

ORIGINAL ARTICLE

Adalimumab with or without Methotrexate in Juvenile Rheumatoid Arthritis

Daniel J. Lovell, M.D., M.P.H., Nicolino Ruperto, M.D., M.P.H., Steven Goodman, M.D., Andreas Reiff, M.D., Lawrence Jung, M.D., Katerina Jarosova, M.U.Dr., Dana Nemcova, M.D., Richard Mouy, M.D., Christy Sandborg, M.D., John Bohnsack, M.D., Dirk Elewaut, M.D., Ph.D., Ivan Foeldvari, M.D., Valeria Gerloni, M.D., Jozef Rovensky, M.D., Ph.D., Kirsten Minden, M.D., Richard K. Vehe, M.D., L. Wagner Weiner, M.D., Gerd Horneff, M.D., Hans-Iko Huppertz, M.D., Nancy Y. Olson, M.D., John R. Medich, Ph.D., Roberto Carcereri-De-Prati, M.D., Melissa J. McIlraith, Ph.D., Edward H. Giannini, M.Sc., Dr.P.H., and Alberto Martini, M.D., for the Pediatric Rheumatology Collaborative Study Group and the Pediatric Rheumatology International Trials Organisation

ABSTRACT

BACKGROUND

Tumor necrosis factor (TNF) has a pathogenic role in juvenile rheumatoid arthritis. We evaluated the efficacy and safety of adalimumab, a fully human monoclonal anti-TNF antibody, in children with polyarticular-course juvenile rheumatoid arthritis.

METHODS

Patients 4 to 17 years of age with active juvenile rheumatoid arthritis who had previously received treatment with nonsteroidal antiinflammatory drugs underwent stratification according to methotrexate use and received 24 mg of adalimumab per square meter of body-surface area (maximum dose, 40 mg) subcutaneously every other week for 16 weeks. We randomly assigned patients with an American College of Rheumatology Pediatric 30% (ACR Pedi 30) response at week 16 to receive adalimumab or placebo in a double-blind fashion every other week for up to 32 weeks.

RESULTS

Seventy-four percent of patients not receiving methotrexate (64 of 86) and 94% of those receiving methotrexate (80 of 85) had an ACR Pedi 30 response at week 16 and were eligible for double-blind treatment. Among patients not receiving methotrexate, disease flares (the primary outcome) occurred in 43% of those receiving adalimumab and 71% of those receiving placebo ($P=0.03$). Among patients receiving methotrexate, flares occurred in 37% of those receiving adalimumab and 65% of those receiving placebo ($P=0.02$). At 48 weeks, the percentages of patients treated with methotrexate who had ACR Pedi 30, 50, 70, or 90 responses were significantly greater for those receiving adalimumab than for those receiving placebo; the differences between patients not treated with methotrexate who received adalimumab and those who received placebo were not significant. Response rates were sustained after 104 weeks of treatment. Serious adverse events possibly related to adalimumab occurred in 14 patients.

CONCLUSIONS

Adalimumab therapy seems to be an efficacious option for the treatment of children with juvenile rheumatoid arthritis. (ClinicalTrials.gov number, NCT00048542.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Lovell at Cincinnati Children's Hospital Medical Center, Division of Rheumatology, Location E, Rm. 2-129, MLC 4010, 3333 Burnet Ave., Cincinnati, OH 45229-3039, or at daniel.lovell@cchmc.org.

Drs. Lovell and Ruperto contributed equally to this article.

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JUVENILE RHEUMATOID ARTHRITIS IS THE most common rheumatic disease of childhood and is an important cause of disability among children.¹ Weekly methotrexate (oral or parenteral), at dosages of up to 15 mg per square meter of body-surface area per week for parenteral administration, has been established as an effective therapy in polyarticular juvenile rheumatoid arthritis.^{2,3} During the past decade, the use of tumor necrosis factor (TNF) antagonists in adult rheumatoid arthritis has shifted the paradigm of care.⁴⁻⁶ More recently, TNF blockade has been shown to be an efficacious treatment option for polyarticular juvenile rheumatoid arthritis.⁷ Adalimumab (Humira, Abbott Laboratories) is a fully human, IgG₁, monoclonal anti-TNF antibody. In patients with adult rheumatoid arthritis, adalimumab, with or without concomitant methotrexate, reduces the signs and symptoms of disease, improves the quality of life and physical functioning, and inhibits radiographic progression.^{5,8-10} Sustained efficacy has been demonstrated during long-term administration.¹¹ We conducted this study to evaluate the efficacy and safety of adalimumab in children with polyarticular-course juvenile rheumatoid arthritis.

METHODS

PATIENTS

Patients 4 to 17 years of age with polyarticular-course juvenile rheumatoid arthritis (with any type of onset) who had active disease (at least five swollen joints and at least three joints with limitation of motion) that had not responded adequately to treatment with nonsteroidal antiinflammatory drugs (NSAIDs) were eligible for enrollment. The patients either had not previously been treated with methotrexate or had been previously treated with methotrexate and had had adverse events or an inadequate response. Patients were excluded from participation if they had clinically significant deviations in hematologic, hepatic, or renal indicators; if they had an ongoing infection or had recently had a major infection requiring hospitalization or intravenous antibiotics; if they had recently received live or attenuated vaccines; or if they had been previously treated with other biologic agents at any time or recently treated with intravenous immune globulin, cytotoxic agents, investigational agents, disease-modifying antirheumatic drugs other than methotrexate, or corticosteroids administered by the intraarticular, intramuscular,

or intravenous route. All sexually active study participants were required to use contraception, and serum pregnancy tests were performed before dosing and during the trial in all girls of reproductive potential.

