A randomized, double-blind, placebo-controlled 12-Week trial of Infliximab in patients with Juvenile-Onset Spondyloarthritis or Enthesitis Related Arthritis

Rubén Burgos-Vargas

Department of Rheumatology, Hospital General de Mexico Dr. Eduardo Liceaga

Adalberto Loyola-Sanchez (✉ adalbert@ualberta.ca)

University of Alberta

Sofia Ramiro

Leiden University Medical Center

Arturo Reding-Bernal

Department of Rheumatology, Hospital General de Mexico Dr. Eduardo Liceaga

Raul Gutiérrez-Suárez

Department of Rheumatology, Hospital General de Mexico Dr. Eduardo Liceaga

Julio C. Casasola-Vargas

Department of Rheumatology, Hospital General de Mexico Dr. Eduardo Liceaga

Everardo Alvarez-Hernandez

Department of Rheumatology, Hospital General de Mexico Dr. Eduardo Liceaga

Désirée Van der Heijde

Leiden University Medical Center

Janitzia Vazquez-Mellado

Department of Rheumatology, Hospital General de Mexico Dr. Eduardo Liceaga

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Abstract

Objective. To assess the efficacy and safety of infliximab versus placebo in the treatment of patients with Juvenile-onset Spondyloarthritis and enthesitis-related arthritis (JoSpA/ERA).

Methods. Phase III, randomised, double-blind, placebo-controlled-trial of 12-weeks that included patients ≤ 18 -year-old with JoSpA/ERA not-responding to nonsteroidal-anti-inflammatory drugs, sulfasalazine, or methotrexate. Patients were randomly assigned 1:1 to the infusion of Infliximab 5mg/kg or placebo; completers entered then an open-label extension (OLE) period of 42 weeks. The primary endpoint was the number of active joints. Secondary outcomes included the assessment of disease activity, tender entheses, spinal mobility, serum C reactive protein (CRP), the Bath Ankylosing Spondylitis Disease Activity and Functional Index, and the Childhood Health Assessment Questionnaire (CHAQ).

Results. We randomized 12 patients to Infliximab and 14 to placebo. No significant differences were found between groups at baseline. At week 12, the mean number of active joints was 1.4 (SD 2.4) in the Infliximab group and 4.1 (SD 3.0) in the placebo group ($p=0.0002$). A repeated measures mixed model analysis that included all endpoints in the study demonstrated sustained favourable outcomes of Infliximab for active joints, tender joints, swollen joints and tender entheses counts, as well as for CHAQ and CRP ($p<0.01$). Adverse events were more frequent in the Infliximab group, including infections and infusion reactions, but none of them were serious.

Conclusion. Infliximab is efficacious for patients with JoSpA/ERA with an inadequate response to conventional treatment. No serious adverse events with the use of infliximab were observed.

Key Messages

- What is already known about this subject?

Few randomised clinical trials about the efficacy and safety of Tumour Necrosis Factor- α inhibitors (TNFi) (ie., etanercept and adalimumab) in patients with Juvenile-onset Spondyloarthritis (JoSpA) and enthesitis-related arthritis (ERA) have been published thus far. Regarding infliximab, there is one randomized clinical trial in children with polyarticular course-Juvenile Idiopathic Arthritis, but no JoSpA/ERA.

- What does this study add?

This is the first randomised clinical trial assessing the efficacy and safety of Infliximab in patients with JoSpA/ERA. At 12-week, the mean number of active joints (primary outcome) was significantly lower in the Infliximab than in the placebo group. Nearly all secondary measures showed the same result. Infliximab efficacy was sustained during a 42-week open-label phase. Adverse events were seen more often in the Infliximab group, but none was serious.

- How might this impact on clinical practice?

Efficacy of Infliximab in this study support its role in the treatment of children and adolescents with JoSpA/ERA.

Background

Juvenile-onset SpondyloArthritis (JoSpA) is the name of a group of HLA-B27 inflammatory disorders seen in children and adolescents equivalent to adult-onset SpondyloArthritis (SpA)(1). Initially, JoSpA patients have recurrent episodes of peripheral enthesitis-related arthrititis (ERA) and rarely axial disease (2, 3). At first glance, this presentation corresponds to one or the categories of juvenile idiopathic arthritis (JIA). Five to ten years later, around 75% of them may have involvement of the spine and sacroiliac joints (4–6) and fulfil the modified New York (mNY) criteria for Ankylosing Spondylitis (AS) or radiographic axial spondyloarthritis (r-axSpA) (7).

In contrast to JoSpA, most patients with adult-onset SpA present with inflammatory back pain and less frequently peripheral arthritis (8). In the past, the recognition of AS and radiographic sacroiliitis could take up to ten years (9). Today, with the use of Magnetic Resonance Imaging (MRI), the recognition of sacroiliitis and management of the disease occur at an earlier stage (10, 11) with the purpose to relieve symptoms and stop the progression of the disease (11, 12). For years, peripheral arthritis and enthesitis have been the most severe manifestations of JoSpA. Akin to adults, there is no beneficial effect of conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) such as sulfasalazine (SSZ) or methotrexate (MTX), particularly on the axial manifestations of the disease (12).

Treatment of JoSpA resembles that of adult-onset SpA and some categories of Juvenile Idiopathic Arthritis (JIA) (13). Among them, the use of biological DMARDs (bDMARDs), specifically tumour necrosis factor- α inhibitors (TNFi) has been a substantial therapeutic advance in JoSpA. Despite so, only four randomized clinical trials, two each on etanercept (14, 15) and adalimumab (16, 17) using different protocols have been published thus far. Infliximab, a monoclonal TNFi, has only been investigated in children with polyarticular course JIA (18, 19). Infliximab indications include several adult axSpA and related disorders, but no JoSpA.

