Assessment of Musculoskeletal Toxicity 5 Years After Therapy With Levofoxacin

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**KEY WORDS**
levofoxacin, fluoroquinolone toxicity, cartilage, articular/growth and development

**ABBREVIATIONS**
DSMC—Data Safety and Monitoring Committee
FDA—Food and Drug Administration
LTU—long-term follow-up
MSAE—musculoskeletal adverse events
NSAID—nonsteroidal antiinflammatory drug
PDMSD—protocol-defined musculoskeletal disorders
SAE—serious adverse event
SPFU—surveillance phase follow-up

Dr Bradley assisted in the design of the outcomes of the data collection, critically reviewed and analyzed study data, and drafted the initial manuscript; Drs Kauffman, Duffy, and Gerbino comprised the primary group to design the outcomes used for data collection to assess musculoskeletal adverse events for this study, critically reviewed and analyzed study data, and reviewed and revised the manuscript; Dr Balis assisted in the design of the data collection instruments, coordinated and supervised data collection, supervised data queries by manuscript authors, and critically reviewed the manuscript; Drs Maldonado and Noel conceptualized and designed the study with the US Food and Drug Administration, carried out the initial analyses, and critically reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

This trial has been registered at www.clinicaltrials.gov (identifier NCT00210639).

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**WHAT’S KNOWN ON THIS SUBJECT:** Animal studies document dose-dependent and duration-of-therapy-dependent fluoroquinolone cartilage toxicity in weight-bearing joints. Preliminary pediatric data collected after fluoroquinolone treatment and up to 1 year posttreatment in blinded and unblinded studies suggest the possibility of cartilage toxicity in children.

**WHAT THIS STUDY ADDS:** These are the first prospectively collected data on fluoroquinolone musculoskeletal safety collected posttherapy from randomized, comparative studies of respiratory tract infections and analyzed at 5 years. Long-term musculoskeletal adverse events occurred with equal frequency in both levofoxacin and comparator groups.

**BACKGROUND:** Safety concerns for fluoroquinolones exist from animal studies demonstrating cartilage injury in weight-bearing joints, dependent on dose and duration of therapy. For children treated with levofoxacin or comparator in randomized, prospective, comparative studies for acute otitis media and community-acquired pneumonia, this 5-year follow-up safety study was designed to assess the presence/absence of cartilage injury.

**METHODS:** Children enrolled in treatment studies were also enrolled in a 1-year follow-up safety study, which; focused on musculoskeletal adverse events (MSAE). Those with persisting MSAEs, protocol-defined musculoskeletal disorders, or of concern to the Data Safety and Monitoring Committee were requested to enroll in four additional years of follow-up, the subject of this report.

**RESULTS:** Of the 2233 subjects participating in the 12-month follow-up study, 124 of 1340 (9%) of the levofoxacin subjects, and 83 of 893 (9%) of the comparator subjects were continued for 5-year posttreatment assessment. From children identified with an MSAE during years 2 through 5 posttreatment, the number that were “possibly related” to drug therapy was equal for both arms: 1 of 1340 for levofoxacin and 1 of 893 for comparator. Of all cases of MSAE assessed by the Data Safety and Monitoring Committee at 5 years’ posttreatment, no case was assessed as “likely related” to study drug.

**CONCLUSIONS:** With no clinically detectable difference between levofoxacin- and comparator-treated children in MSAEs presenting between 1 and 5 years in these safety studies, risks of cartilage injury with levofoxacin appear to be uncommon, are clinically undetectable during 5 years, or are reversible. *Pediatrics* 2014;134:1–8

**abstract**

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Fluoroquinolones represent a class of broad-spectrum antimicrobial agents that have found widespread acceptance for use in a wide variety of infections in adults, but their use in children has not been encouraged, largely because of concerns related to cartilage toxicity. In the mid-1990s, the emergence of multiple drug-resistant pathogens, including pneumococcus, together with the evolving recognition that toxicity observed in fluoroquinolone-exposed juvenile laboratory animals was not clinically evident in children treated with these drugs, provided a basis for initiating US Food and Drug Administration (FDA)-sanctioned, prospective, comparative efficacy and safety clinical trials with fluoroquinolones in children. Clinical trials were subsequently undertaken with trovafloxacin treating children for bacterial meningitis, gatifloxacin for otitis media, ciprofloxacin for complicated urinary tract infections, and levofloxacin for upper and lower respiratory tract infections (otitis media and community-acquired pneumonia). Overall, these comparative clinical trials supported conclusions that fluoroquinolones were effective in treating infectious diseases in children, but there were ongoing concerns regarding a low rate of musculoskeletal adverse events (MSAE). Each of these clinical trials included an assessment of MSAEs during the trial and, in some, for periods of up to 1 year after fluoroquinolone exposure. However, to date, none of these trials has reported on long-term findings beyond 1 year, which is likely to be more clinically relevant in detecting progressive and irreversible injury to cartilage in weight-bearing joints.

