into the study. Diagnosis was confirmed by the presence of either purulent nasal discharge or facial pain and/or pressure and/or tightness for more than 7 but fewer than 28 days. X rays (Waters' view) of the maxillary sinus(es), obtained within 48 h of entry into the study and read by a qualified radiologist, must have been positive at least for one of the following: opacification, air-fluid level, or ≥ 6 mm of mucosal thickening. Key exclusion criteria included allergy or hypersensitivity to any penicillin or macrolide antibiotic, systemic antibiotic therapy for 24 h or longer within 2 weeks prior to enrolling, a history of chronic sinusitis (defined as three or more episodes within the last 6 months), a history of sinus surgery other than for diagnostic procedure, and treatment with systemic histamine (H_1) receptor antagonists.

Treatment and compliance. Subjects were assigned randomly in a 1:1:1, double-blind, and double-dummy fashion. Subjects received 500-mg tablets of AZM or a placebo administered as one tablet once daily for 6 days, and 250-62.5 mg of AMC per 5 ml of liquid suspension or a placebo administered as two teaspoons (500-125 mg) three times daily for 10 days. The suspension formulation of AMC was required to facilitate development of double-blind, double-dummy clinical supplies. Compliance was measured by investigators reporting exact doses taken, reasons for missed doses, and the amounts of study medication returned by subjects at the end of therapy visit.

Study procedures. Study visits included baseline (visit 1) at day 1, telephone contact (visit 2) at day 4 (time range, 3 to 5 days), end of therapy (EOT) at day

10 (time range, 8 to 15 days), and end of study (EOS) at day 28 (time range, 22 to 36 days). At baseline, after subjects provided written informed consent, investigators reviewed the inclusion and exclusion criteria. If the inclusion criteria were met, investigators collected demographic, medical history, and drug and nondrug therapy information. They also performed a targeted physical exam, clinically assessed signs and symptoms of ABS, and checked vital signs. A sinus radiograph was obtained. Chemistry-14 and hematology panels were drawn, and urinalysis was performed. A pregnancy test was performed for women of child-bearing potential. At EOT and EOS visits, investigators globally assessed the clinical response of ABS. Signs and symptoms of ABS were assessed, and vital signs were checked. Subjects reported all adverse events and concomitant drug and nondrug treatments. At EOS, a sinus X ray was taken and compared to the baseline film.

Outcome measures. (i) **Efficacy.** Efficacy was measured by clinical success rates based on the global assessment of the clinical presentation of the subject made by the investigator at an evaluation time point. Clinical success was defined at EOT as cure plus improvement and at EOS as cure. The primary efficacy measure was clinical success at EOS.

Cure was defined as resolution of signs and symptoms of acute sinusitis to the level that existed prior to the occurrence of the acute illness with no worsening in the radiographic appearance of the sinuses (applicable to EOS or where radiographic information was available) and without requirement of antibiotics (other than the study drug) given for treatment of sinusitis. Improvement, applicable only at EOT, was defined as partial but incomplete resolution of the signs and symptoms of acute sinusitis as defined above and no requirement for additional antibiotic use.

Failure was defined as persistence of one or more signs or symptoms of ABS or appearance of new signs or symptoms and/or a need for additional antimicrobials or change in antimicrobial therapy. Subjects assessed as failures during the study were assessed as failures at subsequent visits.

(ii) **Safety.** Safety was analyzed for all subjects who took at least one dose of study medication. All observed adverse events (AEs) as well as AEs reported by patients, categorized as serious or nonserious, were recorded at each visit or contact. Changes to the study drug (temporarily or permanently discontinued) and changes to the study (treatment given, withdrawn from study) were also recorded. Investigators assessed the seriousness and causality of each AE, including its relationship to the study drug; AEs with an unknown relationship to the study drug were classified as treatment related.

Statistical methods. AZM was considered to be as effective as AMC if the lower bound of the two-sided 97.5% confidence interval (CI) for the clinical response rate at EOS between two treatments was greater than or equal to -10% . With two planned comparisons—each AZM arm to AMC—each comparison was performed by using an adjusted Bonferroni approach on a 0.05/2 significance level to ensure that the overall Type I error rate did not exceed 0.05. The clinical success rate of AMC at EOS was assumed to be 85%; therefore, 243 subjects were required in each treatment group to ensure with 80% power that the lower bound of the CI was not less than -10% . Assuming a 20% nonevaluability, a sample size of 304 subjects per treatment group, 912 in total, was planned. No statistical comparisons of efficacy or safety between the two AZM arms were planned.

