Long-term efficacy and safety of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis: findings from an open-label treatment extension

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ABSTRACT

Objective To assess the long-term efficacy and safety of infliximab plus methotrexate in juvenile rheumatoid arthritis (JRA).

Methods Patients eligible for the open-label extension (OLE, weeks 52–204) received infliximab 3–6 mg/kg every 8 weeks plus methotrexate.

Results Of the 78/122 (64%) children entering the OLE, 42 discontinued infliximab, most commonly due to consent withdrawal (11 patients), lack of efficacy (eight patients) or patient/physician/sponsor requirement (eight patients). Infliximab (mean dose 4.4 mg/kg per infusion) was generally well tolerated. Infusion reactions occurred in 32% (25/78) of patients, with a higher incidence in patients positive for antibodies to infliximab (58%, 15/26). At week 204, the proportions of patients achieving ACR-Pedi-30/50/70/90 response criteria and inactive disease status were 44%, 40%, 33%, 24% and 13%, respectively.

Conclusions In the limited population of JRA patients remaining in the study at 4 years, infliximab was safe and effective but associated with a high patient discontinuation rate.

Clinical trials registration number NCT00036374.

Several therapeutic options are now available for treating moderate-to-severe juvenile rheumatoid arthritis (JRA), including methotrexate and biological agents.[1–7] A report from a phase III JRA trial showed that infliximab 3–6 mg/kg had durable efficacy at 1 year, although the primary efficacy endpoint at 14 weeks was not achieved. Safety data indicated that infliximab 6 mg/kg might provide a more favourable benefit/risk profile than 3 mg/kg.[5] In the current evaluation, we assessed the long-term safety and efficacy of infliximab plus methotrexate in a 3-year open-label extension (OLE).

PATIENTS AND METHODS

Patients

To be eligible for the pivotal portion of the trial,[5] patients had to be 4 years or older but less than 18 years of age and have a diagnosis of JRA,[8] a suboptimal response to methotrexate, at least five joints with active arthritis and no active systemic symptoms. Disease-modifying antirheumatic drugs other than methotrexate were prohibited. Patients completing treatment to week 44, and who, in the opinion of the investigator, may have benefited from continued treatment, were eligible for the OLE at week 52. Patients were screened for tuberculosis at baseline and weeks 108 and 156 of the OLE.[9] Patients/parents provided ethics committee-approved assent/consent before the OLE.

Study design

The pivotal portion of the trial[5] was a phase III, international, multicentre, randomised, double-blind, placebo-controlled study of infliximab therapy for 14 weeks, followed by a double-blind, all-active treatment extension to 44 weeks. Patients were randomly assigned to infliximab 3 mg/kg plus methotrexate to week 44 or placebo plus methotrexate for 14 weeks followed by infliximab 6 mg/kg plus methotrexate to week 44. Study medication was administered over a 40–120-minute period.

At the time the OLE was designed, safety information was not available from the pivotal trial. Therefore, all patients entering the OLE received infliximab 3 mg/kg plus methotrexate. During the OLE, dose adjustments were possible for infliximab (from 3 to 6 mg/kg), methotrexate, corticosteroids and non-steroidal anti-inflammatory drugs at the investigator's discretion. The addition of concomitant sulfasalazine/hydroxychloroquine was permitted after week 108. The final study evaluation was at week 204, 8 weeks after the week 196 infliximab infusion. The sponsor did not provide study agent beyond the week 196 infusion.

Results from the pivotal study suggested that paediatric patients might require higher infliximab doses than adults on a mg/kg basis to maintain adequate serum concentrations and minimise the development of antibodies to infliximab and related infusion reactions.[5] Study investigators were informed of these important safety findings, at which time the OLE was already underway. With guidance from regulatory authorities, investigators

were offered several options including infliximab dose increase or discontinuing infliximab and implementing pre-infliximab prophylaxis.

