Gastroenterol Hepatol. 2017;40(2):117–121

Gastroenterología y Hepatología

www.elsevier.es/gastroenterologia

REVIEW

Inflammatory bowel disease as a paradoxical effect of anti-TNF alpha therapy☆

Ainara Iriarte[a,*], Celia Zaera[b], Javier Bachiller-Corral[c], Antonio López-Sanromán[b]

[a] *Servicio de Digestivo, Hospital de Bidasoa, Hondarribia, Guipúzcoa, Spain*
[b] *Servicio de Digestivo, Hospital Ramón y Cajal, Madrid, Spain*
[c] *Servicio de Reumatología, Hospital Ramón y Cajal, Madrid, Spain*

Received 29 October 2015; accepted 27 January 2016
Available online 16 February 2017

KEYWORDS
Inflammatory bowel disease;
Paradoxical effects;
Anti-TNF-α therapies;
Infliximab;
Etanercept;
Adalimumab

Abstract Anti-TNF-α therapies are used in the treatment of different inflammatory conditions, such as inflammatory bowel disease (IBD). However, paradoxical effects may occur during treatment. In other words, these drugs can induce or unmask diseases similar to those they were intended to treat. Etanercept is the main anti-TNF-α agent associated with the development of paradoxical IBD; this drug, moreover, has no proven usefulness in the treatment of the disease. This association, which is not coincidental and meets the criteria for a temporal causal association, is infrequent and is seen particularly in patients with spondyloarthritis. Restarting treatment with etanercept may induce new intestinal symptoms. There are no endoscopic, histopathologic or clinical differences between primary and secondary IBD, and both are diagnosed in the same way. The most frequent presentation is Crohn disease. When a paradoxical event occurs, etanercept is usually replaced with infliximab, which has not been associated with disease recurrence.

PALABRAS CLAVE
Enfermedad inflamatoria intestinal;
Efectos paradójicos;
Anti-TNF-α;
Infliximab;
Etanercept;
Adalimumab

Enfermedad inflamatoria intestinal como efecto paradójico del tratamiento con anti-TNF-α

Resumen Los anti-TNF-α forman parte del tratamiento de distintas enfermedades inflamatorias, como la enfermedad inflamatoria intestinal (EII). Sin embargo, se han descrito los efectos paradójicos, es decir, el desenmascaramiento o producción de enfermedades similares a aquellas para las que se utilizan. Concretamente, en la EII, el fármaco biológico más implicado ha sido etanercept, el cual además no ha demostrado su utilidad como tratamiento de esta enfermedad. Esta asociación, que no es casual, y que cumple el criterio temporal de

☆ Please cite this article as: Iriarte A, Zaera C, Bachiller-Corral J, López-Sanromán A. Enfermedad inflamatoria intestinal como efecto paradójico del tratamiento con anti-TNF-α. Gastroenterol Hepatol. 2017;40:117–121.

* Corresponding author.
E-mail address: airiartr@gmail.com (A. Iriarte).

causalidad, es un cuadro infrecuente que se da especialmente en pacientes con espondiloartritis. Su reintroducción puede inducir nuevos brotes. No hay diferencias clínicas, endoscópicas ni anatomopatológicas que permitan discernirla de la EII primaria, y el proceso diagnóstico es el mismo. La presentación más habitual es la de enfermedad de Crohn. La estrategia terapéutica más extendida consiste en sustituir etanercept por infliximab, con el cual no se ha descrito recidiva de la enfermedad.

Introduction

Anti-TNF-α agents are used to treat various inflammatory diseases, such as inflammatory bowel disease (IBD), rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis (AS). Different anti-TNF-α drugs have different molecular structures.[1–3] Although all anti-TNF-α agents seem to have similar efficacy in musculoskeletal disorders, differences in their molecular structure could explain the differences observed in their immunomodulatory potential, in their efficacy in IBD, and also in their spectrum of adverse effects.

