The "head-to-head" comparison of etanercept and infliximab in treating children with juvenile idiopathic arthritis

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Abstract

Introduction

Our aim was to assess long-term efficacy and tolerability of etanercept and infliximab in patients with JIA.

Materials and methods

This was an observational, retrospective study of 41 patients treated with anti-TNF therapy. We assessed clinical remission, flare, ACR improvement, improvement of DAS-28, and JADAS. Some patients with polyarticular JIA were scored according to the modified SHARP criteria.

Results

Twenty-four weeks after beginning of therapy 35 patients (92.1%) achieved ACR 20, 33 patients (86.8%) ACR 30, 31 patients (81.6%) ACR 50, 28 patients (73.7%) ACR 70 and 20 patients (52.6%) ACR 90. In the same period 19 patients (50%) had good DAS-28 response, 12 patients (31.6%) had moderate response, and 5 patients (13.2%) did not respond to therapy. Statistically significant difference was shown in the average value of JADAS-71 before the beginning and 24 weeks after introduction of anti-TNF therapy. Eleven patients had a flare in the study period (28.9%); five on etanercept (13.1%), three on infliximab (7.9%), and three flared on both of the medications (7.9%). After 12 months, fifteen patients fulfilled criteria for clinical remission on medications. Seven of them were on infliximab and eight on etanercept. Eleven patients have fulfilled criteria for clinical remission off of medications: three were taking etanercept, seven infliximab, and one was switched from etanercept to infliximab.

Conclusion

In our patient cohort, both etanercept and infliximab performed well, since we found no significant difference in the duration, response, flare, resistance or adverse effects between both drugs, however long term remissions are rare.

Key words

juvenile idiopathic arthritis, infliximab, etanercept.

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Introduction

Juvenile idiopathic arthritis (JIA) is a chronic inflammatory disease with a widely variable clinical course and outcome (1). Studies assessing outcome of juvenile idiopathic arthritis have provided inconsistent or conflicting results. Studies in the past 10 years have shown that only 40–60% of patients had inactive disease or clinical remission at follow-up (2-3).

The management of juvenile idiopathic arthritis is based on the combination of pharmacological interventions, physical and occupational therapy, and psychosocial support (4-7). The aim of treatment is to reach complete control of the disease, to preserve the physical and psychological integrity of the child, and to prevent any long-term consequence related to the disease or its therapy (1). Periodic radiograph examination of affected joints is helpful to document progression of erosive disease (8-10). In the last decade or two, there have been major changes in the treatment of patients with JIA, in particular the introduction of methotrexate (MTX) and other disease-modifying anti-rheumatic drugs (DMARDs) and intra-articular corticosteroid injections (11). The introduction of biological medications has provided a very important new therapeutic option for the treatment of patients with juvenile idiopathic arthritis, who are resistant to conventional antirheumatic agents. A controlled study in patients with polyarticular disease course has shown the efficacy of etanercept, at a subcutaneous dose of 0.4mg/kg twice a week (or 0.8mg/kg once a week), in patients who were resistant or intolerant to methotrexate (12). Subsequently, other studies have confirmed the remarkable and rapid efficacy and the good safety profile of the drug (13-14). Etanercept lowers the quantity of free TNF-α available for maintenance of the inflammatory synovitis of JIA (15). Until recently, etanercept was the only anti-TNF agent registered for paediatric use (13). However, controlled trials with other anti-TNF agents such as infliximab and adalimumab have been done, and have shown similar success rates (16-17). Reports of the efficacy of etanercept and infliximab in patients with juvenile spondyloarthritides suggest that these drugs could also play a prominent part in the treatment of these disorders (18-20). Anti-TNF agents in children are usually well tolerated; however, physicians should remain alert for potential side-effects, especially after extended use (21). Since cases of reactivated tuberculosis have been reported during treatment with TNF inhibitors, all children should have documented negative tuberculosis test before any biological therapy is started (22).

Our aim was to assess long-term efficacy and tolerability of etanercept and infliximab in patients with JIA who had experienced an inadequate response to standard therapy of JIA in the routine care setting.

