Case Series

New Onset of Crohn's Disease During Treatment of Active Ankylosing Spondylitis with Etanercept

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ABSTRACT. We describe 3 AS patients treated with etanercept for active AS who developed new onset of CD while AS related symptoms responded well to etanercept. Typical symptoms of active CD occurred 11, 12, and 26 months after start of etanercept therapy, respectively. On colonoscopy, inflammatory lesions highly compatible with CD were found endoscopically and histologically in all patients. Etanercept was stopped, and CD responded well to standard treatment. One of the 3 patients was reexposed to etanercept later on. While the 2 patients without re-exposure to etanercept did not have further CD flares, the third patient flared 6 months after re-institution of etanercept in combination with azathioprine. New onset of CD may be considered as an immune-mediated injury induced by etanercept. Although this is an intriguing hypothesis, any causative role of etanercept remains unproven at this stage. (First Release Jan 15 2008; J Rheumatol 2008;35:532–6)

Key Indexing Terms:
ETANERCEPT CROHN'S DISEASE SIDE EFFECTS ANKYLOSING SPONDYLITIS
TUMOR NECROSIS FACTOR-α INHIBITORS GRANULOMA FORMATION

Tumor necrosis factor (TNF)-α is a proinflammatory cytokine that plays an important pathogenic role in chronic inflammatory diseases such as rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis (AS), but also inflammatory bowel disease (IBD) such as Crohn's disease (CD). Blocking TNF-α in these conditions can be highly effective.

However, TNF-α is also an important molecule for the host defense against a variety of infectious pathogens, as it induces and maintains granuloma formation leading to containment of the pathogen, a key component of the host defense[1]. It may therefore not surprise that the increased clinical use of TNF-α blocking agents was associated with a slight increase of clinical infections overall, and, in particular, of granulomatous infectious diseases[2,3]. Further unusual side effects that can best be described as immune-mediated injuries have been observed with all 3 TNF-α blocking agents: these include the induction of a variety of skin lesions including classic psoriasis[4], systemic lupus erythematosus[5], induction or exacerbation of demyelinating diseases[6], glomerulonephritis[7], sarcoidosis[8], and other granulomatous pulmonary lesions[9]. Thus, it appears that granulomata formation is reduced by TNF blocking agents in some conditions but can also occur as part of an immune-mediated injury induced by these agents.

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CASE REPORTS

We describe 3 patients with AS who developed new onset of CD while being treated with etanercept for their axial symptoms.

All 3 patients had established HLA-B27 positive AS. Data on age, sex, disease duration, treatment and disease activity prior to etanercept therapy, colonoscopy and histological findings, and other measures are summarized in Table 1.

Patient 1. A 46-year-old woman was diagnosed as having AS in 2001. She had short episodes (1-2 days) of mild diarrhea (stool frequency 3-4 times per day) every other month for the last 5 years. A colonoscopy in April 2001 revealed no significant mucosal abnormalities in the colon and terminal ileum either endoscopically or histologically (Figure 1A). Thus, overt IBD was ruled out at that time.

Treatment with etanercept was started in the setting of a placebo-controlled (6 wks with an open extension period) clinical trial in July 2001[10]. During the trial, 2 short periods (1-2 days) of bloody diarrhea and fever occurred.

In early June 2002 the patient was hospitalized because of sudden onset of diarrhea, vomiting, abdominal cramping and fever, with intermittently elevated temperature and elevated C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) values [CRP 159 mg/l (normal < 6 mg/l), ESR 100/ 1st h, leukocytes 18.7/nl] and a stool frequency of 6-8 non-bloody stools per day. Etanercept was stopped. On colonoscopy, acute pancolitis was seen, and histological evaluation revealed signs of severe acute and

Table 1. Demographic data and disease course of AS patients treated with etanercept.