Therefore, we have assessed the efficacy and safety of Infliximab versus placebo in children and adolescents with active JoSpA. Long-term efficacy and safety were assessed in an open-label phase of the trial.

Patients And Methods

Design

This was a phase III, randomised, double-blind, placebo-controlled, twelve-week study followed by a forty-two weeks open-label extension (Fig. 1). The study followed the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice. The Research and Ethics Review Board of the Hospital General de Mexico Dr. Eduardo Liceaga approved the conduction of this trial (Hospital General

de Mexico Research Division Registry: HGM/DIC/02/404-B/02/036). Patients, parents, or legal guardians and two witnesses were informed about the study and if accepted to participate, signed an informed consent form. The protocol was registered in ClinicalTrials.gov (identifier: NCT00591201).

Infliximab in Juvenile onset SpA Trial

Participants

Eligible patients were children and adolescents with active JoSpA who fulfilled the children's validation of the European Spondyloarthritis Study Group (ESSG) classification criteria for SpA (20, 21) and were mainly recruited from the pediatric rheumatology clinics at the Hospital General de México Dr Eduardo Liceaga. Some participants were recruited from private rheumatologist offices and from the Shriners Hospital for children in Mexico City. Recruitment took place from June 2002 to June 2007. Inclusion criteria were age ≤ 16 years at onset of symptoms and ≤ 18 years at screening. Disease activity required four criteria: 1) ≥ 3 active joints (see below); 2) ≥ 3 tender peripheral entheses; 3) ≥ 4 points of pain intensity on a 10 points numerical rating scale (NRS) (0 = no pain, 10 = the worst possible pain); 4) no clinical improvement or intolerance to the administration of ≥ 2 non-steroidal anti-inflammatory drugs (NSAIDs), csDMARDs, and systemic glucocorticoids.

Key exclusion criteria were active extra-musculoskeletal manifestations, such as psoriasis, anterior uveitis, and Crohn's disease; comorbidities or medications interfering with the trial; suspected or confirmed diagnosis of tuberculosis or other chronic infections; lymphoma or any other neoplasia; previous therapy with TNFi; lack of vaccinations, particularly Bacillus Calmette-Guerin (BCG); a positive skin test (> 5 mm) following the subcutaneous injection of the purified protein derivative (PPD); and for sexually active boys and girls, use of less than 2 contraceptive measures.

Patients were allowed to continue on NSAIDs, oral prednisone or its equivalent (≤ 10 mg/day), SSZ (≤ 50 mg/kg/day), and MTX (≤ 15 mg/m²/body surface area) as long as there were no changes in the dosages during the study.

Procedures

During the double-blind phase, patients were randomly assigned 1:1 and allocated to Infliximab 5 mg/kg or placebo infusions at weeks 0, 2, 6, and 12 according to a computer-generated randomization list restricted by blocks of four. Patients, parents, and investigators were blinded to allocation. Patients who finished the double-blind twelve-week period, were invited to participate in the open-label extension. Patients on infliximab continued with infusions every six weeks. Patients on placebo started receiving infliximab on week twelve and then every six weeks. Patients with serious adverse events or worsening of their disease in the double-blind phase were allowed to change to the open label phase or withdraw from the trial.

Outcomes

The primary outcome was the number of active joints (0 to 68), defined by the presence of swelling or range of motion limitation and pain and/or tenderness (22). Secondary outcomes included joint counts for tenderness (0–72), swelling (0–68), and reduced mobility (0–66), number of tender entheses (0–55), serum high-sensitive C reactive protein (hsCRP) in mg/dL, and the following spinal measurements: the modified Schober's test (cm), lateral spinal flexion (cm), chest expansion (cm), and neck and hip rotation (degrees).

We obtained the physician's global assessment (PGA) of disease activity, parent's rating of participants' pain and global well-being, all in 10-point numeric rating scales (NRS), and we calculated the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (23), Bath Ankylosing Spondylitis Functional Index (BASFI) (23), and the Childhood Health Assessment Questionnaire (CHAQ) (24) using cross-culturally adapted instruments. Even though children above 7 years-old could answer most questionnaires on their own, for the purpose of this study, we only included the responses given by parents or legal guardians.

The percentage of patients that achieved the American College of Rheumatology (ACR) Paediatric (Pedi) 30 response (29) was estimated. This response was defined as three of any of six variables (i.e., 1- PGA of disease activity, 2- parent/patient global assessment of overall well-being, 3- functional ability, 4- number of joints with active arthritis, 5- number of joints with limited range of motion and 6- hsCRP) improving 30% or more with no more than one of the remaining variables worsening more than 30%. We also estimated the ACR-Pedi 50, 70, 90, and 100 responses.

The Assessment in Ankylosing Spondylitis (ASAS) 20 (25), ASAS 40 (26), and ASAS 5/6 (26) improvement and ASAS partial remission criteria (25) were calculated according to four domains: 1) patient global assessment of disease activity, 2) spinal pain, 3) function (mean BASFI), and 4) inflammation (mean BASDAI questions 5 and 6). ASAS 5/6 also consider the hsCRP and lateral spinal flexion variables. To fulfil ASAS 20 criteria an improvement of $\geq 20\%$ and ≥ 1 unit in 3 or 4 domains plus no worsening $\geq 20\%$ or ≥ 1 unit in the remaining domain was necessary. The ASAS 40 criteria required improvement of $\geq 40\%$ and ≥ 2 units in 3 or 4 domains plus no worsening in the remaining domain. The ASAS 5/6 criteria required an improvement $\geq 20\%$ in at least 5 domains and the ASAS partial remission criteria required each of the 4 domains to be ≤ 2 units.

