MAJOR ARTICLE

Safety and Efficacy of Gatifloxacin Therapy for Children with Recurrent Acute Otitis Media (AOM) and/or AOM Treatment Failure

Michael E. Pichichero,[1] Adriano Arguedas,[4] Ron Dagan,[5] Larry Sher,[2] Xavier Sáez-Llorens,[6] Kamal Hamed,[3] and Roger Echols[3]

[1]Elmwood Pediatric Group, University of Rochester Medical Center, Rochester, New York; [2]Peninsula Research Institute, Rolling Hills Estates, California; [3]Bristol-Meyers Squibb Pharmaceutical Research Institute, Wallingford, Connecticut; [4]Instituto de Atención Pediátrica, Universidad de Ciencias Medicas, San José, Costa Rica; [5]Soroka University Medical Center, Ben-Gurion University, Beer-Sheva, Israel; and [6]Hospital del Niño, Ciudad de Panamá, Panama

(See the editorial commentary by Marchant on pages 479–80)

Background. Because of concerns about arthrotoxicity, fluoroquinolones are restricted for use in children. This study describes the safety and efficacy of gatifloxacin when used for treatment of children with recurrent acute otitis media (ROM) or acute otitis media (AOM) treatment failure (AOMTF).

Methods. We performed an analysis of 867 children included in 4 clinical trials who had ROM and/or AOMTF and were treated with gatifloxacin (10 mg/kg once daily for 10 days).

Results. Gatifloxacin had adverse event rates that were similar overall to those of a comparator antibiotic (amoxicillin-clavulanate), except for increased diarrhea in children <2 years old receiving amoxicillin-clavulanate. There was no evidence of arthrotoxicity, hepatotoxicity, alteration of glucose homeostasis, or central nervous system toxicity acutely or during 1 year follow-up in any child. Regarding efficacy, in 2 noncomparative trials, the gatifloxacin cure rate of AOM was 89% (95% confidence interval [CI], 83%–95%) at the test of cure (TOC) visit, 3–10 days after completion of therapy. In 2 comparative trials of gatifloxacin versus amoxicillin-clavulanate, the efficacy of gatifloxacin was 88% (95% CI, 82%–94%). Gatifloxacin led to better clinical outcomes than amoxicillin-clavulanate for AOMTF (91% vs. 81%; $P = .029$), for AOMTF and age <2 years old (89% vs. 69%; $P = .009$), and for severe AOM in children <2 years old (90% vs. 75%; $P = .012$). Among children with AOMTF previously treated with amoxicillin-clavulanate or ceftriaxone injections, gatifloxacin cure rates were high (88% and 75%, respectively).

Conclusions. Gatifloxacin appears to be safe for children, with no evidence of producing arthrotoxicity in 867 children exposed to the antibiotic when used as treatment for ROM and AOMTF.

Fluoroquinolone use in children has been limited because of concerns about arthrotoxicity that are based on observations in juvenile animals [1–9]. Arthrotoxicity has not been documented in children despite intense scrutiny of quinolone use in children with cystic fibrosis or life-threatening infections [1, 3]. A review of quinolone use in 7000 children and adolescents revealed no cases of associated arthropathy [2]. In Great Britain, a study of ciprofloxacin use in 9000 children during 1986–1996 revealed an arthralgia incidence of 2.5%, which was reversible (and thus distinct from cases of arthropathy) [10]. In Japan, where norfloxacin has been approved for use in children since 1993, there have been no reports of arthropathy [11]. In a study of tendon and joint disorders in children receiving fluoroquinolones or azithromycin, there were no differences in the types and incidences of adverse events [12]. Ciprofloxacin is now approved in the United States for use in children ⩾1 year of age with complicated urinary tract infections or pyelonephritis.

There are few treatment options for children with recurrent acute otitis media (ROM) who do not re-

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Reprints or correspondence: Dr. Michael E. Pichichero, Dept. of Microbiology, Box 672, University of Rochester Medical Center, 601 Elmwood Ave., Rm. 2-5431, Rochester, NY 14642 (michael_pichichero@urmc.rochester.edu).