Materials and methods

This was an observational, retrospective study of 41 patients treated with anti-TNF therapy in two tertiary paediatric rheumatology centres in Croatia between 2005 and 2009. All patients were diagnosed with various forms of juvenile idiopathic arthritis. In 38 patients we have made assessment after six months and after one year, and in 24 patients after two or more years, regardless whether they stopped taking therapy or not, and they were subject to further analysis. Three patients were taking therapy for less than six months, and were excluded from further analysis. Anti-TNF therapy was administered to patients who fulfilled criteria of the Croatian national health insurance, which included no improvement after six months of therapy with methotrexate or leflunamide, and dependence on daily doses of steroids (0.5mg/kg or more). All patients received anti-TNF therapy along with methotrexate or leflunamide. Leflunamide was used only if patients developed side effects to methotrexate. There are no world accepted criteria on whether a patient should receive etanercept or infliximab (23). In our case, seventeen patients were treated with etanercept, fourteen with infliximab and seven patients were switched from one medication to the other due to the lack of efficacy. Infliximab was administered as an in-

travenous infusion (3–5mg/kg, loading dose + q 6 wks) and etanercept as subcutaneous injection (0.4mg/kg twice a week, or 0.8mg/kg once a week). Data on age, gender, diagnosis, duration of disease, and duration of the therapy were recorded. Core Set Criteria for improvement in Juvenile Idiopathic Arthritis were gathered at the beginning of the treatment, after six months, after one year, as well as after two or more years. Criteria include number of active joints, number of joints with loss of motion, physician's global assessment, parent's global assessment, Croatian version of childhood health assessment questionnaire (C-HAQ) and ESR (24-27). Some patients with hand involvement underwent radiographic imaging of the wrist before the beginning of the therapy, as well as after 24 weeks. Images were scored according to the modified SHARP criteria by one experienced paediatric radiologist in the field (10). After 6, 12 and 24 or more months of treatment clinical remission and ACR improvement according to definition, as well as improvement of DAS-28, and JADAS-71 (see below), were assessed.

Clinical remission on medications was defined as inactive disease for at least 6 consecutive months while the patient is taking medication (28). Clinical remission off of medications was defined as inactive disease for at least 12 consecutive months without the patient taking any anti-arthritis or anti-uveitis medications (27-28). Criteria for inactive disease were as follows: no joints with active arthritis; no fever, rash, serositis, splenomegaly or generalised lymphoadenopathy attributable to JIA; no active uveitis; normal ESR or CRP (if both are tested, both must be normal); physician's global assessment of disease activity indicates no disease activity (24). Disease flare was defined as 40% worsening in two out of six core set items without improvement in more than one core set variable by 30% or more (28).

The American College of Rheumatology has defined ACR 30 improvement as 30% or greater improvement in 3 of 6 items and a worsening of 30% in no more than one item. The ACR Pedi 50, 70 and 90 require a 50%, 70% or 90% improvement in 3 of 6 items with worsening of 30% in no more than 1 item (25).

DAS-28 equitation incorporates a swollen and tender joint count (based on a 28 joint count), erythrocyte sedimentation rate (ESR) and patient's assessment of general health. Good improvement in DAS-28 was achieved if 24 months of therapy DAS-28 values were lower by more than 1.2; moderate if values were lower by 0.6–1.2; and there was no response if the values were lower by 0.6 or less (29-30).

The Juvenile Arthritis Disease Activity Score (JADAS) is a newly developed composite disease activity score for juvenile idiopathic arthritis (JIA) that includes 4 measures: 1) physician's global assessment of disease activity; 2) parent/patient's global assessment of well-being; 3) active joint count; 4) erythrocyte sedimentation rate (31).

