The Journal of Rheumatology Volume 38, no. 7

Development of Inflammatory Bowel Disease in Patients with Juvenile Idiopathic Arthritis Treated with Etanercept

TRUDY D. van DIJKEN, SEBASTIAAN J. VASTERT, VALERIA M. GERLONI, IRENE PONTIKAKI, KRISTINA LINNEMANN, HERMANN GIRSCHICK, WINEKE ARMBRUST, KIRSTEN MINDEN, FEMKE H.M. PRINCE, FREDDY T.M. KOKKE, EDWARD E.S. NIEUWENHUIS, GERD HORNEFF and NICO M. WULFFRAAT

J Rheumatol 2011;38;1441-1446
http://www.jrheum.org/content/38/7/1441

Development of Inflammatory Bowel Disease in Patients with Juvenile Idiopathic Arthritis Treated with Etanercept

TRUDY D. van DIJKEN, SEBASTIAAN J. VASTERT, VALERIA M. GERLONI, IRENE PONTIKAKI, KRISTINA LINNEMANN, HERMANN GIRSCHICK, WINEKE ARMBRUST, KIRSTEN MINDEN, FEMKE H.M. PRINCE, FREDDY T.M. KOKKE, EDWARD E.S. NIEUWENHUIS, GERD HORNEFF, and NICO M. WULFFRAAT

ABSTRACT. ***Objective.*** With the increasing use of etanercept for juvenile idiopathic arthritis (JIA) new possible adverse events are reported including new autoimmune diseases. Our purpose was to examine if the incidence of inflammatory bowel disease (IBD) in patients with JIA using etanercept is higher than in the healthy age-matched population. We give the clinical characteristics of the IBD in patients with JIA using etanercept.

Methods. The national JIA registries for etanercept of The Netherlands, Germany, Finland, Denmark, and Italy were searched for patients with JIA and IBD. The total number of patient-years was used to calculate incidence. The physicians of the identified patients were asked to give clinical details.

Results. Thirteen cases of IBD in JIA patients were identified in the registries between 1999 and 2008. The IBD incidence in JIA patients while using etanercept was 362 per 100,000 patient-years under etanercept, about 43 times higher than in the general pediatric population. Clinical presentation of IBD in JIA patients using etanercept was similar to that in non-JIA patients. The median time between onset of JIA and onset of IBD was 6 years and 10 months. The time between the start of etanercept and the first appearance of IBD symptoms was between 9 days and 4.5 years.

Conclusion. The incidence of IBD in JIA patients using etanercept seems to be markedly increased, analyzing data from European registries. This incidence of IBD in the etanercept registries cannot be compared to the incidence of IBD in JIA patients using other treatment without etanercept, because such registries do not exist yet in all European countries. These findings are in keeping with a report of 8 new IBD cases occurring in French children with JIA using etanercept. These findings illustrate the need for large international disease-specific registries focused on outcome and pharmacovigilance. (First Release April 1 2011; J Rheumatol 2011;38:1441–6; doi:10.3899/jrheum.100809)

Key Indexing Terms:
INFLAMMATORY BOWEL DISEASE
ETANERCEPT
JUVENILE IDIOPATHIC ARTHRITIS
INCIDENCE

Etanercept is one of 3 tumor necrosis factor-α (TNF-α)-blocking agents, along with infliximab and adalimumab, used in treatment of juvenile idiopathic arthritis (JIA). Etanercept is a soluble p75 TNF-α receptor fusion protein; it is the first anti-TNF-α agent approved by the US Food and Drug Administration (FDA) for JIA. Etanercept has proven ther-

From the Department of Pediatric Immunology, University Medical Centre Utrecht, Utrecht, The Netherlands; Dipartimento di Reumatologia, Università di Milano, Istituto Gaetano Pini, Milan, Italy; Abt. Allgemeine Pädiatrie/Rheumatologie, University Hospital Greifswald, Greifswald, Germany; Section of Pediatric Rheumatology, Immunology, Infectious Diseases and Osteology, Kinderklinik der Universität, Würzburg, Germany; Department of Pediatrics, University Medical Centre Groningen, Groningen, The Netherlands; Department of Pediatrics, University Medicine Charité Berlin, Berlin, Germany; Department of Pediatric Rheumatology, Erasmus Medical Center, Sophia Children's Hospital, Rotterdam, The Netherlands; Department of Pediatric Gastroenterology, University Medical Centre Utrecht, Utrecht, The Netherlands; and Department of Pediatrics, Asklepios Klinik Sankt Augustin, Sankt Augustin, Germany.