Safety Evaluation

Adverse events (AEs) were collected from the first infusion of treatments onwards, including infections such as tuberculosis, malignancies and infusion reactions. The definition of AEs followed those of the Medical Dictionary for Regulatory Activities (MedDRA). AEs were expressed as number of patients and percentages. Serious adverse events (SAEs) were also monitored (i.e., death, life-threatening condition, hospital admission, hospital stay extension and disability).

Statistical Analysis

The primary analysis followed an intention to treat (ITT) strategy, including all participants who received at least one infusion of Infliximab. To assess the in-between group differences for number of active joints and continuous secondary outcomes, we used Analysis of Covariance (ANCOVA) adjusted for baseline scores (27). For nominal outcomes, we utilized the Fisher's exact test to assess the differences between groups at week 12. In addition, we performed repeated-measures mixed model analyses for continuous outcomes. These analyses assess group and time interactions in both the double-blind and open label phases of the study. To calculate the sample size, we used the independent means difference method considering an intervention effect size of 1.1 (Cohen's d) on the number of active joints, based on expert opinion since no literature was available when this study was designed. Seeking a statistical power of 80% with a confidence level of 95% in a two-tailed hypothesis, 14 participants were estimated to be needed for each group. All analyses were performed using STATA version 16.

Results

Twenty-six patients were randomised, 14 to placebo and 12 to infliximab (see Fig. 1). All patients completed the randomized controlled phase, and none was switched early to the open phase. Two patients withdrew their consent at weeks 24 and 30 because of family problems at home and unexplained issues, respectively. There were no significant demographic or clinical differences between the groups at baseline (see Table 1). Two patients in each group fulfilled the mNY for AS or r-axSpA, whereas all patients fulfilled the International League of Associations for Rheumatology (ILAR) ERA classification criteria.

Table 1
Baseline demographics and disease characteristics

	Placebo (n = 14)	Infliximab (n = 12)	p!
Demographics			
Males, no. (%)	13 (92.9)	12 (100.0)	1.000
Age, years mean (SD)	14.5 (2.7)	15.0 (1.7)	0.587
Weight, kg mean (SD)	55.2 (19.5)	52.7 (14.5)	0.718
Body mass index, kg/m ² mean (SD)	21.4 (5.1)	19.7 (3.3)	0.339
Radiographic sacroiliitis *, no. (%)	2 (14.3)	2 (6.7)	0.763
Disease characteristics			
Disease duration, years mean (SD)	6.9 (3.5)	6.4 (2.7)	0.689
HLA-B27, no. (%)	13 (92.9)	10 (90.9)	0.859
Family history of SpA**, no. (%)	2 (14.3)	1 (8.3)	0.642
<p>* Radiographic sacroiliitis if at least graded 2 or 3 bilateral or 3 unilateral.</p> <p>** Family history of SpA refers to three cases with axSpA, one to nrSpA, and another to rSpA (AS).</p> <p>! probability values of true differences, utilizing parametric t-tests for continuous variables and non-parametric chi-squared tests for nominal variables.</p> <p>no = number; SD = Standard Deviation.</p>			

Efficacy

At the end of the randomized controlled phase of the trial, the number of active joints was lower in the infliximab [1.4 (SD 2.4)] than in the placebo [4.1 (SD 3.0)] group (p = 0.0002) (Fig. 2A). Similar results were observed for the mean number of swollen (Fig. 2B) and tender joints (Fig. 2C), entheses (Fig. 2D), and hsCRP (Fig. 3A). All these differences were statistically significant (p < 0.01) (See Table 2).

Table 2. Between-group differences in primary and secondary continuous outcomes at baseline and at the end of the RCT phase

	Placebo		Infliximab		
	Baseline	Week 12	Baseline	Week 12	P*
Active joints, no	6.1 (3.7)	4.1 (3.0)	4.5 (1.7)	1.4 (2.4)	0.0002
Tender joints, no	10.6 (6.8)	7.8 (7.9)	6.7 (3.1)	1.0 (2.0)	0.0001
Swollen joints, no	6.5 (3.6)	4.5 (3.0)	5.0 (2.0)	1.5 (2.4)	0.0003
Tender entheses, no	9.2 (4.8)	7.1 (5.9)	9.5 (9.7)	1.4 (2.3)	0.004
CHAQ score, 0-3	2.0 (0.5)	2.0 (0.4)	1.9 (0.5)	1.6 (0.8)	0.1
BASDAI score, 0-10	6.1 (1.9)	5.5 (1.8)	5.5 (2.5)	3.4 (2.3)	0.07
BASFI score, 0-10	5.4 (2.6)	4.9 (2.0)	5.5 (2.8)	3.0 (2.8)	0.12
hsCRP level, mg/dl	30.1 (23.4)	19.7 (17.3)	23.1 (9.5)	3.1 (5.0)	0.003
Modified Schober's, cm	4.5 (1.1)	4.6 (1.3)	4.5 (1.5)	4.7 (1.0)	0.84
Lateral flexion, cm	17.6 (7.0)	16.7 (5.4)	25.4 (14.6)	18.1 (7.1)	0.81
Chest expansion, cm	4.5 (1.5)	4.8 (1.4)	4.4 (1.3)	4.7 (1.5)	0.94
Hip rotation, cm	39.9 (8.9)	42.3 (11.8)	50 (16.1)	47.4 (9.9)	0.92
Physician assessment of disease activity, 10 cm NRS	6.7 (1.6)	5.1 (2.8)	6.4 (1.0)	1.3 (2.1)	0.0006
Physician assessment of health status, 10 cm NRS	3.7 (2.1)	5.0 (2.7)	4.1 (1.3)	7.6 (2.0)	0.01
Parent/patient assessment of well being, 10 cm NRS	6.4 (1.3)	5.3 (2.6)	3.8 (1.9)	2.3 (2.2)	0.39
Pain score, 0-10 NRS	7.5 (1.8)	5.8 (2.7)	7.2 (1.9)	2.4 (1.9)	0.003

Values represent the mean (SD).

