

Tumor Necrosis Factor-blocking Agents for Children with Enthesitis-related Arthritis — Data from the Dutch Arthritis and Biologicals in Children Register, 1999-2010

MARIEKE H. OTTEN, FEMKE H.M. PRINCE, MARINKA TWILT, REBECCA ten CATE, WINEKE ARMBRUST, ESTHER P.A.H. HOPPENREIJS, YVONNE KOOPMAN-KEEMINK, NICO M. WULFFRAAT, SIMONE L. GORTER, KOERT M. DOLMAN, JOOST F. SWART, J. MERLIJN van den BERG, MARION A.J. van ROSSUM, and LISETTE W.A. van SUIJLEKOM-SMIT

ABSTRACT. *Objective.* To evaluate the effectiveness and safety of biological agents in children with enthesitis-related arthritis (ERA).

Methods. All patients with ERA in whom a biological agent was initiated between 1999 and 2010 were selected from the Dutch Arthritis and Biologicals in Children (ABC) register. In this ongoing multicenter observational register, data on the course of the disease and medication use are retrieved prospectively at the start of the biological agent, after 3 months, and yearly thereafter. Inactive disease was assessed in accordance with the Wallace criteria.

Results. Twenty-two patients with ERA started taking 1 or more biological agents: 20 took etanercept, 2 took adalimumab (1 switched from etanercept to adalimumab), and 2 took infliximab (1 switched from etanercept to infliximab). Characteristics: 77% were male, 77% had enthesitis, 68% were HLA-B27-positive. The median age of onset was 10.4 (IQR 9.4–12.0) years; median followup from the start of the biological agent was 1.2 (IQR 0.5–2.4) years. Intention-to-treat analysis shows that inactive disease was achieved in 7 of 22 patients (32%) after 3 months, 5 of 13 patients (38%) after 15 months, and 5 of 8 patients (63%) after 27 months of treatment. Two patients discontinued etanercept because of ineffectiveness, and switched to adalimumab (inactive disease achieved) or infliximab (decline in joints with arthritis after 3 months of treatment). One patient discontinued etanercept because of remission, but had flare and restarted treatment, with good clinical response. No serious adverse events occurred.

Conclusion. Tumor necrosis factor (TNF)-blocking agents seem effective and safe for patients with ERA that was previously unresponsive to 1 or more DMARD. However, a sustained disease-free state could not be achieved, and none discontinued TNF-blocking agents successfully. (First Release Aug 15 2011; *J Rheumatol* 2011;38:2258–63; doi:10.3899/jrheum.110145)

Key Indexing Terms:

JUVENILE IDIOPATHIC ARTHRITIS
ANTI-TUMOR NECROSIS FACTOR

ENTHESITIS-RELATED ARTHRITIS
BIOLOGIC THERAPY
RESPONSE

From the Department of Pediatrics/Pediatric Rheumatology, Erasmus MC Sophia Children's Hospital, Rotterdam; Department of Pediatrics/Pediatric Rheumatology, Leiden University Medical Centre, Leiden; Department of Pediatrics/Pediatric Rheumatology, Beatrix Children's Hospital, University Medical Centre Groningen, Groningen; Department of Pediatrics/Pediatric Rheumatology, St. Maartenskliniek, Radboud University Nijmegen Medical Centre, Nijmegen; Department of Pediatrics, Hagaziekenhuis Juliana Children's Hospital, The Hague; Department of Pediatrics/Pediatric Rheumatology, Utrecht MC Wilhelmina Children's Hospital, Utrecht; Department of Internal Medicine, Rheumatology Subdivision, Academic Hospital Maastricht, Maastricht; Department of Pediatrics/Pediatric Rheumatology, St. Lucas Andreas Hospital; Reade, Centre for Revalidation and Rheumatology, Department of Rheumatology; Department of Pediatrics/Pediatric Rheumatology, VU Medical Centre; and Department of Pediatrics/Pediatric Rheumatology, Emma Children's Hospital/Academic Medical Centre, Amsterdam, The Netherlands.

