Antitumor Necrosis Factor-α Therapy Associated with Inflammatory Bowel Disease: Three Cases and a Systematic Literature Review

Amir Bieber, Abdallah Fawaz, Irina Novofastovski, and Reuven Mader

ABSTRACT. ***Objective.*** Antitumor necrosis factor-α (anti-TNF-α) therapy is the most prescribed biologic agent therapy in rheumatology and gastroenterology. However, a number of serious side effects have been reported with these drugs. Only a handful of cases of new-onset inflammatory bowel disease (IBD), mostly in children diagnosed with juvenile idiopathic arthritis (JIA), have been reported during anti-TNF-α therapy. We present 3 cases of adult IBD following anti-TNF-α therapy and a literature review on this topic.

Methods. We searched PubMed MESH for all relevant terms, papers were reviewed, and patient-specific data were extracted. Relevant clinical data were calculated and presented.

Results. The PubMed search resulted in 137 articles, of which 11 articles and 4 cited publications were included in our analysis. We found 53 cases of IBD after anti-TNF-α therapy reported in the literature; most of them were case series collected retrospectively from national databases or studies. Almost all the patients developed IBD after the introduction of etanercept (ETN); 2 patients with rheumatoid arthritis were also included. The average age at IBD onset was 17.3 years and the average time from ETN introduction to IBD onset was 27 months (± 24). Gastrointestinal symptoms have been reported as improving or subsiding in most of the patients after discontinuing ETN.

Conclusion. Although this manifestation is not common, it should be taken into consideration as an adverse effect of ETN. Rheumatologists, and in particular rheumatologists treating adult patients, should be aware of this possible complication. Further investigation about the pathogenic process underlying this phenomenon is warranted. (First Release April 15 2017; J Rheumatol 2017; 44:1088–95; doi:10.3899/jrheum.160952)

Key Index Terms:
RHEUMATOID ARTHRITIS JUVENILE IDIOPATHIC ARTHRITIS ANTI-TNF-α THERAPY
ETANERCEPT INFLAMMATORY BOWEL DISEASE

Antitumor necrosis factor-α (TNF-α) therapy is the most prescribed biologic agent therapy in rheumatology and gastroenterology. There are various indications for its use in rheumatology, all of which are approved by the US Food and Drug Administration (FDA), and recommended in international clinical guidelines. Anti-TNF-α use is accepted and recommended in the treatment of rheumatoid arthritis (RA), spondyloarthropathies (SpA) including psoriatic arthritis (PsA) and ankylosing spondylosis (AS), and juvenile idiopathic arthritis (JIA), and is regarded as a biologic disease-modifying antirheumatic drug (DMARD)[1]. It has also become part of the standard treatment in inflammatory bowel disease (IBD).

From the Rheumatic Diseases Unit Ha'Emek Medical Center, Afula; The Technion Institute of Technology, Haifa, Israel.

A. Bieber, MD, Rheumatic Diseases Unit Ha'Emek Medical Center; A. Fawaz, MD, Rheumatic Diseases Unit Ha'Emek Medical Center; I. Novofastovski, MD, Rheumatic Diseases Unit Ha'Emek Medical Center; R. Mader, MD, Rheumatic Diseases Unit Ha'Emek Medical Center, and The Technion Institute of Technology.

Address correspondence to Dr. R. Mader, Rheumatic Diseases Unit, Ha'Emek Medical Center, Afula 18101, Israel.
E-mail: mader_r@clalit.org.il

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There are several potential side effects that have been reported with anti-TNF-α agents. These include infectious diseases, tuberculosis, skin reactions, infusion reactions, and exacerbation of congestive heart failure[1]. Gastrointestinal (GI) adverse events have been reported without mentioning new-onset IBD. Only a handful of cases of new-onset IBD, mostly in children diagnosed with JIA, have been reported so far during anti-TNF-α therapy.

Three adult cases, in which anti-TNF-α therapy with etanercept (ETN) for RA and JIA was initiated prior to the diagnosis of IBD, are presented. The association and possible pathogenetic factors are discussed and the literature pertinent for this association has been reviewed.