With respect to levofloxacin, preclinical animal toxicity data were developed and analyzed by Johnson & Johnson and the FDA prior to clinical trials in adults. The no adverse effect level in juvenile beagle dogs was found to be 3 mg/kg/day with intravenous dosing for 14 days, with evidence of erosions on the articular surface of weight bearing joints noted at 4 mg/kg/day. The FDA-approved dose for anthrax post-exposure prophylaxis and for treatment of plague for children weighing <50 kg is 16 mg/kg/day, divided every 12 hours.

The levofloxacin pediatric safety program was designed to focus on events that would reflect the clinical correlate of histopathologic findings in cartilage in experimental animals and address the possibility of involvement of epiphyseal plates. This safety program included protocol-defined musculoskeletal disorders (PDMSD) that included arthritis, arthralgia, gait abnormality, tendinopathy, and growth impairment, which were distinguished from a broader category of any musculoskeletal adverse events (MSAE) that included virtually any abnormality of the musculoskeletal system, including sprains, broken bones, accidental injury, or back pain. Both PDMSD and MSAE observations were collected routinely and analyzed on all children enrolled in the clinical studies during the period of treatment and the month after completion of therapy. In addition, a 12-month surveillance phase follow-up (SPFU) study by Noel and colleagues of both levofloxacin- and comparator-treated children who participated in the 12-month SPFU study. This subset of children was identified as potentially at higher risk of bone or joint toxicity than other children who participated in these trials based on reports of having a PDMSD or a musculoskeletal adverse event, documented delayed growth that might be associated with injury to a growth plate, or any child felt by the investigator or Data Safety and Monitoring Committee (DSMC), for any reason, to require long-term observation. This LTFU study is the subject of this report.

METHODS

The subjects included in the LTFU study (n = 207) were selected from the SPFU study by meeting ≥1 of the following criteria: (1) growth impaired or possibly growth impaired, defined as a documented height <80% of the expected height increase 12 months posttreatment; (2) assessed by the investigator as having abnormal bone or joint signs or symptoms during the 12-month SPFU study; (3) persisting MSAE at the end of the 12-month SPFU study;
or (4) follow-up requested by the DSMC because of concerns for possible joint toxicity associated with a PDMSD. All subjects/care providers who were enrolled in the additional safety study (from years 1 through 5 after treatment) provided written, informed consent for the additional study procedures after institutional review board approval at each participating center (ClinicalTrials.gov Identifier: NCT00210639). These subjects were asked to continue to be evaluated annually for 5 years after their first exposure to study medication to assess ongoing musculoskeletal growth and function or, in the event of a persistent MSAE at the time of the 1-year visit (eg, sprained ankle, broken wrist) for the SPFU study, until the event was considered resolved or 5 years, whichever occurred sooner (Table 1). Subjects were not randomized at the time of entry into the LTFU study. Parents were not blinded in this LTFU study. Site principal investigators were given the option to be blinded in this study. All follow-up visits were to be scheduled within ±30 days of the yearly anniversary of the 1-year follow-up visit. At each follow-up visit, an interval history interview was performed using a standardized questionnaire that focused on assessing the occurrence of any MSAEs, a physical examination (including musculoskeletal examination with evaluation of joints) was performed, and height was measured. Information on serious adverse events (SAEs) was also collected at each visit. Data were collected for analysis of linear growth based on stage of bone development as a function of age and gender, described as prepubescent, pubescent, or postpubescent, as defined by the FDA and Janssen Research and Development, LLC (Table 1).

The DSMC for both the SPFU study and the LTFU study comprised 3 pediatric specialists, in rheumatology, orthopedic surgery, and drug safety. The DSMC reviewed all MSAEs in the 12-month SPFU study and classified them into categories based on the cause of the adverse event, joint involvement, and the results of physical examinations, laboratory findings, or imaging and determined the relationship to study drug: not related, doubtfully related, possibly related, or likely related. PDMSDs were categorized as tendinopathy, arthritis, arthralgia, or gait abnormality. A single subject may have had >1 PDMSD over the 5-year follow-up period. The DSMC was not blinded to drug assignment at the 12-month assessment. The committee also assessed the need for 5-year long-term follow-up based on PDMSD, MSAEs, growth abnormalities, or other concerns and reviewed subjects with emergent musculoskeletal events during years 1 through 5 of the LTFU study by the same criteria as those used for the 12-month SPFU evaluation except they were blinded to study drug assignment at the year 5 evaluation. The DSMC assessments were used for this data analysis.