* p-values reflect the comparison of the outcomes at week 12 and obtained with ANCOVA analysis adjusting for baseline values

BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; CHAQ = Childhood Health Assessment Questionnaire; hsCRP = high-sensitive C Reactive

Protein

The results from repeated measures mixed model analyses showed that the evolution of the continuous outcome measures over time was different between groups and clearly favoured Infliximab throughout the duration of the study (Figs. 3 and 2). This was demonstrated by significant interactions between time and treatment group in these models (active joints count $p = 0.0001$; tender joint count $p < 0.001$; swollen joint count $p < 0.001$; tender entheses count $p < 0.001$; hsCRP levels $p < 0.001$ and also the CHAQ scores $p = 0.004$).

Differences between groups in CHAQ, BASDAI, and BASFI scores and Schober's, lateral flexion, chest expansion, hip rotation and parent assessment of wellbeing were not significant at week 12. Physician's assessment of disease activity, health status and parents' reports on pain yielded significant differences favouring the infliximab group at the end of the RCT phase (see Table 2).

The proportions of patients achieving the ACR-Pedi 30, 50, 70 and 90 responses at the end of the RCT phase were significantly higher in the Infliximab group (Fig. 4). Despite that 33% of the patients in the Infliximab group showed an ACR-Pedi 100 response vs none in the placebo group (Fig. 4), the small number of patients did not allow to achieve statistical significance.

More patients in the Infliximab group achieved ASAS40 and ASAS5/6 responses (Fig. 4). However, differences between groups on ASAS20 (Infliximab = 45% vs Placebo = 14%) and ASAS partial remission (Infliximab = 25% vs Placebo = 0%) responses were not statistically significant, despite a clear higher number of patients achieving them in the Infliximab group (Fig. 5).

Adverse events

The overall number of patients with any AE was nine (75%) in the Infliximab and eight (57%) in the placebo groups (Table 3). Infections were more frequent in patients who received Infliximab (41% vs. 28%) and participants presented with different types of infections during the study, which are described in Table 3. Infusion reactions were more common in the infliximab group (41%) than in the placebo group (7%), but none of them were considered serious (i.e., fever, headache and dizziness). Two patients on Infliximab developed psoriatic plaques and nocturnal back pain after four weeks, and these were considered paradoxical adverse events. Importantly, none of the patients developed SAEs during the study.

Table 3
Adverse events (AEs) during the complete duration of the study (RCT + OLE)

	Infliximab (n = 12)	Placebo (n = 14)
Patients with		
Any adverse event (%)	9 (75)	8 (57.1)
Any infection (%)	5 (41.6)	4 (28.5)
Infusion reactions (%)	5 (41.6)	1 (7.4)
Serious AEs*	0 (0.0)	0 (0.0)
Infection related		
Varicella	1 (8.3)	1 (7.4)
Pharyngitis	3 (25.0)	4 (28.5)
Upper tract infections, including flu	5 (41.6)	5 (35.7)
Diarrhea	2 (16.6)	2 (14.3)
Infusion related		
Fever	3 (25.0)	2 (14.3)
Headache	1 (8.3)	0 (0.0)
Dizziness	1 (8.3)	0 (0.0)
Paradoxical AEs		
Psoriasis	1 (8.3)	0 (0.0)
Back pain	1 (8.3)	0 (0.0)
	0 (0.0)	0 (0.0)
* Serious adverse events monitored included, death, life-threatening condition, hospital admission, hospital stay extension and disability. RCT- randomized controlled trial phase; OLE- open label extension phase.		

Discussion

This study demonstrated that Infliximab is effective and safe in the treatment of JoSpA. The primary endpoint, namely the number of active joints, was significantly lower in patients on infliximab compared to placebo. Moreover, most secondary outcomes, including composite scores and response criteria, showed improvements in favour of Infliximab. The repeated mixed model analyses showed sustained efficacy of infliximab on the primary and most secondary outcomes during the open label phase. AEs were mild and mostly related to infections and infusion reactions.

Although the incidence of JoSpA in Paediatric Rheumatology clinics is relatively low, the disease seems more active and severe than other JIA and adult-onset SpA (28, 29). The risk of developing r-axSpA within 10 years from onset is higher in HLA-B27 boys who are ≥ 8 years old and present with foot arthritis, enthesitis along with hip, sacroiliac, and spinal involvement at onset (30–33). Before the use of bDMARDs, disease remission occurred in only 20% of patients with JoSpA five years after onset. At 15-year follow-up, disease remained active in 50% of the cases, and disease activity at baseline predicted functional impairment at 10 years in 60% of the patients (32, 34, 35). Moreover, patients with JoSpA score higher in the CHAQ (31, 36) and bodily pain (37, 38) than other JIA categories.

Up to date, the efficacy of bDMARDs in children with JoSpA has not been established well in RCTs. The documented efficacy of bDMARDs in patients with a polyarticular JIA and adults with axSpA has contributed to justify their use in children and adolescents with JoSpA and enthesitis-related arthritis (ERA). JIA categories differ from each other regarding prevalence, clinical features, outcome measures, and management. Considering ethical constraints related with conducting RCTs in children, the use of a controlled withdrawal design RCT has become the standard for clinical trials in JIA, even though the appropriateness of this standard has been questioned (39–41). Therefore, most of the clinical trials on the use of TNFi in JoSpA utilized a controlled withdrawal design and only one has utilized a standard RCT design (15), which we implemented in the present study.

Two open-label studies on the efficacy of bDMARDs in the JoSpA population have been published. One open-label study on Etanercept for 24 weeks clearly showed an effect of the TNFi to prevent disease flares (42). Similarly, the open-label CLinical Study in Paediatric Patients of Etanercept for treatment of ERA, PsA, and extended oligoarthritis (CLIPPER)(14, 15, 43) showed efficacy of the biologic to achieve the ACR Pedi 30 response at 12 weeks. This study utilized two historical groups for comparison with the treatment group (14, 17).