STUDY DESIGN

This was a randomized, double-blind, stratified, placebo-controlled, multicenter, medication-withdrawal study with a 16-week open-label lead-in phase, a 32-week double-blind withdrawal phase, and an open-label extension phase. Study visits occurred at screening, at baseline (day 1), between days 2 and 10, at weeks 2 and 4, and every 4 weeks through week 48 or withdrawal from the study. For those who withdrew from the study, another visit occurred 30 days after the last dose of study medication. In the open-label extension phase, visits occurred every 8 weeks through the first year and then every 16 weeks throughout the remainder of the patient's participation in the open-label phase. The dosage was based on body-surface area during the first part of the extension phase; in the later part, patients received a fixed dose based on body weight (20 mg for patients weighing <30 kg, and 40 mg for patients weighing ≥30 kg).

Patients who entered the fixed-dose phase at an increased dosage were also seen 12 weeks after the beginning of that phase. Drs. Lovell, Ruperto, Carcereri-De-Prati, Giannini, and Martini were directly involved in the design of the study. Drs. Lovell, Ruperto, Medich, Carcereri-De-Prati, McIlraith, Giannini, and Martini analyzed the data. The academic authors vouch for the completeness and accuracy of the data and data analyses.

At the beginning of the open-label lead-in phase, the patients underwent stratification into two groups according to methotrexate use. Patients in the stratum not receiving methotrexate either had never received methotrexate or had discontinued methotrexate at least 2 weeks before administration of the study drug. Patients in the methotrexate stratum had received methotrexate at a stable dosage of at least 10 mg per square meter per week for the 3-month period before screening and continued to receive methotrexate at the same dosage during the open-label lead-in and double-blind phases. During the open-label lead-in phase, all patients received 24 mg of adalimumab per square meter (to a maximum of 40 mg) subcutaneously every other week for 16 weeks. The adalimumab dosage was selected with the use of

pharmacokinetic data that determined the effective dosage of adalimumab in adults with rheumatoid arthritis.

Stable dosages of NSAIDs and low-dose corticosteroids (≤ 0.2 mg of prednisone or prednisone equivalent per kilogram of body weight per day to a maximum of 10 mg per day) were permitted. Pain medications were also allowed except for the 12 hours preceding an assessment of the joints.

At week 16, patients with an American College of Rheumatology Pediatric 30% (ACR Pedi 30) response underwent randomization at a 1:1 ratio within their respective strata to receive subcutaneous injections of either adalimumab or placebo every other week in a 32-week, double-blind treatment phase. A separate randomization schedule for each stratum was generated by the study sponsor before the start of the study. The investigators, study coordinators, assessors, patients, and parents were unaware of the treatment assignment during the double-blind phase of the study.

During the double-blind phase, patients were monitored for disease flares. Patients who enrolled in the double-blind phase were eligible to receive open-label treatment with adalimumab in an extension phase of the study.

The study protocol was approved by an independent ethics committee or institutional review board at each study site. Each parent or guardian provided written informed consent, and an independent data and safety monitoring board reviewed adverse events that occurred during the study. The study complied with the Consolidated Standards of Reporting Trials statement.¹²

ASSESSMENT, OUTCOME, AND SAFETY MEASURES

ACR Pedi responses were assessed throughout the study. An ACR Pedi 30 response is defined as an improvement of 30% or more in at least three of the six core criteria for juvenile rheumatoid arthritis and a worsening of 30% or more in no more than one of the criteria. The criteria are the physician's global assessment of disease activity and the patient's or the parent's global assessment of overall well-being (both measured with the use of a 100-mm visual-analogue scale, in which 0 represented no disease activity or an assessment of "very well" for overall well-being, and 100 represented the most disease activity or an assessment of "very poor" for overall well-being), the number of joints with active arthritis (defined as joints with swelling not caused by deformity or joints, in