RESULTS

Of the 2233 subjects participating in the 12-month follow-up study, 124 of 1340 (9%) of the levofoxacin subjects, and 83 of 893 (9%) of the comparator subjects were enrolled in the 5-year posttreatment safety assessment. These 207 subjects were enrolled based on ≥1 of the predefined criteria listed earlier. Demographics of subjects enrolled in the LTFU study in each group, levofoxacin or comparator, are provided in Table 2, with comparable age distributions and subject heights in each group. The median age was 2.9 years, and 97% of all subjects were ≤12 years of age. Of all subjects enrolled in the LTFU study, 49% were from the United States, although only 20% of all subjects enrolled originally in the treatment trials were from sites in the United States. Of all children enrolled in the additional 4 years of observation in the LTFU study, 49% of each group, levofoxacin or comparator, completed the study. Table 3 provides information on the stated reasons for subjects not completing the study, with the largest proportion being “lost to follow-up” over 4 years, with a similar percentage in both treatment and comparator groups.

Data were collected on concomitant medications during the 4 years of additional follow-up, with additional fluoroquinolone use in 3% of those in the levofoxacin-treated group, and 4% of those in the comparator group (Table 4). Corticosteroid use was

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TABLE 1 Data Collected and Analyzed During Participation in the LTFU Study

1. Study completion and withdrawal information
2. Protocol deviations
3. Descriptive statistics (mean, SD, median, and range) were provided for age, weight and height, gender, race, country, age group (6 mo to <2 y, ≥2 to <5 y, ≥5 to <12 y, ≥12 to <17 y)
4. Pubescence stage (prepubescent = male age <11 or female age <9, pubescent = male age 11–15 or female age 9–14, postpubescent = male age >15 or female age >14)
5. Treatment-emergent musculoskeletal adverse events and serious adverse events*
6. Individual patient listing of possible long-term growth impairment was provided for subjects who were deemed growth impaired at the end of the 1 year surveillance phase and had growth data at the 4- or 5-y visit.

*Summarized by system organ class and Preferred Term, coded in accordance with the Medical Dictionary for Regulatory Activities, Versions 9.0, 12.1, and 13.0, used for terminology of MSAEs as the description most closely related to the investigator’s study-requested terminology.

**The z score was calculated after the formula provided by the Centers for Disease Control and Prevention (http://www.cdc.gov/growthcharts/percentile_data_files.htm) based on median population values from smoothed growth curves for gender and length/height by age. z scores were compared for subjects who were deemed growth impaired at the end of the SPFU, to those with growth data at the end of the LTFU study. Subjects were classified based on the difference in z score (final score minus 1 y score) for purposes of this analysis as “Improved” (z difference ≥0.5), “Deteriorated” (z difference ≤−0.5), or “No Change” (z difference <−0.5 to >0.5).
reported in 2% of the levofloxacin group compared with 6% of the comparator group. Nonsteroidal antiinflammatory drug use was equivalent between the 2 groups, at 33% and 31%, respectively.

Although every attempt was made to arrange for annual visits, not all visits were kept, and for those visits attended, not all visits were able to occur within the predefined “window.” 46 levofloxacin-treated children had missed visits during the follow-up period (37% of all 124 levofloxacin-treated children followed); of these 46 children, 27 missed only 1 visit (59%). Twenty-eight comparator-treated children had missed visits (34% of all 83 comparator-treated children followed); of these 28 children, 16 missed only 1 visit (57%). During the period of 1 year after study drug exposure, there were 46 levofloxacin-treated (46 of 1340, 3%) and 16 comparator-treated children (16 of 893, 1%) who had PDMSD or MSAE, with all cases reviewed by the DSMC to assess the adverse event with respect to causality, as previously reported by Noel and colleagues (Fig 1). Five levofloxacin-treated and 2 comparator-treated children in this group were not evaluated after the 1-year evaluation. Each of these children had a normal physical examination at the 1-year visit. Of all children initially treated with levofloxacin or comparator, felt to be at highest risk of a drug-attributable MSAE and followed in the LTFU study, only 8 reported MSAEs that developed during years 2 to 5 of observation (3 levofloxacin treated, 3 comparator treated; Supplemental Table 5). Although no child in the study was assessed to have a “likely” PsMSD caused by either levofloxacin or comparator, the assessment at 12 months by the DSMC considered “possible” drug-attributable PDMSD for 29 children in the levofloxacin group (2% of those exposed) and 10 children in the comparator drug (1% of those exposed). 13 However, by year 5, with 49% in each group completing the 5-year follow-up, only 1 child in each group had ongoing concerns for possible drug toxicity (Fig 1).
levofoxacin-treated child, a 2-year-old boy at the time of drug exposure, complained of transient knee and elbow pain 1 year after drug exposure, with subsequent development of transient right hip synovitis 2.7 years after drug exposure. The comparator-treated child, a 4.3-year-old boy at the time of drug exposure, complained of hip arthralgia starting on the sixth day of therapy and continuing, while on therapy, until day 14, with subsequent development of bilateral musculoskeletal leg pain (diagnosed as “growing pains”) at 1 year after drug exposure (Supplemental Table 5).