Evaluations and analyses

The key efficacy evaluation was the proportion of patients meeting the American College of Rheumatology Pediatric 30 (ACR-Pedi-30) response criteria[10–13] at weeks 76, 100, 124, 148, 172, 196 and 204. Patients were also evaluated using the more stringent definitions of improvement of ACR-Pedi-50/70/90. The number of patients demonstrating inactive disease was also determined, defined in this study as no joints with active arthritis, an erythrocyte sedimentation rate of less than 20 mm/first hour and a physician global assessment of disease activity score of 0 mm on a 100-mm visual analogue scale.[14]

Patients were monitored for adverse events, Tanner staging, antibodies to infliximab, serum infliximab concentrations,[15] antinuclear antibodies and antibodies to double-stranded DNA (anti-dsDNA).[15]

All OLE data were summarised with descriptive statistics; no inferential statistical hypothesis testing was performed.

RESULTS

Baseline patient characteristics and patient disposition

Seventy-eight (64%) of the original 122 patients entered the OLE and were included in safety analyses: 39 patients had received placebo/infliximab 6 mg/kg plus methotrexate and 39 infliximab 3 mg/kg plus methotrexate. Seventy-five (61%) patients were available for the efficacy analysis (figure 1). Reasons for lack of eligibility for, and subsequent discontinuation from, the OLE are shown in figure 1. Most commonly, patients withdrew consent (11 patients) or discontinued due to lack of efficacy (eight patients)