Efficacy was analyzed at both EOT and EOS in two subject populations: intent to treat (ITT) and per protocol (PP). ITT-evaluable subjects included those who were diagnosed with ABS as defined by the protocol and took at least one dose of the active study drug. Subjects included in the PP population were ITT evaluable, satisfied all inclusion and exclusion criteria, took at least 80% and no more than 120% of the active study medication (unless assessed as a clinical failure), were assessed clinically by an investigator unless there was prior failure, did not take a systemic antibiotic for something other than ABS, had an assessment within a protocol-specified window, and had a sinus radiograph with comparison to baseline film (unless assessed as a failure). Comparisons of AE incident and discontinuation rates between treatment groups were performed by using the chi-square test or Fisher's exact test as appropriate.

RESULTS

A total of 941 subjects (316 for the AZM-3 regimen, 311 for the AZM-6 regimen, and 314 for the AMC regimen) were randomized into the study, as shown in Table 1. Nine hundred thirty-six (936) subjects (312 AZM-3, 311 AZM-6, and 313 AMC) received at least one dose of the study drug and were included in the safety analysis. The ITT population consisted

TABLE 1. Study evaluation summary

Regimen	No (%) of patients							
	Randomized to treatment	Treated	Completed 80 to 120% of treatment	Completed treatment as scheduled	Completed study	ITT population	PP EOT	PP EOS
AZM-3	316	312 (98.7)	309 (99.2)	309 (99.2)	297 (95.2)	307 (98.4)	269 (86.2)	272 (87.2)
AZM-6	311	311 (100)	299 (96.1)	292 (93.9)	292 (93.9)	306 (98.4)	271 (87.1)	271 (87.1)
AMC	314	313 (99.7)	269 (85.9)	257 (82.1)	282 (90.1)	307 (98.1)	259 (82.7)	251 (78.0.2)
Total	941	936	877	858	871	920	799	794

of 920 subjects (307 AZM-3, 306 AZM-6, and 307 AMC). Sixteen treated subjects (5 AZM-3, 5 AZM-6, and 6 AMC) were excluded from ITT because they were enrolled by a center deemed ineligible by the FDA. The PP analysis at EOT included 799 subjects (269 AZM-3, 271 AZM-6, and 259 AMC) and at EOS included 794 subjects (272 AZM-3, 271 AZM-6, and 251 AMC).

Most subjects were excluded from clinical evaluability at EOT and EOS due to not meeting entry criteria, having visits outside the protocol-specified windows, or having unknown or missing clinical response evaluation by the investigator. Seven subjects (two AZM-3, two AZM-6, and three AMC) were

excluded from the analyses for using concomitant systemic antibiotics for comorbidities other than ABS.

Eight hundred fifty-eight (91.7%) of the 936 treated subjects completed therapy as scheduled, defined as in a period of 3 days for AZM-3, 6 days for AZM-6, and 10 days for AMC. A statistically significantly higher percentage of AZM-3 (99.2%, $P < 0.0001$) and AZM-6 subjects (93.9%, $P < 0.0001$) completed therapy as scheduled than did AMC subjects (82.1%). Overall, 871 (93.1%) completed the study, defined as completing the EOS visit.

There were no clinically meaningful differences in baseline demographic and disease assessments between the two AZM

