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Contents

Weekly Volume 30 Number 15 April 21, 2024

EDITORIAL

MINIREVIEWS

ORIGINAL ARTICLE

Case Control Study

Retrospective Study

Basic Study

LETTER TO THE EDITOR

World Journal of Gastroenterology

Weekly Volume 30 Number 15 April 21, 2024

Contents

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EDITORIAL

Combination treatment of inflammatory bowel disease: Present status and future perspectives

John K Triantafillidis, Constantinos G Zografos, Manousos M Konstadoulakis, Apostolos E Papalois

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John K Triantafillidis, Inflammatory Bowel Disease Unit, "Metropolitan General" Hospital, Holargos 15562, Attica, Greece

John K Triantafillidis, Hellenic Society for Gastrointestinal Oncology, 354 Iera Odos, Chaidari 12461, Attica, Greece

Constantinos G Zografos, Manousos M Konstadoulakis, The 2nd Department of Surgery, University of Athens, School of Medicine, Aretaieion Hospital, Athens 11528, Greece

Apostolos E Papalois, Unit of Surgical Research and Training, The 2nd Department of Surgery, University of Athens, School of Medicine, Aretaieion Hospital, Athens 11528, Greece

Corresponding author: John K Triantafillidis, PhD, Honorary Associate Professor, Inflammatory Bowel Disease Unit, "Metropolitan General" Hospital, 264 Mesogeion Avenue, Holargos 15562, Attica, Greece. jktrian@gmail.com

Abstract

The treatment of patients with inflammatory bowel disease (IBD), especially those with severe or refractory disease, represents an important challenge for the clinical gastroenterologist. It seems to be no exaggeration to say that in these patients, not only the scientific background of the gastroenterologist is tested, but also the abundance of "gifts" that he should possess (insight, intuition, determination, ability to take initiative, *etc.*) for the successful outcome of the treatment. In daily clinical practice, depending on the severity of the attack, IBD is treated with one or a combination of two or more pharmaceutical agents. These combinations include not only the first-line drugs (*e.g.*, mesalazine, corticosteroids, antibiotics, *etc*) but also second- and third-line drugs (immunosuppressants and biologic agents). It is a fact that despite the significant therapeutic advances there is still a significant percentage of patients who do not satisfactorily respond to the treatment applied. Therefore, a part of these patients are going to surgery. In recent years, several small-size clinical studies, reviews, and case reports have been published combining not only biological agents with other drugs (*e.g.*, immunosuppressants or corticosteroids) but also the combination of two biological agents simultaneously, especially in severe cases. In our opinion, it is at least a strange (and largely unexplained) fact that we often use combinations of drugs in a given patient although studies comparing the simultaneous administration of two or more drugs with monotherapy are very few. As mentioned above, there is a timid tendency in the literature to combine two biological agents in severe cases unresponsive to the applied treatment or patients with severe extraintestinal

manifestations. The appropriate dosage, the duration of the administration, the suitable timing for checking the clinical and laboratory outcome, as well as the treatment side-effects, should be the subject of intense clinical research shortly. In this editorial, we attempt to summarize the existing data regarding the already applied combination therapies and to humbly formulate thoughts and suggestions for the future application of the combination treatment of biological agents in a well-defined category of patients. We suggest that the application of biomarkers and artificial intelligence could help in establishing new forms of treatment using the available modern drugs in patients with IBD resistant to treatment.

Key Words: Biologics for immune-mediated conditions; Dual-targeted treatment; Combination treatment; Inflammatory bowel disease; Crohn's disease; Ulcerative colitis

Core Tip: During the last few years, the combination of two biological agents or a combination of a biological agent and another drug belonging to the category of so-called "small molecules" seems to be steadily gaining ground [dual biologic therapy (DBT)]. Even the combination of a biological agent with a drug belonging for example to the category of immunosuppressants is a therapeutic option that has been applied for several years [combination therapy (CT)]. Finally, in daily clinical practice, various combinations of so-called first-line drugs (mesalazine, corticosteroids, antibiotics, probiotics, *etc.*) are used with satisfactory results in most cases. DBT and CT currently find application in cases of patients resistant to treatment or patients with extraintestinal manifestations that do not respond satisfactorily to classical treatment. The existing data, although encouraging, are not sufficient in terms of the number of patients included so far. The safety of this emerging kind of treatment is another point of interest. Finally, there is a need to carry out more studies regarding this interesting field of research.

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INTRODUCTION

It is known that biological agents, including small molecule drugs, alone or in combination with immunomodulatory drugs, are currently the recommended treatment in cases of moderate or severe inflammatory bowel disease (IBD)[1,2].

However, many patients, some of whom may have concurrently extraintestinal manifestations do not respond to treatment, making the treatment particularly complicated[3]. In recent years, the growth of our pharmaceutical arsenal has decisively influenced the way by which our IBD patients are treated. Certain characteristics of the disease in today's era, such as resistance to medication and the long duration of the disease may have an unsatisfactory therapeutic result. On the other hand, although the available drugs are effective even when they are given alone some patients do not respond favorably to treatment. Also, drugs that have a favorable effect on intestinal disease may not be effective in extraintestinal manifestations. The above assumption is also presumed from the fact that in the era of biological factors that we are going through, the rates of surgical interventions seem to be similar to those of previous years.

There are many inflammatory pathways involved in the pathogenesis of IBD as well as many cytokines involved in the inflammatory cascade. If we succeed in interrupting this cascade not only in one but in more places we expect to achieve a better clinical outcome. For example, tofacitinib improves rheumatoid arthritis and IBD because it inhibits inflammatory factors that contribute to both gut and joint inflammation[4]. It is therefore reasonable to hypothesize that administration of a combination of biological agents or a biological agent with an immunosuppressive or other pharmaceutical agent may increase the proportion of patients who respond to treatment.