T.D. van Dijken, MD; S.J. Vastert, MD, Department of Pediatric Immunology, University Medical Centre Utrecht; V.M. Gerloni, MD; I. Pontikaki, MD, Dipartimento di Reumatologia, Università di Milano, Istituto Gaetano Pini; K. Linnemann, MD, Abt. Allgemeine Pädiatrie/Rheumatologie, University Hospital Greifswald; H. Girschick, MD, PhD, Section of Pediatric Rheumatology, Immunology, Infectious Diseases and Osteology, Kinderklinik der Universität Würzburg; W. Armbrust, MD, Department of Pediatrics, University Medical Centre Groningen; K. Minden, MD, PhD, Department of Pediatrics, University Medicine Charité Berlin; F.H.M. Prince, MD, PhD, Department of Pediatric Rheumatology, Erasmus Medical Center, Sophia Children's Hospital; F.T.M. Kokke, MD; E.E.S. Nieuwenhuis, MD, PhD, Professor, Department of Pediatric Gastro-enterology, University Medical Centre Utrecht; G. Horneff, MD, PhD, Professor, Department of Pediatrics, Asklepios Klinik Sankt Augustin; N.M. Wulffraat, MD, PhD, Associate Professor, Department of Pediatric Immunology, University Medical Centre Utrecht.

Address correspondence to Dr. N.M. Wulffraat, Department of Pediatric Immunology, University Medical Centre Utrecht, Utrecht, The Netherlands. E-mail: n.wulffraat@umcutrecht.nl

Accepted for publication November 23, 2010.

apeutic benefit in patients with JIA who were unresponsive to or were intolerant for methotrexate (MTX)[1].

The most frequent adverse events of etanercept concern infections, local reactions, and neuropsychiatric manifestations. In general, etanercept offers an acceptable safety profile in children with JIA and provides significant and sustainable improvement in disease manifestations.

With the increasing use and longer followup times, new possible adverse events are being reported. Concerns have been raised whether anti-TNF therapy increases the risk of lymphoproliferative disorders[2,3,4]. Another notable concern is the possibly increased risk for developing autoimmune diseases such as vasculitis, systemic lupus erythematosus, and interstitial lung diseases in adults[5]. Several cases of sarcoidosis occurring during etanercept therapy in patients with rheumatoid arthritis (RA) and JIA were also reported[6,7].

Etanercept has been tested for effectiveness in Crohn's disease in adults and has proven to be safe but not effective in the short term[8,9]. In contrast, infliximab, a chimeric TNF-—blocking agent, is widely used as a therapeutic agent in Crohn's disease and has been registered by the FDA for pediatric Crohn's since 2006. Note that some cases of new-onset inflammatory bowel disease (IBD) have also been reported as an adverse event in JIA patients using etanercept in Italy (3 cases) and France (8 cases)[7,10,11,12]. This phenomenon was also reported for adult RA and spondyloarthropathy (SpA)[8,13,14].

In this study we give an overview of cases of IBD in patients with JIA using etanercept reported by the European etanercept registries for JIA. Data on the clinical presentations and intestinal biopsies were obtained from the physicians reporting the IBD as an adverse event to their national registry.

MATERIALS AND METHODS

Registries for the use of etanercept in JIA in The Netherlands, Germany, Italy, Finland, Switzerland, and Denmark were contacted for data on JIA patients (fulfilling ILAR diagnostic criteria[15]) who developed IBD. Patients were selected if they had been reported to the registries between 1999 and 2008 and if the use of etanercept preceded the diagnosis of IBD. Patients in whom the IBD diagnosis preceded the prescription of etanercept were excluded. With use of a short questionnaire (Table 1), data were retrieved on the subtype of JIA, previous medications, medication at time of IBD symptoms, diagnosis and type of IBD (Crohn's disease, ulcerative colitis, or indeterminate colitis), and clinical characteristics of the IBD. Data on disease course between start of JIA, start of etanercept, and appearance of IBD symptoms were also collected.