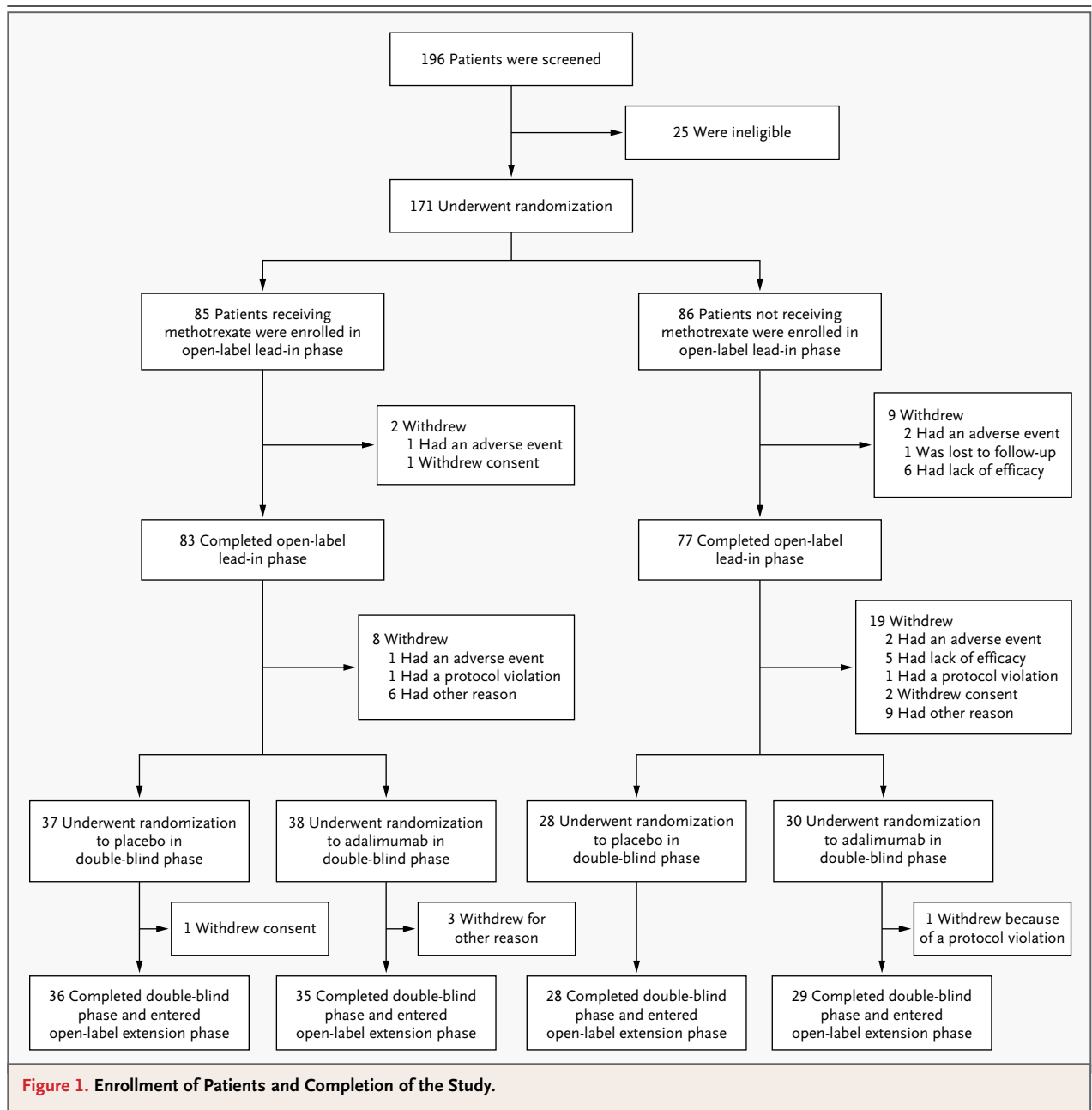
the absence of swelling, with limitation of passive motion accompanied by pain, tenderness, or both), the number of joints with limitation of passive motion, physical function (measured by the Disability Index of the Childhood Health Assessment Questionnaire), and a laboratory assessment of inflammation (C-reactive protein concentrations were used in this study).¹³ ACR Pedi 50, 70, 90, and 100 levels of response also were evaluated and were defined as improvements of 50% or more, 70% or more, 90% or more, and 100%, respectively, in at least three of the six core criteria for juvenile rheumatoid arthritis, with worsening of 30% or more in no more than one criterion.

The primary efficacy end point was the percentage of patients not receiving methotrexate who had a disease flare during the double-blind phase of the study (weeks 16 to 48). A disease flare was defined as a worsening of 30% or more in at least three of the six core criteria for juvenile rheumatoid arthritis and an improvement of 30% or more in no more than one of the criteria. If the number of joints with active arthritis was used as a criterion of flare and the patient initially had no active joints or only one active joint, an increase in the number of active joints to at least two was required. The same approach was used if the number of joints with loss of motion was used as a criterion of flare. If either of the global assessments was used as a criterion of flare, any increase of more than 30% in the visual-analogue scale of 0 to 100 was sufficient, and no minimum clinically important increase was required (e.g., an increase from 2 to 4 would qualify for use of that criterion in the determination of flare).

The safety of adalimumab was evaluated throughout the study on the basis of physical examinations, laboratory results, vital signs, and adverse events. All patients who discontinued study medication were followed for adverse events for 70 days after their last dose.

STATISTICAL ANALYSIS

On the assumption of a 70% rate of response to adalimumab, 42 patients would need to enroll in the open-label lead-in phase to yield the 29 patients needed in each treatment group in the double-blind phase. This estimate was based on a 40% difference in the rate of flare between the placebo and the adalimumab groups and provided a power of 80% at an alpha level of 0.05. Demographic and baseline characteristics were summa-



alized by descriptive statistics. Efficacy analyses were performed on the intention-to-treat population, which was defined as all patients who received at least one dose of the study drug during the phase of the study for which the analysis was being conducted. The following types of imputation were performed. For the primary efficacy end point and for all secondary analyses of disease flare, missing values were treated as disease flares. For secondary analyses of ACR Pedi 30, 50, 70, and

90 responses during the open-label lead-in and double-blind phases, missing values were imputed as nonresponses. In addition, patients in whom a flare occurred according to the protocol definition during the double-blind phase were classified as having no response (ACR Pedi <30) at week 48, regardless of their actual ACR Pedi responses. ACR Pedi response rates during the open-label extension phase were calculated by using the last observation carried forward for missing values. Con-