Statistical analysis

Data compiled from a retrospective chart review of all study patients were extracted by using specially prepared data forms at baseline, after 6 months, 12 months, and 2 or more years. The information extracted, where available, included demographic data, medication history, physician global assessment, parent global assessment, active joint count, restricted joint count, markers of inflammation and functional assessment by the Croatian version of the Childhood Health Assessment Questionnaire (C-HAQ). The Level of significance was set at 0.05. Data comparison of CORE set variables before and after therapy was made using the Mann-Whitney independent samples test. The same test was used for the comparison of DAS-28 and JADAS-71 values before and after therapy, comparison of the modified SHARP score before and after therapy and for comparison of therapy duration. The correlation coefficient was used to analyse the degree of association between the DAS-28 and JADAS-71 tests. ROC analysis for two disease activity scores included a full Roc report with all criterion values and coordinates of the ROC curve. Cut of criterion was chosen based on the best ratio between the positive (+PV) and negative (-PV) predictive value, but also included the best possible specificity/sensitivity ratio. All results are presented with 95% confidence intervals and significance *p*-level for the test, which was considered significant if lower or equal to 0.05 ($p \leq 0{,}05$). It was important to determine the best diagnostic odds (DO) that each of the above mentioned tests has for the specific sample group, which were calculated from measuring the positive and negative likelihood ratio in each case, also presented with 95% confidence intervals. Statistical analysis was done using MedCalc® statistical software (MedCalc 10.1.3.1., Frank Schoonjans, Mariakerke, Belgium).

Results

Between 2001 and 2009, 41 patients received etanercept or/and infliximab in our two paediatric rheumatology clinics. Table I shows demographic and clinical characteristics of the patients, their diagnosis, disease duration, and HLA B27/DR4 positivity. Table I also shows patients distribution according to ILAR classification.

As expected, the majority of patients were RF negative poliarticular patients (41%), followed by persistant oligoarticular patients (20%), RF positive poliarticular patients (15%), extended oligoarticular patients (9%), enthesitis-related patients (9%), psoriatic arthritis (3%), and others (3%). In the last category one patient with diagnosis of polyarticular RF negative JIA was treated with etanercept for 16 months and with infliximab for another 77 months, before the final diagnosis of Blau syndrome based on genetic analysis was made. The patient now has a much better response treated with adalimumab. No patients with systemic-onset JIA were treated with anti-TNF agents at the time of the study. Furthermore, no difference was found in the treatment between etanercept and infliximab.

Measures of disease activity

Improvement. Core set variables were assessed at therapy initiation, after 6 and 12 months, and finally 24 or more months after introduction of therapy. The values are shown in Figure 1.

Table I. The demographic and clinical characteristics of the study patients divided according to ILAR classification.

Diagnosis	No. of patients M/F	Mean age at the beginning of the disease (*yrs, range*)	Mean age at the beginning of anti-TNF therapy (*yrs, range*)	Duration of anti-TNF therapy (*months, range*)	Disease duration at the beginning of the therapy (*yrs, range*)	HLA B27/DR4
Oligoarthritis persistent	8 /6	5.4 (2–8)	8.7 (2–14)	20.55 (10–39)	3.7 (1–8)	1/0
Oligoarthritis extended	3 /2	5.2	11.8	21.5	5	0
Polyarthritis RF+	6 /2	10.2 (2–15)	14,1 (8–18)	23.3 (9–37)	3.7 (1–10)	0/1
Polyarthritis RF-	19 /12	7.2 (1–15)	11.1 (2–18)	34.8 (8–75)	3.6 (1–11)	5/0
ErA	3 /0	7.7 (4–13)	12.7 (7–16)	41.3 (25–65)	6.3 (4–10)	1/2
Psoriatic arthritis	1 /1	2	11	31	8	0
Other	1 /0	1	7	93	6	1/0
TOTAL	41 /25	6.9 (1–15)	11 (2–18)	30.9 (8–93)	4.1 (1–11)	8/3