The Board of Health Insurances financed the ABC register from 2003 until 2006. Pfizer B.V. (formerly Wyeth International B.V.) and Abbott B.V. supported the ABC register unconditionally.

M.H. Otten, MD, Department of Pediatrics/Pediatric Rheumatology, Erasmus MC Sophia Children's Hospital; F.H.M. Prince, MD, PhD, MSCE, Department of Pediatrics/Pediatric Rheumatology, Erasmus MC Sophia Children's Hospital; M. Twilt, MD, PhD, MSCE, Department of Pediatrics/Pediatric Rheumatology, Erasmus MC Sophia Children's Hospital, Department of Pediatrics/Pediatric Rheumatology, Leiden University Medical Centre; R. ten Cate, MD, PhD, Department of Pediatrics/Pediatric Rheumatology, Leiden University Medical Centre; W. Armbrust, Department of Pediatrics/Pediatric Rheumatology, Beatrix Children's Hospital, University Medical Centre Groningen; E.P.A.H. Hoppenreijjs, MD, Department of Pediatrics/Pediatric Rheumatology, St. Maartenskliniek, Radboud University Nijmegen Medical Centre; Y. Koopman-Keemink, MD, Department of Pediatrics, Hagaziekenhuis Juliana Children's Hospital; N.M. Wulffraat, MD, PhD, Department of Pediatrics/Pediatric Rheumatology, Utrecht MC Wilhelmina Children's Hospital; S.L. Gorter, MD, PhD, Department of Internal Medicine, Rheumatology Subdivision, Academic Hospital Maastricht; K.M. Dolman, MD, PhD, Department of Pediatrics/Pediatric Rheumatology, St. Lucas Andreas Hospital; Reade, Centre for Revalidation and Rheumatology, Department of Rheumatology;

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2011. All rights reserved.

J.F. Swart, MD, Department of Pediatrics/Pediatric Rheumatology, VU Medical Centre and the Centre for Revalidation and Rheumatology, Department of Rheumatology; J.M. van den Berg, MD, PhD, Department of Pediatrics/Pediatric Rheumatology, Emma Children's Hospital/Academic Medical Centre and Reade, Centre for Revalidation and Rheumatology, Department of Rheumatology; M.A.J. van Rossum, MD, PhD, Department of Pediatrics/Pediatric Rheumatology, Emma Children's Hospital/Academic Medical Centre and Reade, Centre for Revalidation and Rheumatology, Department of Rheumatology; L.W.A. van Suijlekom-Smit, MD, PhD, MSCE, Department of Pediatrics/Pediatric Rheumatology, Erasmus MC Sophia Children's Hospital.

Address correspondence to Dr. M.H. Otten, Department of Pediatrics, Sp 1546, Erasmus MC Sophia Children's Hospital, PO Box 2060, 3000 CB Rotterdam, The Netherlands. E-mail: m.otten@erasmusmc.nl

Accepted for publication June 8, 2011.

The International League of Associations for Rheumatology (ILAR) has described enthesitis-related arthritis (ERA) as a subgroup of juvenile idiopathic arthritis (JIA)¹. ERA is defined as chronic inflammatory arthritis in combination with enthesitis. When either arthritis or enthesitis is absent, 2 or more of the following criteria are required: a history of sacroiliac joint tenderness and/or inflammatory lumbosacral pain, presence of the HLA-B27 antigen, onset of arthritis in a male over 6 years of age, acute (symptomatic) anterior uveitis, or history of HLA-B27-related disease in a first-degree relative¹. This ERA classification replaces previous definitions such as juvenile ankylosing spondylitis (AS), seronegative enthesopathy and arthropathy (SEA) syndrome, and the more general term juvenile spondyloarthropathy. Sacroiliitis and spondylitis most often develop 5 to 10 years after disease onset, and extraarticular manifestations such as anterior uveitis occur occasionally². A followup study demonstrated that the SEA syndrome frequently progresses to AS; for ERA this is still unknown³.