Table 1. Baseline Demographic and Clinical Characteristics of the Patients.*

| Characteristic | Open-Label Lead-in Phase | | Double-Blind Phase | | | |
|--|--------------------------|----------------------|--------------------|----------------------|-------------------|----------------------|
| | Methotrexate | No Methotrexate | Methotrexate | | No Methotrexate | |
| | adalimumab (N=85) | adalimumab (N=86) | placebo (N=37) | adalimumab (N=38) | placebo (N=28) | adalimumab (N=30) |
| Age — yr | 11.4±3.3 | 11.1±3.8 | 10.8±3.4 | 11.7±3.3 | 11.3±3.8 | 11.1±4.1 |
| Age group — no. (%) | | | | | | |
| 4–8 yr | 19 (22) | 21 (24) | 12 (32) | 6 (16) | 8 (29) | 8 (27) |
| 9–12 yr | 30 (35) | 32 (37) | 10 (27) | 17 (45) | 7 (25) | 10 (33) |
| 13–17 yr | 36 (42) | 33 (38) | 15 (41) | 15 (40) | 13 (46) | 12 (40) |
| Female sex — no. (%) | 68 (80) | 67 (78) | 30 (81) | 30 (79) | 20 (71) | 23 (77) |
| Race — no. (%)† | | | | | | |
| White | 81 (95) | 76 (88) | 36 (97) | 36 (95) | 27 (96) | 26 (87) |
| Black | 0 | 3 (3) | 0 | 0 | 1 (4) | 1 (3) |
| Other | 4 (5) | 7 (8) | 1 (3) | 2 (5) | 0 | 3 (10) |
| Body weight — kg | 43.8±18.3 | 40.9±19.3 | 44.3±18.9 | 42.1±17.9 | 45.4±24.4 | 41.3±17.3 |
| Negative for rheumatoid factor — no./total no. (%) | 64/83 (77) | 67/85 (79) | 30/36 (83) | 27/37 (73) | 21/27 (78) | 24/30 (80) |
| Duration of juvenile rheumatoid arthritis — yr | 4.0±3.7 | 3.6±4.0 | 4.0±3.5 | 4.3±4.1 | 2.9±3.3 | 3.6±4.0 |
| Previous medication use — no. (%) | | | | | | |
| Methotrexate | 85 (100) | 18 (21) | 37 (100) | 38 (100) | 4 (14) | 8 (27) |
| Other disease-modifying antirheumatic drugs | 8 (9) | 8 (9) | 7 (19) | 1 (3) | 3 (11) | 4 (13) |
| Methylprednisolone | 4 (5) | 2 (2) | 2 (5) | 2 (5) | 1 (4) | 0 |

* Plus-minus values are means ±SD.

† Race was determined by the patient or the parent.

tinuous variables were compared by means of analysis of covariance. Categorical data, including those used for the primary end-point analysis, were analyzed with either the Pearson chi-square test or Fisher's exact test, as appropriate. All comparisons were two-sided at an alpha level of 0.05. The safety analyses included all patients who received the study drug during the designated study phase. We report prespecified analyses for the blinded phase and report other analyses, such as that for ACR Pedi 100, for the extension phase.

RESULTS

BASILINE CHARACTERISTICS OF THE PATIENTS

The open-label lead-in and double-blind phases of the study occurred from September 19, 2002, to January 13, 2005; the open-label extension phase was ongoing at the time of publication of this article. A total of 171 patients from 31 study sites participated in the open-label lead-in phase, and 160 completed this phase (Fig. 1). Of these 160 patients, 133 entered the double-blind phase. The rea-

sons for discontinuation of the study are listed in Figure 1. Demographic characteristics and disease activity at baseline are described in Tables 1 and 2. Among patients entering the double-blind phase, there were no significant differences in baseline characteristics between the placebo and the adalimumab groups within either stratum (methotrexate or no methotrexate). Disease duration was shorter and disease activity, as measured by the numbers of affected joints, was greater among patients not receiving methotrexate (statistical comparison not performed). All patients enrolled in the study had chronic, very active, widespread joint inflammation at baseline.

OPEN-LABEL LEAD-IN PHASE

The patients improved according to all levels of ACR Pedi response during the open-label lead-in phase (Fig. 2A). Twenty-two of 86 patients not receiving methotrexate (26%) and 24 of 85 receiving methotrexate (28%) had an ACR Pedi 90 response. The percentage improvements from baseline to week 16 in the core criteria for juvenile rheuma-

Table 2. Changes from Baseline in Disease-Activity Variables during the Open-Label Lead-in Phase of Adalimumab Treatment.*

| Variable | No. of Joints Evaluated | Methotrexate (N=85) | | | No Methotrexate (N=86) | | |
|--|-------------------------|---------------------|-------|---------------|------------------------|-------|---------------|
| | | Baseline | Wk 16 | Mean % Change | Baseline | Wk 16 | Mean % Change |
| Physician's global assessment of disease activity† | | 58.0 | 17.0 | −71 | 59.7 | 19.4 | −64 |
| Parent's or patient's global assessment of disease activity† | | 43.2 | 15.9 | −59 | 53.4 | 20.6 | −49 |
| No. of joints with limitation of passive motion | 69 | 12.7 | 4.5 | −65 | 14.3 | 7.1 | −44 |
| No. of joints with active arthritis | 75 | 15.0 | 4.3 | −71 | 19.4 | 7.3 | −56 |
| Disability Index score in Childhood Health Assessment Questionnaire‡ | | 0.9 | 0.4 | −64 | 1.2 | 0.5 | −34 |
| Serum C-reactive protein (mg/dl)§ | | 0.7 | 0.1 | −72 | 0.8 | 0.1 | −69 |
| No. of swollen joints | 66 | 13.2 | 3.6 | −75 | 16.3 | 6.0 | −61 |
| No. of tender joints | 75 | 9.5 | 2.7 | −51 | 13.3 | 3.1 | −42 |
| No. of joints with pain on passive motion | 75 | 8.0 | 1.6 | −66 | 12.6 | 3.8 | −31 |
| Parent's or patient's assessment of pain¶ | | 43.3 | 13.9 | −60 | 55.7 | 21.3 | −48 |

* All values are means except those for C-reactive protein, which are medians.