	Patient 1	Patient 2	Patient 3
Age, yrs/gender	46/F	37/M	28/F
Disease duration, yrs	15	17	6
Other SpA manifestations	6 episodes of acute iritis	None	Positive family history for SpA
Grading of sacroiliitis*	Grade 2-3 bilateral	Grade 4 bilateral	Grade 3 bilateral
Treatment before initiation of etanercept treatment	4 NSAID, tramadolol and physiotherapy, leflunomide, steroids	NSAID, infliximab	3 NSAID
Disease activity measures prior to etanercept			
BASDAI	7.5	7.7	5.5
CRP, mg/dl	1.8	11.4	2.1
ESR, (mm/h	18	90	44
Initial response (AS) to etanercept (BASDAI 50)	Yes	Yes	Yes
Sustained response (AS) to etanercept	No	Yes	Yes
Time between etanercept start and CD onset	12 mo	11 mo	26 mo
Colonoscopy	Acute pancolitis with multiple aphtheous-like ulcerations (landscape appearance); most severe in descending and transverse colon	Pancolitis with chronic and florid (moderately erosive) inflammation	Inflammatory lesions in terminal ileum, descending and sigmoid colon with ulcerations and partly pseudopolypoid mucosal changes
Histology	Severe acute and chronic colitis with ulcerations, cryptitis, crypt abscesses and non-necrotizing granulomata with giant cells	Ulcerations and granulomatas in terminal ileum	Active granulomatous lesions mainly in sigmoid colon but also in terminal ileum
Imaging	—	Abdominal MRI: moderate thickening of the wall of terminal and preterminal ileum with narrowing and moderate inflammation	Abdominal ultrasound: mural thickening of the descending colon
Treatment of CD	Glucocorticosteroids, mesalazine	Glucocorticosteroids, sulfasalazine	Glucocorticosteroids, mesalazine
Treatment of AS after discontinuation of etanercept	NSAID	Adalimumab, infliximab with prednisone, etanercept with azathioprine	Infliximab
CD flare during followup	No	Yes	No

AS: ankylosing spondylitis; SpA: spondyloarthritis; yrs: years; MRI: magnetic resonance imaging; NSAID: nonsteroidal antiinflammatory drug; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein (reference 0.5 mg/dl); CD: Crohn's disease; * radiographic grading by modified New York criteria.

chronic colitis with granulomatous ulcerations (details in Table 1 and Figure 1B). An infectious origin was ruled out. Based on the clinical presentation, the endoscopic and histological findings, and absence of an infection, a diagnosis of CD was made. Upon treatment with prednisolone and mesalazine, diarrhea improved rapidly, fever disappeared, and CRP and ESR normalized. At discharge from the hospital she had a stool frequency of about twice daily.

On followup the patient did not experience a further flare of CD and mesalazine was discontinued 15 months later in October 2004. Without specific treatment for CD, there were no gastrointestinal signs or symptoms suggesting CD activity until spring 2007 when she was last seen.

Cytokine analysis. Blood samples were available from this patient from various timepoints during the clinical trial with etanercept for cytokine analysis. The cytokines interferon (IFN)-γ and TNF-α were intracellularly stained in CD8+ and CD4+ T lymphocytes according to a described protocol[11,12]. The percentage of cytokine positive T cells was not significantly different at the 3 timepoints before the onset of CD as compared to the 2 timepoints after diagnosis and treatment of CD, although it appears that the lowest level of positive T cells was seen 6 weeks after initiation of prednisolone 60 mg per day (Figure 1).

Patient 2. A 37-year-old man was diagnosed with AS in October 2003 and started taking infliximab 300 mg in November 2003 because of highly active disease. Although he responded very well, infliximab was discontinued in March 2004 because of an allergic reaction during the fourth infusion. Thereafter in April 2004, treatment with etanercept 25 mg twice weekly subcutaneously was started because AS had flared. He also responded very well to etanercept.

Eleven months later (in March 2005) the patient was hospitalized because of chronic non-bloody diarrhea (4-5 times per day) with abdominal pain and fatigue without fever for about 3 weeks. CRP was slightly elevated (3.9 mg/dl; normal < 0.3 mg/dl). Colonoscopy revealed a pancolitis with histologically detectable ulcerations and granulomatas in the terminal ileum. A diagnosis of CD was made, etanercept was stopped, and he was successfully treated with glucocorticosteroids and sulfasalazine. Since AS flared again, he was subsequently treated with adalimumab (July 2005 until October 2005; discontinued because of inefficacy), reintroduction of infliximab with prednisolone (discontinued in September 2006 because of recurrent allergic reactions and secondary loss of efficacy), and eventually with etanercept under concomitant immunosuppressive therapy with azathioprine 200 mg daily. Although AS related symptoms improved again, etanercept had to be discontinued 6 months later because of new CD flare in March 2007.