The total number of patients in the registry was noted and, if possible, total of patient-years was retrieved to calculate the incidence of IBD in JIA patients after use of etanercept. The calculated incidence was compared to the results of a large prospective study with 739 valid reports in the British Isles, which reported an incidence of IBD in childhood of 5.2 new cases/100,000/year during 1998 and 1999[16]. It was not possible to also study the incidence of IBD in JIA patients undergoing MTX therapy only, since largescale MTX registries do not exist. However, since 2005, the German registry also collects data in JIA patients using only MTX as a control for the etanercept-treated patients. According to the registry holder of this German MTX cohort (G. Horneff, one of the coauthors of this report) no case of IBD under MTX treatment was reported in roughly 2000 patient-years[17].

RESULTS

Between 1999 and 2008 a combined total of 1651 patients were enrolled in the Dutch (226 patients, 695 patient-years), Finnish (150 patients), Danish (146 patients), Italian (203 patients, 450 patient-years), and German (1006 patients, 1853 patient-years) registries[7,17,18,19]. The number of patient-years in the Finnish and Danish registries was unknown. No data were available on the English registry.

A total of 17 patients that were also diagnosed with IBD were identified in the national JIA registries for etanercept: 3 Dutch cases, 8 German cases, 5 Italian cases, and one Finnish case. Three patients developed IBD symptoms prior to etanercept and 1 developed IBD 2 years after etanercept was stopped, and these 4 were excluded from further analysis. Data from possible patients who were French or British could not be obtained.

Data were available for total patient-years from the German, Italian, and Dutch registries (1435 enrolled patients, a total of 2998 patient-years). Based on the first 3 registries, we estimate the total patient-years under etanercept treatment for the whole group (n = 1651 patients) to be 3600 patient-years. Therefore, the estimated incidence of IBD (n = 13) occurring in JIA patients using etanercept (etanercept use preceding IBD) is 362/100,000 patient-years.

The median age at onset of IBD in the reported patients was 12 years. Sawczenko, *et al* reported an incidence of IBD of 5.2/100,000 per year from a large prospective survey of childhood IBD in the British Isles[16]. The incidence at age 12 years was 8.3/100,000[16]. Our estimate of incidence of 362/100,000 is therefore about 43 times higher than that for IBD in the normal population of the same age.

The demographic details of the 13 patients from whom sufficient data could be collected are shown in Table 2. Patients were aged between 1 and 16 years at time of diagnosis of JIA; 10 patients were female. Four patients had polyarticular JIA, 5 had oligo-extended JIA, 2 had systemic JIA, and 2 had enthesitis-related arthritis. Etanercept was the only drug used at the time of appearance of IBD symptoms in half the cases. A standard etanercept dose was used in all patients. All patients were HLA-B27-negative. Data on family history were available in 12 of 13 cases and were all negative for IBD.

The median time between onset of JIA and onset of IBD was 5 years and 3 months (Table 2) and ranged between 1 and 17 years. The time between the start of etanercept therapy and the first appearance of IBD symptoms was between 9 days and 4.5 years.

Nine patients in our study developed Crohn's disease, 3 developed ulcerative colitis, and 1 patient had indeterminate IBD. In most cases, upon development of symptoms of IBD,

Table 1. Questionnaire for patient data.

Demographics and JIA Type	Questions on Medications Used	Questions on IBD
Initials	When was MTX started/stopped	Date start IBD symptoms:
Date of birth	Sulfasalazine given? When started/stopped?	What was the medication at time of onset of gastrointestinal complaints?
Gender	Steroids (when started, what dosage)/start/stop	Aspect of stools: blood/mucus/normal
Age of onset JIA	When was etanercept, infliximab, adalimumab or anakinra started (date)	Daily frequency of stools
Subtype JIA	Dosage etanercept	Weight loss/failure to thrive
Family history JIA	Did JIA symptoms improve after starting etanercept	Laboratory examinations: HLA-B27; Blood film, ESR, CRP, OT, PT, LDH, albumin
HLA-B27		Fecal blood/increased protein excretion (for instance alpha 1 antitrypsin)
		Biopsy proven (date)
		What was the pathology report
		Date stop etanercept/infliximab/adalimumab/anakinra
		How and when (date) was the IBD further treated
		Steroid dose and duration of treatment; did GI symptoms improve under steroids or did symptoms develop after stopping steroids?
		Treatment response
		Date of disappearance of IBD symptoms:

Table 2. Demographics and time relation among juvenile idiopathic arthritis (JIA) and inflammatory bowel disease and etanercept.

