A Prospective Study Comparing Celecoxib with Naproxen in Children with Juvenile Rheumatoid Arthritis

IVAN FOELDVARI, ILONA S. SZER, LAWRENCE S. ZEMEL, DANIEL J. LOVELL, EDWARD H. GIANNINI, JEFFERY L. ROBBINS, CHRISTINE R. WEST, GINA STEIDLE, SRIRAM KRISHNASWAMI, and BRADLEY J. BLOOM

ABSTRACT. ***Objective.*** To compare the efficacy and safety of celecoxib and naproxen in children with juvenile rheumatoid arthritis (JRA).

Methods. In this multicenter, randomized, double-blind, noninferiority study, subjects with JRA were randomized to receive a target dose of celecoxib 3 mg/kg bid or 6 mg/kg bid, or a target dose of naproxen 7.5 mg/kg bid for 12 weeks (maximum allowed dose = 600 mg total daily dose). The primary efficacy measure was the percentage of responders at Week 12 attaining the American College of Rheumatology pediatric 30% improvement criterion (ACR Pediatric-30).

Results. Both celecoxib doses were at least as effective as naproxen at Week 12 [ACR Pediatric-30 treatment differences: celecoxib 3 mg/kg bid – naproxen = 1.36% (95% CI –13.08 to 15.80); celecoxib 6 mg/kg bid – naproxen = 13.02% (95% CI –0.22 to 26.25)]. Celecoxib 6 mg/kg bid had a numerically higher response rate than celecoxib 3 mg/kg bid at all postrandomization visits and a numerically higher response rate than naproxen 7.5 mg/kg bid at Weeks 4, 8, and 12. Improvement in each ACR Pediatric-30 core set measure was comparable to or numerically higher for celecoxib 6 mg/kg bid than naproxen or celecoxib 3 mg/kg bid. Adverse event rates were similar for all treatment groups, except that gastrointestinal adverse events were more common in the naproxen group, although the difference was not statistically significant.

Conclusion. Celecoxib 3 mg/kg bid and 6 mg/kg bid were at least as effective as naproxen 7.5 mg/kg bid in treating the signs and symptoms of JRA over 12 weeks. All treatments were generally well tolerated. (First Release Nov 15 2008; J Rheumatol 2009;36:174–82; doi:10-3899/jrheum.080073)

Key Indexing Terms:
JUVENILE RHEUMATOID ARTHRITIS CELECOXIB
NAPROXEN AMERICAN COLLEGE OF RHEUMATOLOGY CRITERIA

Juvenile rheumatoid arthritis (JRA) is a group of disorders characterized by idiopathic inflammatory arthritis ranging from very mild to severe, destructive disease that can be challenging to treat. The term JRA was commonly used to describe these disorders until the late 1990s, when it was largely supplanted by the internationally accepted term "juvenile idiopathic arthritis" (JIA), which also encompasses diagnoses not included in the JRA definition, such as psoriatic arthritis. The JRA definition has been used throughout this report because this study was conceived in the late 1990s when the term JRA was still predominant and because the United States Food and Drug Administration (FDA) until recently used JRA as its preferred terminology for determination of regulatory approvals.

Children with pauciarticular JRA are often candidates for nonsteroidal antiinflammatory drug (NSAID) monotherapy. Such therapy is often used in combination with other medications in polyarticular and systemic JRA. Pain is common in JRA and usually necessitates treatment. This pain may be present despite treatment with disease modifying drugs, such as the anti-tumor necrosis factor (anti-TNF) biologic, etanercept, which has demonstrated efficacy in JRA[1]. Indeed, the pain of JRA does not correlate well with disease activity, and pain may be present despite well controlled arthritis[2]. A survey of pediatric rheumatologists showed that 85% of patients with JRA are treated with NSAID[3], and children with JRA achieve American College of

From the Hamburger Zentrum für Kinder- und Jugendrheumatologie, Hamburg, Germany; Rady Children's Hospital, San Diego, California; Connecticut Children's Medical Center, Hartford, Connecticut; Cincinnati Children's Hospital Medical Center, William S. Rowe Division of Rheumatology, Cincinnati, Ohio; Pfizer Inc., New London, Connecticut; and Pfizer Inc., Ann Arbor, Michigan, USA.

Sponsored by Pfizer Inc.

I. Foeldvari, MD, Hamburger Zentrum für Kinder- und Jugendrheumatologie; I.S. Szer, MD, Rady Children's Hospital; L.S. Zemel, MD, Connecticut Children's Medical Center; D.J. Lovell, MD, MPH; E.H. Giannini, MSc, DrPH, Cincinnati Children's Hospital Medical Center, William S. Rowe Division of Rheumatology; B.J. Bloom, MD; J.L. Robbins, Pfizer Inc., New London, CT; C.R. West; G. Steidle; S Krishnaswami, Pfizer Inc., Ann Arbor, MI.

Address reprint requests to Dr. I. Foeldvari, Kinder- und Jugendrheumatologe, Hamburger Zentrum für Kinder- und Jugendrheumatologie, Am Klinikum Eilbek, Dehnhaide 120, 22081 Hamburg, Germany. E-mail: sprechstunde@kinderrheumatologie.de

Accepted for publication August 15, 2008.

Rheumatology (ACR) Pediatric-30 response rates of about 75% after 12 months of NSAID therapy[4]. However, the use of nonselective NSAID is associated with gastrointestinal (GI) ulcers, bleeding, and impaired renal function, occurring principally as a result of cyclooxygenase-1 (COX-1) inhibition[5]. The COX-2-selective NSAID celecoxib has efficacy equivalent to nonselective NSAID in the treatment of various conditions in adults, including rheumatoid arthritis (RA), but may have a more favorable GI tolerability profile by sparing normal COX-1-mediated physiologic functions (e.g., maintenance of the GI mucosa and platelet-mediated coagulation)[6].

We conducted a randomized clinical trial to evaluate the efficacy, safety, and pharmacokinetics of celecoxib, compared with naproxen, for treating the signs and symptoms of JRA. The pharmacokinetic aspects of the study will be described in a separate report.

