This editorial offers a comprehensive review of the combination treatment approaches for Inflammatory Bowel Disease (IBD), with a specific focus on those patients who have no response to single biologic agents and those facing the challenges of extraintestinal manifestations. It delves into dual biological therapy (DBT) and combination therapy (CT), providing a detailed synthesis of a wide array of clinical trials, systematic reviews, and case reports. These sources have critically assessed the efficacy, safety, and potential side effects of various drug combinations. Furthermore, the manuscript outlines several future research directions in this field, including the evaluation of different dosages, administration methods, treatment durations, and novel drug combinations, with an emphasis on the possibility of adverse effects. It also highlights the innovative application of emerging biomarkers and artificial intelligence to improve therapeutic strategies and outcomes. Given the challenges in managing complex IBD cases, the emphasis on combination treatment is pertinent and aligns well with the current needs. This editorial stands out for its comprehensive review of various studies, logically structured and clearly presented, providing a multidimensional perspective on the topic and enhancing readability. Additionally, there is also a minor drawback in this manuscript could be improved. A concise summary of the extensive studies reviewed in the text, highlighting those results that were widely validated and clinically applicable, would make this manuscript more attractive and practical. Over all, the systematic overview and novel insights make this editorial beneficial for both clinical practice and basic science, which offers guidance for more personalized and effective treatment strategies and charts a path for future academic research.

A summary of the results of the studies, the results of which in the authors' opinion are valid and clinically applicable, is listed below.

Dual Therapy (DT - Combination of two biological agents)

Privitera et al [11], in a retrospective study of 16 patients with active IBD and/or patients with severe extraintestinal manifestations, used DT consisting of a combination of vedolizumab + ustekinumab or vedolizumab + adalimumab. Clinical improvement of intestinal disease and/or extraintestinal manifestations was observed in all patients treated with DT without serious adverse events.

Kwapisz L et al [13] in 14 patients with CD and 1 patient with UC used a combination therapy consisting of two biological agents: Vedolizumab plus anti-TNF agent (8 patients), vedolizumab plus ustekinumab (5 patients) and ustekinumab plus anti-TNF- α agent (2 patients). Symptomatic improvement was noticed in 73%. Moreover, 67% were able to reduce the dose of corticosteroids they were receiving, while in 44%, an improvement in the endoscopic and imaging pictures was noticed. Three patients underwent surgery and 4 developed infections which were treated efficiently with antibiotics.

Miyatani Y et al [18] used a combination of ustekinumab plus upadacitinib, an oral selective Janus kinase inhibitor in 10 patients with CD with refractory active disease accompanied or not by extraintestinal manifestations. Five of the 6 patients with active CD and 2 of the patients with extraintestinal manifestations experienced

clinical remission. Side effects during the 6-month follow-up were minimal (mainly upper respiratory infections).

In a retrospective study of 32 CD and 18 UC patients who received combination therapy with biologic or micromolecular agents, Glassner et al [12] described that significantly more patients under combination therapy were in clinical and endoscopic remission compared to baseline status. Erythrocyte sedimentation rate and CRP also showed significant value reduction. Side effects occurred in 26% mainly related to upper respiratory tract infections.

Interleukins 12 and 23 are known to play an important role in intestinal homeostasis and the pathogenesis of IBD. Their systematic study led to the development of monoclonal antibodies that target the p40 subgroup (ustekinumab and briakinumab) or p19 (risankizumab, guselkumab, brazikumab and mirikizumab). Feagan BG et al [19] investigated the possibility that the combined administration of guselkumab plus golimumab could be superior to monotherapy with either guselkumab or golimumab alone in patients with moderate to severe UC. Patients were randomized to receive guselkumab plus golimumab combination therapy (72 patients), guselkumab alone (72 patients), or golimumab alone (71 patients). At the end of week 12, 83% of the combined treatment subjects achieved clinical remission compared to 61% and 75% of the other two groups, respectively. The most common side effects were upper respiratory infections, fever, anemia, and neutropenia. It therefore appears that combination therapy with guselkumab plus golimumab is superior to monotherapy with guselkumab alone or golimumab alone.

Based on the results of the studies published so far, it appears that the combination of vedolizumab plus ustekinumab and vedolizumab plus anti-TNF-α factors are the preferred combinations in CD patients because they achieve satisfactory clinical results with an acceptable rate of side effects. The corresponding combinations for patients with UC concern the administration of vedolizumab plus anti-TNF-α factor or vedolizumab plus tofacitinib.

Despite the small number of patients included in the studies mentioned above, it appears that the combination of biological agents with a different mechanism of action is safe and effective in the treatment of patients with refractory

IBD or patients with IBD and extraintestinal manifestations. It is clearly emphasized that it is necessary to carry out multicenter studies in a large number of patients as well as studies in rats using experimental models of colitis to investigate the possible effectiveness of the combination treatment, as well as the optimal dosage and duration of the administration of treatment [58].

Combination Treatment (CT - Combination of one biologic agent with one immunosuppressive drug)

The combination of a biologic anti-TNF-α agent (mainly infliximab and to a lesser extent adalimumab) with azathioprine appears to be more effective in CD patients than monotherapy with infliximab or azathioprine [24, 26, 29, 34]. The combination of vedolizumab with calcineurin inhibitors appeared also to be particularly effective in achieving remission in patients with active IBD [36]. Finally, the combination of vedolizumab with corticosteroids was shown to be more effective in inducing remission compared to vedolizumab or corticosteroids alone [37].

The side effects observed in the above studies are largely acceptable compared to the clinical benefit offered. Furthermore, it has long been known that the combination of infliximab plus azathioprine, effectively prevents the formation of antibodies against the biological agent. Clinicians should not avoid the combined use of these drugs when indicated.

Combination of first-line drugs (Step-up therapeutic strategy)

The use of antibiotics in severe UC flares remains a point of contention among experts, the majority of whom, at least theoretically, recommend avoiding their use in severe UC unless there is clear evidence of a septic condition. However, three recently published studies revisit the issue of combination antibiotic administration in UC flares [38,39,40].

In the case of patients with CD, the administration of antibiotics is easier, especially in patients with perianal disease.

In our opinion, in cases of patients with severe UC exacerbation, the possibility of Campylobacter *jejuni* infection should be carefully investigated by the gastroenterologists since this infection may worsen the clinical picture and delay remission of the disease.

The issue of antibiotic administration especially in patients with UC should be investigated in the future with multicenter, well-designed studies, in a large number of patients.

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