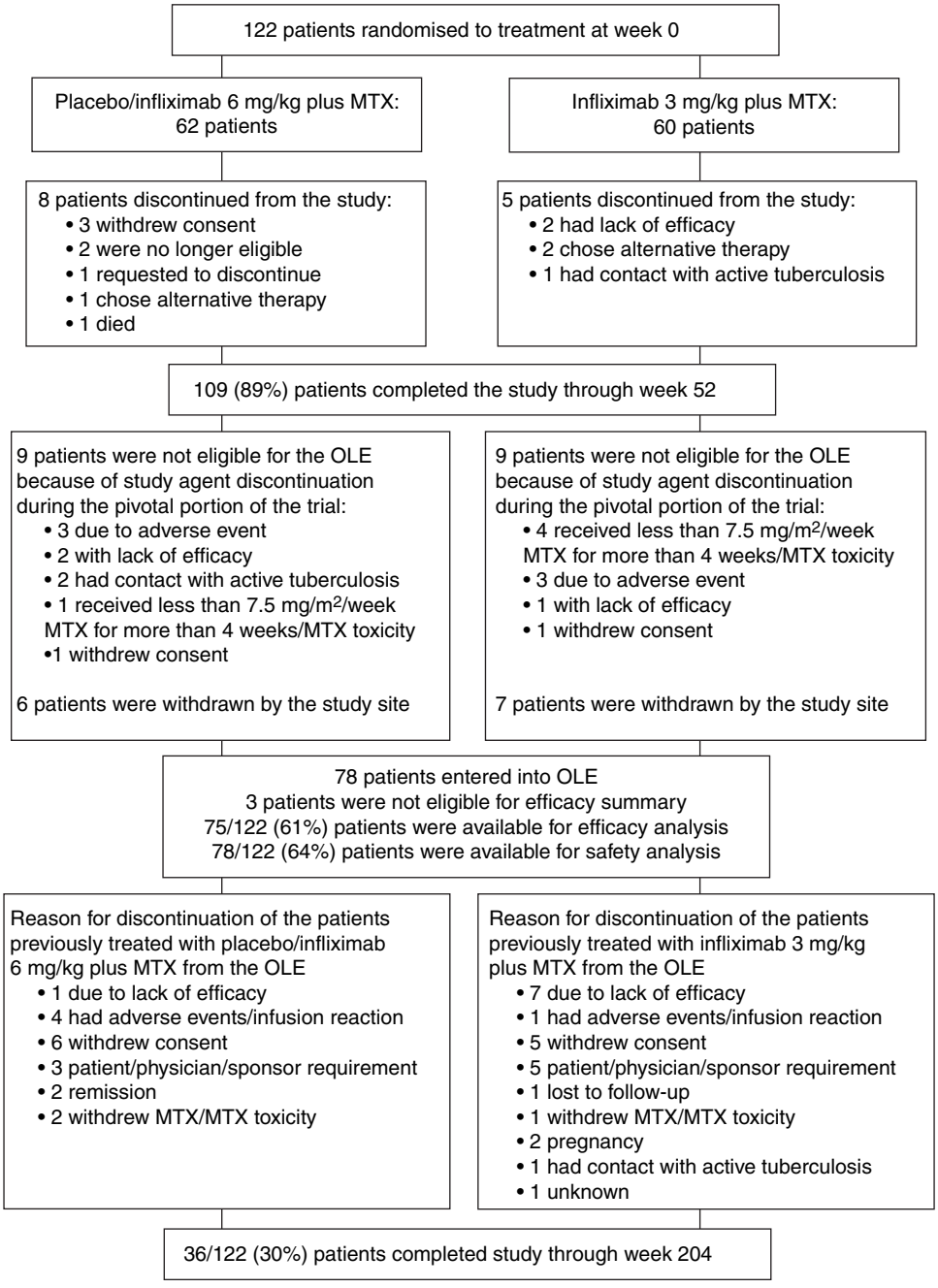

Figure 1 Patient disposition. MTX, methotrexate; OLE, open-label extension.

or a patient/physician/sponsor requirement (eight patients). Overall, 36 (30%) patients completed the study to week 204.

Efficacy

Improvement in the six ACR-Pedi-30 core set parameters from week 0 (before study entry) to week 52 in the 78 patients entering the OLE was greater than that reported for the entire study population,[5] highlighting that the OLE population was 'enriched' with responders (data not shown).

The proportions of patients achieving ACR-Pedi-30/50/70/90 responses and inactive disease during the OLE based on the intent-to-treat patient population (n=75) are shown in figure 2. At week 52 (before the start of the OLE), 64 (85%), 61 (81%), 45 (60%), 31 (41%) and 22 (29%) of infliximab-treated patients achieved ACR-Pedi-30/50/70/90 responses and inactive disease, respectively. By week 204, respective response rates were 33 (44%), 30 (40%), 25 (33%), 18 (24%) and 10 (13%; figure 2).

Immunogenicity and infusion reactions

During the OLE, 26/71 (37%) patients were positive for antibodies to infliximab, 22 (31%) were negative and 23 (32%) had an inconclusive status. Twenty-five (32%) of 78 treated patients had at least one infusion-related reaction, with a higher occurrence among patients classified as positive for antibodies to infliximab (58%, 15/26; table 1). Serious infusion reactions occurred in two patients (one each antibody positive and negative). One patient (antibody positive) had a possible anaphylactic reaction. There were no delayed hypersensitivity reactions.

Newly positive antinuclear antibodies (≥1:320) and anti-ds-DNA occurred in 26% (15/58) and 7% (4/61) of patients from weeks 52 to 204 (table 1). No patient exhibited clinical signs or symptoms suggesting an autoimmune disorder (ie, lupus or lupus-like syndrome).