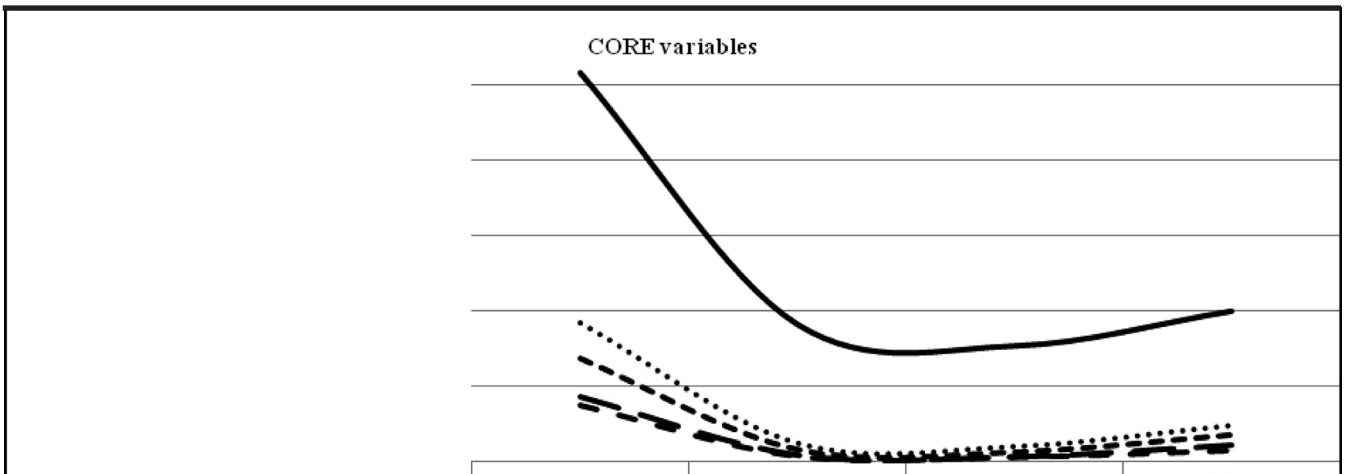
Using the Mann-Whitney statistical test we have found statistical differences ($p \leq 0.05$) in values of core set variables at the beginning of therapy and after 6, 12 and 24 months in the number of active joints, VAS-MD and VAS-PATIENT. There was also a statistically significant difference ($p \leq 0.05$) between values of C-HAQ at the beginning of therapy and after 24 months.

During the study period, seventeen patients received only etanercept and fourteen only infliximab. Due to the lack of efficacy, four patients were switched from etanercept to infliximab, and three from infliximab to etanercept. For the same reason three patients were switched to adalimumab, one after taking only etanercept, and two after taking both etanercept and infliximab (data not shown). Hence, the total number of patients treated with etanercept was twenty-four and the total number of patients treated with infliximab was twenty-one.

Twenty-four weeks after the beginning of therapy we assessed achievement of ACR 20, ACR 30, ACR 50, ACR 70 and ACR 90 in 38 patients on anti-TNF therapy. Thirty-five patients (92.1%) achieved ACR 20, thirty-three patients (86.8%) ACR 30, thirty-one patients (81.6%) ACR 50, twenty-eight patients (73.7%) ACR 70 and twenty patients (52.6%) ACR 90.

The differences between values of the CORE variables among patients starting therapy with etanercept or infliximab are shown in Figure 2.

Nineteen patients (50%) had good DAS-28 response after ≥24 weeks of therapy, twelve patients (31.6%) had moderate response, and five patients (13.2%) did not respond to therapy. In the etanercept group, eleven patients (52.38%) had good response, seven (33.33%) had moderate response, and three (14.29%) did not respond. In the



	At the begining:	After 6 months	After 12 months	After 24 or more months
SE:	33,2	15,8	13,4	15,2
VAS PATIENT:	4,6	0,8	0,7	1,2
VASD MD:	5,1	0,8	0,7	1,4
No. Of joints with limited range of motion:	1,1	0,16	0	0,7
No. Of active joints:	7,5	0,6	0,5	1,40

Fig. 1. Core set variables at the beginning of therapy, and 6, 12, and 24 or more months later.