Case	Age Onset JIA, Type	Time Between JIA and IBD	Time Between Start Etanercept and IBD	Previous Medication	Medication at Onset IBD/Flare	Type IBD	Stop Etanercept After Symptoms	Treatment for IBD	Decrease IBD Symptoms after Stop Etanercept	IBD Still Active	Ongoing Treatment for IBD
1	7 yrs, 1 mo, poly	3 yrs, 3 mo	9 mo	NSAID, MTX	ETA, NSAID	UC	5 mo	Stop: ETA and NSAID. Start: pred pentasa, ferro, CaD3, later infliximab	< 1 mo	No	Infliximab
2	11 yrs, 5 mo, oligo ext	1 yr, 2 mo	9 days	NSAID, MTX, Pred	ETA, NSAID, omeprazol, Pred	CD	3 wk	Stop: ETA. Start: pred, later infliximab	< 1 mo	Yes	Infliximab
3a	1 yr, oligo ext	7 yrs, 4 mo	3 mo	NSAID, MTX, SZP	ETA, MTX, Pred	CD	1 mo	Stop: ETA. Start: pentasa	No	Yes	Pentasa and Pred
3b			Pancreatitis, 1 mo			CD	2.5 mo	Stop: pentasa and ETA Start: Pred, later infliximab	1 mo	Yes	Humira
4	5 yrs, 10 mo, poly	4 yrs, 5 mo	2 yrs, 3 mo	NSAID, MTX, Pred	ETA	CD	3 mo	Stop: ETA. Start: Pred, Mes, Im	1 mo	No	Pred and ADA
5	5 yrs, Systemic	5 yrs, 3 mo	3 yrs	NSAID, MTX, Pred	ETA	CD	7 mo	Stop: ETA. Start Mes	10 mo	No	Yes
6	3 yrs, 9 mo, ERA	4 yrs, 8 mo	1 yr	NSAID, MTX, Rolex SZP	ETA	UC	1 mo	Stop; ETA. Start: Bud + infliximab	1 mo	Yes	Infliximab, Bud, Mes, Pant
7	6 yrs, 8 mo, oligo ext	5 yrs	1 yr, 3 mo	NSAID, MTX, Pred	ETA	CD	1 wk	Stop: ETA. Start: ADA	2 mo	Yes	ADA
8	8 yrs, ERA	9 yrs, 7 mo	9 mo	NSAID, MTX, Pred, SZP	ETA, MTX	CD	Continued	Bud, SZP	1 mo	Yes	ETA, MTX, Pred, SZP, Bud
9	14 yrs, 1 mo, Systemic	12 yrs, 4 mo	4 mo	NSAID, MTX, CSA	ETA, Pred, CSA	CD	4 mo	Stop: ETA. Start: Pred and SZP, infliximab	5 mo	No	No
10	16 yrs, 10 mo, poly	16 yrs, 8 mo	1 yr, 6 mo	NSAID, MTX, gold, SZP, HCQ, infliximab	ETA, Pred	CD	1 mo	Stop: ETA. Start: ADA	1 yr	No	No
11	3 yrs, 4 mo, oligo ext	9 yrs, 4 mo	4 yrs, 6 mo	NSAID, MTX	ETA	ID	3 mo	Stop: ETA. Start: SZP + infliximab, later ADA	1 mo	No	Yes
12	1 yr, 11 mo, oligo ext	11 yrs, 2 mo	1 yr, 6 mo	NSAID, MTX, CSA, chlorambucil	ETA	CD	1 mo	Stop: ETA. Start: Mes, infliximab, later ADA	1 mo	No	Yes
13	1 yr, 7 mo, poly	6 yrs, 5 mo	5 yrs, 10 mo	MTX, CSA	ETA	UC	1 mo	Stop: ETA. Start: infliximab, later ADA	10 mo	No	Yes