Anti-TNF-α drugs have been associated with various paradoxical adverse events, i.e., the unmasking or development of diseases similar to those they are used to treat, such as psoriasis, anterior uveitis, lupus-like disorders or IBD.[4–10]

Specifically, etanercept, which has no demonstrated efficacy in IBD, has been most frequently associated with the occurrence of this disease.[6,7,11] This association, which cannot be considered fortuitous, is particularly common in patients with spondyloarthritis, in whom IBD develops soon after starting treatment with etanercept,[10] while resumption of treatment can cause new flares.[12]

There are no clinical, endoscopic or histopathologic differences between paradoxical and primary IBD. The diagnosis process is the same, and IBD should be suspected when patients with rheumatic diseases treated with anti-TNF-α develop intestinal symptoms.[6,7] The most common presentation is similar to Crohn's disease (CD).[13] Although treatment is not fully established, the most widely used strategy consists of replacing etanercept with infliximab, which is not associated with IBD recurrence.[1,4,7,10,11]

However, paradoxical IBD is a rare, poorly understood event that would not have been attributed to the effect of therapy had it remained unknown. For this reason, we believe that this article may provide information relevant to routine clinical practice.

What is etanercept?

Tumour necrosis factor α (TNF-α) is a pivotal factor in the disordered inflammatory response that characterizes diseases such as CD and ulcerative colitis (UC). The action of this cytokine is highly complex, though it is known to be mainly proinflammatory.[1,14] As a result, TNF-α drives monocytes to differentiate into macrophages, activates macrophages and phagosomes, increases neutrophil and macrophage chemotaxis, promotes granuloma formation and maintains their cell integrity.[1,2] Anti-TNF-α drugs inhibit these actions by directly blocking circulating and transmembrane TNF-α. Nevertheless, it also induces cell-mediated cytotoxicity, which is triggered by the molecule's Fc component, and apoptosis.[2,4,14]

There are basically five anti-TNF-α drugs, three are complete immunoglobulins (infliximab, adalimumab and golimumab), another (certolizumab) is formed only from the Fv fragment of an anti-TNF-α immunoglobulin fused with a stabilizing molecule, and the last, etanercept, is a fusion protein, composed of a dimer formed by fusing a protein (the extracellular domain of human tumour necrosis factor receptor-2 [TNFR2/p75]) to the Fc domain of human immunoglobulin G1 (IgG1).[15] This Fc component contains the hinge, CH2 and CH3 regions, but not the CH1 region of IgG1[2] This molecule, therefore, differs both in structure and mechanism of action from those found in other anti-TNF-α agents, a factor that could explain the differences observed in its efficacy and the safety profile.

Anti-TNF-α agents are used to treat various inflammatory diseases, such as IBD, UC, rheumatoid arthritis, psoriatic arthritis and AS.

Specifically, the European Medicines Agency (EMA) has approved the use of etanercept as a second-line therapy in rheumatic diseases that have not responded to standard therapies (mainly methotrexate).[15] These include rheumatoid arthritis, juvenile idiopathic arthritis (JIA), psoriatic arthritis, AS, non-radiographic axial spondyloarthritis and plaque psoriasis.[15]

However, etanercept is the only anti-TNF-α that has not shown any efficacy in IBD, while infliximab and adalimumab are effective in both inducing and maintaining remission in CD and moderate to severe UC.[11,13,16] Sandborn et al.,[11] who investigated this particular issue, found that etanercept was safe but ineffective for the treatment of moderate to severe CD. One possible explanation for this is the dosage used (25 mg twice weekly), which is the usual dose for rheumatoid arthritis. The authors suggest that higher doses or more frequent administration may be required to attain a response.

Etanercept and paradoxical gastrointestinal reactions

Although anti-TNF-α agents have been shown to be highly effective, they are not without their adverse effects. These drugs increase susceptibility to infections, certain tumours (lymphomas, leukaemia, other haematopoietic malignancies and solid tumours), skin lesions and neurological disorders, among others.[15] They can also produce or unmask diseases similar to those they are used to treat, resulting

in what has been termed paradoxical reactions or effects. This means that they can be used in the treatment of psoriasis, anterior uveitis, rheumatic disease and IBD, but may produce symptoms similar to these diseases.[4,12]

Etanercept, in particular, has been implicated in the emergence of paradoxical IBD,[6,7,10] although the same phenomenon has also been reported in patients receiving golimumab,[17,18] adalimumab and, in rare cases, infliximab.[10,19]

The emergence of IBD in patients treated with etanercept cannot be considered fortuitous, as various studies have reported a clear temporal relationship. In true IBD associated with rheumatic diseases, onset may occur years after the initial diagnosis, while in the case of a paradoxical reaction, IBD will onset a few months after start of etanercept therapy,[10] while resumption of treatment can cause new flares.[12]

The association between anti-TNF-α agents and paradoxical reactions is more common in patients with various forms of spondyloarthritis (AS, JIA, enthesitis-related arthritis, and undifferentiated and non-radiographic spondyloarthritis) and less frequent in psoriatic arthritis.[1,4–8,10,12]

Are these paradoxical gastrointestinal reactions common?