Patient 3. A 28-year-old woman with AS diagnosed in 2001 also partici-

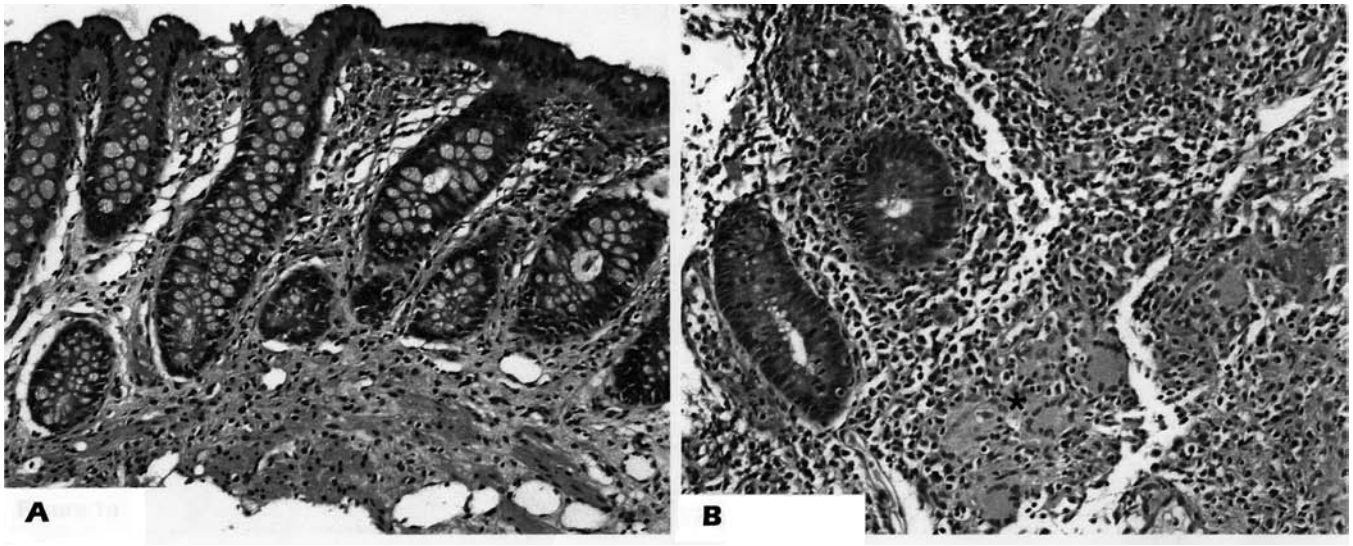

Figure 1. Histology of colonic biopsies performed in patient 1 before (April 2001) and during (July 2002) etanercept therapy. A. Normal colonic mucosa (before initiation of etanercept); B. severe chronic active colitis with epitheloid granuloma and giant cells (*) during etanercept (hematoxylin & eosin, original magnification ×200).