Poly: polyarticular JIA; oligo: oligoarticular JIA; oligo ext: oligo-extended JIA; ERA: enthesistis-related arthritis; CSA: cyclosporin A; Pred: prednisone; MTX: methotrexate; SZP: salazopyrin; ETA: etanercept; ADA: adalimumab; Bud: budesonide; Mes: mesalazine; Pant: pantoprazol; HCQ: hydroxychloroquine; Im: imuran; NSAID: nonsteroidal antiinflammatory drug.

etanercept was stopped, either immediately or later (up to 7 months after onset of IBD symptoms). In one case, etanercept was not stopped, but additional therapy was started. In the third patient in Table 2 etanercept was stopped after the first episode of IBD symptoms (episode 1). Because the arthritis relapsed, etanercept was restarted. One month after

restart, the patient developed acute pancreatitis (episode 2), possibly a serious extraintestinal manifestation of Crohn's disease or an adverse drug reaction. Thereafter, etanercept was stopped for the second time and treatment for IBD was started. The pancreatitis disappeared soon afterward.

As shown in Table 2, 5 patients were treated first with prednisone and later with infliximab, a drug effective for both JIA and IBD. In 5 cases the third TNF-α receptor blocker, adalimumab, was started. In one patient data on the treatment of IBD were not available. In another patient IBD treatment was started with budesonide and sulfasalazine, with continuation of etanercept. Medication used to control the IBD symptoms is noted in Table 2.

The clinical presentation and histology results of the IBD in our patients are described in Table 3. All patients except one developed abdominal pain with chronic diarrhea. In one patient the presenting symptom was a perianal abscess. The fourth patient had no gastrointestinal (GI) complaints but developed erythema nodosum. Other symptoms were bloody stool, weight loss, and vomiting. A flare of arthritis was reported in only one case. Infectious causes of bowel symptoms were ruled out for all patients. The diagnosis including type of IBD was determined from endoscopy and histopathology on biopsy.

DISCUSSION

We estimated an incidence for IBD of 362/100,000 per year in JIA patients undergoing etanercept therapy. This is much higher than the calculated incidence of 8.3/100,000 for pediatric IBD in the general pediatric population aged 12 years[16]. We could not calculate the incidence of IBD in a general JIA cohort because such a registry, including all prevalent JIA cases, does not exist. However, Germany has a (small) JIA registry specifically for MTX and here no IBD cases could be identified[17]. Of course the patient numbers in this MTX registry are too low to calculate any differences with the IBD incidence in the combined etanercept registries. Recently, a French retrospective analysis reported 8 cases of IBD in French patients with JIA using etanercept[10]. In that study the number of etanercept patient-years was unknown, so incidence could not be calculated[10]. Our current study based on registry reports from 5 European countries confirms the reported increased incidence of IBD in children with more severe JIA. The clinical presentation and response to treatment were similar to those of the French report. Together, we now have data from 21 cases in 6 European countries.

International collaboration provided the results of several national etanercept JIA registries that enabled us to per-

Table 3. Clinical presentation and histology results of patients with inflammatory bowel disease (IBD). Patient 3 had the first IBD disease episode (3a) prior to and a relapse (3b) after restarting etanercept.

Patient	Type of IBD	Abdominal Pain	Aspect of Stool	Frequency of Stool	Weight Loss	Other Symptoms	Endoscopy	Pathology
1	UC	+	D, B, M	4/day	2.8 kg in 3 mo	Vomiting	Grade II-III proctosigmoiditis	Colon: active infection, crypt abscess, changed architecture indicative of UC
2	CD	+	D, B, M	6/day	4 kg in 1 mo	More arthritis, Perianal abscess	Skip lesions	Indeterminate, later CD
3a	CD	+	D, B	2–8/day	5 kg in 3 mo	Vomiting and fatigue	Normal	Colon: UC or CD with inflammation, granulomas
3b	CD	++	D	6/day	NA	Abdominal cramps, pancreatitis	NA	
4	CD	–	–	1/day	No	Raised ESR and CRP; erythema nodosum	NA	Esophagitis: with epitheloid cell reaction and isolated giant cells Duodenitis: with microgranulomata Colitis with epitheloid cell reaction
5	CD	+	NA	NA	NA	No	NA	CD
6	UC	+	D, B	25/day	No	No	Ulcers, terminal ilium normal	Colitis with crypt abscess and ulcers, no granulomas
7	CD	+	D, B	6/day	No	No	NA	CD
8	CD	+	D	NA	No	NA	NA	Overall active CD with granulomas
9	CD	+	D	5/day	Yes	Anemia	CD	CD
10	CD	+	D	3/day	Yes	Unknown	NA	CD
11	ID	+	D	3/day	Growth stop, 1 yr	No		Chronic inflammation; colitis with crypt abscess
12	CD	+	D	2/day	6.5 kg in 3 mo	No	CD	CD
13	UC	+	D, B	> 3 x/day	6 kg in 7 mo	No	NA	UC