Fortunately, this association is rare, and is more frequent with etanercept than with other anti-TNF-α agents. In AS, incidence is estimated at 2.3 per 100 patient-years with adalimumab and 2.2 cases per 100 patient-years with etanercept. Incidence was similar when compared to placebo, but differed significantly when each was compared with infliximab.[7] In the case of JIA, the incidence of new cases with etanercept is 1.9 per 100 patient-years.[8,10] More importantly, in patient with a history of IBD, the relative risk of reactivation increases ten-fold in patients treated with etanercept, but not in those taking infliximab or placebo.[7]

AS and IBD are two genetically related diseases.[20] In fact, 6% (5%-10%) of individuals with AS have a history of IBD; moreover, 40%-60% present subclinical endoscopic and histopathological lesions similar to those of IBD. In these patients, CD is more common that UC.[1,7,21] However, emergence of IBD has been reported in patients with AS treated with etanercept and adalimumab, and a clear temporal relationship has been observed between exposure or re-exposure to the drug and the subsequent onset of the disease. Some authors suggest that anti-TNF-α agents could unmask existing subclinical conditions.[4,10]

An important issue in both this and other situations could be the effect of therapy combined with an immunosuppressant.

Braun et al.[7] performed a meta-analysis of 9 clinical trials, 7 of which were placebo-controlled and 2 open-label, with a total of 1514 patients. They found that patients receiving continuous azathioprine presented fewer IBD flares. However, they do not mention whether incidence of IBD differed between patients receiving combination vs monotherapy. The authors also mention that azathioprine and other disease-modifying antirheumatic drugs were allowed in both the etanercept and the larger adalimumab trial, concluding that it is unclear whether and how this may have influenced the results. Neither were the authors able to determine concomitant intake of nonsteroidal anti-inflammatory drugs (NSAIDs), although they suggest this was likely to be similar between the different groups.

Barthel et al.[22] studied patients with JIA to specifically investigate whether concomitant administration of anti-TNF-α and immunosuppressants affects the development of IBD. Of 3071 patients included in the study, 11 had IBD. Patients with IBD more commonly had enthesitis-related arthritis, extended oligoarthritis, psoriatic arthritis, and also rheumatoid factor (RF)-negative polyarthritis. However, no cases of IBD were observed in patients with systemic JIA or RF-positive polyarthritis. They observed that methotrexate seemed to be protective, since IBD incidence was significantly lower in patients receiving combination etanercept + methotrexate than etanercept in monotherapy, leading them to conclude that etanercept as monotherapy, but not in combination, is associated with IBD.

What is the pathogenesis? Why does IBD occur more frequently with this drug?

Different anti-TNF-α drugs have different clinical and biological properties. Various hypotheses have been put forward to explain this phenomenon.

The different molecular structures of these drugs are highly relevant. First, infliximab, adalimumab, certolizumab and golimumab are monoclonal antibodies, whereas etanercept is a fusion protein (an antireceptor).[2] Infliximab and adalimumab bind specifically to TNF-α, but etanercept also binds to lymphotoxin α.[1,2]

In addition, two TNF-α can bind to a molecule of infliximab, and three infliximab molecules can bind to one TNF-α, thus completing all TNF-α domains. In contrast, etanercept dimers only bind to two of these, leaving the third free, thus forming 1:1 complexes.[2] Infliximab, unlike etanercept, binds to TNF-α monomers, which can prevent the formation of bioactive trimers. Etanercept-TNF-α complexes, meanwhile, are less stable than those formed with infliximab, and when they disassociate, TNF-α is released and again becomes biologically active.[1,2]