MATERIALS AND METHODS

Study population. Children aged 2–16 years, inclusive, weighing at least 9 kg, with pauciarticular or polyarticular-course JRA, with or without systemic onset, according to ACR criteria, were eligible. Subjects had ≥ 1 swollen joint and ≥ 1 joint with limited motion, which could be the same joint, and investigator and parent global assessments at screening of ≥ 10 mm on a 100-mm visual analog scale (VAS). Written informed consent from a parent or legal guardian and assent for older children were required. Subjects were excluded if they had active systemic manifestations. Oral corticosteroid doses ≤ 0.2 mg/kg/day or 10 mg prednisone or the equivalent per day, whichever was less (stable for 4 weeks prior to screening), and methotrexate doses < 1 mg/kg/week or a maximum weekly dose of 40 mg (stable for 8 weeks) were allowed. Patients were allowed (but not required) to be taking the following background arthritis medications prior to receiving the first dose of study medication, but the dose had to be stable for disease modifying antirheumatic drugs (DMARD), biologic therapies, or intravenous (IV) immunoglobulins or other immunosuppressives for 12 weeks and for injectable gold salts for 16 weeks.

Study design. This was a 12-week, multicenter, randomized, double-blind, active-controlled, parallel-group noninferiority study, followed by an optional 12-week open-label treatment phase. The study was conducted in 17 centers worldwide. In the double-blind phase, children were randomly assigned to 1 of 3 treatment groups in a 1:1:1 ratio: celecoxib 50 mg/5 ml oral suspension (target dose approximately 3 mg/kg bid); celecoxib 100 mg/5 ml oral suspension (target dose approximately 6 mg/kg bid); or naproxen oral suspension 125 mg/5 ml (target dose approximately 7.5 mg/kg bid). Subjects were assigned to a fixed dose of suspension according to body weight at baseline, and at Week 12 upon entering the open-label phase. The total daily doses for subjects assigned to each treatment are shown in Table 1. The choice of comparator (naproxen) and its dosing (approximately 7.5 mg/kg bid) were based on pediatric rheumatologists' recommendations[7]. The dosing of celecoxib (approximately 3 and 6 mg/kg bid) in JRA subjects was extrapolated from the recommended adult dose of celecoxib for RA. Subjects who completed 12 weeks of double-blind treatment were eligible for open-label treatment — 12 additional weeks of celecoxib at a target dose of 6 mg/kg bid.

Following screening, subjects were examined at a baseline clinic visit (Day 1) and randomized according to the allocation number provided by an interactive voice-response system. Study medication was given following randomization. Subjects had further clinic visits for safety and efficacy determinations at Weeks 2, 4, 8, and 12 or early termination during the double-blind phase, and at Weeks 16 and 24 or early termination during the open-label phase.

Table 1. Dosage of treatment medication based on mass and volume. Target daily dose shown in parentheses based on subject weight.

Weight, kg	Celecoxib, 3 mg/kg bid* Suspension	Celecoxib, 6 mg/kg bid† Suspension	Naproxen, 7.5 mg/kg bid†† Suspension
9–12	25 mg bid (50 mg)	50 mg bid (100 mg)	62.5 mg bid (125 mg)
13–25	50 mg bid (100 mg)	100 mg bid (200 mg)	125 mg bid (250 mg)
26–37	75 mg bid (150 mg)	150 mg bid (300 mg)	187.5 mg bid (375 mg)
38–50	100 mg bid (200 mg)	200 mg bid (400 mg)	250 mg bid (500 mg)
> 50	150 mg bid (300 mg)	300 mg bid (600 mg)	500 mg bid (1000 mg)

* 50 mg/5 ml; † 100 mg/5 ml; †† 125 mg/5 ml.

The study was conducted in accord with the International Conference on Harmonisation Good Clinical Practice guidelines, Institutional Review Board/Independent Ethics Committee (IRB/IEC) informed consent regulations, and the Declaration of Helsinki.

Study endpoints. Efficacy. The primary efficacy endpoint was the percentage of subjects showing an improvement based on the ACR Pediatric-30 definition of improvement at Week 12[8]. According to these criteria, subjects were considered to be responders to treatment if they demonstrated at least a 30% improvement from baseline in a minimum of any 3 of the 6 JRA core set measures, with worsening by more than 30% permitted in only 1 of the measures. Change in the measures was defined in terms of the percentage change from baseline. The JRA core set measures were the following: physician's global assessment of disease activity on a 100-mm VAS (0 = no disease activity; 100 = most severe disease activity); parent's global assessment of overall well-being on a 100-mm VAS (0 = very well; 100 = very poor); daily physical function by Childhood Health Assessment Questionnaire (CHAQ) parent's assessment of physical function (CHAQ Disability Index, 0 = no limitation; 3 = severe limitation); number of joints with active arthritis; number of joints with limited range of motion; and a laboratory marker of inflammation (serum C-reactive protein concentration was used instead of the erythrocyte sedimentation rate cited in the original core set measurements).

Secondary endpoints were change from baseline at each visit for the individual JRA core set measures. Additional assessments reported were parent's assessment of child's arthritis pain on a 100-mm VAS (0 = no pain; 100 = very severe pain) as reported on the CHAQ, assessed at baseline and Weeks 2, 4, 8, and 12 (or at early termination) in the double-blind phase and at Week 24 (or at early termination) in the open-label phase, and health-related quality of life assessed with the Pediatric Quality of Life Inventory (PedsQL™). The PedsQL is a standardized instrument that assesses patients' and parents' perceptions of health-related quality of life in children with chronic health conditions. It was conducted at baseline, at Week 12/early termination in the double-blind phase, and at Week 24/early termination in the open-label phase. The parent/guardian was asked to complete the age-appropriate Parent-Proxy form. Subjects aged 5–18 years were also asked to complete the age-appropriate Child Self-Report form. Post hoc exploratory evaluations included the percentage of subjects who met the ACR Pediatric-50 and -70 criteria. Subjects were considered responders by the ACR Pediatric-50 and -70 definitions of improvement criteria if they demonstrated at least 50% and 70% improvement from baseline, respectively, in a minimum of 3 JRA core set measures, with worsening by more than 30% permitted in only one of the measures.

Safety. Safety was evaluated by reporting the adverse events (AE; graded as mild, moderate, or severe) that occurred during the trial and by monitoring vital signs and routine laboratory test results. Serious AE were those that resulted in death, were life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, or resulted in congenital anomaly/birth defect. Flare of systemic features of JRA was also reported as a serious AE. Subjects who experienced systemic flare had blood tested for fibrinogen, fibrinogen degradation products, and D-dimer. Developmental evaluations were conducted by the investigators at screening and at Weeks 12 and 24. Any adverse change in development or loss of developmental milestones was recorded as an AE. A slit-lamp eye examination to assess for uveitis was performed at screening and at Weeks 12 and 24. Results were recorded as "normal/not clinically relevant" or "abnormal/clinically relevant."