Case 1

A 64-year-old woman was diagnosed with RA in 2008, according to the 1987 American College of Rheumatology criteria. Her disease started with symmetric polyarthritis affecting her wrists, some metatarsophalangeal and proximal interphalangeal joints, and shoulders. Morning stiffness was reported at the beginning of the clinical course lasting at least 2 h. Other organs were not affected throughout the clinical course. No GI symptoms were reported by her, despite

regular questioning during her ambulatory clinical appointments. Therapy with methotrexate (MTX) at a dose of 12.5 mg/week was commenced, but she subsequently developed abnormal liver function and the MTX was stopped. Hydroxychloroquine (HCQ) 300 mg per day and sulfasalazine (SSZ) 2 g per day were prescribed without a significant response. ETN treatment was initiated in March 2010, concomitantly with HCQ and SSZ. With this treatment, disease activity was low, and she needed only occasional intraarticular corticosteroid injections into small joints. On May 2014, she was admitted to the hospital with fever, abdominal pain, and diarrhea. She underwent a thorough investigation including chest and abdominal computed tomography (CT) with intraluminal contrast media (not enterography protocol), and subsequently a colonoscopy with biopsies. The CT revealed 2 thickened colonic wall segments at the descending colon and multiple colonic diverticula. Colonoscopy demonstrated signs of mucosal inflammation beginning at the rectum, with multiple ulcers of different sizes (from tiny ones to 2 cm width). The cecum had a normal appearance, as did the terminal ileum, and no biopsies were taken from the terminal ileum. Histological examination from the inflamed areas in different parts of the colon showed non-necrotizing granulomatous inflammation, distorted crypt architecture, and multinuclear giant cells. Microbiological tests for acid-fast bacilli and PCR examination for 16sRNA, which detects most pathogenic colonic bacteria, were both negative. Periodic acid-Schiff staining and cytomegalovirus tests were also negative. Crohn disease (CD) was the working diagnosis because of granulomas on the biopsies from various parts of the colon. Her blood tests at that time showed normocytic anemia, hemoglobin 10.0 g/dl, and platelets 531 K/mcl with no other significant abnormalities. Erythrocyte sedimentation rate was 78 mm/h. Blood chemistry was normal except for hypoalbuminemia of 2.95 g/dl. C-reactive protein was 112 mg/l (normal ≤ 5 mg/l). The treatment with ETN was stopped and subcutaneous adalimumab (ADA) 40 mg every other week was started concomitantly with prednisone 30 mg/day, which was tapered down rapidly. Her abdominal symptoms subsided, and 7 months after the initial colonoscopy, a repeat colonoscopy was done that demonstrated diverticulosis and no signs of inflammation during the procedure or on the biopsies taken. The blood inflammatory markers and the anemia subsided. At present, she is treated with ADA 40 mg every other week with low disease activity.

Case 2

A 22-year-old woman, diagnosed with JIA[2] since the age of 8 years, first presented with monoarthritis of the left knee. She was treated with naproxen for several years, and then switched to MTX and SSZ because of recurrent exacerbations. She began treatment with ETN in August 2004, after discontinuation of MTX, SSZ, and any nonsteroidal anti-inflammatory drugs (NSAID), with a good clinical response. She was followed up at the pediatric rheumatology outpatient clinic until the age of 19. During that time, she independently discontinued ETN and experienced relapses of the arthritis that resolved quickly after ETN was resumed. There were no systemic complaints or GI symptoms during the followup in childhood. At age 22, upper abdominal pain and nonbloody diarrhea accompanied by iron-deficiency anemia supervened. Serology for celiac disease was negative. Upper GI endoscopy demonstrated esophageal ulcerations and esophagitis, moderate acute gastritis, and multiple duodenal ulcerations. Lansoprazole 30 mg a day was started. CT of the abdomen was suggestive for CD, demonstrating thickened terminal ileum with relative narrowing of the lumen. Colonoscopy showed circular inflammation of the transverse and descending colon with haustra enfacements and ulcerations. Biopsies demonstrated eosinophilic infiltrate in the lamina propria and basal membrane plasmacytosis, insufficient for pathological diagnosis of CD. According to the colonoscopy findings and the biopsies, CD was the working diagnosis within the context of IBD. ETN was stopped accordingly and ADA 40 mg every other week was started with improvement of her GI symptoms and no recurrence of the arthritis. At present, she is treated with ADA alone, and has minimal disease activity and no anemia or elevated acute-phase reactants.