D: diarrhea, B: blood, M: mucus, CD: Crohn's disease; UC: ulcerative colitis; ID: indeterminate; NA: not available.

form this study. Of course we based the calculated incidence rate on a relatively small number of patients that make up a selected group already diagnosed with severe JIA. Future collaboration will possibly enable the formation of large multinational registries focusing on both longterm efficacy and pharmacovigilance of biologics in JIA. Recently, the FDA and the European Medicines Agency confirmed the need for such registries.

This is the first study that reports an increased incidence of IBD symptoms in JIA patients using etanercept. It is unknown whether these cases represent new-onset IBD or reactivation of subclinical symptoms. In adults, the risk for RA was 2.7 (95% CI 2.4–3.0) for adult patients with IBD[20]. Kokkonen, *et al* reported that children with JIA with GI complaints show a lymphoid nodular hyperplasia in the mucosa and an increase in intestinal intraepithelial lymphocytes[11]. Picco, *et al* described that an increased gut permeability was present not just in the juvenile SpA, but also in patients with oligoarticular JIA[21]. This suggested that gut wall inflammation (albeit asymptomatic) can be present in JIA. Indeed, diseases like JIA and IBD could be connected through the gut-synovium axis[22,23]. This has been described for SpA, where the relationship between gut and joint inflammation is well known. The main features are sacroiliitis and inflammatory low back pain, oligoarticular asymmetric synovitis, and genetic linkage with HLA-B27[22]. Gut inflammation occurs in 25%–75% of patients with SpA depending on the subtype, and 6% progress to overt Crohn's disease during followup[23]. Intestinal inflammation in SpA seems to be histologically related to the gut inflammation observed in Crohn's disease[22]. Ileocolonoscopy was performed in 32 adult SpA patients with "late onset pauciarticular JIA." Such patients would now be classified as having enthesitis-related JIA. Eighty-one percent (26/34) presented histological signs of gut inflammation and 19/26 were classified as having active chronic or Crohn-like lesions[24]. SpA affects mostly adults and the type of joint involvement shows a different pattern to that in JIA. In our patient cohort only 2 had enthesitis and all were HLA-B27-negative. A connection in the gut-joint axis for JIA and IBD would represent a new finding.

Extraintestinal manifestations occurred in 6% of pediatric patients prior to diagnosis of IBD. Axial arthritis occurred prior to or during IBD in 3.1% of the children with IBD; peripheral arthritis occurred prior to or during IBD in 11.6% of children with IBD; combined arthritis patterns occurred prior to or during IBD in 3.6% of children with IBD[25]. It seems unlikely, however, that our cases are examples of extraintestinal manifestations of IBD because of the severe expression of the JIA disease course (using ILAR criteria) for which etanercept was given, and the long interval between the first symptoms of JIA and symptoms of IBD.

We reported details of 13 cases in which etanercept could be involved in the development of IBD in children with JIA. Remarkably, all the patients were HLA-B27-negative and also had a negative family history of IBD. IBD-type Crohn's disease developed in 69% of the cases. This percentage is higher than the 55% predicted in pediatric IBD[26]. The retrospective analysis of our study does not enable classification of IBD according to the Montreal classification[27]. The average time between start of etanercept and start of symptoms was between 9 days and 4.5 years. Etanercept was stopped several months after symptoms occurred (Table 2). It is difficult to say whether the IBD regressed upon discontinuation of the etanercept because in most cases other medication (e.g., infliximab) was started. When etanercept was found not to be effective for Crohn's disease, this was explained by different effects on T lymphocytes. Infliximab binds to both soluble and membrane-bound TNF, whereas etanercept binds primarily to soluble TNF[28]. Binding to membrane-bound TNF elicits apoptosis and these in particular can be found in the lamina propria in Crohn's disease[29]. In addition, treatment of patients with RA and ankylosing spondylitis with etanercept may lead to increased peripheral T cell reactivity both to microbial antigens and to self-antigens[30,31,32]. Considered together, such T cell activation and apoptosis of lamina propria T cells could predispose or identify patients susceptible to developing IBD.