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spond to high-dose amoxicillin-clavulanate or to other treatments recommended by the Centers for Disease Control and Prevention and the American Academy of Pediatrics–American Academy of Family Physicians (i.e., cefdinir, cefpodoxime proxetil, cefuroxime axetil, or intramuscular ceftriaxone). Current treatment recommendations, which rotate a small number of antibiotics, offer limited options and may not be effective against the 2 most prevalent pathogens associated with AOM (i.e., *Streptococcus pneumoniae* and *Haemophilus influenzae*). Effective treatment options are further limited for children who are allergic or hypersensitive to penicillin.

In this article, a comprehensive review of all pediatric clinical trials conducted with gatifloxacin for treatment of AOM are described, with particular emphasis on the safety of the drug in children aged 6 months to 7 years. We describe the safety of gatifloxacin with regard to potential arthrotoxicity, hepatotoxicity, glucose homeostasis, phototoxicity, and CNS toxicity.

STUDY DESIGNS

Four pivotal clinical studies involving 1176 children were conducted to evaluate the safety and efficacy of gatifloxacin (10 mg/kg once daily for 10 days) in 867 children aged 6 months to 7 years with ROM (defined as at least 3 episodes of acute otitis media [AOM] in the previous 6 months or ⩾4 episodes in the previous 12 months, including the current episode) and/or AOM treatment failure (AOMTF; defined as AOM that occurred within 14 days after the last dose of antibiotic for a previous episode or as lack of response after at least 2 full days of treatment for the current episode) (table 1). There were 2 phase II noncomparative studies (studies 094 [13] and 076 [14]); both required pretreatment tympanocentesis to identify the pathogens causing AOM. There were 2 phase III comparative studies; one compared gatifloxacin with high-dose amoxicillin-clavulanate (study 078 [15]), and the other compared gatifloxacin with regular-dose amoxicillin-clavulanate (study 084 [16]). Both phase III studies included optional pretreatment tympanocentesis, which was performed in 65% of cases. Of the participants in the 4 studies, 32% had ROM, 37% had AOMTF, 28% had ROM and AOMTF, and 55% had severe AOM (defined below); 52% were <2 years old.

Study procedures and observations. The study procedures in all 4 studies were similar. Assessments were scheduled to occur as follows: before treatment initiation (treatment was started later the same day); 4, 5, or 6 days after treatment initiation; during the test of cure (TOC) visit (4, 5, 6, or 7 days after treatment initiation in studies 076, 078, and 084 and 2, 3, or 4 days after treatment initiation in study 094); during a "late" follow-up examination (between 21 and 28 days after treatment initiation in studies 076, 078, and 084 and between 12 and 18 days after treatment initiation in study 094); and during long-term safety follow-up visits (2, 4, 6, and 12 months after receipt of the final dose of study medication).

Pretreatment evaluations included joint examination; characterization of gait; collection of a blood sample for hematologic analysis, liver function testing, and measurement of blood urea nitrogen, creatinine, and fasting or nonfasting glucose levels; documentation of specific and nonspecific signs and symptoms of AOM; severity scoring of otitis media; pneumatic otoscopy; tympanometry or acoustic reflectometry; and culture of

Table 1. Clinical studies of the safety and efficacy of gatifloxacin for the treatment of recurrent acute otitis media (ROM) and/or acute otitis media (AOM) treatment failure.

Study	Title	No. of subjects, by regimen		Time of tympanocentesis
		Gatifloxacin	Comparator[a]	
Phase II				
076 [13]	Open-Label, Multicenter, Noncomparative Study of Gatifloxacin in the Treatment of Recurrent Otitis Media And Acute Otitis Media Treatment Failure	254	…	Before treatment
094 [14]	Recurrent Acute Otitis Media Occurring within 1 Month after Completion of Antibiotic Therapy: Relationship to the Original Pathogen	160	…	Before and during treatment
Phase III				
078 [15]	Randomized, Investigator-Blinded, Multicenter Comparative Study of Gatifloxacin versus High-Dose Amoxicillin-Clavulanate in the Treatment of ROM/AOM Treatment Failures in Children	176	173	Before treatment (optional)
084 [16]	Randomized, Investigator-Blinded, Multicenter Comparative Study of Gatifloxacin versus Amoxicillin/Clavulanate in the Treatment of ROM/AOM Treatment Failures in Children	277	136	Before treatment (optional)
Total	…	867	309	…

[a] High-dose amoxicillin-clavulanate was used in study 078, and regular-dose amoxicillin-clavulanate was used in study 084.

middle ear fluid (MEF) obtained during tympanocentesis or within 24–48 h after tympanic membrane rupture. Tympanocentesis was optional in the phase III studies (i.e., studies 078 and 084).