† A 100-mm visual-analogue scale was used in which higher scores indicated more active disease.

‡ Scores range from 0 (best) to 3 (worst).

§ The normal median value for C-reactive protein is less than 0.287 mg per deciliter.

¶ A 100-mm visual-analogue scale was used in which higher scores indicated more severe pain.

toid arthritis and other efficacy variables are shown in Table 2.

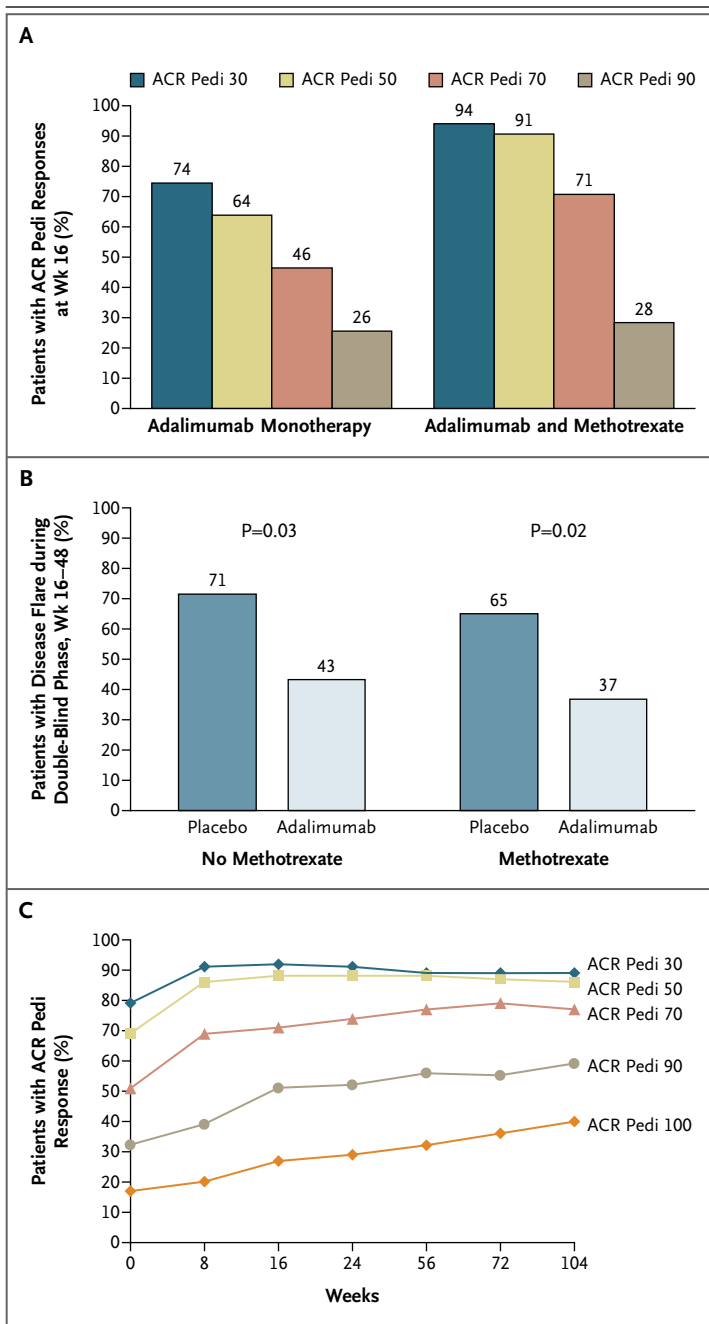
DOUBLE-BLIND PHASE AND OPEN-LABEL EXTENSION PHASE

Sixty-four of 86 patients not receiving methotrexate (74%) and 80 of 85 receiving methotrexate (94%) had an ACR Pedi 30 response at week 16 and were eligible for enrollment in the double-blind phase (Fig. 2A). Six patients in the no-methotrexate stratum and five in the methotrexate stratum met the response criteria for eligibility but did not enroll in the double-blind treatment phase.