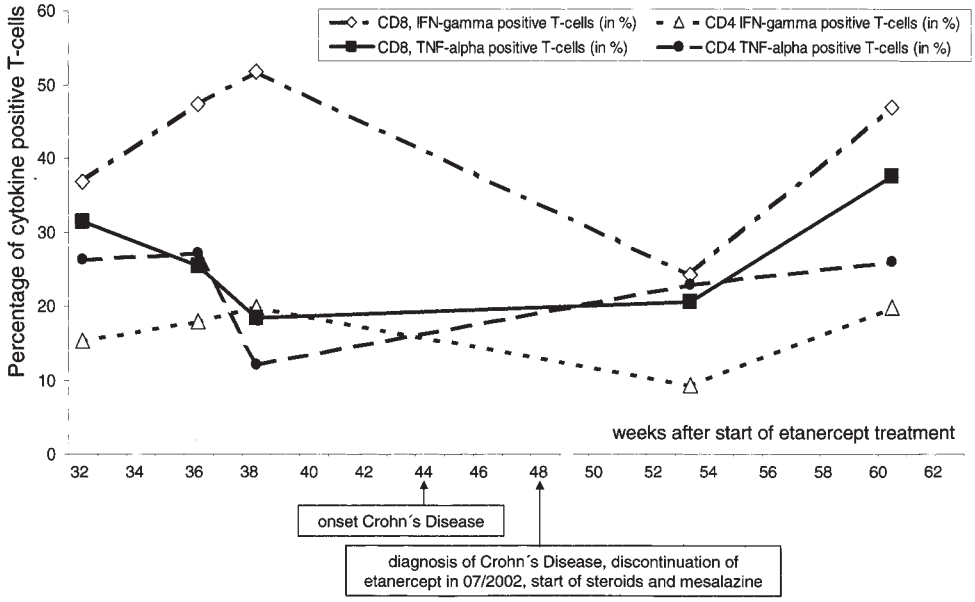

Figure 2. Cytokine (IFN-γ and TNF-α) production by T cells over time in patient 1. The cytokines IFN-γ and TNF-α were intracellularly stained in CD8+ and CD4+ T lymphocytes after nonspecific stimulation as described[11,12]. The percentage of cytokine positive CD8+ or CD4+ T cells is shown. Blood samples during highly active CD were not available.

pated in the clinical trial with etanercept 25 mg twice weekly in July 2001[10]. Twelve weeks after start of etanercept the disease (AS) was very well controlled (clinical remission).

In September 2003 (26 months after start of etanercept), she reported a sudden onset of non-bloody watery diarrhea lasting for 2 weeks with crampy abdominal pain and fever up to 38.5°C. Examination showed a soft abdomen with pain on palpation in the left lower quadrant but was otherwise unremarkable. She was slightly anemic and had elevated CRP. Colonoscopy and subsequent histological investigations revealed typical inflammatory lesions in the terminal ileum and sigmoid colon compatible with CD. Etanercept was stopped, and CD successfully treated with prednisolone, mesalazine, and local steroid foam Formulations. Although not intended, mesalazine therapy was terminated by the patient already after 3 months when CD was in remission. In November 2003, infliximab 200 mg was started because of sustained active AS. She went into clinical remission with regard to AS, and still is in remission regarding AS and CD (summer 2007).

DISCUSSION

Three patients with AS cared for in a single center developed new onset of CD while being treated with etanercept.

The patients were treated with etanercept because of active AS with predominant back pain that was not sufficiently relieved by nonsteroidal antiinflammatory drugs (NSAID) alone. The time interval from start of etanercept therapy until development of CD was 11, 12, and 26 months, respectively. To our knowledge, there is only 1 further case report on new onset of CD during etanercept therapy[13]. This was a patient with psoriatic arthritis who developed CD after 3 years of etanercept treatment.

About 5 to 10% of patients with AS have concomitant IBD, either CD or ulcerative colitis (UC). Further, 40 to 60% of patients with AS may have subclinical gut inflammation according to thorough endoscopic or histological investigations[14]. The first patient with previous episodes of intermittent diarrhea underwent colonoscopy shortly before start of etanercept. At that time, colonoscopy revealed neither endoscopic nor histological evidence of IBD. In the other 2 patients there was no clinical evidence of an underlying IBD at all.

Given the high prevalence of subclinical gut inflammation, the 2 patients who did not have a colonoscopy prior to etanercept therapy could have had subclinical gut inflammation, which may have evolved into clinical IBD. According to Mielants, *et al*[15], however, only a small proportion (about 7%) of SpA patients with subclinical (chronic) gut inflammation progressed to full blown IBD. Thus, the natural evolution from subclinical gut inflammation to clinically overt IBD cannot be excluded but seems unlikely, in particular because the 2 patients with AS did not have the risk profile for evolution into IBD as described by Mielants, *et al*[15]: our patients had purely axial disease without concomitant active peripheral arthritis.

The intriguing question is whether new onset of CD occurred by chance or can rather be considered as an immune mediated injury attributable to the TNF-α blocking agent etanercept. A recent analysis of placebo-controlled randomized trials with TNF-α blocking agents in AS revealed that the incidence of established/new onset of IBD was slightly more frequent in patients with etanercept (14 cases; 2.2 per 100 patient-years) than in patients treated with placebo (2 cases; 1.3 per 100 patient-years) or infliximab (1 case; 0.2 per 100 patient-years)[16]. Among the 8 cases with CD activity during etanercept in these trials, there were 4 flares and 4 new onset cases. Two (patients 1 and 3) of these new onset cases are reported in detail here.