Anti-tumor necrosis factor- α (anti-TNF) agents have been proven to be effective for adult-onset AS and for polyarticular course JIA^{4,5,6,7,8,9,10}. However, the randomized controlled trials conducted in children comparing anti-TNF agents with placebo did not evaluate patients with the ERA subtype^{6,8,9}. Only a few case series focused on the effectiveness of etanercept for patients with the ERA subtype. These studies all showed impressive improvements of etanercept on both the arthritis and enthesitis, with ACRpedi30 improvements in up to 100% of the patients and as early as 6 weeks after start of treatment^{11,12,13}. Limitations of these studies are that most data were retrospective and had a maximum followup of 2 years. Until now no studies focused on other anti-TNF agents (adalimumab or infliximab) for use in this patient group. A multicenter open-label study to evaluate the effect of etanercept in the ERA subtype is pending; however, data regarding the primary outcome in a time-frame of 12 weeks are not expected until 2013¹⁴. The longterm effectiveness of TNF- α -blocking agents in ERA remains unknown. Therefore we conducted this prospective

study to evaluate the (longterm) effectiveness and safety of TNF- α -blocking agents in patients with ERA.

MATERIALS AND METHODS

Our study is embedded in the Arthritis and Biologicals in Children (ABC) register, a multicenter prospective observational study that includes all Dutch patients with JIA in whom a biological agent is prescribed, from the first introduction in 1999. More than 350 patients are included in the register. In 2008 this register was made Web-based¹⁵. The study protocol was approved by the Medical Ethics Committee at Erasmus MC, Rotterdam, and by all participating hospitals. In the register, patient and disease characteristics are collected at baseline. Data on the course of the disease are prospectively retrieved at start of treatment, after 3 months of treatment, and yearly thereafter until transfer to adult care. This includes the variables of the JIA core set: the physician's global assessment of disease activity by visual analog scale (VAS; range 0–100 mm, 0 = best score); the Childhood Health Assessment Questionnaire (CHAQ) test of functional ability (range 0–3, 0 = best score) by patients or parents, including global assessment of well-being by VAS; the number of active and limited joints; and the erythrocyte sedimentation rate (ESR). Additionally, the global assessment of pain by VAS was included. Data on enthesitis and sacroiliac involvement are not included in the JIA disease activity score and therefore are not reported in our study. However, this involvement will be reflected in the physician's assessment of disease activity and the patient's or parent's assessment of well-being and pain.

In addition to entering followup data at 3 months and yearly, data also were entered at the time of any important events, including when biological agents were discontinued or switched or when there were safety concerns. Once patients discontinued their biological agent, data collection was maintained once yearly until the patient transferred to adult care. Safety data included adverse events (AE) and serious adverse events (SAE). SAE were defined as life-threatening or fatal events, events resulting in persistent or significant disability, events requiring intervention to prevent permanent impairment or damage, events that required hospitalization or prolongation of existing hospitalization, or congenital anomalies.

For our study we selected all patients with JIA who had the ERA subtype and who started a biological agent during 1999–2010, and who had at least 3 months of followup. For these patients we collected additional data regarding the diagnostic ILAR criteria for ERA [i.e., occurrence and location of enthesitis, a history of sacroiliac joint tenderness and/or inflammatory pain, presence of HLA-B27 antigen, acute (symptomatic) anterior uveitis, and history of HLA-B27-related disease in a first-degree relative]¹.