Among patients not receiving methotrexate, disease flares — the primary end point — occurred in a significantly lower percentage of those receiving adalimumab than of those receiving placebo (13 of 30 [43%] vs. 20 of 28 [71%], $P=0.03$) (Fig. 2B). Of the patients receiving methotrexate, 14 of 38 who received adalimumab (37%) and 24 of 37 who received placebo (65%) had a disease flare during the double-blind phase ($P=0.02$). At the end of the 48-week study, more patients treated with adalimumab than patients treated with placebo had ACR Pedi 30, 50, 70, or 90 responses in both the methotrexate stratum and the stratum

not receiving methotrexate (Table 3). In the methotrexate stratum, significantly more patients treated with adalimumab than those receiving placebo had ACR Pedi 30, 50, or 70 responses at 48 weeks; the differences between patients treated with adalimumab and those receiving placebo in the stratum not receiving methotrexate were not significant. Although patients met the protocol-defined flare criteria in the double-blind phase of the trial, many continued to show marked improvement as compared with their status at baseline. At the study visit in which a disease flare was judged to have occurred, 73% of patients had an ACR Pedi 30, 61% had an ACR Pedi 50, and 24% had an ACR Pedi 70 response. During the open-label extension phase, ACR Pedi responses were sustained during 2 years of treatment (Fig. 2C). After 104 weeks of treatment, 40% of patients had an ACR Pedi 100 response.

During an exploratory analysis of the primary end point, a logistic-regression analysis was performed to evaluate whether concomitant use of corticosteroids or NSAIDs at study entry influenced the incidence of disease flares among adalimumab-treated patients, and no such effect was found. Because of the small numbers of patients

**Figure 2. Response to Treatment.**

Panel A shows American College of Rheumatology Pediatric (ACR Pedi) response levels among patients receiving open-label adalimumab at week 16 according to whether they were or were not receiving methotrexate. ACR Pedi 30, 50, 70, and 90 responses are defined as improvements of at least 30%, 50%, 70%, and 90%, respectively, in at least three of the six core criteria for juvenile rheumatoid arthritis, with worsening of 30% or more in no more than one criterion. Panel B shows the percentages of patients in the placebo and adalimumab groups with disease flare during the double-blind phase of the study (weeks 16 through 48). Panel C shows ACR Pedi 30, 50, 70, 90, and 100 responses during the first 104 weeks of the open-label extension phase regardless of whether adalimumab was dosed according to body-surface area or body weight. The data are from the intention-to-treat population of 128 patients who entered the open-label extension phase of the study; for missing values, the last observation was carried forward.

Serious adverse events considered possibly related to study drug by the investigator occurred in 14 patients: 6 during the open-label lead-in phase, 1 during the double-blind phase, and 7 during the open-label extension phase. Of these, seven were serious infections (one case each of bronchopneumonia, herpes simplex virus infection, pharyngitis, pneumonia, and unspecified viral infection and two cases of herpes zoster). Nine patients during the open-label lead-in phase, no patients during the double-blind phase, and three patients during the open-label extension phase discontinued treatment because of adverse events. No deaths, malignant conditions, opportunistic infections, cases of tuberculosis, demyelinating diseases, or lupuslike reactions were reported during this study.

IMMUNOGENICITY

Twenty-seven of 171 patients (16%) had at least one positive test for anti-adalimumab antibody during the open-label and double-blind phases: 5 of 85 (6%) receiving methotrexate and 22 of 86 (26%) not receiving methotrexate. Development of anti-adalimumab antibody did not lead to a greater rate of discontinuation of the study drug, nor did it increase the incidence of serious adverse events.

DISCUSSION

Adalimumab, administered with or without methotrexate, improved signs and symptoms of disease in children with juvenile rheumatoid arthritis. Dis-

receiving corticosteroids during the trial (Table 1), analysis of ACR Pedi responses according to corticosteroid use during the trial was not feasible.

SAFETY

The most frequently reported adverse events, after adjustment according to extent of exposure, were infections and injection-site reactions (Table 4). These events were considered mild to moderate.

Table 3. ACR Pedi 30, 50, 70, and 90 Responses of Patients Receiving Placebo or Adalimumab with or without Methotrexate at Week 48.*

| ACR Pedi Response | No Methotrexate | | | Methotrexate | | |
|-------------------|-------------------|----------------------|---------|-------------------|----------------------|---------|
| | Placebo (N=28) | Adalimumab (N=30) | P Value | Placebo (N=37) | Adalimumab (N=38) | P Value |
| | percent | percent | | percent | percent | |
| 30 | 32 | 57 | 0.06 | 38 | 63 | 0.03 |
| 50 | 32 | 53 | 0.10 | 38 | 63 | 0.03 |
| 70 | 29 | 47 | 0.16 | 27 | 63 | 0.002 |
| 90 | 18 | 30 | 0.28 | 27 | 42 | 0.17 |

* A patient who had a flare according to the protocol definition was classified as having no response from that point forward, regardless of the patient's American College of Rheumatology Pediatric (ACR Pedi) response at that time. ACR Pedi 30, 50, 70, and 90 responses are defined as improvements of at least 30%, 50%, 70%, and 90%, respectively, in at least three of the six core criteria for juvenile rheumatoid arthritis, with worsening of 30% or more in no more than one criterion.

ease flares were significantly less frequent among children receiving adalimumab than among those receiving placebo. Disease flare was defined conservatively in this study, with a relatively small degree of worsening exceeding the threshold for a flare. Therefore, many patients met the criteria for a disease flare while showing substantial improvement as compared with baseline disease activity. The ACR Pedi scores at week 48, which defined all patients who had disease flares as having no response, were significantly greater for patients treated with adalimumab than for those receiving placebo, both among patients receiving methotrexate and among all patients regardless of whether they received methotrexate, but not among patients not receiving methotrexate. Of patients treated with adalimumab, 30% not receiving methotrexate and 42% receiving methotrexate had an ACR Pedi 90 response, a measure that we believe has not previously been included in an efficacy trial of juvenile rheumatoid arthritis (Table 3). During 2 further years of adalimumab treatment in the open-label extension phase, ACR Pedi responses were sustained, including achievement of ACR Pedi 100 responses by 40% of the patients.