TABLE 2. Baseline demographics and assessments

Characteristic (unit)	AZM-3 ($n = 312$)	AZM-6 ($n = 311$)	AMC ($n = 313$)
Gender (M/F)	123/189	124/187	134/179
Age			
Mean	40.2	41.3	42.4
Range	18.0–76.0	18.0–80.0	18.0–84.0
Race (n)			
White	271	261	274
Black	20	18	19
Asian	2	9	3
Other	19	23	17
Ht (cm)			
Mean	170.1	170.2	171.2
Range	144.0–201.0	53.0–211.0	150.0–206.0
Wt (kg)			
Mean	82.7	80.6	81.0
Range	39.0–163.3	35.4–154.2	45.4–149.7
Duration of sinusitis symptoms prior to baseline (days)	12.9	12.9	13.0
Protocol-specific signs and symptoms of sinusitis present in ITT population (n [%])			
Postnasal purulent discharge	297 (96.4)	292 (95.4)	292 (95.1)
Facial pain	285 (92.8)	288 (94.1)	289 (94.5)
Hyposalivemia	216 (70.4)	225 (73.5)	215 (70.0)
Jaw pain with mastication	140 (45.6)	131 (42.8)	132 (43.0)
Headache	264 (86.0)	267 (87.3)	271 (88.3)
Halitosis	165 (53.7)	195 (63.7)	184 (59.9)
Nasal congestion	303 (98.7)	302 (98.7)	302 (98.4)
Radiology findings ^a in ITT (n [%])			
Opacification (n [%])	184 (59.9)	164 (53.6)	171 (55.7)
Air-fluid level (n [%])	98 (31.9)	82 (26.9)	89 (29.0)
≥ 6 -mm mucosal thickening (n [%])	197 (64.2)	221 (72.2)	208 (67.8)

^a Subjects may have more than one finding.

TABLE 3. Clinical success rates

	No. of clinically successful patients/total (%) (97.5 CI) ^a		
	AZM-3	AZM-6	AMC
EOT			
PP ^b	239/269 (88.8) (-2.7-10.5)	242/271 (89.3) (-2.2-10.9)	220/259 (84.9)
ITT ^b	268/303 (88.4) (-3.0-9.4)	265/298 (88.9) (-2.5-9.9)	248/291 (85.2)
EOS			
PP ^c	195/272 (71.7) (-8.5-9.2)	199/271 (73.4) (-6.7-10.9)	179/251 (71.3)
ITT ^c	213/298 (71.5) (-8.4-8.3)	218/294 (74.1) (-5.6-10.9)	206/288 (71.5)

^a CI for difference from AMC.

^b Clinical success equals cure plus improvement.

^c Clinical success equals cure only.

and AMC treatment groups (Table 2). Age, weight, height, and mean duration of sinusitis signs and symptoms prior to baseline between all arms were comparable. The distribution of signs and symptoms of sinusitis and radiographic findings at baseline were also comparable between the arms.

Allergic rhinitis was the most frequently reported significant medical disease or syndrome and was comparable across all arms—118 subjects in AZM-3, 133 in AZM-6, and 117 in AMC arms. The use of drug treatments, including systemic antibiotics (12 in total) prior to baseline was also similar in all arms (data not shown).

Clinical success in the AZM arms was equivalent to that of AMC in ITT and PP subjects at EOT and EOS (Table 3). PP cure rates at EOS were 71.7% for AZM-3, 73.4% for AZM-6, and 71.3% for AMC (97.5% CI compared with AMC were as follows: AZM-3, -8.5 to 9.2; AZM-6, -6.7 to 10.9). Clinical ITT analysis at EOT and EOS demonstrated cure rates of each AZM arm that were comparable to that of AMC.

At EOS, the percentages of subjects who reported that post-nasal discharge, facial pain, and nasal congestion had resolved were 72 to 77%, 83 to 89%, and 60 to 64%, respectively. The majority of subjects across all treatment groups had resolution of their radiological findings and were assessed as showing either improvement from baseline or complete resolution at EOS (opacification [63.7 to 66.9%], air fluid level [85.3 to 87.1%], and mucosal thickening of ≥6 mm [56.1 to 59.1%]). The majority of subjects with radiological films taken at EOS were assessed as either showing improvement from baseline or completely resolved (71.7% in AZM-3, 74.2% in AZM-6, and 66.2% in AMC) (data not shown).

AMC subjects reported a significantly higher incidence of at least one treatment-related adverse event than the AZM subjects (Table 4). More AMC subjects discontinued the study due to treatment-related AEs than did subjects from the AZM

arms combined. Diarrhea was the most frequently reported treatment-related AE and led to the most discontinuations (d/c). AMC subjects (32.3%, 14 d/c) reported a higher incidence and more d/c due to diarrhea than did AZM-3 (17.0%, 2 d/c) and AZM-6 (21.2%, 5 d/c) subjects. No treatment-related serious adverse events occurred in any treatment arm.