Statistical analyses. Based on the response rates in previous studies, an approximate response rate of 60% according to the ACR Pediatric-30 was assumed for naproxen[4,9-11]. Given this assumption, and with an expected difference of –2% between subjects treated with celecoxib and those receiving naproxen, 75 pediatric subjects per treatment group would give 81% power to conclude noninferiority of celecoxib with respect to naproxen. All statistical analyses were performed using the intent-to-treat cohort, which included all subjects who were randomized to treatment and took at least 1 dose of the study medication. Missing values were imputed using the last observation carried forward method.

The noninferiority of celecoxib to naproxen was evaluated using 95% 2-sided binomial confidence intervals (large-sample normal approximation) for the difference in the percentage of subjects improved, as defined by the ACR Pediatric-30, at Weeks 2, 4, 8, and 12 (final visit), using these comparisons: celecoxib 3 mg/kg bid – naproxen 7.5 mg/kg bid, and celecoxib 6 mg/kg bid – naproxen 7.5 mg/kg bid. Noninferiority of celecoxib was claimed if the lower limit of the 95% 2-sided confidence interval for the difference in the percentage responders (celecoxib – naproxen) was above –25%. This noninferiority bound was determined by consensus in consultation with members of the pediatric rheumatology community, and has precedence in other pediatric NSAID trials[4,9-11]. Pairwise treatment comparisons using the chi-square test were also performed for the 3 treatment groups. Change from baseline at each visit for the individual JRA core set measures and PedsQL were analyzed using analysis of covariance (ANCOVA), with treatment group as a factor and baseline as a covariate. Treatments were compared using the least-squares mean changes from baseline ($\alpha = 0.05$). Methods for post hoc analyses of the ACR Pediatric-30 response by JRA course (pauciarticular or polyarticular), JRA onset (systemic or not systemic), DMARD/biologic use, oral corticosteroid use, and age and weight subgroups as well as the ACR Pediatric-50 and -70 criteria were similar to those already described.

AE were coded using *Medical Dictionary for Regulatory Activities* (MedDRA; version 2.3) and the incidence of AE was compared between treatment groups with the 2-sided Fisher exact test during the double-blind phase of the study ($\alpha = 0.05$ for all safety endpoints). AE recorded more than 28 days after the last dose of study medication were excluded. An ANCOVA using pairwise treatment comparisons with treatment group as a factor and baseline value as a covariate was used to analyze any between-treatment group differences from double-blind baseline to final in laboratory values. The incidence of extreme laboratory values was compared between treatment groups using the Fisher exact test; vital signs were analyzed similarly. Utilizing the criteria outlined in the Fourth Report on the Diagnosis, Evaluation and Treatment of High Blood Pressure in Children and Adolescents, post hoc analyses of blood pressure were performed to categorize the blood pressure values as normal, prehypertension, stage 1 hypertension, or stage 2 hypertension[12]. The proportion of subjects who experienced (1) a shift from normal at baseline to prehypertension, stage 1 or 2 hypertension at 2 consecutive clinic visits; and (2) a shift from prehypertension at baseline to stage 1 or 2 hypertension at 2 consecutive clinic visits was summarized.

RESULTS

Patients. Two hundred forty-two pediatric subjects were randomized to the double-blind phase, and all received at least 1 dose of the study medication (Figure 1). About 10% of the enrolled subjects had systemic onset of the disease. Sixty-seven (87%) subjects who received celecoxib 3 mg/kg bid, 71 (86.6%) subjects who received celecoxib 6 mg/kg bid, and 74 (89.2%) subjects who received naproxen 7.5 mg/kg bid completed the double-blind phase. AE were the main reason for early withdrawal. Of the 212 eligible subjects, 202 entered the open-label extension; all received at least 1 dose of the study medication. The majority (195/202, 96.5%) completed the open-label phase, with AE again the most common reason for early withdrawal.

There were no major differences among treatment groups with respect to demographics (Table 2). The majority of subjects were Caucasian (140/242, 57.8%), female (171/242, 70.7%), and aged between 8 and 16 years (174/242, 71.9%). About 16% were under the age of 5 years. The percentage of children who received a DMARD, biologic, or combination of the 2 at screening was similar across the 3 treatment groups (Table 2). Oral corticosteroids were used in 16.9%, 19.5%, and 26.5% of subjects, respectively, for celecoxib 3 mg/kg bid, celecoxib 6 mg/kg bid, and naproxen 7.5 mg/kg bid.

Efficacy. Primary and secondary endpoints. Celecoxib 3 mg/kg bid and celecoxib 6 mg/kg bid were both at least as effective as naproxen 7.5 mg/kg bid in terms of the primary endpoint at Week 12, with the ACR Pediatric-30 criterion achieved by 68.8% (53/77), 80.5% (66/82), and 67.5% (67/83) of subjects, respectively (Table 3). Both celecoxib treatment groups were also at least as effective as naproxen at all other timepoints (Figure 2). Numeric differences (nonsignificant) favored treatment with celecoxib 6 mg/kg bid over naproxen 7.5 mg/kg bid at Weeks 4, 8, and 12, with identical treatment response at Week 2. No differences were observed in subgroup analyses of JRA course or onset, DMARD/biologic use, oral corticosteroid use, age, or weight. Subjects in all 3 treatment groups demonstrated improvement from baseline in all 6 JRA core set measures and in all additional measures.