We know that patients treated with biological agents may not respond to the initial treatment (primary non-response) or lose the good therapeutic effect at a later stage of the disease (secondary loss of effect). Anti-tumor necrosis factor (TNF) biological agents are monoclonal antibodies that suppress inflammation by binding to TNF-α[5]. Ustekinumab works by inhibiting the action of the pro-inflammatory cytokines Interleukin-12 and -23. Vedolizumab works by binding to the α4β7 integrin, resulting in an inability of T cells to infiltrate tissues and exacerbate inflammation. Tofacitinib is a small molecule that inhibits Janus kinase. The combination of these drugs, each of which has a different mechanism of action, will result in the inhibition of different inflammatory pathways. In this way and acting synergistically, these drugs can more effectively reduce the degree of the inflammatory process and improve the clinical and laboratory parameters of the patients.

During the last few years, several clinical studies and systematic reviews have been published describing the results of the combined use of biological agents in patients with IBD and patients suffering from severe rheumatological or dermatological diseases[6]. In this editorial, the results of the most important studies (results in patient series of clinical

trials, reviews, meta-analyses, and cases of interest) in which different drug combinations were used are listed. The results and side effects of the combinations are analyzed, with a simultaneous effort to highlight the most effective combinations in daily clinical practice.

A literature search on electronic databases such as PubMed, Medline, and Cochrane CENTRAL databases was performed to identify relevant articles. Keywords included biologics for immune-mediated conditions along with the terms "dual," and "combination." Case reports, case series, randomized controlled trials, systematic reviews, and meta-analyses were included.

RESULTS

Dual biological therapy

Dual biologic therapy (DBT) is a term that refers to the simultaneous administration of two biological agents or a biological and a micromolecular agent in patients with IBD, while the term Combination Therapy (CT) refers to combination of other drugs, mainly immunosuppressants with biological agents. These therapeutic approaches have already been applied to treatment-resistant IBD patients or patients with inactive disease but with difficult-to-treat extraintestinal manifestations[7,8]. Existing data support that DBT is a safe option for IBD patients who have failed treatments with single biologic agents as well as in patients with difficult-to-treat extraintestinal manifestations[9].

So far the most used combinations involve the concurrent administration of anti-TNF agents with vedolizumab or the concurrent administration of ustekinumab with vedolizumab. The combination of these agents emerged based on the satisfactory safety profile they present, as well as on the basis of the satisfactory degree of efficacy when administered as monotherapy[10-13].

DBT trials: A small number of clinical trials regarding the effectiveness and safety of DBT appeared in the literature. These studies are shown in Table 1.

In the first randomized trial published in 2007, the authors studied the safety and efficacy of the combination of natalizumab and infliximab (IFX) in patients with Crohn's disease (CD) unresponsive to IFX therapy[14]. A total of 52 patients received the combination of natalizumab and IFX and 27 patients received IFX and placebo. Regarding safety, adverse events occurred in 92% of patients receiving IFX and natalizumab and in all patients in the placebo group. The most frequently observed side effects were related to the occurrence of headache. No differences were observed in the incidence of infections between the two groups (27% *vs* 30%). After the first 10 wk, no serious side effects (infection, cancer, death) were observed in patients who continued to receive the combination of IFX and natalizumab. Regarding the clinical effectiveness, patients belonging to the group of the combination of biological agents showed better results than the placebo group, but the differences were not statistically significant. Despite the satisfactory results, this combination should be avoided due to the side effects of natalizumab (risk of multifocal leukoencephalopathy).

In a retrospective study, Yang *et al*[15] evaluated the safety and efficacy of DBT in 22 patients with refractory CD by administering seven different combinations of six biological agents that included an anti-TNF-α agent (IFX, adalimumab, golimumab, and certolizumab pegol), in combination with vedolizumab or ustekinumab. Endoscopic improvement and endoscopic remission were noticed in 43% and 26% of trials, respectively, and clinical response in 50%. Clinical improvement in perianal fistulas was also observed. Adverse events were observed in 13% of trials[15].

Two other retrospective studies published in 2020 evaluated DBT in patients with CD and ulcerative colitis (UC). The first of these included 16 patients (11 with CD and 5 with UC). Seven patients received DBT for unresponsive disease and 9 patients received DBT because of persistent extraintestinal manifestations despite remission of intestinal disease. Patients were treated with anti-TNF agents in combination with vedolizumab or ustekinumab while 2 patients received combined treatment with vedolizumab and ustekinumab for 8 wk. Clinical improvement of both intestinal and extra-intestinal manifestations was observed in all patients. Adverse effects were observed in 3 patients, all non-serious[11].

In the second study, 50 IBD patients (32 with CD and 18 with UC) received CT. The majority of patients received concomitant immunosuppressants or corticosteroids. A total of 29 of the 50 patients received combined biologic therapy. Adverse effects were reported in 26% of patients the majority of which were infectious[12].

Vedolizumab represents an effective and safe biological agent in the treatment of IBD patients during pregnancy, in elderly patients, in patients who have undergone surgery in the past, as well as in patients with a previous history of malignancy. Due to the advantages of the drug, mainly in the area of safety, vedolizumab is currently the main biological agent for the application of CT with another biological or small molecule agent[16,17]. The combination of vedolizumab with ustekinumab appears to be the most promising based on data from retrospective studies, descriptions of patient series, and individual cases. This combination should be a major area of future research since this regimen may be effective in both CD and UC patients.

