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SCIENTIFIC LETTER

A high adalimumab induction dosing regimen achieves clinical and endoscopic remission in super-refractory ulcerative colitis

Una pauta de inducción con dosis altas de adalimumab consigue la remisión clínica y endoscópica en colitis ulcerosa superrefractaria

In the following, we report our experience with a high adalimumab (ADA) induction dosing regimen in the context of a super-refractory ulcerative colitis (UC) patient. A 40-year-old female was diagnosed with left-sided UC in 2006 and remained in remission with aminosalicylates. In 2014, she presented with a severe flare with pancolitis progression and a steroid-refractory course. Rescue with ciclosporin obtained a partial response and infliximab (IFX) plus azathioprine (AZA) was administered with a favorable clinical response. However, IFX intensification proved necessary and few months later, secondary loss of response (LOR) was observed. The patient was subsequently included in a pivotal randomized clinical trial evaluating tofacitinib, but, after worsening symptoms, IFX was reintroduced. Three years later, secondary LOR was observed again despite optimal drug levels. Vedolizumab plus AZA was initiated with a poor response. In October 2018, the patient was admitted to hospital for a new severe flare. The patient rejected colectomy so intravenous steroid therapy and a high ADA induction dosing regimen (160 mg at week 0, 80 mg at week 1 and week 2, followed by 80 mg every two weeks) was initiated. Clinical response was achieved at week 4. Clinical, biological, and endoscopic free-steroid remission was achieved at week 16 and maintained through to week 52. At this point ADA levels were 44 mg/L and anti-drug antibodies were absent.

In the context of an anti-tumor necrosis factor (anti-TNF) pharmacodynamic failure, a change in mechanism of action is generally recommended. In this case, after vedolizumab and tofacitinib had failed, no other effective medical options were available, so we decided to try high doses of a second anti-TNF treatment.

ADA has been shown to be effective in UC both in clinical trials and in ''real life'' experience. The efficacy of ADA in UC refractory to IFX has been extensively evaluated, although it is likely to prove less effective than in naïve patients. Specifically, primary non response to the first anti-TNF and low drug levels during induction have been identified as predictors of non-response to ADA as a second anti-TNF.[1] Early measurement of drug concentration and early intervention in patients with low serum concentrations may improve both the rate and the duration of response. Recently, a ''real-life'' retrospective cohort showed that anti-TNF-naïve patients had significantly better long-term outcomes. In this study, the rate of ADA dose escalation was 17.6% for anti-TNF-naïve patients and 55.2% for anti-TNF-experienced patients. ADA dose escalation enabled the recovery of response in nearly half of the patients.[2] Additionally, the benefits of ADA as a second anti-TNF can be maximized by the adjustment of concomitant therapies, close therapeutic drug monitoring (TDM) and the optimization of ADA dosing after LOR. Ungar et al. recently demonstrated that immunogenicity can be reversed in patients with LOR developing anti-adalimumab antibodies (AAA) by intensification to weekly dosing and/or by the addition of immunomodulator therapy.[3] In our case, early or post-induction drug levels were not available. Early TDM during induction to achieve adequate drug levels could potentially overcome the effect of the inflammatory burden of active disease and, in our opinion, is a reasonable strategy.

A recent phase 3, double-blind, randomized, multicenter study (SERENE-UC) evaluated higher vs. standard ADA dosing regimens for induction and maintenance therapy in adult patients with moderately to severely active UC.[4,5] The results of this study failed to demonstrate significant differences in clinical remission between patients who were treated with either a high-dose or a standard-dose of adalimumab. However, this study largely contained bio-naïve UC patients (87%), so it is likely that these results cannot be extrapolated to patients with prior anti-TNF failure. Further, the SERENE-UC study did not include patients with severe UC flare like our patient. Also, we don't know if conventional dosage would have achieved similar results. In severe acute UC, anti-TNF clearance is accelerated due to high serum and mucosal TNF levels, low albumin, and intestinal losses. For these reasons, it is conceivable than better results could be achieved with a high dose and/or an accelerated induction therapy. Whether concomitant steroids add any benefit in this setting is unknown.

In our opinion, high-dose induction of adalimumab may still be an option to consider in selected patients after IFX failure. More data are needed to assess the optimal dosing regimen of a second anti-TNF drug.

Authors' contributions

A.R.C.: patient recruitment, data collection, literature review, writing up of the first draft of the paper, revision of the manuscript; L.R.A.: data collection, literature review, revision of the manuscript; F.R.M.: literature review, revision of the manuscript; J.G.: literature review, revision of the manuscript.

Data availability statement

Data cannot be shared for ethical/privacy reasons. Data available on request. The data underlying this short report cannot be shared publicly in order to protect the privacy of the individual. The data will be shared on reasonable request to the corresponding author.

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Conflicts of interest

Alexandra Ruiz-Cerulla has served as a speaker for Takeda.

Francisco Rodríguez-Moranta has served as a speaker for Abbvie, Takeda, Pfizer, Jansen, and MSD and has served as an advisor for Abbvie, Jansen, MSD, and Pfizer.

Lorena Rodríguez-Alonso has served as a speaker for Takeda, Pfizer and MSD and has served as an advisor for Abbvie.

Jordi Guardiola has served as a speaker and consultant or has received research or education funding from MSD, Abbvie, Kern, Pfizer, Takeda, Janssen, Ferring, Roche and General Electric.

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Usefulness of capsule endoscopy in idiopathic complex perianal disease

Utilidad de la cápsula endoscópica en la enfermedad perianal compleja idiopática

Crohn's disease (CD) can affect any segment of the gastrointestinal tract, with ileocolonic Crohn's being the most frequent (40%), followed by ileal (30%) and Crohn's of the colon (15%–30%). Exclusive involvement of the proximal small intestine, not accessible by ileocolonoscopy, occurs in only 10% of patients.[1,2] Furthermore, about 9% of patients present with perianal disease (PAD) at the time of diagnosis of CD, with incidence varying according to the intestinal location of the disease. Thus, it is 15% when it affects the ileum, 12% with ileocolonic involvement, 40% with involvement of the colon and 92% with rectal involvement.[3] However, the association of PAD in patients with CD exclusive to the upper gastrointestinal tract has been poorly described.

We present two cases of patients with PAD and normal colonoscopy, in whom the capsule endoscopy (CE) study detected lesions suggestive of CD. The endoscopic findings and the few published studies were reviewed.

Case 1

This was a 35-year-old woman with anal fissure and fistula of two years' evolution who underwent a sphincterotomy with persistence of an intersphincteric fistula visualised by pelvic MRI. Despite this, she presented with a torpid evolution, so she was referred in order to rule out CD. Clinically, she did not report digestive symptoms, she denied NSAID intake, and laboratory tests were strictly normal (including C-reactive protein and faecal calprotectin). In the ileocolonoscopy,