Evaluations performed during day 4, 5, or 6 after treatment initiation included joint examination, gait characterization, pneumatic otoscopy, assessment of signs and symptoms of AOM, and culture of MEF obtained during tympanocentesis; the latter evaluation was optional in all studies except study 094. Evaluations performed during the TOC visit included those performed during the second visit, as well as collection of a blood sample for the same laboratory tests performed during the pretreatment evaluation, tympanometry or acoustic reflectometry, and investigator assessment of clinical response. Evaluations performed during the late follow-up visit were joint examination, gait characterization, assessment of signs and symptoms of AOM, pneumatic otoscopy of both ears, tympanometry or acoustic reflectometry, optional culture of MEF obtained during tympanocentesis, investigator assessment of clinical response, time to resolution of signs and symptoms (from subject diaries). Subjects were examined every 2–3 months up to 1 year after treatment initiation, to identify any joint complaints and gait disturbances and to monitor changes in height.

Selection of study population. The key inclusion criteria in the studies were age of 6 months to 7 years (the maximum age was 48 months in study 094), a diagnosis of ROM or AOMTF, and a diagnosis of AOM that was based on acute onset of otalgia symptoms and otoscopic findings (e.g., bulging or redness in the TM). Studies 076, 078, and 084 also required evidence of effusion demonstrated by acoustic reflectometry or tympanometry, if tympanocentesis was not performed. Tympanocentesis yielding fluid or collection of exudate from a TM perforation existing for no longer than 24–48 h was required in studies 094 and 076.

The key exclusion criteria in the studies were presence of tympanostomy tube(s) in the affected ear(s) and receipt of systemic antibiotic therapy $\leq$7 days (or $\leq$3 days, for study 076) before enrollment for reasons other than otitis media prophylaxis or otitis media treatment failure. Presence of spontaneous TM perforation was an additional exclusion criterion for studies 078 and 084.

AOM severity at baseline was scored on the basis of 5 criteria proposed by Dagan et al. [17]. A total score of <3 corresponded to mild AOM, a total of score of 3–7 corresponded to moderate AOM, and a total score of 8–15 corresponded to severe AOM.

Clinical definitions of outcome. Clinical cure was defined as resolution or improvement of all signs and symptoms associated with acute infection and no receipt of additional antimicrobial treatment for otitis media. Clinical failure was defined as $\geq$1 of the following conditions: primary signs and symptoms of otitis media (otalgia, marked redness of the TM, or bulging TM) were the same, worse, or new; primary signs and symptoms of otitis media were improved or had resolved, but an additional systemic antibiotic was prescribed for the infection under study; and development of new primary signs and symptoms in an ear that was unaffected before treatment during the period considered for clinical assessment.

Microbiologic definitions of outcome. For each pathogen isolated from the MEF before treatment, a bacteriologic response at the TOC visit was designated "eradicated," "persisted," or "unable to determine." Responses defined as eradicated were further characterized as "documented eradicated" (i.e., the original pathogen was absent from the posttreatment culture) or "presumed eradicated" (i.e., no culture was obtained after treatment, and the clinical response was clinical cure). Responses defined as persisted were further characterized as "documented persisted" (i.e., the original pathogen was present in the posttreatment culture) or "presumed persisted" (i.e., no culture was obtained after treatment, and the clinical response was clinical failure).

Statistical analysis. Clinical cure rates and 95% CIs (computed by means of the Blyth-Still-Casella method [18, 19]) were calculated for each subgroup. The method of Agresti and Min [20] was used to test the null hypothesis that there was no difference in the clinical cure rates of gatifloxacin and amoxicillin-clavulanate in each subgroup; testing was 2-tailed. All analyses were performed by means of the binomial procedure in StatXact, version 5.1 (Cytel).