Two other RCTs evaluated the efficacy of the bDMARD Adalimumab in the JoSpA population (16, 17). Our trial contributes to reduce the existing gap in the literature with only few placebo-controlled RCTs conducted (40). Conducting placebo-controlled RCTs in the JoSpA population has several advantages. One of the mentioned Adalimumab RCTs included 32 patients with Juvenile-onset Ankylosing Spondylitis (JoAS) and found no statistically significant differences between adalimumab and placebo in the achievement of ASAS 40 response as their primary endpoint (17). The other RCT on Adalimumab included 46 patients with ERA and found a clear positive effect of the TNFi on the percentual change from baseline in the number of active joints in comparison to placebo (16). Utilizing the “percentual change from baseline” to attribute intervention causality in RCTs has been shown ineffective due to this strategy’s high sensitivity to changes in variance, reducing its power to detect true differences (28). Additionally, in our study we opted for ANCOVA adjusting for baseline outcomes for the between group comparison of means at the end of the RCT as a more appropriate manner to assess between group differences.

Moreover, even though we selected the same RCT design as the Adalimumab studies previously referred, we implemented more stringent criteria to select patients with higher disease activity. We believe that our disease activity parameters are more in line with what is currently used to identify children with JoSpA/ERA who require bDMARDs. Inclusion criteria of other studies have been typically more permissive including a wider range of disease activity, which could go from two active joints in CLIPPER (14) to a combination of sacroiliac, spinal, oligoarthritis, and imaging studies in the JoAS trial (17).

With respect to our primary outcome selection, the ACR Pedi 30 response criteria has been the primary endpoint of RCT withdrawal trials, which included the ACR criteria for flare (42). The Adalimumab trials included ASAS40 response as a primary outcome (16, 17). We selected the number of active joints as our primary outcome, due to its clinical implications, which strongly indicates the disease severity in this population. In addition, our results demonstrate that this outcome is sensitive to change, and clinically important differences can be found even in small samples.

There were no SAEs reported in this study. However, more patients on Infliximab had infectious and infusion-related reactions compared with placebo. In contrast, a trial of Infliximab in 122 patients with polyarticular-course juvenile rheumatoid arthritis randomised to 3 mg/kg or 6 mg/kg yielded AEs in 95% of the patients (18, 19), including serious AEs in 32% of infliximab users. The Pharmachild (n = 2022; all licensed bDMARDs) and Biker (n = 1697; all licensed bDMARDs) registries barely mention the use of Infliximab suggesting low utilization of this TNFi in the paediatric population in some countries (44–48). Interestingly, few AEs have been reported with the use of high doses of Infliximab in refractory cases of JIA extra musculoskeletal manifestations such as uveitis (49, 50).

The limitations of our study could be related with potential comparability with future studies, particularly the fact that we did not use composite measures as our primary outcome. Some of the newest composite measures, such as the AS Disease Activity index (51, 52), the juvenile SpA Disease Activity index (53), and the Juvenile Arthritis Disease Activity Index (JADAS) (54) were not available when we designed the study, and have since been developed to improve the assessment of patients with JoSpA and can be used in future clinical trials. Another limitation was related with the sample size calculation, as by the time we planned the study there were no clinical trials on the use of TNFi for JoSpA in the literature. Therefore, the power of our study was determined by experts' opinion on the significant difference expected among groups. The fact that our sample size was enough to detect significant differences between groups on our primary outcome, makes this limitation less relevant for the conclusions that emerge from our findings.

Conclusions

In summary, the infusion of Infliximab at a loading dose of 5 mg/kg for 12 weeks and then every six weeks up to 54 weeks was effective to reach a lower number of active joints, tender joints, swollen joints, tender entheses, hsCRP levels and better levels of physical function in children and adolescents with

active JoSpA/ERA. Consequently, we conclude that infliximab is efficacious is a good treatment alternative for JoSpA/ERA.

Abbreviations

ACR- American College of Rheumatology

AEs-Adverse events

ANCOVA- Analysis of Covariance

ASAS- Assessment in Ankylosing Spondylitis

BASDAI- Bath Ankylosing Spondylitis Disease Activity and Functional Index

BASDAI-Bath Ankylosing Spondylitis Disease Activity Index

BASFI- Bath Ankylosing Spondylitis Functional Index

BCG- Bacillus Calmette-Guerin

CHAQ- Childhood Health Assessment Questionnaire

CLIPPER- CLinical Study in Paediatric Patients of Etanercept for treatment of ERA, PsA, and extended oligoarthritis

CRP- serum C reactive protein

csDMARDs- conventional synthetic disease modifying anti-rheumatic drugs

ERA- enthesitis-related arthirtis

ESSG- European Spondyloarthropathy Study Group

hsCRP- high-sensitive C reactive protein

International League of Associations for Rheumatology (ILAR)

ITT intention to treat

JADAS- Juvenile Arthritis Disease Activity Index

JIA- juvenile idiopathic arthritis

JoAS- Juvenile-onset Ankylosing Spondylitis

JoSpA- Juvenile-onset SpondyloArthritis

JoSpA/ERA- Juvenile-onset Spondyloarthritis and enthesitis-related arthritis

MedDRA- Medical Dictionary for Regulatory Activities

mNY AS- modified New York criteria for Ankylosing Spondylitis

MRI- Magnetic Resonance Imaging

MTX- methotrexate

NRS- numerical rating scale

OLE- open-label extension phase

Pedi- Paediatric

PGA- physician's global assessment

PPD- purified protein derivative

r-axSpA- radiographic axial spondyloarthritis

SpA- SpondyloArthritis

SSZ- sulfasalazine

TNFi- Tumour Necrosis Factor- α inhibitors

Declarations

Ethical Approval and Consent to participate

The Research and Ethics Review Board of the Hospital General de Mexico Dr. Eduardo Liceaga approved the conduction of this trial (Hospital General de Mexico Research Division Registry: HGM/DIC/02/404-B/02/036). Patients, parents, or legal guardians and two witnesses were informed about the study and if accepted to participate, signed an informed consent form.