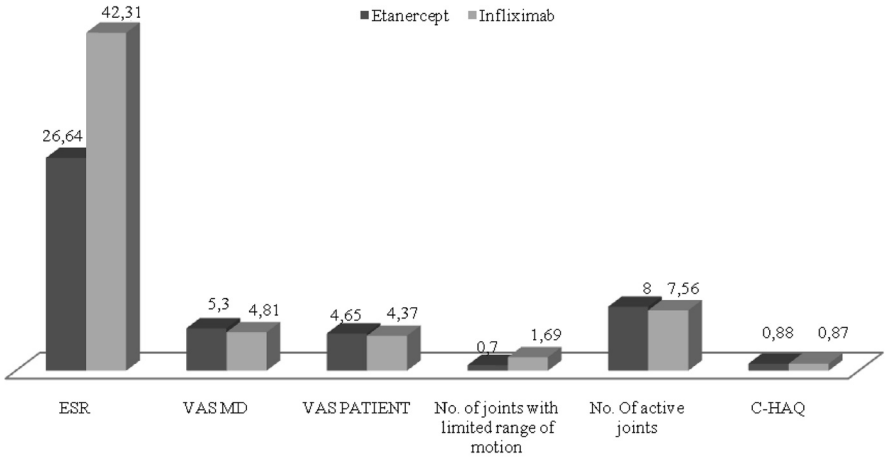


Fig. 2. Differences in values of CORE variables among patients at the beginning of treatment with infliximab or etanercept.

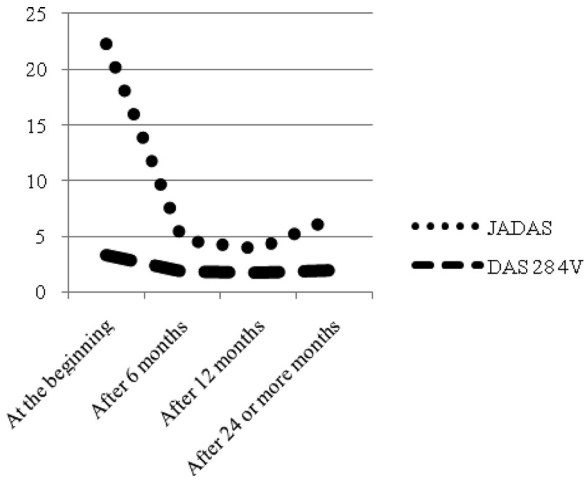


Fig. 3. Differences in DAS28 and JADAS-71 before the therapy, after 6 months, after 12 months and 24 or more months after the beginning of therapy.

group of infliximab patients eight (50%) had good response, five (31.25%) had moderate response, and three (18.75%) did not respond. There was a statistically significant difference between the average value of DAS-28 at the beginning of therapy compared to 24 or more weeks later, DAS-28 dropping from 3.31 to 1.97 (p<0.0001). Similarly, a statistically significant difference was shown in DAS-28 before and 24 weeks after the beginning of therapy with either etanercept (p=0.0003) or infliximab (p=0.0016).

In addition, statistically significant difference was shown in the average value of JADAS-71 before the beginning and 24 weeks after introduction of anti-TNF therapy; JADAS-71 dropped from 19 to 4.71 (±SD, p<0.0001) and similarly to DAS-28 significant difference was also found for either therapy with etanercept (p<0.0001) or infliximab (p<0.0001), respectively. The comparative differences between DAS-28 and JADAS-71 before starting therapy with etanercept and infliximab and 24 or more months after starting therapy are shown in Figure 3.

Flares. Eleven patients had a flare in the study period (28.9%); five on etanercept (13.1%), three on infliximab (7.9%), and three flared on both medications (7.9%). One patient flared in oligo extended group, one in poli RF positive, eight in poli RF negative, and one patient with Blau syndrome.

Remissions. After twelve, months, fifteen patients fulfilled criteria for clinical remission on medications, which was 35.9% of patients in the study: five of them were from the group diagnosed with persistent oligoarthritis, three were from RF positive polyarthritis group, five were from RF negative polyarthritis group, and two were from group of patients diagnosed with enthesitis related arthritis. Out of these fifteen patients, seven of them were on infliximab and eight on etanercept. Furthermore, eleven patients have fulfilled criteria for clinical remission off of medications, and that stands for 28,9% of patients in the study: five of them were in oligoarthritis persistant group, one in RF positive polyarthritis group, four in RF negative polyarthritis group, and two in group of patients diagnosed with enthesitis related arthritis. Of those eleven patients, three were taking etanercept, seven infliximab, and one was switched from etanercept to infliximab, because of the flare while taking etanercept. Average duration of therapy for those eleven patients was 19 months.