RESULTS

Safety of gatifloxacin

The primary data supporting the safety of gatifloxacin in the pediatric population were derived from the 2 phase II and 2 phase III studies of subjects with ROM and/or AOMTF described in this article, in which 867 children aged 6 months to 7 years were treated with gatifloxacin. The duration of exposure to drugs was 10 days. The overall rates of adverse events and drug-related adverse events were similar for gatifloxacin in the phase II and III studies and for gatifloxacin and the comparators in the phase III studies (table 2). In the phase II studies, the relatively high rate of gatifloxacin discontinuation because of adverse events (31 [8%] of 414 subjects) was primarily due to vomiting caused by the bitter taste and high volume of an early oral suspension formulation introduced in these studies (25 subjects [6%]). An improved oral formulation of gatifloxacin was introduced in the phase III studies, and there were no serious adverse events, compared with 5 adverse events associated with the comparators. In the phase III studies, the rates of discontinuation due to adverse events were similar for gatifloxacin and the comparators (~2%). The majority of ad-

Table 2. Adverse events due to gatifloxacin for all treated subjects with recurrent acute otitis media and/or acute otitis media treatment failure in phase II and phase III studies.

Adverse event	No. (%) of subjects who received gatifloxacin, by study type		No. (%) of subjects who received comparator in a phase III study[a]
	Phase II (n = 414)	Phase III (n = 453)	(n = 309)
Any	232 (56.0)	259 (57.2)	188 (60.8)
Drug related	86 (20.8)	91 (20.1)	66 (21.4)
Resulted in discontinuation of study regimen	31 (7.5)	7 (1.5)	7 (2.3)
Severe	10 (2.4)	0	5 (1.6)
Drug related, severe	1 (0.2)[b]	0	1 (0.3)
Death	1 (0.2)[c]	0	0

[a] High-dose amoxicillin-clavulanate was used in study 078, and regular-dose amoxicillin-clavulanate was used in study 084.
[b] Hospitalized on day 1 after treatment initiation for diarrhea, vomiting, and dehydration. The investigator judged these conditions to be possibly related to the study regimen.
[c] Died on day 25 after treatment initiation. The subject had Down syndrome and pneumonia, sepsis, and shock. The investigator judged these conditions to be unrelated to the study regimen.

verse events associated with gatifloxacin were mild or moderate in severity, with 41 (5%) of 867 gatifloxacin-treated children experiencing at least 1 event that was judged by the investigator as severe. The most frequently reported severe adverse event was vomiting (7 subjects [1%]).

In the 2 phase III comparator studies, 453 children were treated with gatifloxacin; 188 were aged <2 years. Among 309 children treated with amoxicillin-clavulanate, 137 were <2 years old. Among the 453 gatifloxacin recipients, the incidence of drug-related adverse events was similar for children <2 years of age (16%) and for children ⩾2 years of age (23%). However, for amoxicillin-clavulanate, the incidence of drug-related adverse events was higher for children aged <2 years (31%) than for children aged ⩾2 years (14%). Drug-related diarrhea was about 4 times as common among children <2 years of age who received amoxicillin-clavulanate (22%), compared with those who received gatifloxacin (5%).

Arthropathy. Transient arthralgia occurred in 12 (1.4%) of 867 gatifloxacin-treated children and resolved without requiring treatment (typically within 2 weeks). Seven of these 12 children were examined by an orthopedist or a pediatric rheumatologist per protocol; no abnormal findings were detected. Two of the 12 children underwent MRI, which showed no evidence of arthrotoxicity. One child discontinued therapy because of transient left knee arthralgia associated with joint swelling (but not effusion) and abnormal gait with no history of trauma; an MRI performed at the time of the event revealed no joint abnormalities, and multiple subsequent joint examinations during a 12-month follow-up period revealed no joint abnormalities. In the phase III comparator studies, the incidence of arthralgia was 1.5% for gatifloxacin (7 of 453 subjects) and 1.3% for amoxicillin-clavulanate (4 of 309 subjects). None of the arthralgia events were associated with a joint abnormality, and none led to discontinuation of treatment.

One-year safety follow-up data were collected for 671 gatifloxacin-treated children, primarily to monitor the potential development of delayed arthropathy. No evidence of arthropathy was reported. For these 671 children, the study had 80% power to detect events occurring at a rate of ⩾0.25%. Also, children treated with gatifloxacin grew at normal rates, according to standardized growth charts. In the phase III studies, the mean heights of children <2 years of age increased at a similar rates during the 12-month observation period for children treated with gatifloxacin or amoxicillin-clavulanate.

None of 351 children exposed to gatifloxacin in pediatric phase I studies experienced an adverse event associated with tendinopathy. In the phase II and phase III studies, a 4-year-old girl developed Achilles tendon pain 5 days after completing treatment with gatifloxacin. The investigator judged the severity of tendon pain to be moderate and possibly related to the study drug. The event resolved within 5 days, without treatment other than rest and ice. Multiple assessments of joints performed during the 12-month follow-up period revealed no abnormalities.