Consent for publication

All authors agree to the terms of the BioMed Central Copyright and License Agreement for the publication of this manuscript.

Availability of supporting data

The anonymized database utilized in the analysis of this manuscript is available upon request.

Competing interests

Dr. Rubén Burgos Vargas received funding from Schering Plough, Mexico to complete the data collection of this study. None of the other authors received any compensation from this or any other pharmaceutical company for the analysis or interpretation of the results.

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Authors' contributions

RBV contributed with the conception, implementation of data collection, analysis and drafting of this manuscript.

ALS, SR and ARB contributed with the analysis and drafting of the manuscript.

RGC, JCV and EAH contributed with implementation of data collection.

DVH and JVM contributed with the drafting of the manuscript.

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Authors' information

Rubén Burgos-Vargas (RBV), email: r.burgos.vargas@gmail.com; Adalberto Loyola-Sanchez (ALS) (corresponding author), email: adalbert@ualberta.ca; Sofia Ramiro (SR), email: sofiaramiro@gmail.com; Arturo Reding-Bernal (ARB), email: reding_79@yahoo.com; Raul Gutierrez-Suarez (RGS), email: ragusu@gmail.com; Julio C Casasola-Vargas (JCV), email: cassvarg@hotmail.com; Everardo Alvarez-Hernandez (EAH), email: everalvh@yahoo.com.mx; Désirée van der Heijde (DVH), email: mail@dvanderheijde.nl; Janitzia Vázquez-Mellado (JVM), email: jvazquezmellado@gmail.com

References

1. Burgos-Vargas R. The juvenile-onset spondyloarthritides. Rheum Dis Clin North Am. 2002;28(3):531 – 60, vi.
2. Jacobs JC, Berdon WE, Johnston AD. HLA-B27-associated spondyloarthritis and enthesopathy in childhood: clinical, pathologic, and radiographic observations in 58 patients. J Pediatr. 1982;100(4):521–8.

3. Rosenberg AM, Petty RE. A syndrome of seronegative enthesopathy and arthropathy in children. *Arthritis Rheum.* 1982;25(9):1041–7.
4. Burgos-Vargas R, Clark P. Axial involvement in the seronegative enthesopathy and arthropathy syndrome and its progression to ankylosing spondylitis. *J Rheumatol.* 1989;16(2):192–7.
5. Cabral DA, Oen KG, Petty RE. SEA syndrome revisited: a longterm followup of children with a syndrome of seronegative enthesopathy and arthropathy. *J Rheumatol.* 1992;19(8):1282–5.
6. Burgos-Vargas R, Vázquez-Mellado J. The early clinical recognition of juvenile-onset ankylosing spondylitis and its differentiation from juvenile rheumatoid arthritis. *Arthritis Rheum.* 1995;38(6):835–44.
7. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum.* 1984;27(4):361–8.
8. Sieper J, Braun J, Dougados M, Baeten D. Axial spondyloarthritis. *Nat Rev Dis Primers.* 2015;1:15013.
9. Rudwaleit M, van der Heijde D, Khan MA, Braun J, Sieper J. How to diagnose axial spondyloarthritis early. *Ann Rheum Dis.* 2004;63(5):535–43.
10. Lambert RG, Bakker PA, van der Heijde D, Weber U, Rudwaleit M, Hermann KG, et al. Defining active sacroiliitis on MRI for classification of axial spondyloarthritis: update by the ASAS MRI working group. *Ann Rheum Dis.* 2016;75(11):1958–63.
11. Aouad K, Maksymowych WP, Baraliakos X, Ziade N. Update of imaging in the diagnosis and management of axial spondyloarthritis. *Best Pract Res Clin Rheumatol.* 2020;34(6):101628.
12. Burgos-Vargas R, Vázquez-Mellado J, Pacheco-Tena C, Hernández-Garduño A, Goycochea-Robles MV. A 26 week randomised, double blind, placebo controlled exploratory study of sulfasalazine in juvenile onset spondyloarthropathies. *Ann Rheum Dis.* 2002;61(10):941–2.
13. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol.* 2004;31(2):390–2.
14. Horneff G, Burgos-Vargas R, Constantin T, Foeldvari I, Vojinovic J, Chasnyk VG, et al. Efficacy and safety of open-label etanercept on extended oligoarticular juvenile idiopathic arthritis, enthesitis-related arthritis and psoriatic arthritis: part 1 (week 12) of the CLIPPER study. *Ann Rheum Dis.* 2014;73(6):1114–22.
15. Horneff G, Foeldvari I, Minden K, Trauzeddel R, Kümmerle-Deschner JB, Tenbrock K, et al. Efficacy and safety of etanercept in patients with the enthesitis-related arthritis category of juvenile idiopathic arthritis: results from a phase III randomized, double-blind study. *Arthritis Rheumatol.* 2015;67(8):2240–9.
16. Burgos-Vargas R, Tse SM, Horneff G, Pangan AL, Kalabic J, Goss S, et al. A Randomized, Double-Blind, Placebo-Controlled Multicenter Study of Adalimumab in Pediatric Patients With Enthesitis-Related Arthritis. *Arthritis Care Res (Hoboken).* 2015;67(11):1503–12.
17. Horneff G, Fitter S, Foeldvari I, Minden K, Kuemmerle-Deschner J, Tzaribacev N, et al. Double-blind, placebo-controlled randomized trial with adalimumab for treatment of juvenile onset ankylosing