Upadacitinib is a second-generation selective Janus kinase inhibitor targeting the JAK1 enzyme approved for the treatment of severe rheumatoid arthritis that is unresponsive to first-line therapy. Ten CD patients refractory to medical therapy were treated with a combination of Upadacitinib and Ustekinumab. Patients were followed-up for 10 months. The median number of prior biologic treatment exposures was 4. Indications for the use of DBT were active CD (6 patients), extraintestinal manifestations (2 patients), and both active CD and extraintestinal manifestations (2 patients). The results showed that 5 out of 6 patients with active CD achieved clinical remission and 2 patients with severe arthritis showed significant clinical improvement. Side-effects included mild respiratory symptoms and nausea. It seems that DBT with Upadacitinib and Ustekinumab may be effective and safe in refractory CD as well as for patients with extraintestinal manifestations[18].

Table 1 Results of clinical trials with dual biologic therapy in patients with active inflammatory bowel disease

Ref.	No. of patients/disease	Kind of DBT	Efficacy	Side-effects
Sands *et al* [14], 2007	79 (two arms: 52 and 27 respectively) CD	IFX + Natali-zumab *vs* IFX + placebo	Better results in DBT but not significant	Headache, infections (27%), nausea, nasopharyngitis
Privitera *et al*[11], 2020	16 (11 with CD & 5 with UC)	anti-TNF + VDZ or UST or VDZ & UST for 8 wk	Clinical improvement (intestinal and extraintestinal manifestations): In all patients	In 3 patients, all non-serious
Glassner *et al*[12], 2020	50 IBD patients (32 CD, 18 UC)	29 out of 50 patients received DBT	DBT: More patients in clinical and endoscopic remission at follow-up *vs* baseline	In 26% of pts. Infections: In patients on DBT. Lower risk in those not on a concomitant immunomodulator
Yang *et al* [15], 2020	22 patients with CD with 24 therapeutic trials of DBT	Six biologic agents were used in: Anti-TNF + UST or VDZ	Endoscopic improvement: In 43% of trials. Endoscopic remission: 26%. Clinical response: 50%. Clinical remission: 41%	Similar rates of adverse events (13% of trials)
Kwapisz *et al*[13], 2021	15 (14 CD, 1 UC)	Various biologics VDZ + anti-TNF/UST; UST + anti-TNF/VDZ	DBT may be effective. Anti-TNF or VDZ plus UST were most effective	DBT may be safe
Feagan *et al* [19], 2023	Severe UC	GUS + GOL (71) *vs* GUS alone (72) *vs* GOL alone (71 pts)	At week 12, 83% of DBT patients had clinical response *vs* 61% and 75% on GOL and GUS monotherapy, respectively	At week 50, 63%, 76% and 65% of patients experienced at least one side-effect (infections, fever, nasopharyngitis, neutropenia
Miyatani *et al*[18], 2024	CD	UPA + UST	5/6 patients, achi-evedremission. Two with severe arthritis: Signifi-cant improvement	Mild respiratory symptoms and nausea

CD: Crohn's disease; GOL: Golimumab; GUS: Guselkumab, IBD: Inflammatory bowel disease; IFX: Infliximab; TNF: Tumor necrosis factor; UC: Ulcerative colitis; UST: Ustekinumab; UPA: Upadacitinib; VDZ: Vedolizumab; DBT: Dual biologic therapy.

In a randomized, double-blind, controlled trial[19], Feagan *et al*[19] investigated whether DBT with Guselkumab (antagonist of the p19 subunit of IL-23) and Golimumab (TNF-a inhibitor) is superior to monotherapy with these two drugs separately administered to patients with moderately to severely active UC. DBT consisted of sc golimumab 200 mg at week 0, sc golimumab 100 mg at weeks 2, 6, and 10, and iv guselkumab 200 mg at weeks 0, 4, and 8, followed by sc monotherapy with guselkumab 100 mg every 8 wk for 32 wk, whereas golimumab monotherapy consisted of sc golimumab 200 mg at week 0 followed by sc golimumab 100 mg at week 2 and every 4 wk thereafter for 34 wk, and guselkumab monotherapy consisted of iv guselkumab 200 mg at weeks 0, 4 and 8, followed by scguselkumab 100 mg every 8 wk thereafter for 32 wk. Of the 214 patients who were finally included, 71 patients received DBT, 72 patients received golimumab monotherapy, and 71 patients received guselkumab monotherapy. Results showed that at week 12, 83% of DBT patients showed a clinical response compared to 61% of patients in the golimumab monotherapy group, and 75% of the guselkumab monotherapy group. At week 50, 63%, 76%, and 65% of patients in the three groups reported at least one side effect such as respiratory infections, nasopharyngitis, neutropenia, and fever. It therefore appears that DBT with guselkumab and golimumab is superior to treatment with one agent alone.

Safety of DBT: An element of DBT that is equally important as its effectiveness concerns the degree of safety provided. Safety has been an important element of the available studies with several of them claiming to have found no serious adverse effects, with most of which referred to an increased risk of infections[15]. In a retrospective observational study, the efficacy and safety of DBT with the combination of two biological agents or the combination of one biological agent with a small molecule was studied. The results showed clinical and endoscopic improvement in 50% of patients with parallel improvement of extraintestinal manifestations. However, a significant percentage of adverse effects (42%) and an increased risk of infections were observed, which necessitated hospitalization in 10%[20].

According to Privitera *et al*[11] adverse effects with DBT with ustekinumab and vedolizumab were observed in 13% to 30% of patients with infections being the most common side effect[11]. The results of a recent systematic review and meta-analysis agree with this percentage[8]. It therefore appears that DBT with vedolizumab and ustekinumab has a tolerable rate of side effects apparently as a result of the low rate of side effects shown by each of these drugs individually. It is recommended that patients be systematically monitored for any unwanted effects, mainly infections and even infections due to rare causes. The exact magnitude of the risk of side effects is expected to be determined in future multicenter studies.