Hepatotoxicity. The aspartate transaminase level was elevated in 14% of children who received either gatifloxacin or amoxicillin-clavulanate, the alanine transaminase level was elevated in 5% of children who received either gatifloxacin or amoxicillin-clavulanate, and the total bilirubin level was elevated in 1% of children who received gatifloxacin or amoxi-

Table 3. Clinical cure rates of gatifloxacin at the test-of-cure visit in phase II studies involving subjects with recurrent otitis media and/or acute otitis media treatment failure.

	Study 076		Study 094		Pooled data	
Population	Proportion of subjects cured	Cure rate (95% CI)	Proportion of subjects cured	Cure rate (95% CI)	Proportion of subjects cured	Cure rate
Clinically evaluable subjects	175/198	88 (83–92)	103/114	90 (83–95)	278/312	89
All treated subjects	217/254	85 (80–89)	117/160	73 (66–80)	334/414	81

cillin-clavulanate. No subject developed simultaneous elevations in liver enzyme levels and total bilirubin levels that were >2 times the upper limit of normal. None of the children who developed elevated liver enzyme or total bilirubin levels had clinical symptoms suggestive of hepatotoxicity, and all symptoms resolved after drug discontinuation.

Glucose homeostasis. The overall incidence of low fasting and nonfasting serum glucose levels in children with a normal pretreatment serum glucose level was higher in gatifloxacin-treated children (5.8% [21 of 360 subjects]), compared with amoxicillin-clavulanate–treated children (2.5% [6 of 239 subjects]). However, none of the low serum glucose levels in either treatment group were clinically relevant (i.e., <40 mg/dL) or associated with clinical symptoms of hypoglycemia. For gatifloxacin-treated children, the overall frequency of abnormally low glucose levels was similar before and after treatment. High fasting and nonfasting serum glucose levels (116–160 and 161–199 mg/dL, respectively) were observed in 1 gatifloxacin-treated child (0.3%).

Phototoxicity. There were no adverse events associated with phototoxicity in the subjects. Analysis of adverse events potentially associated with phototoxicity (i.e., rash, erythema, and sunburn) in the phase III studies indicated that the incidence of such events was similar for children who received gatifloxacin (3.1%) and those who received amoxicillin-clavulanate (3.6%). The events were mild to moderate in severity, were transient in nature, and did not result in discontinuation of treatment.

CNS toxicity. In the phase II studies, a 3-year-old child had convulsions (referred to as "febrile seizures" by the investigator) 11 days after completing treatment with gatifloxacin. The event resolved the same day and was rated as nonserious, severe, and unrelated to study drug in the phase III studies. The only instance of convulsion, which was judged by the investigator as being drug-related, occurred in a child treated with amoxicillin-clavulanate.

Efficacy of gatifloxacin

Overall clinical outcomes for ROM and AOMTF. At the TOC visit, the cure rate of the pooled phase II studies for gatifloxacin was 89% among clinically evaluable children and 81% among all treated children (table 3). The difference in cure rate between clinically evaluable children and all treated children in study 094 (90% vs. 73%) was due to discontinuations associated with the oral suspension formulation of gatifloxacin (11% of subjects; vomiting was the most common adverse event); this formulation was subsequently replaced with a more pleasant tasting formulation in phase III studies.

In phase III study 084, gatifloxacin had a cure rate at TOC of 90% among clinically evaluable children, compared with 84% for regular-dose amoxicillin-clavulanate. The cure rate among clinically evaluable subjects in phase III study 078 was 85% for gatifloxacin, compared with 79% for high-dose amoxicillin-clavulanate (table 4). Consistent with the results of the individual phase III studies, the pooled phase III data show a consistent trend favoring gatifloxacin, both for clinically evaluable children and all treated children. This consistency of

Table 4. Clinical cure rates of gatifloxacin at the test-of-cure visit in comparative phase III studies involving subjects with recurrent acute otitis media and/or acute otitis media treatment failure.