DISCUSSION

In this study utilizing rigorous clinical and statistical criteria, the 3- and 6-day regimens of AZM were shown to each yield clinical efficacy equal to that of the standard 10-day AMC regimen in the treatment of ABS and also showed fewer adverse events and better subject compliance. All subjects had both clinical and radiological evidence of ABS, consistent with current FDA guidance to demonstrate clinical efficacy (5). A prespecified noninferiority delta of 10% was also used. Although no statistical comparisons were made between the two AZM treatment groups, overall efficacy, safety, and compliance rates were similar whether AZM was administered over 3 or 6 days. Because therapy with three doses over 3 days of AZM was as efficacious as 30 doses over 10 days of AMC, further discussion will focus upon comparison of these two treatment arms.

Completion of study therapy as scheduled was significantly higher for AZM-3 subjects than for AMC subjects, consistent with compliance rates of orally administered antimicrobials (14). Compliance has been reported to correlate with dosing frequency: 80% for once-daily regimens but falling to 60% for twice-daily and 38% for three-times-daily regimens (15). It has also been noted that subjects tend to discontinue prescribed antimicrobials 2 to 5 days after initiation due to improvement in or resolution of symptoms. Failure to complete the full

TABLE 4. Safety analysis of treatment-related AEs^a

Regimen (no. of patients)	No. (%) of patients:				
	With at least one treatment-related AE	Who discontinued treatment because of AE	With indicated most frequent AE (>5% of subjects)		
			Diarrhea	Nausea	Flatulence
AZM-3 (312)	97 (31.1)	7 (2.2)	53 (17.0)	23 (7.4)	17 (5.4)
AZM-6 (311)	117 (37.6)	11 (3.5)	66 (21.2)	27 (8.7)	11 (3.5)
AMC (313)	160 (51.1)	28 (8.9)	101 (32.3)	38 (12.1)	6 (1.9)

^a Subjects were counted once and included through 35 days from the last dose of active therapy.

treatment regimen is believed to be a major contributing factor in the development of antimicrobial resistance (14).

Diarrhea was the most frequently reported treatment-related AE across all arms; however, its incidence was 90% higher in the AMC arm than in the AZM-3 arm. The incidence is consistent with the current labeling for three-times-daily administration of AMC suspension (34.3%) to children in doses of 40-10 mg/kg of body weight/day for 10 days and higher for once-daily administration of AZM for 3 days (5 to 9%). Seven times more subjects in the AMC arm than the AZM-3 arm discontinued the study drug due to diarrhea, although comparative data from the labeling of each antibiotic could not be elucidated (Augmentin package insert, GlaxoSmithKline; Zithromax package insert, Pfizer Inc.).

Twice-daily AMC for 10 days is also indicated for ABS, including its suspension and tablet formulations. The incidence of diarrhea as reported in the labeling of twice-daily AMC suspension given to children as 45-6.4 mg/kg/day for 10 days was 14.3%, lower than that noted for three-times-daily AMC (Augmentin package insert, GlaxoSmithKline). This is numerically similar to that reported in the AZM-3 arm of the present study; however, a direct comparison is not possible due to differences in age groups and study design.

AZM-3 and AMC results in this study paralleled findings by Karpov, who recently demonstrated that 3-day AZM therapy for patients with acute sinusitis provided faster clinical cure, better drug tolerance, fewer adverse events, lower cost, and fewer relapses than 10-day AMC therapy (10). It should be noted that this study was designed to detect efficacy equivalence rather than superiority. The results of this study are consistent with other recent clinical and pharmacokinetic ABS studies. Clinical success (cure plus improvement) rates for AZM ranged from 87 to 89% and were comparable to those of AMC (83 to 91%) (3, 11), amoxicillin (97%) (4), and penicillin (88%) (6). AZM (1.5 g) sustained therapeutic concentrations in sinus fluid and mucosa up to 4 days after completing treatment for ABS (9). AZM delivery to and concentrations in sinus fluid may be enhanced due to phagocyte delivery of drug during acute inflammatory conditions, such as ABS (9).