Combination therapy of IBD

We currently distinguish two forms of CT of anti-TNF-α agents and immunosuppressants. In the first combination, called de novo, the combination of the two drugs is done right from the beginning, *i.e.* from the start of the treatment. The purpose of co-administration from the outset is to prevent the formation of antibodies against the biological agent. In the second CT, the so-called "selective", the immunosuppressant is added quite later and only in patients who show a secondary loss of response during anti-TNF-α monotherapy due to the development of antibodies against the biological

agent[21].

It is known that the combination of IFX and thiopurines is superior to monotherapy in inducing and maintaining remission in IBD patients both at the clinical level and in the generation of antibodies against IFX, but at the cost of an increased risk of infections and neoplasms (*e.g.* lymphoproliferative disease). This risk could be partially avoided by reducing the dose, but this needs to be proven in the future. Even the combined treatment could be used for a short period (*e.g.* one year) since it is known that antibodies against the biological agent usually develop during the first months of treatment.

Several studies have proven the truth of the above. In a recently published network meta-analysis and systematic review, the authors evaluated the efficacy and safety of CT with IFX and azathioprine versus IFX monotherapy in CD patients. The study included 15 Randomized clinical trials (RCT) with a total of 1586 CD patients. The results showed that both therapeutic strategies are comparable in terms of their efficacy and safety since no differences were observed in the induction and maintenance of remission between the two combinations. No treatment was significantly safer than the others[22].

Clincal trials concerning CT in IBD patients are shown in Table 2.

CT of IFX with immunosuppressants: A randomized, double-blind study evaluated the efficacy and safety of combined administration of IFX with azathioprine (AZA), compared with AZA or IFX alone in patients with moderate to severe UC. It was found that patients treated with IFX with AZA had a greater rate of disease remission as well as higher rates of mucosal healing compared to patients treated with AZA alone or the biologic agent alone[23].

In 2015 Colombel *et al*[24] published the results of the post hoc analysis of the SONIC trial. The results of the study showed that the CT of IFX with AZA was more effective compared to monotherapy with AZA or IFX, suggesting that mucosal healing can be achieved with CT in a high percentage of patients with early CD[24].

Regarding the dose of AZA in IBD patients in whom disease remission was achieved with CT of IFX with AZA, Roblin *et al*[25] observed that reducing the dose of AZA but not stopping it in patients receiving CT (IFX with AZA) has the same efficacy as the efficacy of continuing full-dose AZA[25].

The anti-TNF agent IFX has also been used as CT with methotrexate. In a double-blind, placebo-controlled study lasting 50 wk, in which IFX was administered with Methotrexate or IFX alone, it was shown that the combination of the two drugs, although safe, did not significantly differ in efficacy from the administration of IFX alone[26].

It is a fact that there is widespread reluctance among gastroenterologists to administer immunosuppressants or biologic agents to elderly IBD patients because of the increased potential for side effects. In a relevant study, Singh *et al* [27] evaluated the effect of age in CD patients older than 60 years, in terms of efficacy and side effects over 2 years. Patients were randomized to receive early combined immunosuppression (173 patients) or conventional management (138 patients). During the 24-month follow-up period, 10% of elderly patients developed CD-related complications (early combined immunosuppression 6.4% versus conventional treatment 14.5%). No difference was found regarding the safety and efficacy of early combined immunosuppression compared with conventional management in both elderly and younger patients. Therefore, early combined immunosuppression is indicated as a therapeutic option in selected elderly CD patients who do not show a satisfactory therapeutic response[27].

In the SONIC and UC-success study, the combination of IFX and AZA was superior to treatment with IFX alone in both UC and CD patients[28]. Therefore, the combined administration of IFX and AZA in patients at low risk of toxicity and patients with limited therapeutic options is expected to provide significant help under the terms and conditions mentioned above.

Louis *et al*[29] compared the relapse rate and duration of remission over two years in the group of CD patients who continued DCT therapy with IFX plus AZA (n = 67) and the group of patients who discontinued treatment with IFX while maintaining AZA (n = 71), as well as the group that maintained IFX therapy but discontinued AZA (n = 69). A total of 39 patients relapsed (12% of the DBT group, 35% of the IFX discontinuation group, and 9% of the AZA discontinuation group). The 2-year relapse rates were 14% in the combination group, 36% in the IFX withdrawal group, and 10% in the immunosuppressant withdrawal group. A total of 31 serious adverse events were observed in 20 patients, with no difference between groups. The most common serious side effects were infections. No death or malignancy occurred. It therefore appears that in CD patients in remission on CT with IFX and AZA, discontinuation of IFX should only be done on a case-by-case basis while withdrawal of AZA is the preferred de-escalation strategy[29].

Roblin *et al*[30] compared two therapeutic strategies, namely changing the anti-TNF agent to another, or adding an immunosuppressant to the initial treatment while maintaining the same anti-TNF agent in 90 patients with IBD in clinical relapse who presented undetectable anti-TNF trough levels and antidrug antibodies. The rate of clinical failure and occurrence of adverse pharmacokinetic curves were higher in monotherapy compared to CT. At a follow-up of 24 months, the survival rates without clinical failure or adverse pharmacokinetics of the biological agents were 22% *vs* 77% and 22% *vs* 78% (monotherapy *vs* CT)[30]. The authors recommend the use of CT after switching to the anti-TNF agent to have favorable clinical outcomes.

A practical question that arises after the successful administration of CT in patients with IBD concerns the duration of maintenance therapy. Lambrescak *et al*[31] investigated the likelihood of disease recurrence two years after achieving remission with CT in 139 patients with a median follow-up of 18.9 months. They noticed that in the 26 relapsed cases shorter duration of CT was not associated with an increased risk of treatment failure. The results do not support the view of continuing CT for more than 12 months after achieving clinical remission in IBD patients[31].

Regarding the route of administration of IFX (subcutaneous or intravenous administration) D'Haens *et al*[30] found that the pharmacokinetics, efficacy, and immunogenicity of the two routes of administration were comparable in the group of patients who underwent monotherapy with sc IFX and DBT in biologic-naïve IBD patients[32].