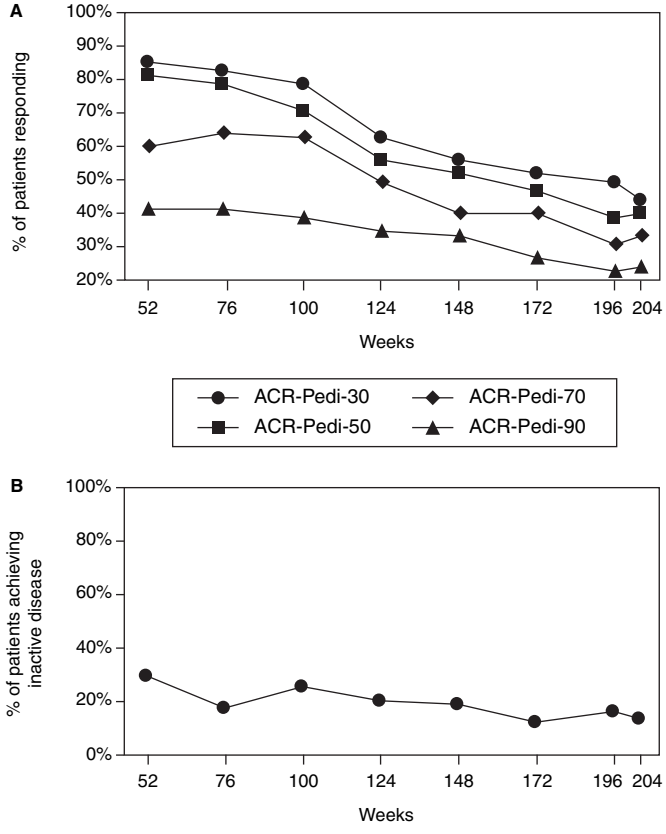

Figure 2 Proportions of juvenile rheumatoid arthritis (JRA) patients meeting the American College of Rheumatology Pediatric 30 (ACR-Pedi-30), ACR-Pedi-50, ACR-Pedi-70 and ACR-Pedi-90 response criteria (A) and with inactive disease (B) over time. These efficacy summaries are based on the intent-to-treat efficacy population (n=75). For these intent-to-treat summaries, patients who did not return for efficacy evaluations or who had no efficacy data available to assess their JRA core set response were considered non-responders.

Table 1 Summary of safety findings for the OLE (week 52 to week 204)

	Open-label infliximab plus methotrexate (N=78)
Average weeks of follow-up	114.1
Adverse events	71 (91.0%)
Common adverse events (>20% of patients)	
Upper respiratory tract infection	31 (39.7%)
Pharyngitis	30 (38.5%)
Headache	19 (24.4%)
Fever	18 (23.1%)
Rhinitis	18 (23.1%)
Vomiting	17 (21.8%)
Patients with adverse events leading to discontinuation of study agent	11 (14.1%)
Adverse events leading to discontinuation	
Infusion syndrome	5 (6.4%)
Pneumonia	2 (2.6%)
Anaphylactoid reaction	1 (1.3%)
Chills	1 (1.3%)
Coughing	1 (1.3%)
Fever	1 (1.3%)
Urticaria	1 (1.3%)
Uveitis	1 (1.3%)
Unintended pregnancy	1 (1.3%)
Vomiting	1 (1.3%)
Serious adverse events*	17 (21.8%)
Infections	57 (73.1%)
Common infections (≥10% of patients)	
Upper respiratory infection	25 (32.1%)
Pharyngitis	23 (29.5%)
Rhinitis	12 (15.4%)
Bronchitis	8 (10.3%)
Fever	8 (10.3%)
No of infusions with infusion reactions†	60/1079 (5.6%)
Positive for antibody to infliximab‡	48/359 (13.4%)
Negative for antibody to infliximab‡	7/317 (2.2%)
Inconclusive for antibody to infliximab‡	3/364 (0.8%)
No of patients with infusion reactions†	25/78 (32.1%)
Positive for antibody to infliximab‡	15/26 (57.7%)
Negative for antibody to infliximab‡	5/22 (22.7%)
Inconclusive for antibody to infliximab‡	3/23 (13.0%)
Serious infusion reaction	2 (2.6%)
Possible delayed hypersensitivity reaction	0 (0.0%)
Possible anaphylactic reaction	1 (1.3%)
Antinuclear antibodies (titre ≥1:320)	
Newly positive from weeks 52 to 204	15/58 (25.9%)
Antibody to double-stranded DNA	
Newly positive from weeks 52 to 204	4/61 (6.6%)

*A serious adverse event was any adverse event that resulted in death, a life-threatening event, inpatient hospitalisation or prolongation of existing hospitalisation, persistent or significant disability/incapacity, or congenital anomaly/birth defect.
†An infusion reaction was any adverse event that occurred during an infusion or within 1 h after the completion of an infusion.
‡Any positive antibody response was classified as positive, regardless of the presence or absence of infliximab in the last serum sample(s) evaluated following an infusion; negative antibody responses were classified as negative if the patient had no measurable concentrations of infliximab in the sample(s) or inconclusive if infliximab was detected in the sample(s). In this analysis of infusion reactions by antibody status, the occurrence of infusion reactions was assessed among the 71 patients with appropriate samples for testing antibody to infliximab.
OLE, open-label extension.