It has also been hypothesized that some of the inflammatory phenomena observed in CD could be due to macrophage dysfunction.[3] Granulocyte chemotaxis towards the bowel wall would clearly be diminished, causing impaired faecal matter and bacteria clearance and promoting the formation of granulomas.[3] Macrophage TNF-α secretion in these patients would be abnormally low due to lysosomal destruction of this substance. Thus, decreased local TNF-α activity following administration of anti-TNF-α agents could precipitate IBD-like symptoms.[1] This is even thought to occur in two stages. In the first, shortly after administration, the aforementioned TNF-α depletion takes place. Subsequently, a chronic change occurs over weeks or months, which predominantly affects T lymphocytes, and can be reversed by the administration of TNF-α. In this regard, monoclonal antibodies (not etanercept) are known to induce circulating and lamina propria T lymphocyte apoptosis by binding directly to transmembrane TNF-α and by caspase 3 activation.[1,2,10,16] Infliximab may also lyse TNF-α-secreting cells by inducing complement-mediated cytolysis. Etanercept, however, due

to its counterregulatory properties, increases T cell levels in peripheral blood, thereby inducing TNF-α and interferon gamma (IFNγ) synthesis, both of which promote inflammation of the intestinal mucosa, IFNγ synthesis, and granuloma formation.[2,7,16]

These differences do not seem to be relevant in musculoskeletal diseases, where all anti-TNF-α agents show similar efficacy. However, it could explain the differences observed in their immunomodulatory potential and in their efficacy in IBD.

According to one hypothesis, the introduction of a TNF-α blocker, mainly etanercept, in genetically predisposed patients, such as carriers of genetic variants NOD2/CARD15, would lead to cytokine imbalance and in increase in interferon αlevels, which may lead to the development of IBD.[1,5,6,9,10,12]

Is there a specific pattern? Does paradoxical IBD differ from primary IBD?

Toussirot et al.[10] classified IBD following anti-TNF-α administration as CD, UC and indeterminate colitis. Other authors have described a fourth group, similar to Crohn's disease (CD-like), defined as an atypical histopathological pattern with endoscopic findings and an extension suggestive of CD.[13] In the study in question, the authors found that IBD most commonly presents as CD (50%) or CD-like disease (43.7%) but rarely as UC (6.25%). A French study found that the prevalence of a family history of IBD and age at onset were similar in primary and paradoxical IBD.[8]

No clinical, endoscopic or histopathological differences have been found that would differentiate primary and paradoxical IBD.

Is diagnosis the same? When should it be suspected?

Diagnosis is carried out in the same way as in other cases of IBD. The main difference is that the first step is to establish a specific clinical suspicion. Thus, the possibility of IBD should be investigated in patients with rheumatic disease (mainly spondyloarthritis) treated with anti-TNF-α (particularly etanercept) who develop intestinal symptoms (such as abdominal pain, diarrhoea, weight loss and others), including perianal abscess.[6,7] Time to onset after initiating etanercept varies greatly, but is usually 8 months.[7,10]

How should it be treated?

Once diagnosed, the best treatment strategy remains unclear, though various options have been suggested. The most widespread therapeutic strategy is to replace etanercept with infliximab, which has not been associated with disease recurrence. This strategy has been reported to achieve clinical remission with no new flares.[1,4,6,7,10] However, reintroducing etanercept is associated with a recurrence of symptoms.[10,12]

Braun et al.[7] describe two therapeutic options in patients with rheumatic disease and etanercept therapy presenting with paradoxical UC: if they are treated concomitantly with other disease-modifying antirheumatic drugs, etanercept can be withdrawn without adding new drugs; if not, the addition of corticosteroids and azathioprine has been shown to be effective.

A more unusual practice is to maintain etanercept without further changes,[7] although the addition of oral mesalazine[4] or, in the case of CD, sulfasalazine[7] has also been described.

Does it re-emerge after switching to other anti-TNF-α agents?

In the observational study carried out by Toussirot et al.[10] no recurrence occurred after switching to another anti-TNF-α. However, new intestinal symptoms occurred after restarting etanercept.[12]

Can it be prevented?

In this type of treatment it is important to individualize indications before weighing the risks and benefits, taking into account the spectrum of adverse effects. In AS patients, some authors suggest that a personal or family history of IBD should first be ruled out, as etanercept is contraindicated in these cases. In case of doubt, an ileocolonoscopy should be performed before starting etanercept.[7,10] Some even suggest avoiding adalimumab in AS,[7] although clinical experience in our setting suggests that this is not necessary. Infliximab is the biological treatment of choice in patients with AS and IBD activity.[1,7,15]

Conflicts of interest

The authors declare that there are no conflicts of interest.