Table 2 Results of clinical trials with combination therapy in patients with active inflammatory bowel disease

Ref.	Disease	Kind of CT	Efficacy
Colombel *et al* [24], 2015	Severe UC	IFX + AZA *vs* IFX alone *vs* AZA alone	CT was more effective compared to monotherapy with AZA or IFX. High rate of mucosal healing with CT
Feagan *et al* [26], 2014	CD	IFX + MTX *vs* IFX alone *vs* MTX alone	No significant differences. Safe combination
Louis *et al*[29], 2023	CD	IFX + AZA *vs* AZA alone *vs* IFX alone	Relapse rate: 12% in the DBT group compared to 35% (IFX group) and 9% in the AZA group. Most frequent side-effects: Infections
Roblin *et al*[30], 2020	IBD 90 patients	Therapeutic strategies: Change of anti-TNF agent to another or adding immunosuppressant	The rate of clinical failure and occurrence of adverse pharmacokinetic curves were higher in monotherapy compared to CT. Use of CT after switching to the anti-TNF agent is recommended
Matsumoto *et al* [34], 2016	CD	Monotherapy *vs* combination group (ADA + AZA *vs* ADA alone)	Remission rate at week 26 did not differ between the two groups. Thus, combination of ADA with AZA offers no benefit compared to ADA alone
Christensen *et al* [36], 2019	9 patients with CD and 11 with UC	VDZ + calcineurin inhibitors	CT of VDZ with calcineurin inhibitors is a safe and effective combination to induce remission in IBD
Sands *et al*[37], 2019	CD	VDZ + CS *vs* VDZ alone *vs* CS alone	CT: Higher rates of clinical remission compared to the other groups. Similar adverse events

ADA: Adalimumab; anti-TNF: Anti-tumor necrosis factor; AZA: Azathioprine; CD: Crohn's disease; CT: Combination treatment; CS: Corticosteroids; IBD: Inflammatory bowel disease; IFX: Infliximab; UC: Ulcerative colitis; VDZ: Vedolizumab; DBT: Dual biologic therapy.

CT of adalimumab with immunosuppressants: Regarding the combined administration of adalimumab with immunosuppressants (thiopurines) as a maintenance treatment, according to the data of an earlier study, the continuation of the administration of thiopurines for a period longer than 6 months does not offer a substantial benefit compared to monotherapy with adalimumab[33].

In contrast to IFX with AZA CT, the combination of adalimumab with AZA appears to offer no additional benefit compared to adalimumab alone. In an open-label prospective study Matsumoto *et al*[34], evaluated the efficacy of adalimumab with or without AZA in 176 patients with active CD who had not previously been treated with biological agents for 52 wk. It was found that the remission rate at week 26 did not differ between the two groups although the endoscopic improvement rate at week 26 was significantly higher in the CT group compared to the monotherapy group. Furthermore, the clinical efficacy of AZA with adalimumab CT at week 26 did not differ from that of adalimumab monotherapy[34].

Vedolizumab with calcineurin inhibitors: Vedolizumab is a potentially effective maintenance regimen after salvage therapy achieved with calcineurin inhibitors in acute severe UC and DTT is recommended as a potential option in these patients[35]. The combination of vedolizumab with calcineurin inhibitors in patients with UC or CD has been used for at least six years. Christensen *et al*[36] published the results of CT of vedolizumab plus calcineurin inhibitors in 20 patients with IBD (9 with CD and 11 with UC) for 12 months after starting treatment with vedolizumab. In the first 12 wk of treatment, 44% of CD patients and 55% of UC patients achieved clinical remission without using corticosteroids. After one year of treatment, 33% of CD patients and 45% of UC patients were in clinical remission without steroids. The 3 serious adverse events that occurred were related to the calcineurin inhibitors and not to the biological agent. These results, although in a small number of patients, suggest that CT of vedolizumab with calcineurin inhibitors is a safe and effective combination in terms of inducing and maintaining remission in patients with IBD for at least one year[36].

Vedolizumab with corticosteroids: Sands *et al*[37] evaluated the efficacy and safety of vedolizumab co-administered with corticosteroids as induction therapy in patients with moderate-to-severe active CD. The data of this retrospective study evaluated the results of induction therapy after 6 and 10 wk of the GEMINI 2 and GEMINI 3 studies. The results showed that the combination of vedolizumab with corticosteroids resulted in higher rates of clinical remission compared to the CT of corticosteroids with placebo, as well as compared to the vedolizumab-only group. The combination of vedolizumab and corticosteroids achieved significantly higher rates of clinical response compared to the administration of corticosteroids compared to patients who received vedolizumab alone. Adverse event rates were similar between groups. It thus appears that vedolizumab in combination with corticosteroids improves remission or clinical response rates in patients with moderately to severely active CD[37].

Combination treatment with drugs used as a first-line therapy of patients with IBD

In daily clinical practice, combinations of two, three, or even more drugs are often used as the first line of treatment for patients with IBD depending on the severity and extent of the disease (*e.g.*, mesalazine, corticosteroids, antibiotics, probiotics, *etc*). For the combinations of these drugs, the existing data seem to be relatively insufficient. The most important of the existing studies regarding combinations of these drugs are listed below.

CT with antibiotics in severe UC: It is generally accepted that the administration of antibiotics in UC flares lacks a favorable clinical outcome. Their administration is required only in cases in which there is "serious suspicion of septic complications". This aphorism, however, lacks practical significance since in the event of a serious relapse, both stool and blood cultures will be available after at least three days during which the patient experiences symptoms characterized by bloody diarrhea with fever, anorexia, vomiting, abdominal pain, *etc.*, and on the other hand because it is not certain that any microbial sepsis will necessarily be demonstrated in the culture. For this reason, the vast majority of clinical gastroenterologists dealing with the treatment of IBD worldwide prefer, in case of severe UC, the "blind" administration of a combination of antibiotics (mainly metronidazole and ciprofloxacin) for at least five days, alongside the administration of the intense treatment regimen.