Other. Three patients continued with the treatment, and because of the age (>18 years) were switched to the division of adult rheumatology. We had one case of an unplanned pregnancy, and due to possible causative effects of anti-TNF therapy on congenital anomalies (32), we immediately stopped therapy with etanercept. After the birth, the baby was fine, with no congenital anomalies.

Measurement of the joint damage. In patients with polyarticular JIA (n=9) we found no statistically significant difference between modified SHARP score before and after 24 weeks of anti-TNF therapy (p=0.5715, although this analysis is poorly significant due to the small number of patients. (Data not shown).

Correlation between DAS-28 and JADAS-71. The correlation coefficient r between DAS-28 and JADAS-71was 0,8431 at the beginning of therapy (p<0.0001) and 0.228 twenty-four or more months after that (p<0.0001).

ROC analysis for two disease activity scores DAS-28 and JADAS-7. Comparison of DAS 28 and JADAS-71 by ROC analysis showed no significant difference in specificity, sensitivity or predictive values for detecting remission or flare in the sample group of patients on and off of the biological therapy (Table II).

Evaluation of positive and negative predictive values of DAS-28 and JADAS-71 were limited. Nevertheless,

Table II. Comparative ROC analysis of DAS28 and JADAS–71.

	AUC	LST	DO	+PV	–PV	Specificity	Sensitivity
ROC analysis for remission in patients on biological therapy							
A	0.827 (0.655–0.935)	0.0013	8.33 (1.276–54.42)	71.40 (74.8–98.8)	92.30 (74.8–98.8)	92.31%	71.43%
B	0.897 (0.749–0.972)	0.0001	33.75 (3.815–298.5)	93.3 (77.9–99.0)	83.3 (36.1–97.2)	71.43%	96.55%
C	*0.0632 (-0.0667–0.193)*	*0.340*	–	–	–	–	–
ROC analysis for remission in patients off of biological therapy							
A	0.715 (0.532–0.857)	0.0182	17.5 (1.701–180)	71.4 (29.3–95.5)	76.9 (56.3–91.0)	90.91%	45.45%
B	0.711 (0.536–0.849)	0.0150	7.714 (0.850–69.99)	52.4 (29.8–74.3)	86.7 (59.5–98.0)	56.52%	84.62%
C	*0.0558 (-0.0817–0.193)*	*0.427*	–	–	–	–	–
ROC analysis detecting flair in patients on biological therapy							
A	0.647 (0.462–0.804)	0.154	12.1 (1.315–111.3)	45.5 (24.4–67.8)	81.8 (48.2–97.2)	42.86%	83.33%
B	0.660 (0.483–0.809)	0.1117	2.8 (0.6718–11.67)	60.0 (26.4–87.6)	76.9 (56.3–91.0)	83.33%	50.0%
C	*0.00397 (-0.134–0.142)*	*0.95*	–	–	–	–	–
ROC analysis detecting flair in patients off of biological therapy							
A	0.760 (0.576–0.892)	0.0066	4.091 (0.71–23.61)	52.9 (27.9–77.0)	86.7 (59.5–98.0)	61.90%	81.82%
B	0.775 (0.603–0.898)	0.0020	6.857 (1.412–33.29)	60.0 (32.3–83.6)	85.0 (62.1–96.6)	73.91%	75.0%
C	*0.0087 (-0.128–0.145)*	*0.901*	–	–	–	–	–

A: DAS28; B: JADAS-71; C: Differences between DAS28 and JADAS-71; AUC: Area under ROC curve; LST: Level of significance of the test; DO: Diagnostic odds. +PV: Positive predictive value; -PV: Negative predictive value.

DO for JADAS-71 score are greatly higher in detecting remission in patients on anti-TNF-α therapy, while the DAS-28 score is more precise in detecting remission in patients off of biological therapy and flare in patients still receiving therapy. In the case of evaluating both scores for detecting a clinical flare in patients in remission and off of biological therapy, the JADAS-71 score is low but with significant DO, while the DAS-28 score is inadequate for detecting flare in clinical practice.