	Study 078, by regimen			Study 084, by regimen			Pooled data, by regimen	
Population	Gatifloxacin	Comparator[a]	95% CI[c]	Gatifloxacin	Comparator[b]	95% CI[c]	Gatifloxacin	Comparator
Clinically evaluable subjects	105/124 (85)	92/117 (79)	(−2.8 to 16.4)	222/246 (90)	102/121 (84)	(−1.9 to 12.9)	327/370 (88)	194/238 (82)
All treated subjects	140/176 (80)	139/173 (80)	(−8.8 to 7.5)	246/277 (89)	111/136 (82)	(−0.9 to 13.8)	386/453 (85)	250/309 (81)

NOTE. Data are proportion (%) of subjects cured, unless otherwise indicated.

[a] High-dose amoxicillin-clavulanate (2 doses per day, for a total of 80 mg/kg).

[b] Regular-dose amoxicillin-clavulanate (2 doses per day, for a total of 40 mg/kg).

[c] Measures the precision of the difference in cure rates between gatifloxacin and comparator regimen, adjusted for age category at the time of randomization.

Table 5. Clinical cure rates at the test-of-cure visit among clinically evaluable subjects with recurrent acute otitis media (AOM) and/or AOM treatment failure (AOMTF) in comparative phase III studies, by prognostic factors.

Prognostic factor	Proportion (%) of subjects cured, by regimen		
	Gatifloxacin (n = 370)	Comparator[a] (n = 238)	P[b]
AOMTF	193/211 (91)	102/126 (81)	.005
Recurrent otitis media	104/120 (87)	73/89 (82)	.368
Severe AOM	197/221 (89)	116/144 (81)	.023
Age <2 years	130/150 (87)	81/103 (79)	.094
Age <2 years, severe AOM	96/107 (90)	49/65 (75)	.012
AOMTF, severe AOM	115/126 (91)	68/84 (81)	.029
AOMTF, age <2 years	62/70 (89)	33/48 (69)	.009

[a] High-dose amoxicillin-clavulanate was used in study 078, and regular-dose amoxicillin-clavulanate was used in study 084.

[b] The null hypothesis was that there is no difference in the clinical cure rates of gatifloxacin and amoxicillin-clavulanate. No adjustment to control for α was performed in these post hoc analyses.

results was maintained across several subgroups, including age, sex, and race.

Protocol predefined baseline prognostic failures. To further define the efficacy of gatifloxacin relative to amoxicillin-clavulanate, analyses were conducted to identify subsets of children who might derive the most benefit from gatifloxacin therapy. These analyses were based on pooled data of clinically evaluable children from phase III studies using prespecified prognostic factors from the protocols. Pooling of these data was statistically justifiable, because the designs of both studies were essentially identical, and the direction of the difference between gatifloxacin and the comparator was similar in both studies.

Gatifloxacin led to better clinical outcomes than amoxicillin-clavulanate in the difficult-to-treat cases (i.e., children with AOMTF or severe AOM, children aged <2 years with AOMTF, and children aged <2 years with severe AOM; table 5). Figure 1 shows the 95% CIs for the observed clinical cure rates for gatifloxacin and amoxicillin-clavulanate per subgroup (P< .05 for all). These data indicate that gatifloxacin was associated with a better clinical response than amoxicillin-clavulanate in the difficult-to-treat cases, specifically for children who did not respond to treatment or who had severe AOM, including those <2 years of age. This treatment advantage for gatifloxacin was also evident at the follow-up visit (between days 21 and 28 after treatment initiation) among children with AOMTF who were <2 years of age (69% for gatifloxacin vs. 46% for comparators; data not shown).

Amoxicillin-clavulanate treatment failures. The gatifloxacin cure rate among 42 subjects who did not respond to amoxicillin-clavulanate was 88%. The bacteriologic outcome was