The study was not statistically powered to detect differences between patients receiving and those not receiving methotrexate; however, the proportions of patients with ACR Pedi 30, 50, 70, or 90 responses were somewhat higher among those receiving adalimumab in combination with methotrexate than among those receiving adalimumab without methotrexate. Although these results are consistent with findings of studies in adult patients with rheumatoid arthritis,^{8,14} any

differences between patients in the two strata (those receiving and those not receiving methotrexate) are difficult to interpret, because the patients underwent randomization within each stratum but not across strata. Eleven of 86 patients not receiving methotrexate withdrew from the study before undergoing randomization, because of lack of efficacy of adalimumab.

A small percentage of patients withdrew because of adverse events. The most frequently reported adverse events were infections and injection-site reactions. Serious adverse events considered possibly drug-related by the investigator occurred in 14 patients, 7 of whom had serious infections. No deaths, opportunistic infections, malignant conditions, demyelinating diseases, or lupuslike reactions occurred in this study. The size of the study population and the length of the study were not sufficient to determine the risks of rare adverse events.

Approximately 16% of the patients had at least one positive test for anti-adalimumab antibody during the study. This percentage is greater than the 5% observed during clinical trials of adult patients with rheumatoid arthritis.¹⁴ There were no increases in discontinuations of the study drug or adverse events associated with the presence of anti-adalimumab antibody. Positive anti-adalimumab antibody tests were less frequent among patients receiving concomitant methotrexate than among those receiving adalimumab monotherapy, a finding consistent with the findings of trials in adult patients with rheumatoid arthritis.

Conducting placebo-controlled trials in pediatric populations requires special consideration of

Table 4. Summary of Adverse Events per Patient-Year of Exposure.

| Variable | Methotrexate | | | | No Methotrexate | | | |
|---|---|--|---|--|--|---|--|--|
| | Open-Label Lead-in Phase | Double-Blind Phase | Open-Label Extension Phase | Open-Label Lead-in Phase | Double-Blind Phase | Open-Label Extension Phase | Open-Label Extension Phase | |
| | adalimumab (N = 85; 27.3 patient-years) | placebo (N = 37; 15.0 patient-years) | adalimumab (N = 38; 18.3 patient-years) | adalimumab (N = 71; 127.4 patient-years) | placebo (N = 28; 10.6 patient-years) | adalimumab (N = 30; 14.4 patient-years) | adalimumab (N = 57; 102.6 patient-years) | |
| Any adverse event | 422 (15.5) | 155 (10.3) | 234 (12.8) | 694 (5.4) | 153 (14.4) | 171 (11.9) | 581 (5.7) | |
| Most frequently reported adverse events | | | | | | | | |
| Related to injection-site reaction | 142 (5.2) | 57 (3.8) | 73 (4.0) | 224 (1.8) | 20 (1.9) | 71 (4.9) | 149 (1.4) | |
| Contusion | 14 (0.5) | 7 (0.5) | 12 (0.7) | 4 (<0.1) | 5 (0.5) | 2 (0.1) | 7 (0.1) | |
| Nasopharyngitis | 6 (0.2) | 6 (0.4) | 5 (0.3) | 9 (0.1) | 5 (0.5) | 0 | 7 (0.1) | |
| Upper respiratory tract infection | 9 (0.3) | 5 (0.3) | 6 (0.3) | 32 (0.2) | 6 (0.6) | 6 (0.4) | 42 (0.4) | |
| Viral infection | 9 (0.3) | 3 (0.2) | 7 (0.4) | 26 (0.2) | 4 (0.4) | 8 (0.6) | 9 (0.1) | |
| Vomiting | 4 (0.2) | 2 (0.1) | 4 (0.2) | 5 (<0.1) | 1 (0.1) | 0 | 4 (<0.1) | |
| Excoriation | 5 (0.2) | 1 (0.1) | 10 (0.6) | 12 (0.1) | 2 (0.2) | 6 (0.4) | 8 (0.1) | |
| Serious adverse events, possibly related to study drug* | 3 (0.1) | 1 (0.1) | 0 | 7 (0.1) | 0 | 0 | 2 (<0.1) | |
| Abdominal pain | 0 | 0 | 0 | 1 (<0.1) | 0 | 0 | 0 | |
| Bronchopneumonia | 0 | 0 | 0 | 0 | 0 | 0 | 1 (<0.1) | |
| Gastroduodenitis | 0 | 1 (0.1) | 0 | 0 | 0 | 0 | 0 | |
| Hematochezia | 0 | 0 | 0 | 1 (<0.1) | 0 | 0 | 0 | |
| Herpes simplex infection | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Herpes zoster infection | 0 | 0 | 0 | 1 (<0.1) | 0 | 0 | 1 (<0.1) | |
| Hydrocephalus | 0 | 0 | 0 | 1 (<0.1) [†] | 0 | 0 | 0 | |
| Juvenile rheumatoid arthritis disease flare | 1 (<0.1) | 0 | 0 | 1 (<0.1) | 0 | 0 | 0 | |
| Leukopenia | 1 (<0.1) | 0 | 0 | 0 | 0 | 0 | 0 | |
| Neutropenia | 1 (<0.1) | 0 | 0 | 0 | 0 | 0 | 0 | |
| Pharyngitis | 0 | 0 | 0 | 1 (<0.1) | 0 | 0 | 0 | |
| Pneumonia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Viral infection | 0 | 0 | 0 | 1 (<0.1) [†] | 0 | 0 | 0 | |
| Adverse events leading to discontinuation of drug | 5 (0.2) | 0 | 0 | 2 (<0.1) | 0 | 0 | 2 (<0.1) | |
| Arthralgia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Dizziness | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Hydrocephalus | 0 | 0 | 0 | 1 (<0.1) [†] | 0 | 0 | 0 | |

