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EDITORIAL

Intensification of maintenance therapy with infliximab in ulcerative colitis

In the past few years the pharmacopeia used for the treatment of ulcerative colitis has become notably more extensive and diverse, the introduction of biologics being the most significant novelty. Biologic drugs are produced from a biologic source (1). For ulcerative colitis approved biologics currently include monoclonal antibodies targeting tumour necrosis factor alpha (TNFα), specifically infliximab (IFX), adalimumab and golimumab. Clinical guidelines from a number of scientific societies recommend their use for moderate to severe active ulcerative colitis in patients failing to respond to conventional therapy (2,3), a setting where clinical trials such as ACT for IFX (4), ULTRA for adalimumab (5), and PURSUIT for golimumab (6) have shown an effectiveness significantly superior to that of placebo.

Despite the success attributed to IFX in ulcerative colitis, its effectiveness is limited by induction failures or loss of response after induction. In this respect predictive factors for poor response to IFX have been identified, including older age, genotype profile, and serum IFX trough levels (7,8). This has led to the development of various strategies devised to improve IFX response, including combined treatments, dose escalation, and approaches based on the detection of serum IFX levels or the development of antibodies against IFX. Concomitant immunomodulators, particularly azathioprine, have been shown to be associated with lower IFX activity and lower need for changing to adalimumab (9). Recent observations suggest that in ulcerative colitis combined maintenance therapy with IFX and thiopurines for over 9 months is effective to prevent flare-ups and IFX failure (10). As IFX trough levels and the presence of anti-IFX antibodies are associated with loss of response to IFX (11), another suggested approach is supplementing empiric therapy with measurement of IFX trough levels, which allows detection of subtherapeutic levels and improves therapy-related decision making (12). Another strategy used for loss of response to IFX is dose escalation, whether by increasing dose per body weight or by reducing dose intervals, which results in clinical response within the first year in 69% of patients, even though loss of intensification effectiveness is subsequently reported at 43% per patient and year in the setting of Crohn's disease (13).

In order to establish in our setting the need for IFX therapy intensification in ulcerative colitis, a single-centre, prospective study of 38 patients was recently carried out, which showed that 42% of patients required intensification after a median follow-up of 6 months (14). Compared to a cohort of patients with Crohn's disease, the need for IFX intensification was most common and developed earlier in ulcerative colitis (14). To assess the efficacy of IFX intensification in ulcerative colitis a retrospective, multicenter, national study in 79 patients followed up for a median of 15 months revealed that intensification provides long-term clinical benefits in 70% of patients, with a decreased relative risk of colectomy by 86% (15).

Despite the well known fact that infliximab therapy intensification is effective when ulcerative colitis stops responding to this drug, some aspects such as predictive factors for intensification or the outcome of intensified patients remain somewhat unclear. This prompted Dr. Fernández-Salazar and colleagues to perform the ECIA (*Estudio de Colitis e Infliximab de ACAD*) trial, the results of which are reported in the present issue of *The Spanish Journal of Gastroenterology (Revista Española de Enfermedades Digestivas)* (16). The ECIA study derives from a collaboration of 10 hospitals in the autonomous regions of Cantabria, Castilla-La Mancha, Castilla y León, and Madrid in a retrospective project that collected follow-up data from 144 patients with ulcerative colitis for 38 months. In all, 37% of patients required IFX therapy intensification, which was implemented by shortening dose intervals in 50% of cases, by increasing doses to 10 mg/kg, or by using double intensification (10 mg/kg every 6 weeks). Of all 53 patients who required therapy intensification deintensification was subsequently attempted for 14 (26%), and could be maintained to the end of follow-up in 9 (64%). Patients with sustained IFX deintensification had a lower rate of loss of response and reduced colectomy need. In order to establish factors associated with intensification need a multivariate analysis was carried out, which identified time of immunomodulation onset as the sole independent variable predictive of intensification among all considered variables.

Several aspects may be highlighted in the present manuscript. On the one hand it confirms the high cumulative frequency of IFX intensification needs in ulcerative colitis, which suggests that ulcerative colitis seems more "resistant" to IFX than Crohn's disease. On the other hand, this multicenter retrospective study reveals the use of different IFX intensification strategies –increased doses, shortened intervals, and both. The study design allows no comparisons between these strategies, but all seem to display similar deintensification rates. The study also identifies intensification need as an aggravation of ulcerative colitis, statistically associated with steroid reintroduction and higher colectomy rates. The study also reveals that concomitant immunomodulators introduced with IFX is associated with a lower risk for intensification (a benefit not observed when immunomodulators were

introduced either before or after IFX). Finally, from the experience gathered by the authors, a significant number of patients with ulcerative colitis who required IFX intensification could be deintensified long-term. However, some questions remain unanswered for patients with ulcerative colitis on IFX –which type of escalation is most effective, whether the same type should be used for all patients, predicting which patients would benefit from temporary intensification for a limited period of time, etc. Although information is increasingly available on this topic, including the paper reported in the present issue of *The Spanish Journal of Gastroenterology (Revista Española de Enfermedades Digestivas)*, further studies are needed to respond to all the questions arising when caring for patients with ulcerative colitis who are candidates to biologic therapy.

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