- spondylitis (JoAS): significant short term improvement. *Arthritis Res Ther*. 2012;14(5):R230.
18. Ruperto N, Lovell DJ, Cuttica R, Wilkinson N, Woo P, Espada G, et al. A randomized, placebo-controlled trial of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis. *Arthritis Rheum*. 2007;56(9):3096–106.
 19. Ruperto N, Lovell DJ, Cuttica R, Woo P, Meiorin S, Wouters C, et al. 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. *Ann Rheum Dis*. 2010;69(4):718–22.
 20. Dougados M, van der Linden S, Juhlin R, Huitfeldt B, Amor B, Calin A, et al. The European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy. *Arthritis Rheum*. 1991;34(10):1218–27.
 21. Prieur AM, Listrat V, Dougados M, Amor B. [Criteria for classification of spondylarthropathies in children]. *Arch Fr Pediatr*. 1993;50(5):379–85.
 22. Cassidy JT, Levinson JE, Bass JC, Baum J, Brewer EJ, Fink CW, et al. A study of classification criteria for a diagnosis of juvenile rheumatoid arthritis. *Arthritis Rheum*. 1986;29(2):274–81.
 23. Cardiel MH, Londoño JD, Gutiérrez E, Pacheco-Tena C, Vázquez-Mellado J, Burgos-Vargas R. Translation, cross-cultural adaptation, and validation of the Bath Ankylosing Spondylitis Functional Index (BASFI), the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Dougados Functional Index (DFI) in a Spanish speaking population with spondyloarthropathies. *Clin Exp Rheumatol*. 2003;21(4):451–8.
 24. Duarte C, Ruperto N, Goycochea MV, Maldonado R, Beristain R, De Inocencio J, et al. The Mexican version of the Childhood Health Assessment Questionnaire (CHAQ) and the Child Health Questionnaire (CHQ). *Clin Exp Rheumatol*. 2001;19(4 Suppl 23):S106-10.
 25. Anderson JJ, Baron G, van der Heijde D, Felson DT, Dougados M. Ankylosing spondylitis assessment group preliminary definition of short-term improvement in ankylosing spondylitis. *Arthritis Rheum*. 2001;44(8):1876–86.
 26. Brandt J, Listing J, Sieper J, Rudwaleit M, van der Heijde D, Braun J. Development and preselection of criteria for short term improvement after anti-TNF alpha treatment in ankylosing spondylitis. *Ann Rheum Dis*. 2004;63(11):1438–44.
 27. Vickers AJ. The use of percentage change from baseline as an outcome in a controlled trial is statistically inefficient: a simulation study. *BMC Med Res Methodol*. 2001;1:6.
 28. Smith JA, Burgos-Vargas R. Outcomes in Juvenile-Onset Spondyloarthritis. *Front Med (Lausanne)*. 2021;8:680916.
 29. Jadon DR, Ramanan AV, Sengupta R. Juvenile versus adult-onset ankylosing spondylitis – clinical, radiographic, and social outcomes. a systematic review. *J Rheumatol*. 2013;40(11):1797–805.
 30. Flatø B, Smerdel A, Johnston V, Lien G, Dale K, Vinje O, et al. The influence of patient characteristics, disease variables, and HLA alleles on the development of radiographically evident sacroiliitis in juvenile idiopathic arthritis. *Arthritis Rheum*. 2002;46(4):986–94.

31. Selvaag AM, Flatø B, Dale K, Lien G, Vinje O, Smerdel-Ramoya A, et al. Radiographic and clinical outcome in early juvenile rheumatoid arthritis and juvenile spondyloarthritis: a 3-year prospective study. *J Rheumatol.* 2006;33(7):1382–91.
32. Minden K, Niewerth M, Listing J, Biedermann T, Bollow M, Schöntube M, et al. Long-term outcome in patients with juvenile idiopathic arthritis. *Arthritis Rheum.* 2002;46(9):2392–401.
33. Weiß A, Minden K, Listing J, Foeldvari I, Sieper J, Rudwaleit M. Course of patients with juvenile spondyloarthritis during 4 years of observation, juvenile part of GESPIC. *RMD Open.* 2017;3(1):e000366.
34. Minden K, Kiessling U, Listing J, Niewerth M, Döring E, Meincke J, et al. Prognosis of patients with juvenile chronic arthritis and juvenile spondyloarthritis. *J Rheumatol.* 2000;27(9):2256–63.
35. Flatø B, Aasland A, Vinje O, Førre O. Outcome and predictive factors in juvenile rheumatoid arthritis and juvenile spondyloarthritis. *J Rheumatol.* 1998;25(2):366–75.
36. Duarte-Salazar C, Guzmán-Vázquez S, Soto-Molina H, Cháidez-Rosales P, Ilizaliturri-Sánchez V, Nieves-Silva J, et al. Disability impact on quality of life in Mexican adults with juvenile idiopathic arthritis and juvenile ankylosing spondylitis. *Clin Exp Rheumatol.* 2007;25(6):922–7.
37. Weiss PF, Beukelman T, Schanberg LE, Kimura Y, Colbert RA, Investigators CR. Enthesitis-related arthritis is associated with higher pain intensity and poorer health status in comparison with other categories of juvenile idiopathic arthritis: the Childhood Arthritis and Rheumatology Research Alliance Registry. *J Rheumatol.* 2012;39(12):2341–51.
38. Rumsey DG, Lougee A, Matsouaka R, Collier DH, Schanberg LE, Schenfeld J, et al. Juvenile Spondyloarthritis in the CARRA Registry: High Biologic Use, Low Prevalence of HLA-B27, and Equal Sex Representation in Sacroiliitis. *Arthritis Care Res (Hoboken).* 2020.
39. Ruperto N, Lovell DJ, Quartier P, Paz E, Rubio-Pérez N, Silva CA, et al. Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. *Lancet.* 2008;372(9636):383–91.
40. Ruperto N, Giannini EH, Pistorio A, Brunner HI, Martini A, Lovell DJ. Is it time to move to active comparator trials in juvenile idiopathic arthritis?: a review of current study designs. *Arthritis Rheum.* 2010;62(11):3131–9.
41. Giannini EH, Lovell DJ, Silverman ED, Sundel RP, Tague BL, Ruperto N. Intravenous immunoglobulin in the treatment of polyarticular juvenile rheumatoid arthritis: a phase I/II study. *Pediatric Rheumatology Collaborative Study Group. J Rheumatol.* 1996;23(5):919–24.
42. Wallace CA, Giannini EH, Huang B, Irt L, Ruperto N, Alliance CARR, et al. American College of Rheumatology provisional criteria for defining clinical inactive disease in select categories of juvenile idiopathic arthritis. *Arthritis Care Res (Hoboken).* 2011;63(7):929–36.
43. Foeldvari I, Constantin T, Vojinović J, Horneff G, Chasnyk V, Dehoorne J, et al. Etanercept treatment for extended oligoarticular juvenile idiopathic arthritis, enthesitis-related arthritis, or psoriatic arthritis: 6-year efficacy and safety data from an open-label trial. *Arthritis Res Ther.* 2019;21(1):125.