The most common starting symptoms in our patients were abdominal pain and diarrhea. These symptoms are aspecific for IBD and very common in JIA, because of the use of medication such as MTX and nonsteroidal antiinflammatory drugs. Our study shows that after exclusion of infectious causes the pediatric rheumatologist needs to consider the possibility of IBD, especially when using etanercept, irrespective of the duration of therapy. We advise stopping etanercept when serious GI complaints occur in a patient and carrying out stool analysis and colonoscopy. If IBD is diagnosed in a child with JIA, infliximab or adalimumab may be a good therapy.

ACKNOWLEDGMENT

This study would not have been possible without international collaboration among the national etanercept registries for JIA. We acknowledge the support of Dr. N. Ruperto (Italy), Dr. S. Nielsen (Denmark), and Dr. P. Lahdenne (Finland) in identifying individual patients.

REFERENCES

1. Lovell DJ, Giannini EH, Reiff A, Cawkwell GD, Silverman ED, Nocton JJ, et al. Etanercept in children with polyarticular juvenile rheumatoid arthritis. New Engl J Med 2000;342:763-9.
2. Brown SL, Greene MH, Gershon SK, Edwards ET, Braun MM. Tumor necrosis factor antagonist therapy and lymphoma development: Twent-six cases reported to the Food and Drug Administration. Arthritis Rheum 2002;46:3151-8.
3. Dekker L, Armbrust W, Rademeker CM, Prakken B, Kuis W, Wulffraat NM. Safety of anti-TNF alpha therapy in children with juvenile idiopathic arthritis. Clin Exp Rheumatol 2004;22:252-8.
4. Nair B, Raval G, Mehta P. TNF-α inhibitor etanercept and hematologic malignancies: report of a case and review of the literature. Am J Hematol 2007;82:1022-4.