no. of events (no. of events per patient-year)

| | | | | | | | | | |
|--------------------------------------|-----------|---|---|---|-----------|----------|---|---|----------|
| Juvenile rheumatoid arthritis | 1 (<0.1) | 0 | 0 | 0 | 0 | 4 (0.1) | 0 | 0 | 2 (<0.1) |
| Leukopenia | 1 (<0.1) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Alanine aminotransferase elevation | 1 (<0.1)‡ | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Aspartate aminotransferase elevation | 1 (<0.1)‡ | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Neutropenia | 1 (<0.1) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Pneumonia | 0 | 0 | 0 | 0 | 0 | 1 (<0.1) | 0 | 0 | 0 |
| Viral infection | 0 | 0 | 0 | 0 | 1 (<0.1)† | 0 | 0 | 0 | 0 |

* Serious adverse events were death or any event that was life-threatening; required hospitalization or prolongation of existing hospitalization; resulted in persistent or significant disability, congenital anomaly, or spontaneous or elective abortion; or required medical or surgical intervention to prevent another serious outcome. In addition to the serious adverse events listed, the following serious adverse events also occurred (in 1 patient each, except where noted) but were not considered to be possibly related to the study drug: abdominal pain, abortion, adenoidal and tonsillar hypertrophy (2 patients), arthritis (2 patients), appendicitis (2 patients), diabetic ketoacidosis, femur fracture, unspecified injury, malabsorption, joint contracture, joint dislocation, juvenile rheumatoid arthritis disease flare (12 patients), osteoarthritis, speech disorder, retinal detachment, urinary tract infection, and vomiting.

† The patient entered the study with a ventricular peritoneal shunt in place because of preexisting hydrocephalus and had concurrent viral infection and shunt malfunction.

‡ Values returned to normal within weeks after discontinuation of study drug.

the ethical issues associated with denying active treatment during a double-blind phase. At the time the adalimumab trial was designed, two other trials of TNF antagonists in pediatric patients were ongoing. Our trial of adalimumab was designed after considering both parallel and randomized approaches to withdrawal, in consultation with the Food and Drug Administration (FDA). The FDA and the study designers agreed that the blinded, randomized medication-withdrawal design provided acceptable scientific rigor while minimizing exposure to placebo in this population of children with severe, active juvenile rheumatoid arthritis and that the primary end point should be a comparison, in the no-methotrexate stratum, between the percentages of patients with disease flares in the group receiving adalimumab and the group receiving placebo during the double-blind phase.

Although the double-blind phase, and thus the primary end-point analysis, was conducted in patients who had a response, the open-label lead-in approach is generalizable to clinical practice, given that treatment decisions are made in an open-label setting after a reasonable trial with a new active treatment. If a patient does not have a response to an active treatment after a period of time (16 weeks or so, as in the current trial), a physician will probably consider other treatment options. For patients who do have a response, treatment will be continued.

Adalimumab, alone or in combination with methotrexate, appears to be an efficacious option for the treatment of children with polyarticular juvenile rheumatoid arthritis. Responses were sustained through 2 years of continued treatment.

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APPENDIX

From the Cincinnati Children's Hospital Medical Center, Cincinnati (D.J.L., E.H.G.); Istituto di Ricovero e Cura a Carattere Scientifico G. Gaslini, Pediatric Rheumatology International Trials Organisation, Genoa, Italy (N.R., A.M.); Arthritis Associates of South Florida, Delray Beach (S.G.); Children's Hospital, Los Angeles (A.R.); Creighton University Medical Center and Children's Hospital, Omaha, NE (L.J.); Revmatologický ústav (K.J.) and First Faculty of Medicine and General Faculty Hospital (D.N.) — both in Prague, Czech Republic; Hôpital Necker Enfants Malades, Paris (R.M.); Stanford University Medical Center, Stanford, CA (C.S.); University of Utah Health Sciences Center, Salt Lake City (J.B.); Ghent University Hospital, Ghent, Belgium (D.E.); Hamburger Zentrum für Kinder- und Jugendrheumatologie, Hamburg, Germany (I.F.); Istituto Gaetano Pini, Milan (V.G.); the National Institute of Rheumatic Diseases, Piastany, Slovak Republic (J.R.); Charité University Hospital, Berlin (K.M.); University of Minnesota, Minneapolis (R.K.V.); Larabida Hospital, University of Chicago, Chicago (L.W.W.); Zentrum für Allgemeine Pädiatrie und Neonatologie, Sankt Augustin, Germany (G.H.); Klinikum Bremen-Mitte, Bremen, Germany (H.-I.H.); University of Kansas Medical Center, Kansas City (N.Y.O.); Abbott Laboratories, Parsippany, NJ (J.R.M.); and Abbott Laboratories, Ludwigshafen, Germany (R.C.-D.-P., M.J.M.).

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