44. Swart J, Giancane G, Horneff G, Magnusson B, Hofer M, Alexeeva E, et al. Pharmacovigilance in juvenile idiopathic arthritis patients treated with biologic or synthetic drugs: combined data of more than 15,000 patients from Pharmachild and national registries. *Arthritis Res Ther*. 2018;20(1):285.
45. Giancane G, Swart JF, Castagnola E, Groll AH, Horneff G, Huppertz HI, et al. Opportunistic infections in immunosuppressed patients with juvenile idiopathic arthritis: analysis by the Pharmachild Safety Adjudication Committee. *Arthritis Res Ther*. 2020;22(1):71.
46. Thiele F, Klein A, Windschall D, Hospach A, Foeldvari I, Minden K, et al. Comparative risk of infections among real-world users of biologics for juvenile idiopathic arthritis: data from the German BIKER registry. *Rheumatol Int*. 2021;41(4):751–62.
47. Klein A, Becker I, Minden K, Hospach A, Schwarz T, Foeldvari I, et al. Biologic Therapies in Polyarticular Juvenile Idiopathic Arthritis. Comparison of Long-Term Safety Data from the German BIKER Registry. *ACR Open Rheumatol*. 2020;2(1):37–47.
48. Klein A, Klotsche J, Hügler B, Minden K, Hospach A, Weller-Heinemann F, et al. Long-term surveillance of biologic therapies in systemic-onset juvenile idiopathic arthritis: data from the German BIKER registry. *Rheumatology (Oxford)*. 2020;59(9):2287–98.
49. Tambralli A, Beukelman T, Weiser P, Atkinson TP, Cron RQ, Stoll ML. High doses of infliximab in the management of juvenile idiopathic arthritis. *J Rheumatol*. 2013;40(10):1749–55.
50. Arepalli S, Rosenbaum JT. The use of biologics for uveitis associated with spondyloarthritis. *Curr Opin Rheumatol*. 2019;31(4):349–54.
51. van der Heijde D, Lie E, Kvien TK, Sieper J, Van den Bosch F, Listing J, et al. ASDAS, a highly discriminatory ASAS-endorsed disease activity score in patients with ankylosing spondylitis. *Ann Rheum Dis*. 2009;68(12):1811–8.
52. Machado P, Landewé R, Lie E, Kvien TK, Braun J, Baker D, et al. Ankylosing Spondylitis Disease Activity Score (ASDAS): defining cut-off values for disease activity states and improvement scores. *Ann Rheum Dis*. 2011;70(1):47–53.
53. Zanwar A, Phatak S, Aggarwal A. Prospective validation of the Juvenile Spondyloarthritis Disease Activity Index in children with enthesitis-related arthritis. *Rheumatology (Oxford)*. 2018;57(12):2167–71.
54. Consolaro A, Ruperto N, Bazso A, Pistorio A, Magni-Manzoni S, Filocamo G, et al. Development and validation of a composite disease activity score for juvenile idiopathic arthritis. *Arthritis Rheum*. 2009;61(5):658–66.

Figures

Figure 1

CONSORT flowchart Infliximab in Juvenile onset SpA trial.

Figure 2

Mean active joint counts, swollen joint counts, tender joint counts and tender enthesis counts registered during the entire duration of the study (RCT + OLE phases) by treatment group according to randomization. **A**, mean active joint count (primary outcome). **B**, **C**, and **D**, mean number of swollen joints, tender joints, and tender enthesis, respectively. All comparisons showed a significant difference between Infiximab and placebo by week 12. In the open label extension, in which all patients received infiximab, the mean of each outcome showed a sustained response to Infiximab.

Figure 3

Mean level of high-sensitive C reactive protein (hs-CRP) and Childhood Health Assessment Questionnaire score (CHAQ) registered during the entire duration of the study (RCT + OLE phases) by treatment group according to randomization. **A**, mean hsCRP serum levels in mg/dL. **B**, mean CHAQ scores. Lines showed a significant and sustained positive effect of Infliximab over time.

Figure 4

Percentage of patients reaching the American College of Rheumatology (ACR) Paediatric 30 (Pedi 30), 50, 70, 90, and 100 response criteria per treatment group at week 12 (end RCT phase).

Figure 5

Percentage of patients reaching the Assessment of Spondyloarthritis international Society (ASAS) 20, 40, partial remission, and 5/6 response criteria per treatment group at week 12 (end RCT phase).