Response was assessed using the American College of Rheumatology (ACR) Pediatric 30 and 70 criteria (ACRpedi 30/70). This definition states that there should be at least 30% improvement (or 70% improvement depending on the score) from baseline in 3 or more variables of the JIA core set with no more than 1 variable worsening by > 30%¹⁶. Further, the Wallace criteria for inactive disease were used, defined as no active arthritis, no uveitis, normal ESR (values < 20 mm/h), and a physician's global assessment of disease activity indicating no disease activity (defined as VAS score < 10 mm)¹⁷.

Descriptive statistics were reported as absolute frequencies or as median values with an interquartile range (IQR) or minimum and maximum range. We compared the patient and disease characteristics of the patients with ERA by sex and by duration of followup (more or less than 1 year).

Depending on the tested variable, Mann-Whitney U test and chi-square test were used to perform comparisons. A p value < 0.05 was considered statistically significant. SPSS version 17.0.1 was used for all analyses.

RESULTS

Patients. From 1999 through 2010, a total of 22 pediatric patients with ERA used 1 or more biological agents in The Netherlands. Twenty patients started etanercept as a first

biological agent, 1 adalimumab, and 1 infliximab. Two patients, after failure of etanercept, switched to a second anti-TNF agent; 1 started adalimumab and 1 infliximab. No other biological agents were introduced in this patient group. Median followup from start of first anti-TNF agent was 1.2 (IQR 0.5–2.4) years, with a total of 38.7 patient-years.

Patient and disease characteristics are shown in Table 1. The commonest diagnostic criteria were enthesitis (in 77% of patients), onset of arthritis in males over age 6 years (73%), HLA-B27 antigen (68%), and sacroiliac joint tenderness and/or inflammatory lumbosacral pain (55%). Sacroiliac joint tenderness and/or inflammatory lumbosacral pain were not present in female patients with ERA, but were present in 75% of male patients ($p = 0.014$, chi-square). There were no differences between female and male patients with ERA for the remaining ERA classification criteria.

Prior to the introduction of the first anti-TNF agent, 92% of the patients used methotrexate and 77% sulfasalazine. Most patients used > 1 disease-modifying antirheumatic drug (DMARD) without sufficient effect.

Table 1. Patient and disease characteristics (n = 22). All data are n (%) unless otherwise indicated.

Characteristics	N (%)
Demographic characteristics	
Male	17 (77)
Median age at onset of arthritis, yrs (IQR)	10.4 (0.4–12.0)
Median disease duration before start of anti-TNF, yrs (IQR)	3.1 (1.1–5.9)
Disease characteristics	
Presence of HLA-B27 antigen	15 (68)
≤ 4 active joints at start of anti-TNF	7 (32)
> 4 active joints at start of anti-TNF	15 (68)
Enthesitis	17 (77)
In Achilles tendon	13 (76)
History of sacroiliac joint tenderness and/or inflammatory lumbosacral pain	12 (55)
Onset of arthritis in male > 6 yrs old	16 (73)
Anterior uveitis	0 (0)
Family history of HLA-B27-related disease	12 (55)
Medication history before start of anti-TNF therapy	
NSAID	21 (96)
Systemic glucocorticoids	8 (36)
Intraarticular glucocorticoids	4 (18)
Methotrexate	21 (96)
Sulfasalazine	17 (77)
Leflunomide	2 (9)
Azathioprine	1 (5)
Concomitant medications at start of anti-TNF therapy	
NSAID	19 (86)
Systemic glucocorticoids	3 (14)
Methotrexate	17 (77)
Sulfasalazine	2 (9)
Leflunomide	0 (0)
Azathioprine	0 (0)

IQR: interquartile range; TNF: tumor necrosis factor; NSAID: nonsteroidal antiinflammatory drugs.

The median duration between initiation of last synthetic DMARD and introduction of anti-TNF agent was 6.8 months (IQR 3.8–24.8 mo). No patients started concomitant synthetic DMARD in the 3-month interval before or the 3-month interval after the start of anti-TNF-blocking agents.