Side effects. Serious adverse events were recorded in only two patients. One girl developed osteomyelitis six months after beginning of therapy with etanercept. She was admitted to the hospital and treated with combined intravenous and *per os* antibiotics for 6 weeks, while etanercept was temporarily discontinued. However, since her arthritis flared, she was successfully restarted with etanercept one month after stopping the antibiotics. She had no further side effects and is currently still on etanercept. The other patient experienced reactivation of EBV infection, splenomegaly and hypersplenism after 9 months on etanercept. Splenectomy was preformed after which etanercept was continued and no further adverse events were recorded. No other patient taking etanercept or infliximab required hospitalisation during the time of treatment. Only five patients had mild infusion-related reactions (with infliximab), which resolved with a decreased rate of infusion, and only one patient had those reactions more than once. None of the patients required discontinuation of therapy due to infusion-related reactions. The presence of anti-infliximab antibodies, which might contribute to those infusion reactions, was not assessed. One patient got pregnant while on etanercept therapy. Unfortunately, the pregnancy was not reported until the second trimester, when therapy was discontinued immediately, and according to collected information's both baby and mother are doing well. No case of malignancy was reported. Side effects are shown in Table III.

Discussion

This study describes the experience of the two major paediatric rheumatology tertiary centres in Croatia with anti-TNF therapy in JIA patients. Although significantly improved in recent years, the outcome for children with JIA is still far from ideal. Early aggressive control of inflammation is essential in order to prevent long-term disability. For those children that are resistant to standard therapy, the introduction of biologic therapy offers new hope. However, very few "head-to head" studies are available for evaluation of disease activity (disease flare, improvement, and remission), long-term efficacy, side-effects of biologics and finally, the outcome of JIA patients (12-14, 33). In our patient cohort both etanercept and infliximab performed well, since we found no significant difference in the duration, response, flare, resistance or adverse effects between both drugs. The majority of patients reached remission on medications (*e.g.* inactive disease); however the likelihood of

Table III. Side effects of etanercept[1] or infliximab[2].

Type of reaction	No. of patients	No. of episodes
Infusion related: chest pain, chills, shortness of breath[2]	5	9
Severe hypertension[2]	2	5
Vomiting, fever[1]	1	1
Osteomyelitis[1]	1	1
Hypersplenomegaly, hypersplenizm[1]	1	1

continued remission off of medication diminished with time. Four out of six core set variables (*e.g.* number of active joints, VAS-MD, VAS-PATIENT and CHAQ, respectively) significantly improved, and remained improved after 24 weeks of anti-TNF therapy. Using ACR indices, we found that thirty-five patients (92.1%) achieved ACR 20, thirty-three patients (86.8%) ACR 30, thirty-one patients (81.6%) ACR 50, twenty-eight patients (73.7%) ACR 70 and 20 patients (52.6%) ACR 90, respectively, after twenty-four weeks on anti-TNF therapy. Eleven patients had a flare on anti-TNF therapy; five on etanercept, three on infliximab and three flared on both of the medications. After twelve months of therapy, fifteen patients fulfilled criteria for clinical remission on medications; seven of them were on infliximab and eight on etanercept. Out of twenty-four patients who were assessed after 24 or more months, only eleven patients fulfilled criteria for clinical remission off of medications. Of those eleven patients, three were taking etanercept, seven infliximab and one was switched from etanercept to infliximab, because of the flare while taking etanercept. The average duration of therapy for those eleven patients was 19 months. Therefore, it seems that both etanercept and infliximab are curative only in the minority of patients. There are many possible explanations for that; firstly we use biologics in general as the third line therapy, rather late in the course of the disease, because we lack reliable biomarker(s) which would be helpful in adjusting patients who would benefit from biologics early in the course of the disease. Similarly to adults, the combination of steroids and anti-TNF therapy early in the course of disease might prove to be an alternative solution for children, and therefore results of the "TREAT-Trial of Early Aggressive Drug Therapy in Juvenile Idiopathic Arthritis" are expected with great hopes (34). The recent expansion of genomic and proteomic research will hopefully provide solution(s) for that paramount clinical dilemma. Secondly, "our hands on" and disease activity indices are not sensitive enough to provide crucial information on "who and when" will flare on any medication. We strongly believe that inclusion of ultrasound (US) in the routine daily care might help us in that regard. Paediatric literature on that topic is still scarce, but a recent prospective study on newly diagnosed JIA patients with knee joint involvement has showed that US is more sensitive than both clinical examination and MRI in detecting disease activity (35). Furthermore, the study from Italy showed that subclinical synovitis as detected by US is common in children with JIA; of the 1,560 clinically normal joints, 86 (5.5%) had subclinical synovitis (*i.e.*, had synovitis on US) (36). US led to classifying 5 patients as having polyarthritis who were classified as having oligoarthritis or were found to have no synovitis on clinical evaluation. The data from the adult literature are definitely pointing towards the same direction, and gray-scale US in conjunction with power Doppler ultrasound (PDU) has become wildly used in assessing disease activity in RA patients (36-38).