Results from the JRA core set measures at Week 12 are shown in Table 3. Treatment with either celecoxib dose resulted in improvements that were either comparable to or numerically higher than those with naproxen. With the exception of the Week 2 results comparing celecoxib 3 mg/kg bid with naproxen 7.5 mg/kg bid in the physician's global assessment of disease activity [least-squares mean changes from baseline –8.70 (SE 1.47) and –13.77 (SE 1.42), respectively; $p = 0.0138$ favoring naproxen], there were no significant differences between either celecoxib dose and naproxen for the core set measures at any timepoint. There were comparable improvements in the parent's assessment of child's arthritis pain (CHAQ subsection) in

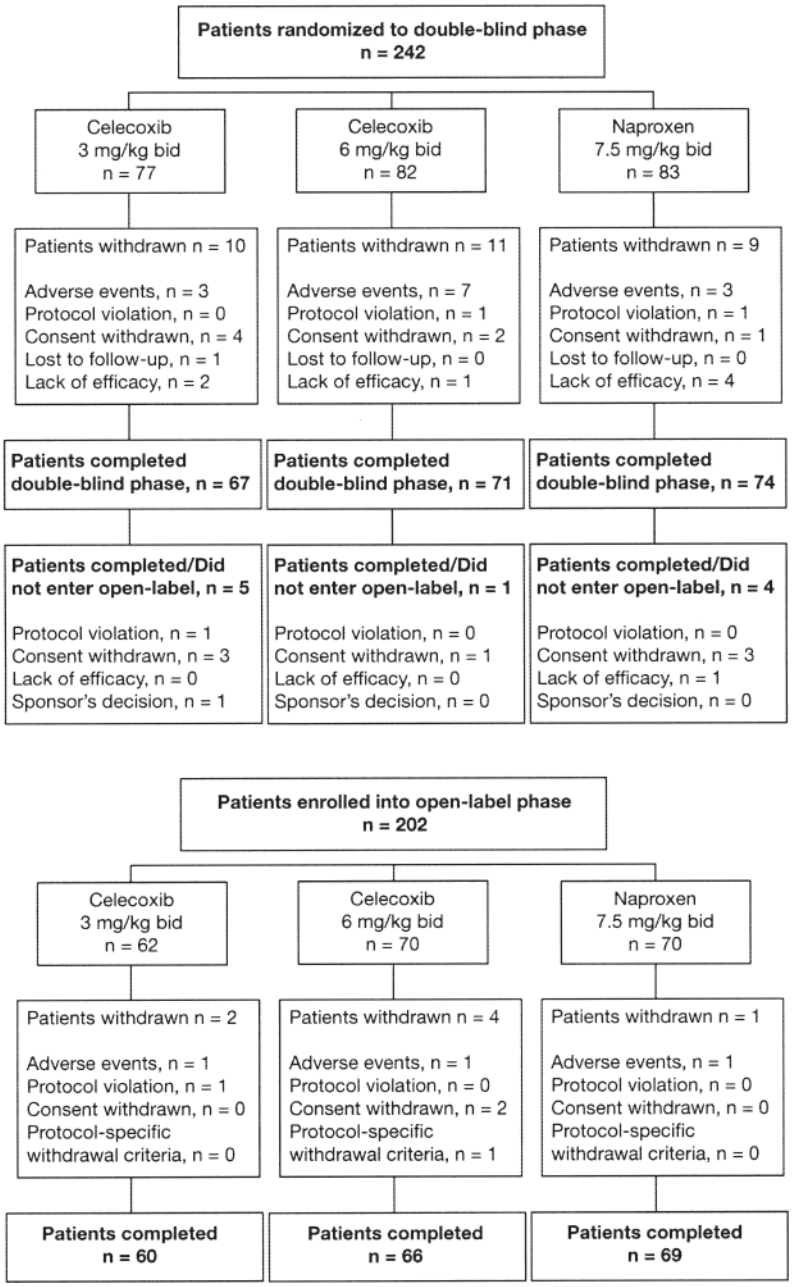

Figure 1. Disposition of the subjects in the double-blind and open-label phases of the study.

each treatment group, with no statistically significant differences among any of the treatment groups. PedsQL scores improved in all treatment groups; improvements in subjects treated with celecoxib 6 mg/kg bid or naproxen 7.5 mg/kg bid were numerically higher than those receiving celecoxib 3 mg/kg bid (p = nonsignificant, data not shown). Persistence of treatment effect with celecoxib 6 mg/kg bid was observed from Weeks 12 to 24 during the open-label phase for all secondary efficacy variables and parent's assessment of child's arthritis pain.

Celecoxib 3 mg/kg bid and celecoxib 6 mg/kg bid were both at least as effective as naproxen 7.5 mg/kg bid in terms of the percentage of subjects who met the ACR Pediatric-50 [55.8% (43/77), 61.0% (50/82), and 55.4% (46/83), respectively] and the ACR Pediatric-70 [24.7% (19/77), 36.6% (30/82), and 32.5% (27/83), respectively] criteria at Week 12. The ACR Pediatric-50 treatment differences for celecoxib 3 mg/kg bid – naproxen and celecoxib 6 mg/kg bid – naproxen were 0.42% (95% CI –14.98 to 15.83) and 5.56% (–9.47 to 20.58), respectively, while those for the ACR Pediatric-70 were –7.85% (–21.79 to 6.08) and 4.06% (–10.45 to 18.56), respectively.

Table 2. Demographics and baseline characteristics of all randomized subjects.

	Celecoxib, 3 mg/kg bid, n = 77	Celecoxib, 6 mg/kg bid, n = 82	Naproxen, 7.5 mg/kg bid, n = 83
Age, yrs, mean (SD)	10.44 (4.09)	10.16 (4.24)	10.39 (3.92)
Distribution by age category, years; n (%)			
2–4	13 (16.9)	16 (19.5)	10 (12.0)
5–7	9 (11.7)	9 (11.0)	11 (13.3)
8–12	31 (40.3)	35 (42.7)	35 (42.2)
13–16	24 (31.2)	22 (26.8)	27 (32.5)
Sex, n (%)			
Female	59 (76.6)	53 (64.6)	59 (71.1)
Male	18 (23.4)	29 (35.4)	24 (28.9)
Race, n (%)			
Caucasian	41 (53.2)	47 (57.3)	52 (62.7)
Black	9 (11.7)	7 (8.5)	4 (4.8)
Asian	1 (1.3)	3 (3.7)	1 (1.2)
Not listed	26 (33.8)	25 (30.5)	26 (31.3)
Height, cm, mean (SD)	136.6 (22.38)	134.6 (24.07)	138.3 (21.76)
Weight, kg, mean (SD)	36.2 (15.35)	36.2 (18.34)	37.3 (15.62)
Duration of JRA, yrs, mean (SD)	2.71 (2.80)	3.77 (3.42)	3.41 (3.23)
Onset with systemic features, n (%)	4 (5.2)	10 (12.2)	8 (9.6)
Course, n (%)			
Pauciarticular	37 (48.1)	45 (54.9)	46 (55.4)
Polyarticular	40 (51.9)	37 (45.1)	37 (44.6)
Received DMARD/biologic/combination therapy, n (%)	39 (50.6)	40 (48.8)	43 (51.8)
Azathioprine	0 (0)	1 (1.2)	0 (0)
Hydroxychloroquine	3 (3.9)	2 (2.4)	5 (6.0)
Methotrexate	30 (39.0)	29 (35.4)	28 (33.7)
Sulfasalazine	1 (1.3)	3 (3.7)	3 (3.6)
Etanercept	0 (0)	1 (1.2)	0 (0)
Azathioprine/infliximab	0 (0)	0 (0)	1 (1.2)
Methotrexate/hydroxychloroquine	3 (3.9)	2 (2.4)	2 (2.4)
Methotrexate/sulfasalazine	0 (0)	0 (0)	1 (1.2)
Methotrexate/etanercept	2 (2.6)	0 (0)	1 (1.2)
Methotrexate/infliximab	0 (0)	2 (2.4)	1 (1.2)
Methotrexate/hydroxychloroquine/sulfasalazine	0 (0)	0 (0)	1 (1.2)

DMARD: disease modifying antirheumatic drugs.