At the start of the first TNF- α -blocking agent, female patients with ERA (n = 5) had higher CHAQ total scores (median 2.2, minimum 1.5, maximum 2.6) and higher VAS pain scores (median 88, minimum 61, maximum 96) than male patients with ERA (n = 17), with a median CHAQ total score of 1.1 (minimum 0.1, maximum 2.1) and a median VAS pain score of 47 (minimum 3, maximum 90; $p = 0.003$ and $p = 0.039$, respectively, Mann-Whitney U test). This difference decreased after 3 months of treatment, and disappeared after 15 months of treatment.

Effectiveness analysis. Figure 1 shows the disease activity scores from the introduction of first anti-TNF agent until 4 years of followup, on the basis of an intention-to-treat analysis.

Because of this ongoing study design (i.e., an open cohort) the total followup duration varied between patients. One patient was lost to followup after 9 months of treatment, 8 patients were transferred to adult care, and some patients started anti-TNF agents more recently. With regard to patient and disease characteristics, the patients with > 1 year of followup did not differ from those with < 1 year of followup.

As Figure 1 shows, the disease activity declines rapidly after initiation of the first anti-TNF agent. At 3 months of treatment, 19 of the 22 patients (86%) reached an ACRpedi30 response, and 16 of the 22 patients (73%) an ACRpedi70 response. All patients continued the anti-TNF agent after 3 months of treatment. The percentage of patients achieving ACRpedi30 and 70 responses and inactive disease at the different timepoints is also shown in Figure 1. One patient discontinued etanercept when remission was reached, but experienced flare 1.3 years later and restarted etanercept, with good effect. No other patients discontinued biological treatment.

Two patients switched to a second anti-TNF agent after failure of the first. Adalimumab was introduced in a patient after 7 months of ineffective etanercept treatment. All 22 joints that had been active before start of adalimumab treatment responded, and inactive disease was achieved after only 5 months of adalimumab treatment. This patient withdrew adalimumab temporarily due to atypical AE. However, after 1 month the arthritis flared and adalimumab was reintroduced, again with good response. The second patient switched to infliximab after 16 months of etanercept treatment, and a remarkable decline in the number of joints with arthritis (from 7 to 2) was seen after 3 months.

Methotrexate could be discontinued in 4 of the 17 patients and sulfasalazine in 1 of the 2 patients who had been using it concomitantly at the start of the biological agent. Three patients used concomitant systemic glucocorti-