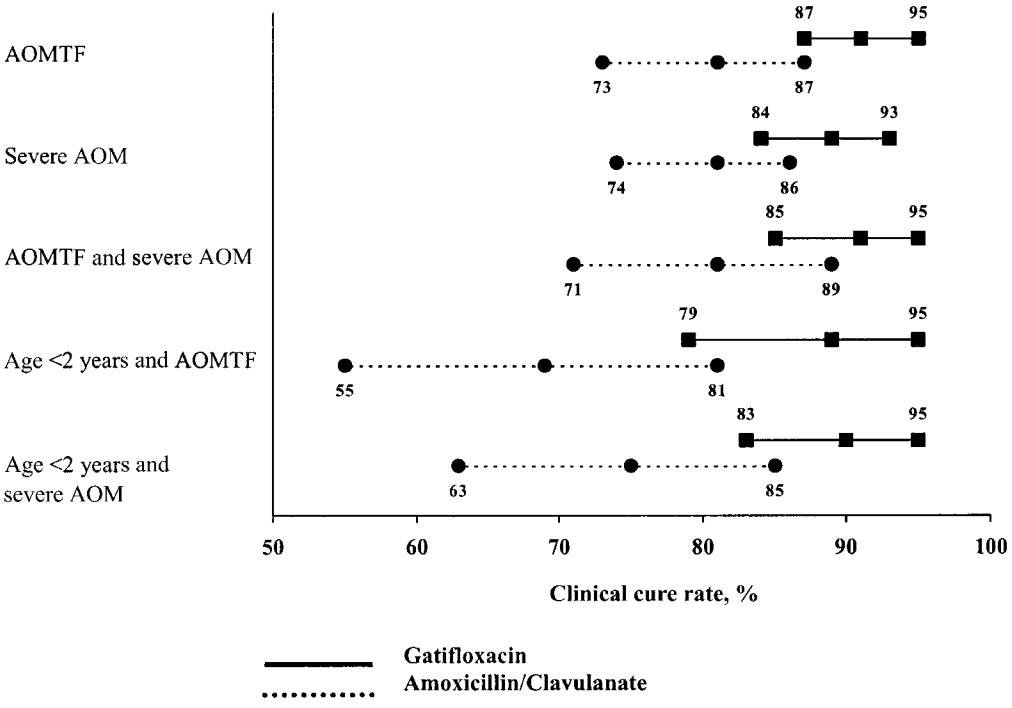

Figure 1. Exact 95% CIs for clinical cure rates among clinically evaluable subjects with recurrent acute otitis media (AOM) and/or AOM treatment failure (AOMTF) at the test-of-cure visit in comparative phase III studies. Exact 95% CIs were calculated according to the methods of Blyth and Still [18] and Casella [19].

Table 6. Gatifloxacin clinical cure rates at the test-of-cure visit among clinically evaluable subjects with recurrent acute otitis media and/or acute otitis media treatment failure who were previously treated with amoxicillin-clavulanate in phase II and phase III studies, according middle ear fluid culture results.

Variable	Proportion (%) of subjects cured
No. of infecting agents	
Any number	20/24 (83)
1 Pathogen	14/18 (78)
⩾2 Pathogens	6/6 (100)
Streptococcus pneumoniae	
Total	8/8 (100)
Penicillin susceptible	2/2 (100)
Penicillin intermediate	1/1 (100)
Penicillin resistant	5/5 (100)
Haemophilus influenzae	
Total	17/19 (89)
β-Lactamase positive	6/7 (86)
β-Lactamase negative	11/12 (92)
Moraxella catarrhalis, β-lactamase positive	0/2 (0)
Streptococcus pyogenes	1/1 (100)

NOTE. A subject may have had >1 pathogen isolated before treatment.

similar to the clinical cure rates; of 24 patients with a pathogen isolated, pathogens were eradicated from 20 (83%) at the TOC (table 6).

Ceftriaxone treatment failures. Gatifloxacin achieved a clinical cure rate at the TOC visit of 75% (9 of 12 subjects) in those who did not respond to ceftriaxone treatment (9 had received intramuscular ceftriaxone for at least 3 days, and 7 had pathogens that were recovered from culture of MEF). The bacteriologic outcome was similar to the clinical cure rate; of 8 subjects with a pathogen isolated (which included 4 *S. pneumoniae* isolates, 3 *H. influenzae* isolates, and 1 *Moraxella catarrhalis* isolate), pathogens were eradicated from 6 (75%) at the TOC.

***Efficacy against drug-resistant* S. pneumoniae.** All MEF pathogens were susceptible to gatifloxacin. This agent achieved high clinical cure rates for children with *S. pneumoniae* that was resistant to 1 or to ⩾2 antibiotics (table 7). Bacteriologic eradication rates were identical to the clinical cure rates: 88% of penicillin-nonsusceptible *S. pneumoniae* isolates (61 of 69) were eradicated with gatifloxacin, including 22 (88%) of 25 penicillin-resistant *S. pneumoniae* (PRSP) strains (14 isolates were documented, and 8 were presumed to be eradicated). Of the 3 cases of PRSP bacteriologic persistence, only 1 was documented (on day 5 of treatment) in a subject who was clinically cured, with pre- and posttreatment gatifloxacin MICs of 0.25 and 0.5 μg/mL, respectively.