Table 3. Results for the ACR Pediatric-30 responders and the ACR Pediatric-30 core set measures at Week 12.

Characteristic	Celecoxib, 3 mg/kg bid, n = 77	Celecoxib, 6 mg/kg bid, n = 82	Naproxen, 7.5 mg/kg bid, n = 83
ACR Pediatric-30 responders, n (%)	53 (68.8)	66 (80.5)	56 (67.5)
Treatment difference (celecoxib – naproxen), %	1.36	13.02	
95% CI for treatment difference	–13.08 to 15.80	–0.22 to 26.25	NA
p value vs naproxen	0.854	0.057	
ACR Pediatric-30 core set measures: LS mean change from baseline (SE)			
Physician global assessment of disease activity (100 mm VAS)	–21.07 (1.86)	–23.27 (1.80)	–21.88 (1.79)
Parent global assessment of overall well-being (CHAQ subsection, 100 mm VAS)	–17.96 (2.42)	–20.45 (2.34)	–18.25 (2.33)
Parent assessment of physical function (CHAQ disability index, grades 0–3*)	–0.28 (0.05)	–0.32 (0.05)	–0.31 (0.05)
No. of joints with active arthritis	–1.94 (0.49)	–3.54 (0.47)	–2.93 (0.47)
No. of joints with limited range of motion	–1.14 (0.43)	–2.58 (0.42)	–1.56 (0.42)
Laboratory marker of inflammation: CRP, mg/l	–3.64 (2.87)	–2.67 (2.72)	–0.01 (2.74)

* CHAQ disability index: 0 = without any difficulty, 1 = with some difficulty, 2 = with much difficulty, 3 = unable to do. LS: least-squares; VAS: visual analog scale; CHAQ: Childhood Health Assessment Questionnaire; CRP: C-reactive protein; NA: not applicable.

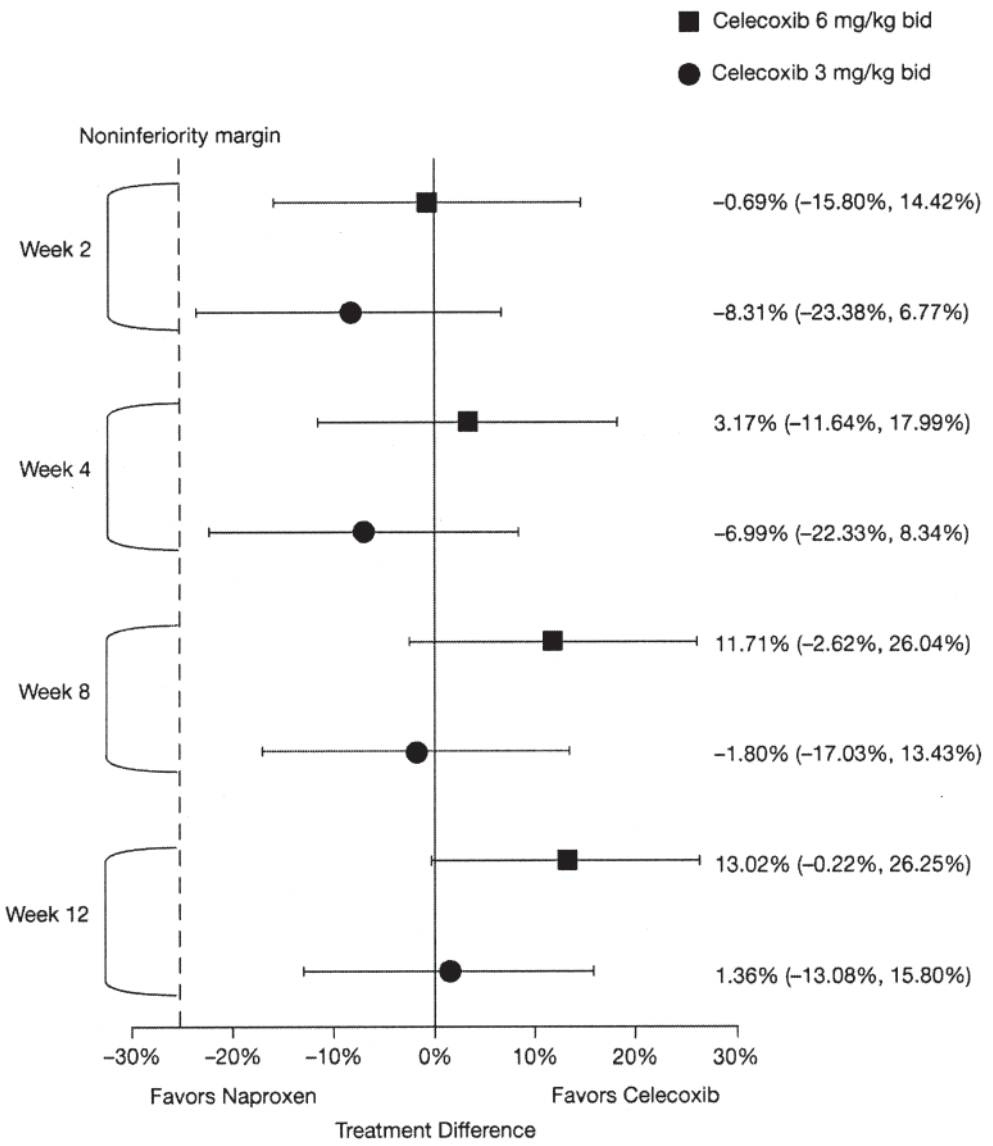

Figure 2. ACR Pediatric-30 definitions of improvement, celecoxib – naproxen (95% CI) at Weeks 2, 4, 8, and 12 in the intent-to-treat population, last observation carried forward.