Case 3

A 24-year-old male patient had been diagnosed with JIA and familial Mediterranean fever (FMF; M694V/M694V) since the age of 12. His symptoms were predominantly arthralgia and fever, mostly affecting his right hip or ankle. He had been treated with colchicine 1.5 mg/day, sporadic per oral corticosteroids, NSAID, and intraarticular corticosteroid injections from 2004 to 2007. In 2007 he began MTX treatment, 25 mg per week, concomitant with his colchicine treatment. After 6 months of MTX, he was still symptomatic, having mainly arthritis of the right ankle and hip. MTX was stopped and ETN treatment 25 mg twice a week was initiated with a good clinical response and resolution of his articular symptoms. Self-discontinuation of ETN resulted in an arthritis flare, which required a corticosteroid injection in his right ankle. It is of note that the independent colchicine discontinuation in 2010 had resulted in pleuritic pain and fever, which resolved spontaneously after 3 days. His articular flares during followup were without fever, lasted more than 3 days, and resolved with NSAID or corticosteroid injection, suggesting that they were not related to FMF, but to JIA. From 2008 until 2011, he was almost asymptomatic with ETN and colchicine treatment. In 2011, arthritis of the right hip, supported by magnetic resonance imaging (MRI), recurred during treatment. A short systemic corticosteroid therapy followed by azathioprine (AZA) 100 mg/day was initiated. When he was 21 years of age, he began to have diarrhea and abdominal pain. After excluding colchicine as the cause of his complaints, MRI enterography demonstrated terminal ileitis with lumen narrowing and thickening of the

cecal wall and infiltration of the mesenteric fat, compatible with IBD. He denied any use of over-the-counter NSAID. ETN was stopped and colonoscopy and gastroscopy demonstrated noncommunicating erosions and ulcers from 15 cm above the dentate line and throughout the colon, including the terminal ileum. Biopsies taken from erosion demonstrated chronic severe colitis, cryptitis, fibrin-coated ulcerations with granulation tissue, without dysplasia, and without granulomas, all compatible with IBD not otherwise classified. ADA treatment 40 mg every other week was started after the biopsy results were clear. Three months after treatment with ADA, he was free of both GI and musculoskeletal symptoms. AZA was stopped and he has been in good clinical remission since then.

The decision to switch from ETN to ADA in all the above described cases took into account that ADA is approved for the treatment of IBD as well as for JIA and RA. Further, ADA is not known to exacerbate or to be associated with IBD exacerbation and targets TNF-α by a different mechanism from ETN.

MATERIALS AND METHODS

We searched PubMed MeSH terms using this string search: ((("Arthritis, Rheumatoid"[MeSH] OR "Arthritis, Juvenile"[MeSH])) AND (((((("etanercept"[MeSH Terms]) OR "adalimumab"[MeSH Terms]) OR "certolizumab pegol"[MeSH Terms]) OR "infliximab"[MeSH Terms]) OR golimumab)) AND "inflammatory bowel diseases"[MeSH Terms].

The papers were reviewed by the first author (AB). Studies, case reports, or series that reported suspected or proven IBD concomitantly with the use of ETN were included. Cited articles were screened in the same manner and included in our analysis if they met the same inclusion requirements. The data were extracted for the relevant clinical and laboratory data for our review. Studies or case reports that investigated the involvement of ETN treatment in IBD alone or in any other diseases except RA or JIA were excluded from our analysis.

We confirm that patient agreement was received for publication of their cases without identifying details. We also declare that our institutional research ethics board does not deal with case report publications because its mandate is for clinical trials approval and research only.