Because no single measure has been identified that is adequate to evaluate outcomes in JIA, and misclassification of active versus inactive disease not uncommon, we attempted to validate on our patient cohort two clinically commonly used indices; DAS-28 commonly used in adult population and recently validated in children, and JADAS-71 recently developed to monitor disease activity in JIA patients, or in those JIA patients treated with either etanercept or infliximab (30, 39-40). Due to a too wide confidence intervals and a small sample size, evaluating positive and negative predictive values between those two tests were obviously limited. Nevertheless, diagnostic odds for JADAS-71 score are greatly higher in detecting remission in patients on anti-TNF-α therapy, while DAS-28 score is more precise in detecting remission in patients off of biological therapy and flair in patients still receiving therapy. JADAS-71 score has low but significant DO for detecting a clinical flair in patients in remission and off of biological therapy, while DAS-28 score is inadequate for detecting flare in clinical practice.

Anti-TNF therapy is generally well-tolerated by both adults and children, and data from long-term studies have not revealed any cumulative toxicities. However, infections, neoplastic complications, hematologic complications, and multiple-sclerosis like neurologic disease have been identified in a small number of patients during post-marketing surveillance and concerns regarding these events exist because long-term experience is still limited (41-42). In particular, the recent FDA boxed warning for a possible increased malignancy risk associated with anti-TNF drugs has put tremendous pressure on both parents and physicians. This action was based on the analysis of 48 malignancies in children treated with anti-TNF drugs (half of which were lymphomas); however, it remains unclear which proportion of the increased risk can be attributed to the use of anti-TNF drugs, to underlying disease, or to other immunosuppressive medications used in the majority (88%) of analysed patients (43). In the past ten years, since we started using anti-TNF therapy, we have seen no cases of malignancy. Until new valid data about the background risk of lymphoma in children and adolescents with JIA is available, we will continue to use those medications with great caution, but it will not prohibit us from using those medications in any way. On line with what is already widely accepted, both etanercept and infliximab were safe in our patients and very few serious adverse events were noted; no reactivation of TB was found in our patients, and the generally seen predisposition to minor viral infections did not interfere with normal daily activities of our patients. We have noted only five infusion reactions in two patients receiving infliximab; both patients were able to successfully continue with therapy with addition of premedication.

This study has several limitations. The patient cohort is rather small, but represents the true clinical experience and challenge given the real life difficulties in availability of those drugs, price and insurance reimbursement problems. In a country with centralised, government-owned insurance company like Croatia, as well as lack of well established, and

world-wide accepted criteria for starting patients on anti-TNF-therapy, the use of biologic therapy is still a challenge in day-to-day clinical practice. The fact that in our patient cohort we use only etanercept and infliximab, and no adalimumab is also a limiting factor. However, recent studies of adalimumab in JIA have showed similar results to ours, in terms of efficacy, flare rate and patient outcome (17). In addition, at the time of the study we had no patients with systemic JIA; therefore we could not evaluate the performance of those two drugs in systemic JIA. However, it is well established that anti-TNF therapy alone or in combination with MTX is markedly less effective in those patients (16).

As the pathogenesis of JIA becomes better understood, the inclusion of various biomarkers, as well as diagnostic methods like bed-side ultrasound performed by a rheumatologist, will certainly have huge impact on the sensitivity and specificity of various outcome measures in children with JIA that would lead to much more improved clinical practice and ultimately, to a tailor-made therapy and much better patient outcomes.

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