Recently, three clinical studies have been published regarding the administration of combination antibiotics in patients with active UC. The first of these evaluated the administration of a combination of three oral antibiotics (500 mg amoxicillin, 500 mg tetracycline, and 250 mg metronidazole three times daily) in 30 patients with active UC-resistant or dependent on corticoids. The results showed that 19 of 30 steroid-resistant patients and 47 of 64 steroid-dependent patients showed a clinical response at 2 wk. After 3 and 12 months the percentages of patients with clinical remission in the first group were 60% and 66.6% respectively and in the second group 56.3% and 51.6% respectively. Ten percent of the first group and 6.3% of the second group underwent colectomy. This study, although lacking a control group, supports that the combined administration of these three antibiotics is effective and safe in patients with active steroid-resistant or steroid-dependent UC[38]. It is worth mentioning that these patients were given a combination of antibiotics used in *Helicobacter pylori* eradication therapy. The paper does not mention this parameter or the status of any *Helicobacter pylori* infection.

The possibility that the favorable effect of the administration of these three antibiotics was due to a long-term change in the intestinal flora of UC patients was investigated in a subsequent multicenter, randomized, double-blind, placebo-controlled study. For this purpose, mucosal samples were taken from 20 patients at the beginning of the treatment and 3 months after its completion to detect terminal restriction fragment length polymorphism in mucosa-associated bacterial components. The researchers found changes in mucosa-associated bacterial components in 10 of 12 patients in the treatment group and none of 8 in the placebo group. These changes persisted for more than three months after completion of treatment, suggesting that treatment with these antibiotics results in long-term changes in the microbiota of patients with UC that may contribute to the favorable therapeutic outcome[39].

The second study evaluated the combined administration of two drugs (ceftriaxone and metronidazole or placebo) as adjunctive therapy in 50 patients with severe UC exacerbation. The authors found that the addition of the two antibiotics in addition to standard care, did not improve outcomes in patients with severe UC exacerbation. However, it should be taken into account that the evaluation of the results was done on the third day of treatment and that the number of cases of fulminant colitis was twice as high in the antibiotic group, which objectively implies that the exacerbation was more severe in the patients in the antibiotic group[40].

In the third study, Rhodes *et al*[41] investigated the efficacy and safety of a combination of antibiotics (ciprofloxacin 500 mg *bd*, plus doxycyclin 100 mg *bd*, plus hydroxychloroquine 200 mg *tds* for 4 wk, followed by doxycycline 100 mg *bd* and hydroxychloroquine 2 mg *tds* for 20 wk in 39 patients with CD) versus budesonide (9 mg peros for 8 wk, 6 mg/d for 2 wks and 3 mg/d for 2 wk in 39 patients with CD). Results were promising with 9/24 patients receiving antibiotics/hydroxychloroquine per protocol maintained in remission by week 24. The overall results with the antibiotic/hydroxychloroquine combination were not impressive, but long-term remission was observed in some patients, which warrants further studies. Withdrawals from the study due to adverse events were observed in 15 patients who received the antibiotic combination and in 6 of those who received budesonide[41].

CT of corticosteroids with mesalazine in severe UC: In a randomized, controlled, investigator-blinded, clinical trial in patients with severe UC exacerbation, 149 patients were treated with corticosteroids alone (73 patients) or corticosteroids plus mesalazine 4 g/d (76 patients). The results showed that 72.6% of patients who received corticosteroids and mesalamine responded to treatment compared to 76.3% of patients treated with corticosteroids alone. The need for administration of biological agents was numerically lower in the group of patients who received corticoids and mesalazine, but the differences did not reach statistical significance. It therefore appears that the combination of mesalamine with corticosteroids does not provide a statistically greater benefit than corticosteroids alone in patients with severe UC exacerbation[42].

CT of oral and rectal mesalazinein UC: In patients with mild to moderate UC, the combined administration of 4 g/d oral and 1 g rectal mesalazine for 8 wk resulted in significantly higher remission rates compared with 4 g/d oral mesalazine and placebo from the rectum (64% *vs* 43%, respectively, PINCE study). All the indices (*e.g.* disease activity index, speed of bleeding elimination, mucosal healing, and quality of life level) were significantly improved in the combined treatment group[43].

CT of antibiotics with vedolizumab in pouchitis: Pouchitis is a major complication occurring in 50% of UC patients who have undergone Ileo Anal Pouch Anastomosis (IAPA). In 20% of patients with pouchitis, the disease becomes chronic. The treatment of this complication presents significant difficulties with high failure rates in several cases. In a recent RCT, Travis *et al*[44] evaluated the effect of vedolizumab (300 mg iv as a loading dose and every 8 wk thereafter) *vs* placebo in 102 patients with chronic pouchitis, while ciprofloxacin administration was maintained in both groups for the first 4 wk. The results showed significant superiority of the combined administration of vedolizumab and ciprofloxacin compared to ciprofloxacin and placebo (remission rate at week 14 31% *vs* 10%). The data regarding the adverse effects of the drugs were also of interest. Serious adverse events occurred in 6% of the vedolizumab group and 8% of patients in the placebo

group[44].

CT of adalimumab and ciprofloxacine in perianal fistula: The combined administration of adalimumab 40 mg every other week with ciprofloxacin 500 mg or placebo twice daily for 12 wk was significantly superior to monotherapy with adalimumab to achieve fistula closure in CD. In a randomized, double-blind, placebo-controlled trial, 76 patients with CD and active perianal fistula were enrolled. At 12 wk the degree of clinical response, reduction in Crohn's Disease activity index (CDAI), and increase in quality of life, were significantly superior in the group of patients who received adalimumab plus ciprofloxacin CT. No differences were observed regarding the rate of side effects. However, the favorable effect was not maintained after discontinuation of the antibiotic[45].