RESULTS

The search resulted in 137 articles, of which 11 articles and 4 cited articles were included in our final analysis, and from which patients' data were extracted (Tables 1A–D)[3–12,13,14,15,16,17]. Another single article that reviewed the data from the FDA adverse events reporting system (FAERS) was not included in our review because it lacked specific patients' data[18]. We found 53 cases reported in the literature; most of them were case histories collected retrospectively from national databases or studies. Nearly all the patients who developed IBD after the introduction of ETN were diagnosed primarily with JIA (53/55), including our cases. Two patients with RA were also reported. Data from the FAERS, not included in our analysis, revealed more than 100 cases of patients with RA in whom ETN preceded the presentation of IBD, but the authors could not determine with certainty a causal relationship between the 2 entities. The average age of rheumatic disease onset was 9.2 years, and the average age for IBD onset was 17.3 years. The average time from ETN introduction to IBD onset was 27 months (± 24). The majority of the patients were treated concomitantly with other therapies such as NSAID or conventional DMARD, for example, MTX, SSZ, AZA, or others (29/39 cases with available data). GI symptoms have been reported to improve or subside in most patients after discontinuation of ETN (data available for 32 patients, of whom only 5 had persistent IBD symptoms despite ETN discontinuation). The time elapsing from discontinuation of ETN to IBD symptomatic relief was variable, ranging from days to 10 months. CD was diagnosed in most of the patients (38/56), ulcerative colitis (UC) was diagnosed in another 9 patients, and undifferentiated IBD was diagnosed in 10 patients.

DISCUSSION

Of the 15 articles reviewed, we extracted 53 reported cases (not including data from the FAERS[18]), in which IBD onset occurred after the initiation of ETN. Most of the cases were JIA and only 3 cases including ours were RA. The average age of IBD onset was 17 years, making it clear that rheumatologists taking care of adults with JIA may encounter this phenomenon. The extracted data are summarized in Tables 1A–D.

ETN is a recombinant dimer of human TNF receptor proteins fused and bound to human IgG1 that acts competitively to inhibit the binding of TNF to its cell surface receptor.

A large retrospective study based on national JIA registries for ETN in the Netherlands, Germany, Finland, Denmark, and Italy extracted 13 patients with JIA and IBD[3] already treated with ETN for JIA. Three of the patients had UC and 1 had unidentified IBD. The scope of the study was to assess the incidence of IBD in JIA. In fact, that study reported an increased incidence of 362 IBD cases/100,000 JIA patient-years, which is about 43× higher than that reported for IBD in the normal population of the same age. The median age at IBD onset was 12 years, and the incidence has been compared with an age-matched pediatric population.

Another work from Germany aiming to find drug exposure influence on IBD incidence in patients with JIA identified 11 patients with JIA who developed IBD during their disease course, 9 of whom were treated with ETN[4]. The median age of IBD disease onset was 11 years, and time from ETN introduction to IBD onset was 1.3 years (median).

A study investigating adverse events during ETN treatment of 95 patients with JIA found 5 new cases of CD, 2 of which had histological confirmation. The investigators were convinced that the GI symptoms' onset was associated with ETN treatment, and resolution of the symptoms occurred as soon as the ETN treatment was stopped or switched to infliximab (IFX)[5].

A retrospective study from France found another 8 cases of patients with JIA who developed IBD, mostly CD, after

Table 1A. Studies included in review.

Study	Dallocchio, *et al*[6]					Gerloni *et al*[5]							
Publish yr	2010								2008				
Study design	Observational								Observational				
Sex	M	F	F	F	M	F	F	F	NS	NS	NS	NS	NS
Age at IBD onset, yrs	14.8	17.8	13.5	12.6	14	14.7	13.5	17	NS	NS	NS	NS	NS
Underlying disease	Oligo JIA	ERA JIA	Poly JIA	Oligo JIA	ERA JIA	Oligo JIA	Oligo JIA	Systemic JIA	JIA NOS	JIA NOS	JIA NOS	JIA NOS	JIA NOS
Age at rheumatic disease onset, yrs	3	10.3	3.5	7.5	13	11.5	4	6	NS	NS	NS	NS	NS
Duration of ETN treatment, yrs	0.6	1	6.5	4.1	1	0.8	2	2	NS	NS	NS	NS	NS
Time from disease diagnosis to ETN start, yrs	11.2	6.5	3.5	1	0	2.5	7.5	9	NS	NS	NS	NS	NS
Time from ETN to IBD, yrs	0.6	1	6.5	4.1	1	0.8	2	2	NS	NS	NS	NS	NS
CD/UC	CD	CD	CD	ID	ID	ID	CD	CD	CD	CD	ID	ID	ID
Biopsy	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y
Concomitant treatment	NSAID	NSAID, MTX, SSZ, PSL	NSAID, PSL	PSL, NSAID, MTX	NSAID, SSZ, MTX	NSAID, MTX	NSAID, MTX	NSAID	NS	NS	NS	NS	NS
Decrease in IBD symptoms	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
IBD treatment after	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
IBD progression: penetrating, stricturing, inflammatory	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS

IBD: inflammatory bowel disease; ETN: etanercept; CD: Crohn disease; UC: ulcerative colitis; NS: not specified; oligo: oligoarticular; JIA: juvenile idiopathic arthritis; ERA: enthesitis-related arthritis; poly: polyarticular; NOS: not otherwise specified; ID: undifferentiated IBD; NSAID: nonsteroidal antiinflammatory drugs; MTX: methotrexate; SSZ: sulfasalazine; PSL: prednisone.

the introduction of ETN. The time elapsing from the first ETN administration to the diagnosis of CD was 7 to 78 months[6].

An article from France reported on cases treated with ETN for rheumatologic disorders and developed *de novo* CD during anti-TNF-α treatment. Out of the 3 cases reported, 2 fulfilled the criteria for JIA and 1 was a case of an 83-year-old woman with RA who developed new-onset CD after ETN initiation[7]. That was the oldest patient so far reported.

A study investigating a cohort of 346 adult patients with JIA revealed 2 cases of new-onset IBD (without specification for CD), which started after ETN treatment[8].

A few other sporadic reports linked ETN treatment in JIA to a new-onset CD. All responded to discontinuation of ETN and/or switching the treatment to anti-TNF-α antibodies[9,10,11,12,13,14,15,16,17].

There is no conclusive or sufficient data on anti-TNF-α treatment for RA associated with new-onset IBD. An attempt to search the FDA adverse effect database revealed postmarketing data about adverse effects from the FAERS concerning IBD after anti-TNF-α treatment. There were no definite cases of IBD following anti-TNF-α therapy, but 40 cases of JIA treated with ETN were reported to be associated with the emergence of IBD. A moderate association was defined in patients with RA, but without proven causality[18].

IBD might be associated with inflammatory arthritis in childhood. A Finnish study reported that pediatric patients already having chronic diseases, and in particular JIA, are prone to experience IBD later in life[19]. The self-reported study estimated that the OR for the development of IBD in patients with JIA were elevated (6 for CD and 3.2 for undifferentiated IBD). It can be postulated that at least some of the newly diagnosed patients with IBD had articular symptoms before its onset that were classified as JIA.

The cited work from Germany showed an association between ETN monotherapy and the risk of IBD in patients with JIA. MTX was found to be protective against IBD in the JIA population[4]. Patients with IBD more commonly had enthesitis-related arthritis, protracted oligoarthritis, PsA, and rheumatoid factor-negative polyarthritis. In our current study, the incidence of new IBD cases per JIA patient-year was also higher among patients with JIA relative to other pediatric

Table 1B. Studies included in review.