Additional safety assessments

From weeks 52 to 204, 71/78 (91%) patients had adverse events and 11 (14%) discontinued study agent due to adverse events (table 1). There were no deaths during the OLE; as previously reported,[5] two pivotal study patients died (one due to septic shock while receiving placebo and one systemically ill patient due to cardiac arrest 3 months after the last infliximab infusion).

Serious adverse events occurred in 17 (22%) patients. The most commonly reported serious adverse events were worsening of arthritis (six patients), pneumonia (two patients) and infusion syndrome (two patients). As previously reported,[5] one patient was diagnosed with asymptomatic tuberculosis (reported as pulmonary infiltration) following repeat screening before week 108. This patient had resolution of the interstitial infiltrates as well as negative follow-up skin test results following quadruple antituberculosis therapy and cessation of infliximab therapy. There were no reports of congestive heart failure or malignancy in the OLE.

New-onset uveitis was reported in four (5%) patients during the OLE. Annual Tanner staging was age appropriate and within the expected range. Markedly abnormal changes in haematology and chemistry parameters were infrequent.

Infliximab dosing and pharmacokinetics

On average, OLE patients received 13.8 infliximab infusions. The mean infliximab dose was 4.4 mg/kg per infusion.

Trough infliximab concentrations before infusion were below the limit of detection in most cases. The number of patients with pharmacokinetic data available at the end of the follow-up period is too limited to allow inference of a dose–concentration relationship.

DISCUSSION

This study reports the safety and efficacy of up to 4 years of infliximab plus methotrexate therapy in patients with polyarticular-course JRA continuing with open-label treatment following participation in the randomised, placebo-controlled portion of the trial.[5]

The distribution and types of adverse events observed with long-term infliximab (weeks 52–204) were similar to those observed in the first 52 weeks of therapy.[5] In particular, infusion-related reactions occurred in one-third of patients overall, with a higher occurrence (58%) in patients who had positive test results for antibodies to infliximab. The one patient diagnosed with asymptomatic tuberculosis based on repeat screening before week 108 underscores the importance of vigilance in tuberculosis screening for all patients receiving anti-TNF therapies. Newly positive antinuclear antibodies occurred in 26% and newly positive anti-dsDNA in 7% of patients from weeks 52 to 204; no autoimmune disorders (ie, lupus or lupus-like syndrome) were observed.

The diminished infliximab efficacy observed during the 3-year OLE is related to the high rate of patient discontinuation, because over half of the patients entering the OLE discontinued by week 204 and response rates were calculated using an intent-to-treat approach. Efficacy evaluations were performed 8 weeks after the previous dose, which also could have influenced response rates.

As noted, 52-week data showed that higher percentages of patients receiving infliximab 3 mg/kg plus methotrexate developed antibodies to infliximab and had infusion reactions compared with patients receiving 6 mg/kg,[5] suggesting that children might require higher infliximab doses on a mg/kg basis, or a shorter interval between doses, to maintain adequate serum concentrations and minimise the development of antibodies to infliximab.

Efficacy results must be interpreted with caution based on the high discontinuation rate. The ability to adjust the infliximab dose in the OLE could have influenced numbers of patients discontinuing from the OLE, as well as the actual infliximab dose administered to patients remaining in the OLE.

In summary, in the limited population of JRA patients who remained in the study at 4 years, infliximab was safe and effective but was associated with a high patient discontinuation rate.

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Competing interests EHG, DJL, AM, NR and PW served as members of the Steering Committee, as well as consultants for Centocor Ortho Biotech, Inc. The members of the Steering Committee had full access to analysis reports from Centocor Ortho Biotech, Inc. SX, Y-KS, SV, AF and AM are employees of Centocor Ortho Biotech, Inc.

Ethics approval This study was conducted with the approval of the independent ethics committee at each centre, which approved the protocol.

Patient consent Obtained.

Contributors RC, SM, CW, EDS, ZB, MH, JD, IF, LI, GS, JO, also authors on the paper, served as investigators for this study.

Provenance and peer review Not commissioned; externally peer reviewed.

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