DISCUSSION

On the basis of results described here, the clinical effectiveness of gatifloxacin appears to be clear. Gatifloxacin rapidly eradicated the causative pathogens of AOM, as demonstrated in double tympanocentesis studies, and it achieved MEF eradication rates that were higher than those reported for most US-marketed antibiotics in similar studies. Gatifloxacin effectively treated cases of ROM and AOMTF caused by penicillin-resistant *S. pneumoniae* (including strains resistant to high-dose amoxicillin-clavulanate), multidrug-resistant *S. pneumoniae* (including strains resistant to 3–4 classes of antibiotics), and β-lactamase–producing *H. influenzae* and *M. catarrhalis*.

However, the potential use of gatifloxacin in children is controversial, with the major concern being risk of arthropathy and the possibility of widespread bacterial resistance to this class of antibiotics, which could limit the future effectiveness of fluoroquinolones in the adult population [2, 8, 21]. Consequently, until 2004, fluoroquinolones were contraindicated in children, growing adolescents, pregnant women, and new mothers who are lactating [22]. Although fluid-filled blisters, fissures, and erosions typically occur in the articular cartilage in weight-bearing joints of juvenile animals after quinolone administration [21], published data suggest that prolonged therapy with fluoroquinolones has been well tolerated by children [2, 22].

Pefloxacin was reported to induce arthropathy in 1 adolescent [23]. However, no unequivocal evidence was obtained for this patient or any other child treated with fluoroquinolones [2, 22]. Furthermore, in an observational study involving >6000 patients <19 years of age, the incidence of verified tendon or

Table 7. Gatifloxacin clinical cure rates at the test-of-cure visit among microbiologically evaluable subjects with recurrent acute otitis media and/or acute otitis media treatment failure from whom drug-resistant *Streptococcus pneumoniae* was isolated—phase II and phase III studies.

S. pneumoniae strain	Proportion (%) of subjects cured
Resistant to penicillin	
MIC ⩾2 μg/mL	22/25 (88)
MIC ⩾4 μg/mL	9/10 (90)
Resistant to macrolides	18/23 (78)
Resistant to second-generation cephalosporins	29/33 (88)
Resistant to trimethoprim-sulfamethoxazole	15/16 (94)
Resistant to multiple drugs	
Overall	25/28 (89)
2 drug classes[a]	9/9 (100)
3 or 4 drug classes[a]	16/19 (84)

[a] Any combination of penicillin (or second-generation cephalosporin), macrolide, and trimethoprim-sulfamethoxazole.

joint disorders within 60 days after fluoroquinolone administration was <1%, equivalent to that for azithromycin.

Antibiotic resistance in microorganisms implicated in otitis media has become a global problem and has probably contributed to the increased incidence of ROM and AOMTF [24, 25]. In particular, the rates of antimicrobial resistance among clinical isolates of *S. pneumoniae* are increasing [26]. Moreover, pneumococcal resistance rates among children <5 years of age are significantly higher for penicillin, other β-lactams, macrolides, and trimethoprim-sulfamethoxazole than they are among older children or adults [27]. The increase in the prevalence of antibiotic resistance among the most important AOM pathogens, along with the increase in the prevalence of multidrug resistance among pathogens, substantially complicates the treatment of AOM and is associated with therapeutic failures. An advantage of gatifloxacin is that, by virtue of structural properties of the molecule, resistance requires 2 mutations in a bacterium. Therefore, there is a decreased propensity for the emergence of fluoroquinolone resistance with this drug. However, although no significant upward shifts in MICs have been reported for gatifloxacin since it received US licensure in 1998, and no resistant strains were identified among AOM isolates or concomitant nasopharyngeal isolates during or 1 month after gatifloxacin treatment in the trials described here (data not shown), increased indiscriminate use in a pediatric population could unfavorably impact currently low fluoroquinolone resistance rates [28].

CONCLUSIONS

Gatifloxacin appeared to be safe for children with ROM or AOMTF who did not respond to currently recommended first- and second-line antibiotics. Gatifloxacin exhibited consistent activity against the important pathogens responsible for AOM. The potential risks of fluoroquinolone use in children can be mitigated by selective use for those who do not respond to second-line antimicrobial therapy or who are hypersensitive to β-lactams.

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