

# Secukinumab-associated inflammatory bowel disease?

RODRÍGUEZ RAMALLO H<sup>1</sup>, BÁEZ GUTIÉRREZ N<sup>1</sup>, DESONGLES CORRALES T<sup>2</sup>

1 Residente de Farmacia Hospitalaria

2 Farmacéutica Especialista en Farmacia Hospitalaria

Servicio de Farmacia. Hospital Universitario Virgen del Rocío. Sevilla (España)

Fecha de recepción: 03/01/2020 - Fecha de aceptación: 09/01/2020

To the Editor:

Ulcerative colitis (UC) and Crohn's disease (CD) represent the two main types of inflammatory bowel disease (IBD)<sup>1</sup>. Both are chronic idiopathic inflammatory bowel disease condition but UC affects the rectum and the colon, whereas CD can affect the entire gastrointestinal tract from the mouth to the anus. Classic symptoms of IBD include fatigue, prolonged diarrhea with abdominal pain, weight loss, and fever, with or without gross bleeding. IBD annual incidence ranges from 3 to 30 cases per 100,000 in North America, Oceania, and many countries in Europe<sup>2</sup>. The risk factors for the development of IBD remains unknown, environmental, genetic, and immunologic causes have been suggested<sup>1</sup>.

Several drug classes has been associated with IBD, such as antibiotics, NSAIDs, oral contraceptives and IL-17-inhibitors and specifically secukinumab<sup>3</sup>.

Secukinumab is a fully human monoclonal antibody that inhibits interleukin (IL)-17A and has shown significant efficacy in the treatment of psoriasis (PsO), psoriatic arthritis (PsA) and ankylosing spondylitis (AS). Interleukin (IL)-17 is a pro-inflammatory cytokine that has been demonstrated to be involved in the pathogenesis of inflammatory bowel disease (IBD). It has been showed that IL-17A is increased in the inflamed areas of patients with Inflammatory bowel disease (IBD)<sup>4</sup>, so it will be rational to think IL-17A inhibitors could be an effective treatment for IBD. However, increased adverse effects among IBD patients undergoing treatment with IL-17 inhibitors have been described.

Even though IL-17 inhibition has been associated with worsening symptoms in Crohn's disease, it remains uncertain whether IL-17 blockade increases the risk of new-onset IBD or it just put in evidence cases of subclinical or latent disease.

Following this line of thought, it is possible that in contrast to its proinflammatory role in other diseases and locations, IL-17A may function as a negative regulator of immunity in the gut mucosa. Whether IL-17A has pathogenic or protective roles in the gut mucosa is highly controversial, alterations of intestinal microbiome and chronic mucocutaneous candidiasis has been described in patients with autosomal recessive deficiency in interleukin-17 receptor A<sup>5</sup>. It has been hypothesized that alterations in the intestinal microbiome could potentially worsen disease activity in IBD.

This theory is particularly controversial because chronic immune-mediated inflammatory diseases such as PsO, PsA and AS shows significant co-heritability with IBD. It is estimated that patients diagnosed with PsO, PsA and AS have a 1–4-fold increased risk of developing IBD<sup>6,7</sup>. Thus the association between secukinumab and IBD could be due to this confounding factor.

First indications of a possible correlation between the blockade of IL-17 and the appearance of IBD were found in secukinumab clinical trials. Schreiber et al in a systematic review published in 2018, analyzed the results of 21 clinical health trials that included more than 7,300 patients. The incidence of IBD after treatment

with secukinumab varies according to the pathology studied: 21 cases of ulcerative colitis, 16 cases of crohn's disease and 5 cases of IBD unclassified were identified in this systematic review<sup>8</sup>.

Real-world-data reports of IBD secukinumab-associated, appear to be uncommon. Recently Fries W et al. review identified five case reports of eight newly diagnosed IBD in secukinumab-treated subjects published since its approval and up to the end of December 2018 (three IBD undefined cases, four UC, one CD). They also identify four additional newly IBD diagnosed sicilian patients after being treated with secukinumab (three CD and one UC)<sup>8</sup>.

New onset IBD during secukinumab treatment seems to occur in approximately 1 per 100 patients-year both on clinic trials and real world patients<sup>3,8</sup>.

The correlation between the duration of treatment with the appearance of the adverse effect has not being established. The published cases described the occurrence of IBD with heterogeneous time to onset, from a rapid onset days after the administration of the first dose of secukinumab, to a late onset after months of treatment.

In conclusion, despite the low incidence of emerging cases of IBD secondary to secukinumab, clinicians should pay attention to the presence of gastrointestinal symptoms in patients treated with IL-17 inhibitors, especially in patients with risk factors for IBD. In these patients, drugs directed to different biological targets such as vedolizumab, ustekinumab or infliximab may be preferable.

*Conflicts of interest: The authors declare that they have no conflict of interest.*

## BIBLIOGRAPHY

1. Baumgart DC, Carding SR. Inflammatory bowel disease: cause and immunobiology. *Lancet*. 2007 May 12;369(9573):1627-40.
2. Ng SC, Shi HY, Hamidi N, Underwood FE, Tang W, Benchimol EI, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet*. 2017 Dec 3;390(10114):2769-78.
3. Schreiber S, Colombel J-F, Feagan BG, Reich K, Deodhar AA, McInnes IB, et al. Incidence rates of inflammatory bowel disease in patients with psoriasis, psoriatic arthritis and ankylosing spondylitis treated with secukinumab: a retrospective analysis of pooled data from 21 clinical trials. *Ann Rheum Dis*. 2019;78(4):473-9.
4. Rovedatti L, Kudo T, Biancheri P, Sarra M, Knowles CH, Rampton DS, et al. Differential regulation of interleukin 17 and interferon production in inflammatory bowel disease. *Gut*. 2009 Dec;58(12):1629-36.
5. Puel A, Cypowyj S, Bustamante J, Wright JF, Liu L, Lim HK, et al. Chronic mucocutaneous candidiasis in humans with inborn errors of interleukin-17 immunity. *Science*. 2011 Apr 1;332(6025):65-8.
6. Cohen AD, Dreiherr J, Birkenfeld S. Psoriasis associated with ulcerative colitis and Crohn's disease. *J Eur Acad Dermatology Venereol*. 2009 May;23(5):561-5.
7. Makredes M, Robinson D, Bala M, Kimball AB. The burden of autoimmune disease: a comparison of prevalence ratios in patients with psoriatic arthritis and psoriasis. *J Am Acad Dermatol*. 2009 Sep;61(3):405-10.
8. Fries W, Belvedere A, Cappello M, Orlando A, Trifirò G. Inflammatory Bowel Disease Onset During Secukinumab Treatment: Real Concern or Just an Expression of Dysregulated Immune Response? *Clin Drug Investig*. 2019 Aug 1;39(8):799-803.