Study	Zeitz *et al*[12]	Barthel *et al*[4]									Minden *et al*[8]		Toussirot *et al*[7]		
Publish yr	2015	2015									2012		2012		
Study design	Observational										Pros. cohort		Observational		
Sex	M	F	M	F	F	F	F	F	F	F	NS	NS	M	F	M
Age at IBD onset, yrs	19	8.2	16.4	11.4	11.8	17.2	12.2	11.7	12	10.2	> 21	> 21	11	83	17
Underlying disease	ERA JIA	Poly RF-JIA	ERA JIA	Oligo JIA	Poly RF-JIA	ERA JIA	Poly RF-JIA	Oligo JIA	Oligo JIA	RF-JIA	Poly JIA	ERA JIA	ERA JIA	RA	ERA JIA
Age at rheumatic disease onset, yrs	7	2.7	12.4	9.6	3.1	10	2	6.7	4.1	5.4	NS	NS	10	71	11
Duration of ETN treatment, yrs	3	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	0.8	0.8	1.5
Time from disease diagnosis to ETN start, yrs	9	3.8	3.3	0.5	7.1	5.5	9.8	2.3	6.3	3.5	NS	NS	0.3	11.3	4.5
Time from ETN to IBD, yrs	3	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	0.8	0.8	1.5
CD/UC	CD	CD	CD	CD	UC	UC	CD	CD	UC	CD	ID	ID	CD	CD	CD
Biopsy	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	NS	NS	Y	Y	Y
Concomitant treatment	IFX, PSL	PSL	MTX, PSL, NSAID	None	PSL, NSAID	SSZ, NSAID	None	NSAID	LEF	None	NS	NS	NS	NS	NS
Decrease in IBD symptoms	IBD improved	IBD improved	IBD improved	IBD persisted	IBD improved	NS	IBD persisted	IBD improved	IBD improved	IBD persisted	NS	NS	NS	NS	NS
IBD treatment after	NS	SSZ	ETN cont + MTX, PSL, NSAID	MTX, PSL SSZ	MTX, IFX, SSZ	SSZ	ADA, AZA, PSL	ADA, SSZ, PSL	MSZ, ADA, PSL	ADA, PSL, MSZ	NS	NS	IFX	ADA	ADA
IBD progression: penetrating, stricturing, inflammatory	Fistulating	Inflammatory	NS	Inflammatory	Inflammatory	Inflammatory	Inflammatory	Inflammatory	Inflammatory	Inflammatory	NS	NS	NS	NS	NS

IBD: inflammatory bowel disease; ETN: etanercept; CD: Crohn disease; UC: ulcerative colitis; pros. cohort: prospective cohort; NS: not specified; ERA: enthesitis-related arthritis; JIA: juvenile idiopathic arthritis; poly: polyarticular; RF: rheumatoid factor; oligo: oligoarticular; RA: rheumatoid arthritis; ID: undifferentiated IBD; IFX: infliximab; PSL: prednisone; MTX: methotrexate; NSAID: nonsteroidal antiinflammatory drugs; SSZ: sulfasalazine; LEF: leflunomide; ETN cont.: ETN continuous; ADA: adalimumab; AZA: azathioprine; MSZ: mesalazine.

populations. Because of the higher prevalence of IBD in patients with JIA, a cause-and-effect relationship between ETN and the emergence of IBD cannot be determined with certainty. However, in most cases where this association has been described, discontinuation of ETN treatment led to improvement in the IBD, suggesting a possible relationship.

New-onset CD has been described in patients with AS, as well as other seronegative SpA treated or not treated with ETN[20,21]. The authors suggested that CD in these patients may be considered an immune-mediated injury induced by ETN.

IBD is known to be associated with SpA and to have its own articular features[22]. It is reasonable to think that some of the reported patients with JIA had clinically silent IBD that manifested clinically only after ETN initiation and not because of ETN treatment, which in itself is known to be ineffective in IBD[23].

The longterm outcome of adult patients diagnosed with JIA during childhood and not treated with anti-TNF-α drugs or other biologic agents is often poor[24]. In recent years, biologic therapy, and specifically anti-TNF-α therapy, is indicated for both JIA and RA. In JIA, this treatment continues often into adulthood when they are followed up and treated as adults by rheumatologists.

The effect of ETN on IBD was investigated. It was found that ETN is ineffective in the treatment of active CD[23]. Few mechanisms were suggested for this observation. One of the assumptions was that instead of leading to apoptosis of T cells in the lamina propria as IFX and ADA do, ETN leads to cytokine production, which includes TNF-α and interferon-γ[23]. Binding of TNF-α to ETN is known to prolong the plasma half-life of the cytokine, which in its turn may favor the bowel mucosa inflammatory response and promote granuloma formation leading to the development of new-onset IBD[25].

It has been shown in CD that inborn errors in macrophages

Table 1C. Studies included in review.