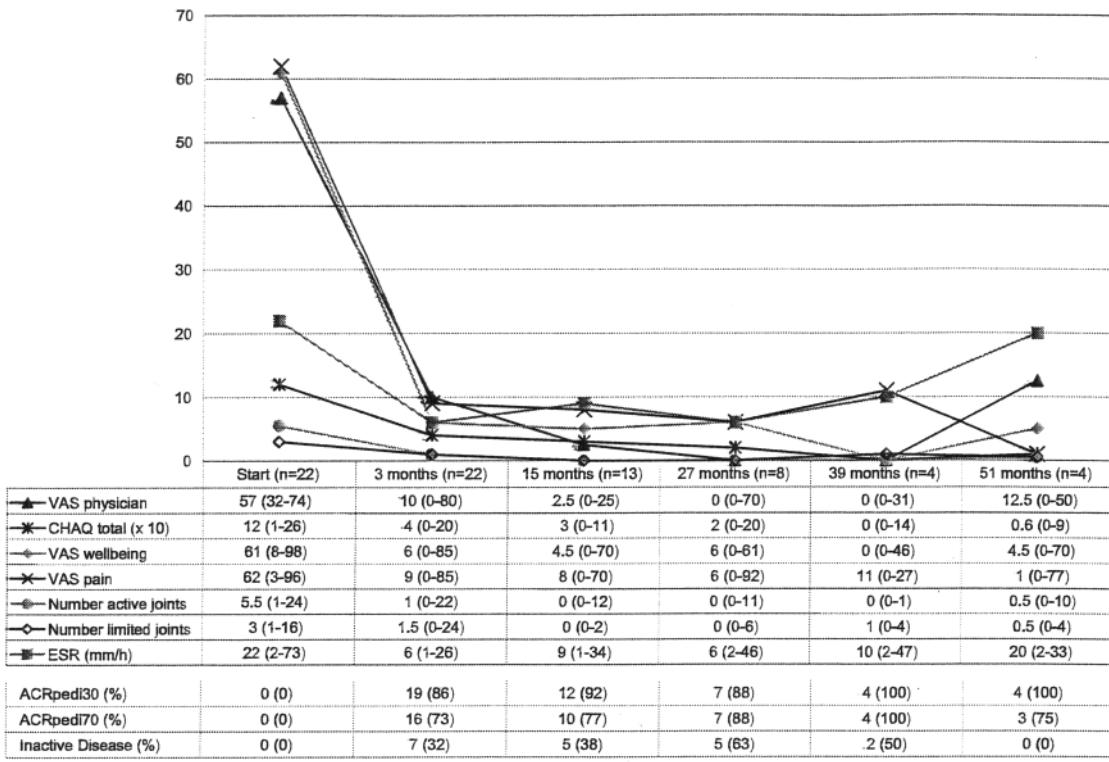


Figure 1. Disease activity scores from introduction of first tumor necrosis factor-blocking agent. VAS: visual analog scale; CHAQ: Childhood Health Assessment Questionnaire; ESR: erythrocyte sedimentation rate; ACRpedi: American College of Rheumatology Pediatric 30 and 70 criteria.

costeroids at the start and only 1 patient was able to stop them. No patients started systemic glucocorticosteroids during followup.

Safety analysis. During etanercept use, a total of 16 AE were reported: 4 mild infections, 2 fevers of unknown origin, 2 headaches, 2 injection-site reactions, 1 case of fatigue, 1 syncope, 1 transient case of hematochezia, 1 nosebleed, 1 report of atypical skin lesions, and 1 discordant pain sensation. This resulted in a rate of 0.45 AE per patient-year of etanercept use.

One patient reported 6 AE during adalimumab treatment: allergic reaction, injection-site reaction, headache, mild infections, pneumonia, and pain while breathing. Adalimumab was temporarily discontinued; however, the pain while breathing remained, and adalimumab was restarted.

No AE were seen in the 2 patients taking infliximab.

No SAE were reported during any of the anti-TNF agent treatment periods.

DISCUSSION

In our prospective observational study, we evaluated the effectiveness and safety of TNF-blocking agents in all Dutch pediatric patients with ERA from 1999 to 2010. Although all available TNF-blocking agents were included, most patients started etanercept, and these results therefore mainly reflect the effectiveness of etanercept.

A remarkable decline in all measures of disease activity was seen after as few as 3 months of treatment, and all patients continued their first anti-TNF agent after 3 months of treatment. After 3 months of treatment, 19 of the 22 patients reached an ACRpedi30 response, 16 an ACRpedi70 response, and one-third achieved inactive disease. This rapid and high response, not accountable to recent changes in synthetic DMARD, is especially impressive considering that these patients were previously unresponsive to 1 or more synthetic DMARD, and is also comparable with a previously published case series in patients with ERA treated with etanercept^{11,12,13}. To date, for patients we have followed on therapy for 15 months (n = 13) and 27 months (n = 8), the response appears to be maintained. This is comparable to a publication from our register in 2009 with inclusion of all JIA subtypes⁷. However, not all patients achieved inactive disease, even though some patients were treated for many years with anti-TNF agents. No patients were able to discontinue anti-TNF agents successfully and most concomitant medications (including glucocorticosteroids) were continued during treatment. Further, the inactive disease rate at 27 months was not sustained in the few patients with a longer followup. It seems that for this patient group, despite the rapid response to TNF-blocking agents, complete disease control is still difficult to achieve. This is also seen in adult-onset AS, with only one-third of patients treated with

TNF-blocking agents achieving <20% disease activity in all 4 domains after 1 to 2 years of treatment^{18,19,20}.