Safety. In the double-blind phase of the study, treatment-emergent AE were recorded in 63.6% of subjects treated with celecoxib 3 mg/kg bid, 69.5% of the celecoxib 6 mg/kg bid treatment group, and 72.3% of the naproxen 7.5 mg/kg bid treatment group (Table 4). Serious AE were experienced by 3 subjects (3.9%) in the celecoxib 3 mg/kg bid group and 2 subjects (2.4%) in the celecoxib 6 mg/kg bid group during the double-blind phase of the study; no subject in the naproxen group developed a serious AE during the double-blind phase. There were no deaths.

Most AE were mild or moderate in severity. AE occurring in ≥ 5% of subjects in any treatment group are listed in Table 4. The AE with the highest incidence across all treatment groups included headache (31/242, 12.8%), pyrexia (22/242, 9.1%), upper abdominal pain (19/242, 7.9%), cough (18/242, 7.4%), and nausea (17/242, 7.0%). Withdrawal due to an AE occurred in 3.9% (3/77), 8.5% (7/82), and 3.6% (3/83) of the celecoxib 3 mg/kg bid, celecoxib 6 mg/kg bid, and naproxen 7.5 mg/kg bid groups, respectively. AE considered to be related to the study medication were recorded for 14.3% (11/242), 12.2% (10/242), and 12.0% (10/242) of subjects in the celecoxib 3 mg/kg bid group, celecoxib 6 mg/kg bid, and naproxen 7.5 mg/kg bid groups, respectively.

GI disorders were observed more frequently in subjects treated with naproxen (30/83, 36.1%) than in either of the celecoxib groups (24.4%–26.0%). In particular, nausea, vomiting, and diarrhea were observed more frequently in the

Table 4. Incidence of adverse events occurring in ≥ 5% of subjects in any treatment group during the double-blind phase of the study.

System Organ Class, n (%)	Celecoxib, 3 mg/kg bid, n = 77	Celecoxib, 6 mg/kg bid, n = 82	Naproxen, 7.5 mg/kg bid, n = 83
Any event	49 (63.6)	57 (69.5)	60 (72.3)
Eye disorders	4 (5.2)	4 (4.9)	4 (4.8)
Gastrointestinal disorders	20 (26.0)	20 (24.4)	30 (36.1)
Abdominal pain (NOS)	3 (3.9)*	6 (7.3)	6 (7.2)
Upper abdominal pain	6 (7.8)	5 (6.1)	8 (9.6)
Vomiting (NOS)	2 (2.6)	5 (6.1)	9 (10.8)
Diarrhea (NOS)	4 (5.2)	3 (3.7)	7 (8.4)
Nausea	5 (6.5)	3 (3.7)	9 (10.8)
General disorders and administration site conditions	10 (13.0)	9 (11.0)	15 (18.1)
Pyrexia	6 (7.8)	7 (8.5)	9 (10.8)
Infections and infestations	19 (24.7)	16 (19.5)	22 (26.5)
Nasopharyngitis	4 (5.2)	5 (6.1)	4 (4.8)
Injury and poisoning	3 (3.9)	5 (6.1)	4 (4.8)
Investigations	2 (2.6)	9 (11.0)	6 (7.2)
Musculoskeletal, connective tissue, and bone disorders	6 (7.8)	8 (9.8)	14 (16.9)
Arthralgia†	2 (2.6)	6 (7.3)	3 (3.6)
Nervous system disorders	13 (16.9)	9 (11.0)	17 (20.5)
Headache (NOS)	10 (13.0)	8 (9.8)	13 (15.7)
Dizziness (excluding vertigo)	1 (1.3)	1 (1.2)	6 (7.2)
Respiratory, thoracic, and mediastinal disorders	6 (7.8)	12 (14.6)	12 (14.5)
Cough	5 (6.5)	6 (7.3)	7 (8.4)
Skin and subcutaneous tissue disorders	8 (10.4)	6 (7.3)††	15 (18.1)

* Serious adverse event. † Some investigators recorded signs of lack of efficacy as an adverse event. †† $p \leq 0.10$ from pairwise comparison with naproxen using Fisher exact test. NOS: not otherwise specified.

naproxen group. Nausea was severe in 1 subject treated with celecoxib 3 mg/kg bid and in 1 subject treated with naproxen 7.5 mg/kg bid; there were no severe incidents of vomiting or diarrhea. One subject in the celecoxib 3 mg/kg bid group developed abdominal pain that was reported as a serious AE. Other serious AE included acute cytomegalovirus hepatitis and viral infection in the celecoxib 3 mg/kg bid group, and exacerbations of JRA and asthma in the celecoxib 6 mg/kg bid group. The abdominal pain and asthma serious AE were considered related to study treatment.

Developmental delays were not observed in any subject, and there were no statistically significant differences between treatment groups for subjects' height or weight. At Week 12, abnormal slit-lamp eye examinations consistent with uveitis were observed in 1 (1.8%) child in the celecoxib 3 mg/kg bid group, 2 (3.3%) children in the celecoxib 6 mg/kg bid group, and 3 (5.1%) in the naproxen group.

Overall, safety-related analyses of laboratory values and vital signs during the double-blind phase of the study did not indicate any clinically significant differences between the 3 treatment groups. The least-squares mean changes in systolic and diastolic blood pressure were 0.91, 0.76, and 1.60 mm Hg and –0.80, –0.49, and –1.25 mm Hg, respectively, for the celecoxib 3 mg/kg bid treatment group, the celecoxib 6 mg/kg bid treatment group, and the naproxen 7.5 mg/kg bid treatment group. Similarly, no treatment differences were observed in the post hoc analyses of blood pressure.

During the open-label phase of the study, no increase in AE relative to the double-blind phase of the study was observed. Serious AE were experienced by 4 subjects (2.0%). One of the events, epigastric pain and vomiting following an intentional overdose of celecoxib and erythromycin, was considered to be related to the study medication. No new safety findings became apparent in the open-label phase. However, 1 subject, who had also received celecoxib 6 mg/kg bid during the double-blind phase of the study, experienced a flare of systemic features of JRA, developing inflammatory myopericarditis. Clinical data confirmed that the etiology of the chest pain experienced by the subject was not ischemic in origin.