Study	Flemming, *et al*[17]	Pontikaki, *et al*[15]			Actis, *et al*[14]	Tarkiainen, *et al*[13]			Current Study			Ruemmele, *et al*[11]	Quartier, *et al*[10]	Wiegering, *et al*[9]	Oikonomou, *et al*[16]
Publish yr	2013	`2006			2012	2011			2016			2004	2003	2010	2010
Study design	Case	Case			Case	Case			Case			Case	Observa-tional	Case	Case
Sex	M	F	F	M	M	F	M	F	M	F	F	M	NS	F	F
Age at IBD onset, yrs	12.3	32	28	15	21	14.8	12.6	15.2	21	22	62	6	8	11	17
Underlying disease	ERA JIA	Poly RF-JIA	Oligo JIA	Oligo JIA	JIA NOS	JIA NOS	ERA JIA	Poly RF-JIA	Oligo JIA	Poly RF-JIA	RA	Oligo JIA	Oligo JIA	Poly RF-JIA	Oligo JIA
Age at rheumatic disease onset, yrs	12	16	1.5	2	8	4.3	9	9.8	12	8	56	2.5	3	7	2
Duration of ETN treatment, yrs	0.4	1.3	NS	1.5	2.3	4.4	2.8	2.1	7	10	4.2	6	0	1	4
Time from disease diagnosis to ETN start, yrs	NS	14.7	NS	13.5	13	5.9	0.8	3.3	3	2	2	4	5	3	11
Time from ETN to IBD, yrs	0.4	1.3	NS	1.5	2.3	4.4	2.8	2.1	7	10	4.2	0	0	1	4
CD/UC	CD	CD	CD	CD	UC	UC	CD	UC	ID	CD	CD	CD	CD	CD	CD
Biopsy	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Concomitant treatment	MTX, PSL	NS	NS	NS	LE	MTX	HCQ	HCQ, LEF	AZA, colchi-cine	None	SSZ, HCQ	PSL, AZA	NS	None	LEF
Decrease in IBD symptoms	IBD improved	IBD improved	IBD improved	IBD improved	IBD improved	IBD persisted	IBD improved	IBD persisted	IBD improved	IBD improved	IBD improved	IBD improved	IBD improved	IBD improved	NS
IBD treatment after	IFX	ADA	IFX	IFX	BUD, PSL	SSZ, BUD	MSZ, HCQ	MSZ, PSL	ADA	ADA	ADA	IFX	NS	ADA	ADA
IBD progression: penetrating, stricturing, inflammatory	NS	NS	NS	NS	Inflam-matory	NS	NS	NS	Inflam-matory	Stric-turing	Mild inflam.	Fistu-lating	NS	Inflam-matory	NS

IBD: inflammatory bowel disease; ETN: etanercept; CD: Crohn disease; UC: ulcerative colitis; NS: not specified; ERA: enthesitis-related arthritis; JIA: juvenile idiopathic arthritis; poly: polyarticular; RF: rheumatoid factor; oligo: oligoarticular; NOS: not otherwise specified; RA: rheumatoid arthritis; ID: undifferentiated IBD; MTX: methotrexate; PSL: prednisone; LEF: leflunomide; HCQ: hydroxychloroquine; AZA: azathioprine; SSZ: sulfasalazine; IFX: infliximab; ADA: adalimumab; BUD: budesonide; MSZ: mesalazine.

cause less production of TNF, interfering with bacteria salvaging from the gut[26]. ETN treatment resembles this lack of TNF while it is used for the treatment of other chronic inflammatory diseases, especially for a long period of time as has been hypothesized by Smith, *et al*, showing different cytokine levels between acute and chronic gut inflammation[26]. Anti-TNF-α monoclonal antibodies (ADA, IFX) bind transmembrane TNF as well, whereas ETN does not. Further, ETN is less specific for TNF-α and also binds TNF-β (lymphotoxin-a)[1]. This might explain the difference in their effect on different immune cells.

In patients with RA, increased peripheral T cell activity both to self-antigens and to microbial antigens has been shown after ETN therapy[27]. It might be assumed that this lymphocytic hypersensitivity is responsible for the ETN effect in those patients who already have RA.