SYSTEMATIC REVIEWS AND METAANALYSES

So far, 5 systematic reviews with or no meta-analyses have been published investigating the efficacy and safety of DBT in patients with IBD. A meta-analysis of 7 studies with a total of 18 patients under DBT (vedolizumab with anti-TNF or ustekinumab) found that all study patients (100%) achieved clinical improvement while 93% showed endoscopic improvement. No significant adverse effects were observed during the 14-month follow-up[46]. Another meta-analysis evaluated the safety and efficacy of DBT and CT with a small molecule agent in patients with refractory IBD (anti-TNF with Vedolizumab, anti-TNF with Ustekinumab, and Ustekinumab with Vedolizumab). A total of 279 patients with refractory IBD and/or extraintestinal manifestations participated. The main indications for DBT administration were drug-resistant disease (81%) and concomitant extraintestinal manifestations of rheumatologic disease (12%). After a median follow-up of 32 wk, the results showed that 59% of patients achieved clinical remission and 34% endoscopic remission, while 12% required surgery. Serious side effects (mainly infections) occurred in 6.5%. Of interest was the fact that the success rate was higher in patients who were given DBT because of treatment-resistant extraintestinal manifestations. Both of these systematic reviews conclude that DBT is a satisfactory treatment option in specialized centers in selected patients with refractory disease or patients with extraintestinal manifestations not controlled by a single biological agent[8].

In a meta-analysis published in the same as the previous year (2022), the authors evaluated the safety and efficacy of the administration of two biological agents or one biological agent and a small molecule (vedolizumab plus anti-TNF-α (56 patients) or vedolizumab plus tofacitinib (57 patients). A total of 13 studies (mostly observational) involving 266 patients with 7 different combinations were included. Median follow-up ranged from 16 to 68 wk. The rate of adverse events for the combination of vedolizumab plus anti-TNF-α was 9.6% while for the combination of vedolizumab plus tofacitinib, the rate of side effects was 1%! The results of this meta-analysis also confirm that DBT is generally safe and effective[47].

In a recent systematic review, the authors analyzed the results of 29 studies in 288 patients with IBD who were given DBT for incompletely responding or non-responding. These patients were given a combination of anti-TNF plus anti-integrin (14 studies, 113 patients), vedolizumab plus ustekinumab (12 studies, 55 patients), vedolizumab plus tofacitinib (9 studies, 68 patients), anti-TNF plus tofacitinib (5 studies, 24 patients), anti-TNF plus ustekinumab (6 studies, 18 patients), and ustekinumab plus tofacitinib (3 studies, 13 patients). Again the authors concluded that DBT administration is a promising therapeutic approach for patients with partial or no response to targeted monotherapy[48].

Finally in a very recently published systematic review the authors analyzed 13 clinical trials evaluating eight biologic agents in patients with CD. Among the biologic agents evaluated, upadacitinib, vedolizumab, adalimumab, guselkumab, mirikizumab, ustekinumab and risankizumab showed statistically significant efficacy concerning various clinical and laboratory parameters (including biomarkers, histology, endoscopy and quality-of-life). Regarding safety it was noticed that all biologic agents were well tolerated with a good safety profile. The authors of this systematic review conclude that DBT could be considered as an effective and safe therapeutic modality for patients with active CD non-responding to conventional treatment[49].

CASE REPORTS AND CASE SERIES

Many case reports or case series have been published regarding the use of DBT in patients with resistant IBD. The majority of these descriptions focus on the use of an anti-TNF-α in combination with vedolizumab. A case series study included 10 patients (6 with UC and 4 with CD)[50]. The authors concluded that CT with vedolizumab and IFX or vedolizumab and adalimumab is probably a safe long-term regimen in patients with refractory CD. The study by Biscaglia *et al*[51] found that the administration of DBT (ustekinumab and vedolizumab in two patients with IBD resulted in improvement of intestinal disease and extraintestinal manifestations, while no adverse events were reported during the two-year follow-up under DBT treatment[51]. In another series of cases in which vedolizumab and other biological agents were administered for 5-37 months, the authors achieved clinical remission and improvement of extraintestinal manifestations. A small percentage of infections were observed, which were, however, not serious[52]. Bethge *et al*[53]. described a patient with enteropathic seronegative spondyloarthritis and refractory UC who eventually underwent IAPA. In this patient with refractory pouchitis, the combination of vedolizumab and etanercept resulted in endoscopic and histological remission with complete resolution of joint symptoms without significant adverse effects[53]. Roblin *et al*[54] described a case of a patient with severe, treatment-resistant UC and human leukocyte antigens-B27 positive

spondyloarthropathy treated with vedolizumab[54]. The patient responded satisfactorily to the addition of golimumab to the regimen. In the long term, both UC and spondyloarthropathy were maintained in remission after one year of CT with vedolizumab and golimumab. Liu *et al*[55] described a case of a young patient with ileocolic CD who, after 10 months of treatment with a combination of ustekinumab and vedolizumab, achieved mucosal healing for the first time after 13 years of persistent disease. During the six-month combined administration of the two biological agents, no significant side effects were found[55]. Huff-Hardy *et al*[56] combined vedolizumab with ustekinumab in a patient with refractory CD. The patient (female, aged 22 years) with severe, stenotic, fistula refractory to treatment showed significant improvement in perianal disease after 8 weeks of DBT while achieving deep remission after 1 year of treatment[56]. Finally, a recent multicenter study from Finland analyzed data from 16 patients (15 with CD) treated with a combination of two biologic agents. The DBT combination used in most patients was adalimumab plus ustekinumab with a median follow-up of nine months. Seven patients (32%) were in remission at the end of follow-up. In all centers from which data were collected, DBT reduced the need for corticosteroids. The majority of patients who achieved a response to DBT were treated with a combination of adalimumab and ustekinumab (56%). At the end of the follow-up, all nine (41%) DBT responders continued treatment. Infections occurred in three patients (19%). The experience of using DBT in this small number of patients is encouraging[57].