DISCUSSION

This study supports the efficacy and tolerability of celecoxib in children with JRA. Both doses of celecoxib (3 mg/kg bid and 6 mg/kg bid) were at least as effective as naproxen 7.5 mg/kg bid in treating the signs and symptoms of JRA, based on the ACR Pediatric-30, and results were substantiated by those from the secondary endpoints. The additional findings of sustained efficacy during the open-label 12-week extension phase support the efficacy of celecoxib for chronic usage in JRA. The ACR Pediatric-50 and -70 treatment responses in this study was generally comparable to those observed in a study of the efficacy of meloxicam in children with JRA[4].

An important consideration when comparing the noninferiority findings of celecoxib with naproxen relates to the effective dose of study drug administered to each subject. Since subjects were assigned to subgroups of a certain weight range rather than receiving a dosage regimen customized to the individual child's body weight, subjects in each group had the potential to receive more or less than the target daily dose (TDD) per kilogram of body weight. Thus, for a weight at the upper end of any given weight band, subjects in the naproxen group would have received a dose of approximately 10 mg/kg/day, whereas very few subjects would have received 15 mg/kg/day, thereby potentially influencing efficacy in the group as a whole. A similar scenario exists for celecoxib 3- and 6-mg/kg bid target doses, with the actual doses administered ranging from 4 to 7.6 mg/kg/day and from 8 to 15.4 mg/kg/day, respectively. Thus, in each treatment assignment, the only subjects receiving the target dose would be those at the lower end of the 13- to 25-kg weight band, with any subject outside this band receiving a lower than target dose. However, balancing any concern over treatment comparisons, the efficacy of naproxen at a dose of 10 mg/kg/day has been confirmed in previous studies of subjects with JRA[13,14] and has been found to be bioequivalent to a 500-mg bid dose in adults. Since the publication of the results of an observational trial[11], in which naproxen was prescribed at dosages ranging from 9 to 20 mg/kg/day, pediatric rheumatologists have commonly used doses as high as 20 mg/kg/day. However, the efficacy of 20 mg/kg/day of naproxen has not been directly compared with 10 or 15 mg/kg/day in randomized double-blind clinical trials[4,9]. Similarly, because of the distribution of doses around the target dose, differential effects in AE between doses of celecoxib or among naproxen doses could be under- or overestimated in some cases.

The course of treatment was generally well tolerated in all 3 treatment groups, with headache, fever, upper abdominal pain, cough, and nausea being the most common AE. Most AE were mild to moderate and did not result in the withdrawal of large numbers of subjects. None of the treatments resulted in growth delay, and there were no reports of altered neurodevelopmental status. GI disorders were the most frequently reported AE, with the highest incidence in subjects assigned to naproxen. However, there was a serious AE of abdominal pain in the celecoxib 3 mg/kg bid group.

GI AE have been observed in a number of clinical trials in children with JRA using NSAID[4,9-11,15-23]. A number of clinical trials and observational studies have also been conducted to determine the prevalence of GI complications of NSAID therapies over time, in a real-world clinical setting. Estimates of NSAID-associated gastropathy in subjects with JRA range from 0.7% to 75%, depending on differences in study design[24-29]. The most comprehensive of these studies followed 570 children, 303 of whom (53%) had JRA, in a pediatric rheumatology clinic over a mean of 22.1 months[28]. Overall, 49% of children taking NSAID versus 42% of those not taking NSAID developed abdominal pain, which was evaluated radiographically and/or endoscopically. Of these, 34% of subjects with abdominal pain taking NSAID had evidence of gastroduodenal injury, while only 7% of those with abdominal pain without NSAID use had such evidence; however, endoscopy can cause GI injury in healthy children. After controlling for prednisone and DMARD use, this yielded a relative risk of 4.8 for gastroduodenal injury in JRA subjects with abdominal pain in NSAID users versus nonusers.

In 2005, the US FDA required all NSAID, including celecoxib, to carry a boxed warning indicating potential increased cardiovascular risk. This was based on concerns that arose as a result of the withdrawal of rofecoxib from the market, and interim results from the Prevention of Sporadic Colorectal Adenomas with Celecoxib (APC) trial[30] in adults with sporadic adenomatous polyposis, which demonstrated a significant increase in the risk for serious cardiovascular events. Due to these concerns, an external data-safety monitoring board (whose proceedings were blinded to the sponsor) was convened to review all safety data from this trial, which was still under way. Based on the evaluation, no changes were made regarding how the study was conducted.

With regard to cardiovascular risk, although hypertension may be an unusual complication during pediatric NSAID use, it could evolve as children continue NSAID use into adulthood and develop other cardiovascular risk factors such as obesity or smoking. Further, recent evidence suggests an increase in the background prevalence of cardiovascular risk factors such as increased body mass index and increased blood pressure among children and adolescents, which may continue into adulthood[31,32]. This epidemiologic factor may further increase the chances of NSAID treatment causing cardiovascular complications as children progress into adulthood.

Reports of renal-related AE in children with JRA receiving NSAID are relatively rare, as corroborated by large observational cohorts and previous clinical trials. The most common of such events appears to be acute, idiosyncratic renal failure, which generally occurs early in therapy and is reversible[33]. Other reported renal complications include renal papillary necrosis, nephrotic syndrome, and interstitial nephritis.

Although followup studies into potential adverse events are warranted, our study indicates that celecoxib therapy is at least as effective as naproxen, and is well tolerated relative to naproxen, for the treatment of the signs and symptoms of JRA.

ACKNOWLEDGMENT

Editorial support was provided by Katherine Ayling-Rouse of Parexel and was funded by Pfizer Inc. We thank the large group of additional investigators in this trial.