Etanercept, infliximab, and adalimumab appear to be similarly effective in treating signs and symptoms attributable to sacroiliitis, spondylitis, and peripheral arthritis in patients with active AS. Etanercept and infliximab are also effective in treating rheumatic symptoms in patients with IBD[17,18]. However, with respect to the gut in CD, infliximab and adalimumab have been effective whereas etanercept has been ineffective[19-21].

The mechanisms underlying the differential efficacy of etanercept and infliximab in IBD are not entirely clear. Among others, defective T cell apoptosis appears to play a role in the development of inflammation in patients with CD[22]. While infliximab binds to both soluble and membrane-bound TNF-α, etanercept binds primarily to soluble TNF-α[23]. Only binding to membrane-bound TNF-α but not to soluble TNF-α seems to affect apoptosis as studies in monocytes and lamina propria cells of CD patients have revealed.

Infliximab and etanercept also have differential effects on the cytokine production of T lymphocytes upon nonspecific stimulation. After 12 weeks of infliximab therapy of patients with AS, the production by T lymphocytes of TNF-α and IFN-γ by CD4+ and CD8+ cells was significantly reduced[12], whereas etanercept led to a significant increase of T cell cytokine production[11]. Monocyte production of TNF-α was not affected by TNF-α inhibitor administration in either study[11,12]. Another group also observed that during etanercept therapy of patients with rheumatoid arthritis[24], T cells stimulated by microbial antigens produced increased levels of IFN-γ. We hypothesized that etanercept that primarily neutralizes soluble TNF-α may result in a counterregulatory increase of cytokines, since T cells themselves remain unaffected by etanercept[11]. Thus, in certain susceptible patients with AS who *per se* have a predisposition to develop subclinical gut lesions or overt CD, an increased counterregulatory production of cytokines upon etanercept therapy may contribute to the onset of CD. In patient 1 we had the opportunity to follow up the cytokine response. Overall, there was no significant change in cytokine production by T cells during the disease course, although the lowest cytokine levels were found during steroid therapy of CD.

Immune mediated injuries are uncommon adverse events that have been observed with all 3 TNF-α blocking agents. The mechanisms of these injuries are poorly understood. Limited data suggest that under certain circumstances, TNF-α blocking agents promote the activation of autoreactive T cells, leading to tissue damage via autoimmune mechanisms[25]. This is exemplified by the induction of antinuclear antibodies in some patients receiving TNF-α inhibitor treatment and the occurrence of autoimmune syndromes, such as cutaneous lupus erythematosus or systemic lupus erythematosus-like syndromes[26]. Moreover, induction of granulomatous diseases such as sarcoidosis has been reported during TNF-α blocking therapy including 2 patients with AS, one treated with etanercept[8], the other one with infliximab[27]. Some of these immune-mediated injuries respond well to cessation of the TNF-α blocking agent with or without a short course of steroids.

In our case series CD went into remission in all 3 patients upon cessation of etanercept and standard CD therapy. Mesalazine was discontinued after 27 months in patient 1, after 12 months in patient 2, and within less than 3 months in patient 3. Interestingly, after cessation of any CD therapy,

there were no further CD flares over a followup period of 30 months in patient 1 and 48 months in patient 2. AS symptoms in patient 1 were treated with NSAID on demand only, while patient 3 has been treated with infliximab for 4 years now. In contrast, in patient 2, who failed trials of adalimumab and infliximab, etanercept was reintroduced with concomitant azathioprine at a time when the gut was quiescent. His AS related symptoms again responded well, but a CD flare occurred 6 months later in March 2007. This circumstantial observation may further support a role of etanercept in inducing an immune mediated injury in this patient.

It remains unresolved whether etanercept had a causative role in induction of CD in the patients with AS described here. However, the finding of 3 AS patients with new onsets of CD in a single center is an intriguing observation and should prompt further monitoring in clinical trials and clinical practice.

Added in Proof

During preparation of this manuscript, a fourth case of new onset of Crohn's disease during etanercept therapy was observed in our department; a 34-year-old male patient with AS who also participated in the clinical trial 10 developed new onset of CD 66 months after initiation of etanercept. A pancolitis was found endoscopically, with typical granulomata microscopically. CD symptoms responded well to steroids, etanercept was stopped, and AS-related symptoms were treated with infliximab.

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