Switching between TNF-blocking agents occurred twice in our study. Both those patients (1 to adalimumab and 1 to infliximab after failing etanercept) improved remarkably. Until now, introduction of a second anti-TNF agent for JIA has been evaluated once. In that retrospective cohort study, 73 patients with JIA (one-third of the total cohort) switched to a second biological agent²¹. The second biological agent was discontinued in 53% of the patients because of ineffectiveness or AE. No detailed information was given on the treatment response after initiation of the second agent. No conclusions can be drawn about whether switching between biologicals is effective for patients with ERA; however, it seems a valuable option, especially because few alternative treatments are available.

It is remarkable that at the start of anti-TNF treatment, female patients with ERA report higher VAS pain and CHAQ scores than males. This is in accord with a cross-sectional study of patients with JIA who transferred to adult care showing significantly higher CHAQ scores in females with ERA²². In a case-control study comparing ERA with oligoarticular and polyarticular subtypes, female sex was found to be a predictor of failure to achieve remission²³. In our study, sex was not a predictor of a lack of treatment response because the differences in male and female patients disappeared after 15 months of treatment, and the numbers are small.

Etanercept seemed to be well tolerated, with a favorable safety profile, for this poorly described subset of patients with JIA. Our AE rate of 0.45 AE/patient-year of etanercept use seems to be higher than reports for all JIA subtypes (0.09–0.21 AE/patient-year)^{5,7}. However, these results should be interpreted with care, because only 38.7 patient-years of followup were included. No safety profile of adalimumab and infliximab for its use in patients with ERA can be given because only 4 patients used those drugs.

Our study has some limitations. First, the number of patients included was low and the number of patients with followup data beyond 15 months dropped quickly. The 22 patients included in our study were all patients in The Netherlands with ERA who started biological agents in an 11-year treatment period. Although the number is small, for this indication it is the largest case-series published to date.

The second limitation is that, because our register focuses on all patients in The Netherlands with JIA, detailed information about the responses of axial involvement and enthesitis was beyond the scope of our study. However, we expect that these signs will be reflected in the physician's global and patient's global assessment for well-being and pain. Burgos-Vargas, *et al* have proposed a tool for clinical evaluation for ERA containing 12 variables, including spinal and sacroiliac joint pain and tenderness and enthesitis, but this tool has not been validated yet²⁴.

TNF-blocking agents seem effective and safe for patients with ERA who at first do not respond to synthetic DMARD. As in adults, however, a sustained disease-free state could not be achieved, and none of the patients discontinued the biological agents successfully. The agents' effects on enthesitis and spinal involvement remain to be determined.