REFERENCES

1. Lahdenne P, Vahasalo P, Honkanen V. Infliximab or etanercept in the treatment of children with refractory juvenile idiopathic arthritis: an open label study. Ann Rheum Dis 2003;62:245-7.
2. Schanberg LE, Anthony KK, Gil KM, Maurin EC. Daily pain and symptoms in children with polyarticular arthritis. Arthritis Rheum 2003;48:1390-7.
3. Cron RQ, Sharma S, Sherry DD. Current treatment by United States and Canadian pediatric rheumatologists. J Rheumatol 1999;26:2036-8.
4. Ruperto N, Nikishina I, Pachanov ED, et al. A randomized, double-blind clinical trial of two doses of meloxicam compared with naproxen in children with juvenile idiopathic arthritis: short- and long-term efficacy and safety results. Arthritis Rheum 2005;52:563-72.
5. Allison MC, Howatson AG, Torrance CJ, Lee FD, Russell RI. Gastrointestinal damage associated with the use of nonsteroidal antiinflammatory drugs. N Engl J Med 1992;327:749-54.
6. Moore RA, Derry S, Makinson GT, McQuay HJ. Tolerability and adverse events in clinical trials of celecoxib in osteoarthritis and rheumatoid arthritis: systematic review and meta-analysis of information from company clinical trial reports. Arthritis Res Ther 2005;7:R644-65.
7. Cassidy JT. Medical management of children with juvenile rheumatoid arthritis. Drugs 1999;58:831-50.
8. Giannini EH, Ruperto N, Ravelli A, Lovell DJ, Felson DT, Martini A. Preliminary definition of improvement in juvenile arthritis. Arthritis Rheum 1997;40:1202-9.
9. Reiff A, Lovell DJ, Adelsberg JV, et al. Evaluation of the comparative efficacy and tolerability of rofecoxib and naproxen in children and adolescents with juvenile rheumatoid arthritis: a 12-week randomized controlled clinical trial with a 52-week open-label extension. J Rheumatol 2006;33:985-95.
10. Gedalia A, Espada G, Johnson P, Kovacs B, Wood C, Padula S. Meloxicam in JRA Study Group. Efficacy and safety of meloxicam oral suspension in the treatment of juvenile rheumatoid arthritis (JRA): results from a twelve-week active-controlled (naproxen oral suspension), multinational trial [abstract]. Arthritis Rheum 2004;50 Suppl:S95.
11. Laxer RM, Silverman ED, St. Cyr C, Tran MT, Lingam G. A six-month open safety assessment of a naproxen suspension formulation in the therapy of juvenile rheumatoid arthritis. Clin Ther 1988;10:381-7.
12. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics 2004;114 Suppl 2:1-22.
13. Kvien TK, Hoyeraal HM, Sandstad B. Naproxen and acetylsalicylic acid in the treatment of pauciarticular and polyarticular juvenile rheumatoid arthritis. Assessment of tolerance and efficacy in a single-centre 24-week double-blind parallel study. Scand J Rheumatol 1984;13:342-50.
14. Leak AM, Richter MR, Clemens LE, Hall MA, Ansell BM. A crossover study of naproxen, diclofenac and tolmetin in seronegative juvenile chronic arthritis. Clin Exp Rheumatol 1988;6:157-60.
15. Giannini EH, Brewer EJ, Miller ML, et al. Ibuprofen suspension in the treatment of juvenile rheumatoid arthritis. Pediatric Rheumatology Collaborative Study Group. J Pediatr 1990;117:645-52.
16. Goodman S, Howard P, Haig A, Flavin S, MacDonald B. An open label study to establish dosing recommendations for nabumetone in juvenile rheumatoid arthritis. J Rheumatol 2003;30:829-31.
17. Levinson JE, Baum J, Brewer E Jr, Fink C, Hanson V, Schaller J. Comparison of tolmetin sodium and aspirin in the treatment of juvenile rheumatoid arthritis. J Pediatr 1977;91:799-804.
18. Moran H, Hanna DB, Ansell BM, Hall M, Engler C. Naproxen in juvenile chronic polyarthritis. Ann Rheum Dis 1979;38:152-4.
19. Bass J, Athreya B, Brandstrup N, et al. Flurbiprofen in the treatment of juvenile rheumatoid arthritis. J Rheumatol 1986;13:1081-3.
20. Bass JC, Athreya BH, Brewer EJ, et al. A once-daily antiinflammatory drug, oxaprozin, in the treatment of juvenile rheumatoid arthritis. The Pediatric Rheumatology Collaborative Study Group. J Rheumatol 1985;12:384-6.
21. Bhettay E, Thomson AJ. Double-blind study of ketoprofen and indomethacin in juvenile chronic arthritis. S Afr Med J 1978;54:276-8.
22. Haapasaari J, Wuolijoki E, Ylijoki H. Treatment of juvenile rheumatoid arthritis with diclofenac sodium. Scand J Rheumatol 1983;12:325-30.
23. Williams PL, Ansell BM, Bell A, et al. Multicentre study of piroxicam versus naproxen in juvenile chronic arthritis, with special reference to problem areas in clinical trials of nonsteroidal anti-inflammatory drugs in childhood. Br J Rheumatol 1986;25:67-71.
24. DeWitt EM, Sherry DD, Cron RQ. Pediatric rheumatology for the adult rheumatologist. I: Therapy and dosing for pediatric rheumatic disorders. J Clin Rheumatol 2005;11:21-33.
25. Keenan GF, Giannini EH, Athreya BH. Clinically significant gastropathy associated with nonsteroidal antiinflammatory drug use in children with juvenile rheumatoid arthritis. J Rheumatol 1995;22:1149-51.
26. Mulberg AE, Linz C, Bern E, Tucker L, Verhave M, Grand RJ. Identification of nonsteroidal antiinflammatory drug-induced gastroduodenal injury in children with juvenile rheumatoid arthritis. J Pediatr 1993;122:647-9.
27. Hermaszewski R, Hayllar J, Woo P. Gastro-duodenal damage due to non-steroidal anti-inflammatory drugs in children. Br J Rheumatol 1993;32:69-72.
28. Dowd JE, Cimaz R, Fink CW. Nonsteroidal antiinflammatory drug-induced gastroduodenal injury in children. Arthritis Rheum 1995;38:1225-31.
29. Menniti-Ippolito F, Traversa G, Da Cas R. Gastroduodenal adverse reactions to drugs in children in Italy [abstract]. Pharmacoepidemiol Drug Saf 2004;13:S141.
30. Bertagnolli MM, Eagle CJ, Zauber AG, et al. Celecoxib for the prevention of sporadic colorectal adenomas. N Engl J Med 2006;355:873-84.
31. Muntner P, He J, Cutler JA, Wildman RP, Whelton PK. Trends in blood pressure among children and adolescents. JAMA 2004;291:2107-13.
32. Juonala M, Jarvisalo MJ, Maki-Torkko N, Kahonen M, Viikari JS, Raitakari OT. Risk factors identified in childhood and decreased carotid artery elasticity in adulthood: the Cardiovascular Risk in Young Finns Study. Circulation 2005;112:1486-93.
33. Cassidy JT, Petty RE. Textbook of pediatric rheumatology. 5th ed. Philadelphia: W.B. Saunders; 2005.