5. Ramos-Casals m, Brito-Zeron P, Soto MJ, Cuadrado MJ, Khamashta MA. Autoimmune diseases induced by TNF-targeted therapies. Best Pract Res Clin Rheumatol 2008;22:847-61.
6. Toussirot E, Pertuiset E, Kantelip B, Wendling D. Sarcoidosis occuring during anti-TNF-alpha treatment for inflammatory rheumatic diseases: report of two cases. Clin Exp Rheumatol 2008;26:471-5.
7. Prince FHM, Twilt M, ten Cate R, van Rossum MAJ, Armbrust W, Hoppenreijs EPAH, 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.
8. Haraoui B, Krelenbaum M. Emergence of Crohn's disease during treatment with the anti-tumor necrosis factor agent etanercept for ankylosing spondylitis: Possible mechanisms of action. Semin Arthritis Rheum 2009;39:176-81.
9. Sandborn WJ, Hanauer SB, Katz S, Safdi M, Wolf DG, Baerg RD, et al. Etanercept for active Crohn's disease: A randomized, double-blind, placebo-controlled trial. Gastroenterology 2001;121:1088-94.
10. Dallocchio A, Canioni D, Ruemmele F, Quesne A, Coazec JY, Bouvier R, et al. Occurrence of inflammatory bowel disease during treatment of juvenile idiopathic arthritis with etanercept: a French retrospective study. Rheumatology 2010;49:1694-8.
11. Kokkonen J, Arvonen M, Vahasalo P, Karttunen T. Intestinal immune activation in juvenile idiopathic arthritis and connective tissue disease. Scand J Rheumatol 2007;36:386-9.
12. Ruemmele FM, Prieur AM, Talbotec C, Goulet O, Schmitz J. Development of Crohn disease during anti-TNF-alpha therapy in a child with juvenile idiopathic arthritis. J Pediatr Gastroenterol Nutrition 2004;39:203-6.
13. Oh J, Arkfeld DG, Horwitz DA. Development of Crohn's disease in a patient taking etanercept. J Rheumatol 2005;32:752-3.
14. Fouache D, Goeb V, Massy-Guillemant N, Avenel G, Bacquet-Deschryver H, Kozyreff-Meurice M, et al. Paradoxical adverse events of anti-tumour necrosis factor therapy for spondyloarthropathies: a retrospective study. Rheumatology 2009;48:761-4.
15. 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.
16. Sawczenko A, Sandhu BK, Logan RFA, Jenkins H, Taylor CJ, Mian S, et al. Prospective survey of childhood inflammatory bowel disease in the British Isles. Lancet 2001;357:1093-4.
17. Horneff G, De Bock F, Foeldvari I, Girschick HJ, Michels H, Moebius D, et al. Safety and efficacy of combination of etanercept and methotrexate compared to treatment with etanercept only in patients with juvenile idiopathic arthritis (JIA): preliminary data from the German JIA Registry. Ann Rheum Dis 2009;68:519-25.
18. Gerloni V, Pontikaki I, Gattinara M, Fantini F. Focus on adverse events of tumour necrosis factor alpha blockade in juvenile idiopathic arthritis in an open monocentric long-term prospective study of 163 patients. Ann Rheum Dis 2008;67:1145-52.
19. Lahdenne P, Vahasalo P, Honkanen V. Infliximab or etanercept in the treatment of children with refractory juvenile idiopathic arthritis: an open label study. Ann Rheum Dis 2003;62:245-7.
20. Cohen R, Robinson D, Paramore C, Fraeman K, Renahan K, Bala M. Autoimmune disease concomitance among inflammatory bowel disease patients in the United States, 2001-2002. Inflamm Bowel Dis 2008;14:738-43.
21. Picco P, Gattorno M, Marchese N, Vignola S, Sormani MP, Barabino A, et al. Increased gut permeability in juvenile chronic arthritides. A multivariate analysis of the diagnostic parameters. Clin Exp Rheumatol 2000;18:773-8.
22. Baeten D, De Keyser F, Mielants H, Veys EM. Immune linkages between inflammatory bowel disease and spondyloarthropathies. Curr Opin Rheumatol 2002;14:342-7.
23. Mielants H, Veys EM, Cuvelier C, Devos M. Course of gut inflammation in spondylarthropathies and therapeutic consequences. Baillieres Clin Rheumatol 1996;10:147-64.
24. Mielants H, Veys EM, Joos R, Cuvelier C, De Vos M, Proot F. Late onset pauciarticular juvenile chronic arthritis: relation to gut inflammation. J Rheumatol 1987;14:459-65.
25. Jose FA, Garnett EA, Vittinghoff E, Ferry GD, Winter HS, Baldossano RN, et al. Development of extraintestinal manifestations in pediatric patients with inflammatory bowel disease. Inflamm Bowel Dis 2009;15:63-8.
26. Zaag-Loonen HJ, Casparie M, Tarniniau JAJM, Escher JC, Pereira RR, Derkx HHF. The incidence of pediatric inflammatory bowel disease in the Netherlands: 1999-2001. J Pediatr Gastroenterol Nutrition 2004;38:302-7.
27. Satsangi J, Silverberg MS, Vermeire S, Colombel JF. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. Gut 2006;55:749-53.
28. Scallon B, Cai A, Solowski N, Rosenberg A, Song XY, Shealy D, et al. Binding and functional comparisons of two types of tumor necrosis factor antagonists. J Pharmacol Exp Ther 2002;301:418-26.
29. Sieper J, van den Brande J. Diverse effects of infliximab and etanercept on T lymphocytes. Semin Arthritis Rheum 2005;34:23-7.
30. Zou JX, Brown J, Sieper J. Immunological basis for the use of TNF alpha-blocking agents in ankylosing spondylitis and immunological changes during treatment. Clin Exp Rheumatol 2002;20 Suppl 28:S34-S37.
31. Berg L, Lampa J, Rogberg S, van Vollenhoven R, Klareskog L. Increased peripheral T cell reactivity to microbial antigens and collagen type II in rheumatoid arthritis after treatment with soluble TNF alpha receptors. Ann Rheum Dis 2001;60:133-9.
32. Van den Brande JMH, Braat H, van den Brink GR, Versteeg HH, Bauer CA, Hoedemaeker I, et al. Infliximab but not etanercept induces apoptosis in lamina propria T-lymphocytes from patients with Crohn's disease. Gastroenterol 2003;124:1774-85.