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Comment on: Dual advanced therapy in inflammatory bowel disease. Why, when and how?

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Dear Editor,

We have read with great interest the article by Diz-Lois Palomares MªT et al. "Effectiveness and safety of dual advanced therapy in inflammatory bowel disease: A multicenter series from Galicia, Spain" recently published in the Revista Española de Enfermedades Digestivas (1). In this retrospective, multicenter study, the authors show that advanced combination therapy (ACT) is an effective and safe option for the treatment of patients with inflammatory bowel disease (IBD).

Advances in understanding inflammatory pathways, particularly the cytokines and immunological signals involved in IBD, have led to the availability of drugs with different mechanisms of action. However, experience has shown that a significant percentage of patients treated with biological therapy may not respond to induction therapy or lose therapeutic effectiveness at a later stage. In this context, ACT has emerged as an emerging strategy for challenging clinical scenarios. The available evidence comes mainly from retrospective studies and case reports of refractory patients with clinical and endoscopic remission rates of approximately 60% and 30%, respectively (2,3).

The authors adequately answer two key questions: when to consider ACT? and how to use this strategy?. Their study included 24 patients with refractory IBD or had extraintestinal manifestations or an associated immune-mediated disease. The results showed that clinical and endoscopic remission was achieved in 41.1% and 31% of cases, respectively, with greater effectiveness when the indication was an associated immune-mediated disease. Three patients were hospitalized due to a serious infection. Others have reported rates of serious adverse events and infections in 12.4% and 7.6% of patients, respectively (3). Diz-Lois Palomares MªT et al. classified ACT according to the mechanism of action (overlapping, synergistic, or complementary effect), without observing significant differences in effectiveness between the different approaches (1), which constitutes a relevant conceptual contribution. Although the authors do not mention factors that could influence the effectiveness of ACT, long-standing IBD, moderate to severe inflammatory activity, the presence of perianal disease, and

concomitant use of corticosteroids could negatively affect the results of this strategy (3).

Although the incidence and prevalence of IBD have been increasing in Latin America, experience with the use of ACT is limited (4). A recently published article by our group, which included three patients with difficult-to-manage IBD, showed that the combination of anti-TNF with Janus kinase inhibitors was effective and safe in reducing intestinal inflammatory activity (5). A fourth patient treated with vedolizumab and upadacitinib has achieved clinical remission (Table 1).

In conclusion, the article by Diz-Lois Palomares MªT et al. and our limited experience support the use of ACT in complex IBD. However, this is still an emerging strategy that requires prospective, controlled studies to better define its indication, duration, effectiveness, and safety.

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Table 1. Clinical characteristics of inflammatory bowel disease patients treated with advanced combination therapy.

	Disease (Montreal classification), duration	Previous advanced therapy	Advanced combined therapy, duration	Treat to target	Adverse events
Male, 40 yo	Crohn disease (L2, B1, P), 14 years	Adalimumab, infliximab, ustekinumab	Adalimumab + upadacitinib, 24 weeks	Clinical and endoscopic response	no
Male, 32 yo	Crohn disease (L2, B1, P), 2 years	Infliximab, etrasimod	Infliximab + upadacitinib, 12 weeks	Clinical and endoscopic response, FC remission (120 ug/g)	no
Female, 32 yo	Ulcerative colitis (E3), 1 year	Infliximab optimized and accelerate scheme	Infliximab + tofacitinib, 8 weeks	Clinical, FC (54 ug/g) and endoscopic remission	no
Female, 54 yo	Crohn disease (L2, B1, P), 15 years	Infliximab, natalizumab, adalimumab, ustekinumab	Vedolizumab + upadacitinib, 24 weeks	Clinical remission, FC response (252 ug/g) and endoscopic response	no