For subjects with clinically and radiologically documented ABS, AZM given in a 500-mg dose once daily for 3 days was shown to be as efficacious as AMC given as 500-125 mg three times daily for 10 days. Results of this study further demon-

strated that AZM provides a better safety profile and better patient compliance than AMC for the treatment of ABS. Future investigations of ABS requiring baseline culturing are necessary to determine the bacteriological response rates of AZM.

ACKNOWLEDGMENT

This work was supported by a grant from Pfizer Pharmaceuticals Group, Pfizer Inc.

REFERENCES

1. Brook, I. 2002. Antimicrobial management of acute sinusitis: a review of therapeutic recommendations. *Infect. Med.* **19**:231-237.
2. Chen, D. K., A. McGeer, J. C. de Azavedo, D. E. Low, et al. 1999. Decreased susceptibility of *Streptococcus pneumoniae* to fluoroquinolones in Canada. *N. Engl. J. Med.* **341**:233-239.
3. Clement, P. A., and J. B. de Gandt. 1998. A comparison of the efficacy, tolerability and safety of azithromycin and co-amoxiclav in the treatment of sinusitis in adults. *J. Int. Med. Res.* **26**:66-75.
4. Felstead, S. J., R. Daniel, et al. 1991. Short-course treatment of sinusitis and other upper respiratory tract infections with azithromycin: a comparison with erythromycin and amoxicillin. *J. Int. Med. Res.* **19**:363-372.
5. Food and Drug Administration. 1998. FDA Guidance for Industry. Acute bacterial sinusitis—developing antimicrobial drugs for treatment, July 1998. Center for Drug Evaluation and Research, Bethesda, Md.
6. Haye, R., E. Lingaas, H. O. Hoivik, and T. Odegard. 1996. Efficacy and safety of azithromycin versus phenoxymethylpenicillin in the treatment of acute maxillary sinusitis. *Eur. J. Clin. Microbiol. Infect. Dis.* **15**:849-853.
7. Henry, D. C., A. Sydnor, Jr., G. A. Settignano, J. Allen, S. Burroughs, M. M. Cobb, and H. P. Holley, Jr. 1999. Comparison of cefuroxime axetil and amoxicillin/clavulanate in the treatment of acute bacterial sinusitis. *Clin. Ther.* **21**:1158-1170.
8. Hickner, J. M., J. G. Bartlett, R. E. Besser, R. Gonzales, J. R. Hoffman, and M. A. Sande. 2001. Principles of appropriate antibiotic use for acute rhinosinusitis in adults: background. *Ann. Intern. Med.* **134**:498-505.
9. Karma, P., J. Pukander, and M. Penttila. 1991. Azithromycin concentrations in sinus fluid and mucosa after oral administration. *Eur. J. Clin. Microbiol. Infect. Dis.* **10**:856-859.
10. Karpov, O. I. 1999. The clinical and economic efficacies of short courses of azithromycin in acute sinusitis. *Antibiot. Khimioter.* **44**:28-32.
11. Klapan, I., J. Culig, K. Oreskovic, M. Matrapazovski, and S. Radosevic. 1999. Azithromycin versus amoxicillin/clavulanate in the treatment of acute sinusitis. *Am. J. Otolaryngol.* **20**:7-11.
12. Murray, J. J., E. Solomon, D. McCluskey, J. Zhang, R. Palmer, and G. Notario. 2000. Phase III, randomized, double-blind study of clarithromycin extended-release and immediate-release formulations in the treatment of adult patients with acute maxillary sinusitis. *Clin. Ther.* **22**:1421-1432.
13. Nudelman, J. 2001. How should we treat acute maxillary sinusitis? *Am. Fam. Physician* **64**:837-839.
14. Pichichero, M. E. 2000. Short course of antibiotic in acute otitis media and sinusitis infections. *J. Int. Med. Res.* **28**:25A-36A.
15. Sclar, D. A., T. A. Tartaglione, and M. J. Fine. 1994. Overview of issues related to medical compliance with implications for the outpatient management of infectious diseases. *Infect. Agents Dis.* **3**:266-273.
16. Snow, V., C. Mottur-Pilson, and J. M. Hickner. 2001. Principles of appropriate antibiotic use for acute sinusitis in adults. *Ann. Intern. Med.* **134**:495-497.