REFERENCES

- 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;31:390-2.
- Hofer M. Spondylarthropathies in children — are they different from those in adults? *Best Pract Res Clin Rheumatol* 2006; 20:315-28.
- 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;19:1282-5.
- Davis JC Jr, van der Heijde DM, Braun J, Dougados M, Clegg DO, Kivitz AJ, et al. Efficacy and safety of up to 192 weeks of etanercept therapy in patients with ankylosing spondylitis. *Ann Rheum Dis* 2008;67:346-52.
- Horneff G, Schmeling H, Biedermann T, Foeldvari I, Ganser G, Girschick HJ, et al. The German etanercept registry for treatment of juvenile idiopathic arthritis. *Ann Rheum Dis* 2004;63:1638-44.
- Lovell DJ, Giannini EH, Reiff A, Cawkwell GD, Silverman ED, Nocton JJ, et al. Etanercept in children with polyarticular juvenile rheumatoid arthritis. Pediatric Rheumatology Collaborative Study Group. *N Engl J Med* 2000;342:763-9.
- Prince FH, Twilt M, ten Cate R, van Rossum MA, Armburst W, Hoppenreijns EP, et al. Long-term follow-up on effectiveness and safety of etanercept in juvenile idiopathic arthritis: the Dutch national register. *Ann Rheum Dis* 2009;68:635-41.
- Lovell DJ, Ruperto N, Goodman S, Reiff A, Jung L, Jarosova K, et al. Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. *N Engl J Med* 2008;359:810-20.
- 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;56:3096-106.
- Barr A, Keat A. Spondyloarthritis: evolving therapies. *Arthritis Res Ther* 2010;12:221.
- Henrikson M, Reiff A. Prolonged efficacy of etanercept in refractory enthesitis-related arthritis. *J Rheumatol* 2004;31:2055-61.
- Sulpice M, Deslandre CJ, Quartier P. Efficacy and safety of TNF-alpha antagonist therapy in patients with juvenile spondyloarthropathies. *Joint Bone Spine* 2009;76:24-7.
- Tse SM, Burgos-Vargas R, Laxer RM. Anti-tumor necrosis factor alpha blockade in the treatment of juvenile spondylarthropathy. *Arthritis Rheum* 2005;52:2103-8.
- Study Evaluating Etanercept in 3 Subtypes of Childhood Arthritis (CLIPPER). [Internet. Accessed June 30, 2011.] Available from: <http://clinicaltrials.gov/ct2/show/NCT00962741>
- Prince FH, Ferker IS, Kamphuis S, Armburst W, Ten Cate R, Hoppenreijns EP, et al. Development of a web-based register for the Dutch national study on biologics in JIA: www.ABC-register.nl. *Rheumatology* 2008;47:1413-6.
- Giannini EH, Ruperto N, Ravelli A, Lovell DJ, Felson DT, Martini A. Preliminary definition of improvement in juvenile arthritis. *Arthritis Rheum* 1997;40:1202-9.
- Wallace CA, Ruperto N, Giannini E. Preliminary criteria for clinical remission for select categories of juvenile idiopathic arthritis. *J Rheumatol* 2004;31:2290-4.

18. Brandt J, Listing J, Haibel H, Sorensen H, Schwebig A, Rudwaleit M, et al. Long-term efficacy and safety of etanercept after readministration in patients with active ankylosing spondylitis. *Rheumatology* 2005;44:342-8.
19. van der Heijde D, Dijkmans B, Geusens P, Sieper J, DeWoody K, Williamson P, et al. Efficacy and safety of infliximab in patients with ankylosing spondylitis: results of a randomized, placebo-controlled trial (ASSERT). *Arthritis Rheum* 2005; 52:582-91.
20. van der Heijde D, Schiff MH, Sieper J, Kivitz AJ, Wong RL, Kupper H, et al. Adalimumab effectiveness for the treatment of ankylosing spondylitis is maintained for up to 2 years: long-term results from the ATLAS trial. *Ann Rheum Dis* 2009;68:922-9.
21. Tynjala P, Vahasalo P, Honkanen V, Lahdenne P. Drug survival of the first and second course of anti-tumour necrosis factor agents in juvenile idiopathic arthritis. *Ann Rheum Dis* 2009;68:552-7.
22. Gare BA, Fasth A. The natural history of juvenile chronic arthritis: a population based cohort study. II. Outcome. *J Rheumatol* 1995;22:308-19.
23. Flato B, Hoffmann-Vold AM, Reiff A, Forre O, Lien G, Vinje O. Long-term outcome and prognostic factors in enthesitis-related arthritis: a case-control study. *Arthritis Rheum* 2006;54:3573-82.
24. Burgos-Vargas R, Pacheco-Tena C, Vazquez-Mallado J. The juvenile-onset spondyloarthritides: rationale for clinical evaluation. *Best Pract Res Clin Rheumatol* 2002;16:551-72.