Failure to achieve 80% of predicted height was subsequently considered by the DSMC to be not drug related in 101 of 1340 (8%) levofoxacin-treated, and 66 of 893 (8%) comparator-treated children.

**Growth-Related Entry Criteria**

Among all study participants identified for study participation by the growth criteria (n = 174), subsequent growth was assessed by z score–defined height–percentile categories. Children from levofoxacin and comparator treatment groups displayed similar growth characteristics at the 5-year assessment, with equal percentages of children from each treatment group having (1) no change in height percentile, (2) increase in percentile, or (3) decrease in percentile. Of the 9 children demonstrating less growth than predicted based on population expectations (6 of 104 children in the levofoxacin group [6%] and 3 of 70 children in the comparator group [4%]), no child was felt by the DSMC to have drug-attributable growth changes system.

**Incidence of SAE**

SAEs occurred in 2 of 122 children (2%) of the levofoxacin group (hospitalizations for inguinal hernia repair and mononucleosis), and 3 of 80 children (4%) in the comparator group (hospitalization for tonsillectomy, tympanostomy tube placement, and adenoidectomy with tympanostomy tube placement). No SAE was related to the musculoskeletal system.

**DISCUSSION**

In animal models of fluoroquinolone skeletal toxicity, damage to the cartilage is directly proportional to the dose and duration of therapy but varies with the particular fluoroquinolone, animal model, and age of the animal. Most of the animal studies document changes in cartilage at the highest dosages, most easily detected in weight-bearing joints. Injury is particularly apparent in the most sensitive model, juvenile beagle dogs, both histologically and clinically (eg, limp or lameness). The clinical
Evidence of joint tenderness that develops with exposure to fluoroquinolones in this model is reversible if the fluoroquinolone exposure is stopped once these signs of joint involvement are apparent. Theoretical concerns have been raised that joint damage could evolve even after symptoms resolve, based on observations in dogs. Experiments with ciprofloxacin-exposed beagle pups documented evidence of erosions of the weight-bearing articular joint surface as long as 5 months after therapy, despite resolution of joint symptoms that occurred at the time of dosing in these animals.16 These gross anatomic and histologic data concerning articular cartilage, as well as histologic data documenting abnormalities of the epiphyseal cartilage at the highest doses of trovafloxacin and ofloxacin tolerated in rats,17 prompted concerns that a better understanding of risk associated with fluoroquinolone use in children would require evaluation of children well beyond the period of exposure. Although animal data strongly supported that fluoroquinolone-related damage to cartilage would be evident during or immediately after drug exposure, it was reasoned in designing the levofoxacin pediatric program that clinically apparent, drug-related injury to joint cartilage or to the epiphyseal plate in children could take months to manifest.

Initial pediatric clinical trials studying efficacy and safety of fluoroquinolones involved children with invasive pneumococcal disease, including acute bacterial meningitis and recurrent bacterial otitis media. The first large prospective, comparative safety database of fluoroquinolones in children involved the study of ciprofloxacin in the treatment of complicated urinary tract infections, reported on the ciprofloxacin package label.18 This large, international, comparative study documented, for a broad range of all potential bone/joint/tendon/muscle abnormalities (including “arthralgia, abnormal gait, abnormal joint exam, joint sprains, leg pain, back pain, arthrosis, bone pain, pain, myalgia, arm pain, and decreased range of motion in a joint”), a small but statistically significant higher rate of adverse events in ciprofloxacin-treated children (31 of 335, 9.3%) compared with children treated with standard agents (21 of 349, 6%), 95% confidence interval −0.8% to +7.2%, by 6 weeks after treatment. These events were largely mild or moderate in intensity, usually resolving within 30 days of the end of treatment. Using the same assessment criteria at 1 year after treatment, ciprofloxacin-treated children still had an increase in reported adverse events (46 of 335, 13.7%) compared with standard therapy (33 of 349, 9.5%), 95% confidence interval −0.6% to +9.1%.