References

1. 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.
2. Benucci M, Saviola G, Manfredi M, Sarzi-Puttini P, Atzeni F. Tumor necrosis factors blocking agents: analogies and differences. Acta Biomed. 2012;83:72–80.
3. Smith AM, Rahman FZ, Hayee B, Graham SJ, Marks DJ, Sewell GW, et al. Disordered macrophage cytokine secretion underlies impaired acute inflammation and bacterial clearance in Crohn's disease. J Exp Med. 2009;206:1883–97.
4. Oh J, Arkfeld DG, Horwitz DA. Development of Crohn's disease in a patient taking etanercept. J Rheumatol. 2005;32:752–3.
5. 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 (Oxford). 2009;48:761–4.
6. Dallocchio A, Canioni D, Ruemmele F, Duquesne A, Scoazec JY, Bouvier R, et al. Occurrence of inflammatory bowel disease during treatment of juvenile idiopathic arthritis with etanercept: a French retrospective study. Rheumatology (Oxford). 2010;49:1694–8.
7. Braun J, Baraliakos X, Listing J, Davis J, van der Heijde D, Haibel H, et al. Differences in the incidence of flares or new onset of inflammatory bowel diseases in patients with ankylosing spondylitis exposed to therapy with anti-tumor necrosis factor alpha agents. Arthritis Rheum. 2007;57:639–47.

8. Oikonomou KA, Kapsoritakis AN, Tsiopoulos FD, Tsikouras AN, Potamianos S. Emergence of Crohn's disease in juvenile idiopathic arthritis during treatment with etanercept: a causal link or a mere coincidence? J Gastrointestin Liver Dis. 2010;19:342.
9. Khirfan K, Kistin M. Colitis associated with biological agents. Dig Dis Sci. 2014;59:1112–4.
10. Toussirot E, Houvenagel E, Goeb V, Fouache D, Martin A, le Dantec P, et al. Development of inflammatory bowel disease during anti-TNF-alpha therapy for inflammatory rheumatic disease: a nationwide series. Joint Bone Spine. 2012;79:457–63.
11. 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.
12. Song IH, Appel H, Haibel H, Loddenkemper C, Braun J, Sieper J, et al. New onset of Crohn's disease during treatment of active ankylosing spondylitis with etanercept. J Rheumatol. 2008;35:532–6.
13. Silverberg MS, Satsangi J, Ahmad T, Arnott ID, Bernstein CN, Brant SR, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. Can J Gastroenterol. 2005;19 Suppl. A:5A–36A.
14. Georgopoulos S, Plows D, Kollias G. Transmembrane TNF is sufficient to induce localized tissue toxicity and chronic inflammatory arthritis in transgenic mice. J Inflamm. 1996;46:86–97.
15. Agency EM. Etanercept-Enbrel Product information. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000262/WC500027361.pdf [accessed 24.02.15].
16. 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.
17. Bawany MZ, Rafiq E, Thotakura R, Lay R, Silverman AL, Nawras A. Golimumab may induce exacerbation of inflammatory bowel disease when it is used for the treatment of ankylosing spondylitis: a case report with a review of literature. Am J Ther. 2014;21:e26–7.
18. Fiehn C, Vay S. Induction of inflammatory bowel disease flares by golimumab: report of three patients with enteropathic spondylarthritis or ankylosing spondylitis and comorbid colitis. Arthritis Rheum. 2011;63:3640–1.
19. Fernandez Salazar L, Barrio Andres J, Gonzalez Hernandez JM. Crohn's disease diagnosis during adalimumab treatment. Scand J Gastroenterol. 2013;48:254–5.
20. Robinson D Jr, Hackett M, Wong J, Kimball AB, Cohen R, Bala M. Co-occurrence and comorbidities in patients with immune-mediated inflammatory disorders: an exploration using US healthcare claims data, 2001–2002. Curr Med Res Opin. 2006;22:989–1000.
21. García-Vicuña R, Zarco P, González CM, Vanaclocha F, Marín-Jiménez I, Cea-Calvo L. Two-year incidence of psoriasis, uveitis and inflammatory bowel disease in patients with spondyloarthritis: a study in the AQUILES cohort. Reumatol Clin. 2015;12:22–6.
22. Barthel D, Ganser G, Kuester RM, Onken N, Minden K, Girschick HJ, et al. Inflammatory bowel disease in juvenile idiopathic arthritis patients treated with biologics. J Rheumatol. 2015;42:2160–5.