IBD can be diagnosed in childhood as early as 5 years of age, and it peaks during the second and third decades of life. The reported peak occurrence of IBD is between 15 and 30 years of age[28]. There are no data examining the age variation of IBD-associated arthropathy, but it can either precede or follow the IBD GI symptoms. One article showed that sacroiliitis was asymptomatic in 32% of IBD patients with sacroiliitis, as demonstrated by CT[29]. Taking the age of IBD onset in the population, and especially the fact that axial IBD–associated arthropathy does not correlate with GI symptoms, it can be assumed that young adult patients in their second and third decades of life will be treated by a rheumatologist for their arthropathy and by a gastroenterologist for their IBD. Rheumatologists treating adults should be aware of this possibility, and that ETN is not a treatment option for IBD, while it may contribute to its initiation as previously discussed. We suggest that the occurrence of IBD following treatment with ETN might be more common than previously reported. It is particularly important for rheumatologists to continue to follow up with these patients as they grow older. Discontinuation or the switching of ETN to another treatment may improve both the arthritis and the IBD.

There are some limitations that should be considered when interpreting our review. The cases were collected retrospectively and were not extracted from randomized controlled trials, with the exception of a single article. It could well be

Table 1D. Studies included in review.

Study	van Dijken, *et al*[3]												
Publish yr	2011												
Study design	Observational												
Sex	F	F	F	F	F	F	F	F	F	F	M	M	M
Age at IBD onset, yrs	8	13.1	12.7	33.5	26.4	17.6	11.7	8.4	15.3	10.3	8.3	12.5	10
Underlying disease	Poly JIA	Oligo JIA	Oligo JIA	Poly JIA	Systemic JIA	ERA JIA	Oligo JIA	ERA JIA	Systemic JIA	Poly JIA	Oligo JIA	Oligo JIA	Poly JIA
Age at rheumatic disease onset, yrs	1.6	1.9	3.3	16.8	14.1	8	6.7	3.3	5.8	5.8	1	11.4	7.08
Duration of ETN treatment, yrs	5.9	1.3	4.8	1.5	0.7	0.8	1.3	1.1	3.6	2.5	0.3	0.1	1.3
Time from disease diagnosis to ETN start, yrs	0.6	9.9	4.8	16.6	12	16.8	10.4	4.2	9.3	3.3	8.1	12.4	2.8
Time from ETN to IBD, yrs	5.8	1.3	4.5	1.4	0.3	0.8	1.3	1	3	2.3	0.1	0	0.4
CD/UC	UC	CD	ID	CD	CD	CD	CD	UC	CD	CD	CD	CD	UC
Biopsy	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Concomitant treatment	None	None	Nons	PSL, CSA	PSL, CSA	ETN cont.	ADA	None	None	None	MTX, PSL	NSAID, omeprazole, PSL	NSAID
Decrease in IBD symptoms	IBD improved	IBD improved	IBD improved	IBD improved	IBD improved	NS	NS	IBD improved	IBD improved	NS	IBD persisted	IBD improved	IBD improved
IBD treatment after	IFX, ADA	MSZ, IFX, ADA	NS	ADA	IFX, SSZ	ETN, MTX, PSL, SSZ	ADA	IFX, BUD, MSZ	MSZ	PSL, ADA	PSL	IFX, BUD, MSZ	IFX
IBD progression: penetrating, stricturing, inflammatory	NS	NS	Inflam-matory	NS	NS	NS	NS	Inflam-matory	NS	Inflam-matory	Inflam-matory	NS	Inflam-matory

IBD: inflammatory bowel disease; ETN: etanercept; CD: Crohn disease; UC: ulcerative colitis; NS: not specified; poly: polyarticular; JIA: juvenile idiopathic arthritis; oligo: oligoarticular; ERA: enthesitis-related arthritis; ID: undifferentiated IBD; PSL: prednisone; CSA: cyclosporine; ETN cont.: ETN continuous; ADA: adalimumab; MTX: methotrexate; NSAID: nonsteroidal antiinflammatory drugs; IFX: infliximab; MSZ: mesalazine; SSZ: sulfasalazine; BUD: budesonide.

that in randomized controlled trials done with ETN, diarrhea or other GI symptoms or signs were not reported or diagnosed as IBD. Our study did not incorporate the data from the FAERS, which found 104 patients with RA, of whom 53 received ETN. Although there were no "definite" cases of anti-TNF-α–induced IBD according to the Naranjo scale used for our assessment, it might be that IBD following ETN or other anti-TNF-α therapies for RA and JIA is more prevalent than previously reported[18].

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