In addition to this experience with ciprofloxacin, gatifloxacin was extensively studied in children with acute bacterial otitis media.19 However, no musculoskeletal safety issues were raised in the investigator-blinded, published pediatric studies of gatifloxacin, with similar rates of reported and observed musculoskeletal events occurring in gatifloxacin and amoxicillin-clavulanate over 1 year of follow-up.4–7 Of 108 children treated with trovafloxacin and 95 treated with ceftriaxone for acute bacterial meningitis, only 1 child in the trovafloxacin-treated arm and 3 in the ceftriaxone arm demonstrated any joint abnormalities during the 6 to 12 months after therapy. No long-term bone or joint sequelae were noted during the follow-up period in either arm.3

Soon after its launch in 1997, levofoxacin was considered to have the potential to address an evolving unmet medical need in children related to infections caused by multidrug-resistant Streptococcus pneumoniae. However, given the observation in preclinical toxicology experiments that a dose of levofoxacin as low as 4 mg/kg/day was associated with erosion on the articular surface of weight-bearing joints in juvenile beagle dogs11 and that 4 mg/kg/day dosing in these laboratory animals was below the estimated exposure needed to treat children with serious infections, the levofloxacin safety program was designed to detect specific PDMSDs that might reflect the clinical and histologic correlates of findings in cartilage and epiphyses seen in animal experiments.

This design included comparative evaluation (levofloxacin vs nonfluoroquinolone comparator) of children assessed for as long as 5 years after drug exposure. In this experience, it was observed that MSAEs occurred in a similar percentage of children in levofloxacin-treated and comparator-treated groups during the follow-up interval. However, this study had a number of limitations. The study did not involve blinded evaluations by clinicians or parents and therefore represented an open-label study. Nearly half of the children identified for follow-up at 1 year left the trial before 5 years of evaluation, and there may have been children not identified by PDMSDs, MSAEs, investigators, or the DSMC at 1 year, who may have subsequently developed a drug-attributable musculoskeletal event. Despite these shortcomings, the data collected documented that children did not have “likely” fluoroquinolone-attributable persistent musculoskeletal symptoms or clinical sequelae, nor did they have growth abnormalities as assessed by the DSMC at 12 months or at 5 years into the study. Importantly, for all children with “possible” MSAEs during the first year after treatment, only 1 child in each treatment group had an additional MSAE during the subsequent 4 years of follow-up, with neither child having the subsequent event in the originally symptomatic joint. For the levofoxacin-treated 2-year-old boy, the first arthralgia event did not occur until 309 days after drug exposure.
far longer than expected from observations of joint toxicity in the animal model, but the comparator-treated child, a 4.3-year-old boy, experienced arthralgia that started on day 6 and resolved on day 14 of therapy, at the time of the end of antibiotic treatment. The finding that specific joints identified during the first year of follow-up did not cause symptomatic disease during years 2 through 5 of follow-up suggests that progressive degenerative injury is unlikely to occur to a joint that might possibly be detected during the first year of follow-up.

CONCLUSIONS
No prospective, randomized, double-blind, controlled fluoroquinolone study with extended long-term follow-up that has assessed the potential risks of joint toxicity in children has yet been published. Additional prospectively collected data will be important to assess overall fluoroquinolone safety, particularly with the knowledge that each fluoroquinolone may have a different MSAE profile. The findings of this study should be considered alongside earlier findings of the 12-month SPFU study of levofloxacin and provide additional evidence to support the relative safety of levofloxacin in children with respect to cartilage toxicity. If long-term injury occurs with levofloxacin, the rate of these events is low; if injury occurs, it appears to be reversible as assessed at 5 years. Given the common musculoskeletal injuries that occur in children, as well as underlying diseases that may manifest during several years of follow-up, comparative, blinded trials are essential in assessing specific drug-attributable adverse events. Current risk assessments and recommendations by the American Academy of Pediatrics are consistent with the best available published evidence. Careful use of fluoroquinolones for children in situations for which other classes of antibiotics are not available or tolerated, particularly when oral therapy can be used instead of parenteral therapy, is supported by these levofloxacin LTFU study data.

REFERENCES
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*Pediatrics;* originally published online June 2, 2014;
DOI: 10.1542/peds.2013-3636

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Pediatrics; originally published online June 2, 2014;
DOI: 10.1542/peds.2013-3636

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