Summary of the results

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 (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 dual therapy (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 *et al*[13] in 14 patients with CD and 1 patient with UC used a CT 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 patients developed infections which were treated efficiently with antibiotics.

Miyatani *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 CT with biologic or micromolecular agents, Glassner *et al*[12] described that significantly more patients under CT were in clinical and endoscopic remission compared to baseline status. Erythrocyte sedimentation rate and C-reactive protein 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 *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 CT (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 CT 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 (combination of one biologic agent with one immunosuppressive drug): The combination of a biologic anti-TNF-α agent (mainly IFX and to a lesser extent adalimumab) with azathioprine appears to be more effective in CD patients than monotherapy with IFX 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 IFX 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[38-40].

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.

FACING THE FUTURE

As mentioned above, studies related to DBT are constantly being published, which combine biologics with small molecule agents (tofacitinib). Future studies should evaluate different dosages and combinations of drugs, different ways of administration, and different duration of treatment, emphasizing the possibility of adverse effects. The length of time of DBT administration should also be investigated, whether it should be administered only to induce remission or should also be administered as maintenance therapy. If DBT is used as a maintenance treatment then for how long and at what dosage should be administered? The type of administration should be at the same as in the induction phase or at reduced doses?

Another important field of research should be the possible combination of new pharmaceutical products that will equip our pharmaceutical quiver and which work with different mechanisms of action. Such drugs may be anti-IL-23 agents such as mirikizumab, risankizumab (Skyrizi, AbbVie), brazikumab and guselkumab, newer anti-integrin drugs such as etrolizumab and ontamalimab, as well as phosphodiesterase-4 inhibitors and sphingosine-1-phosphate receptor agonists. Currently, these drugs have good efficacy when administered individually, but it remains unknown whether they will work better in combination with older biological agents.

CONCLUSION

The need for the administration of combination biologic agents is constantly being established. After all, in daily clinical practice, regardless of whether there is not a sufficient number of randomized clinical studies investigating the effect of the simultaneous administration of established pharmaceutical agents (*e.g.*, corticoids, mesalazine, antibiotics, probiotics or immunosuppressants), this practice is widely applied. Patients with IBD require long-term and expensive treatment that should achieve important and difficult therapeutic goals such as the absence of symptoms, avoidance of complications and surgeries, prevention of disability and restoration of their quality of life.

Combination therapies appear to be effective in certain categories of patients, such as patients with refractory disease or patients with extraintestinal manifestations, although the treatment may be associated with an increased risk of adverse effects and malignancies.

The use of newer combinations, the application of new biomarkers and artificial intelligence, and clinical trials to establish efficacy during follow-up are necessary to implement with the aim of adopting new more effective therapeutic strategies in patients with resistant IBD.

The existing studies of combined use of biological agents lack the evidence of perfection that characterizes studies of single agents probably because there is no adequate financial support. Long-term safety data are also lacking. There is an urgent need in the near future for studies in sufficient numbers of patients with resistant disease and/or difficult-to-treat extraintestinal manifestations in which all possible combinations of biologic agents or biologic agents with other already established pharmaceutical agents, including immunosuppressants, are used.

At present the majority of studies suggest that no particularly serious adverse effects have been observed as a result of the use of DBT. On the other hand, it becomes apparent that with the explosive increase in the number of available biological agents, the possibilities of creating many and different combinations will become much easier in the future.

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Country/Territory of origin: Greece

ORCID number: John K Triantafillidis 0000-0002-9115-232X; Constantinos G Zografos 0000-0002-8203-6407; Manousos M Konstadoulakis 0000-0002-9999-5022; Apostolos E Papalois 0000-0001-8339-7426.

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REFERENCES

1 **Feuerstein JD**, Isaacs KL, Schneider Y, Siddique SM, Falck-Ytter Y, Singh S; AGA Institute Clinical Guidelines Committee. AGA Clinical Practice Guidelines on the Management of Moderate to Severe Ulcerative Colitis. *Gastroenterology* 2020; **158**: 1450-1461 [PMID: 31945371 DOI: 10.1053/j.gastro.2020.01.006]
2 **Feuerstein JD**, Ho EY, Shmidt E, Singh H, Falck-Ytter Y, Sultan S, Terdiman JP; American Gastroenterological Association Institute Clinical Guidelines Committee. AGA Clinical Practice Guidelines on the Medical Management of Moderate to Severe Luminal and Perianal Fistulizing Crohn's Disease. *Gastroenterology* 2021; **160**: 2496-2508 [PMID: 34051983 DOI: 10.1053/j.gastro.2021.04.022]
3 **Greuter T**, Rieder F, Kucharzik T, Peyrin-Biroulet L, Schoepfer AM, Rubin DT, Vavricka SR. Emerging treatment options for extraintestinal manifestations in IBD. *Gut* 2021; **70**: 796-802 [PMID: 32847845 DOI: 10.1136/gutjnl-2020-322129]
4 **Danese S**, Solitano V, Jairath V, Peyrin-Biroulet L. The future of drug development for inflammatory bowel disease: the need to ACT (advanced combination treatment). *Gut* 2022; **71**: 2380-2387 [PMID: 35701092 DOI: 10.1136/gutjnl-2022-327025]
5 **Gold SL**, Steinlauf AF. Efficacy and Safety of Dual Biologic Therapy in Patients With Inflammatory Bowel Disease: A Review of the Literature. *Gastroenterol Hepatol (N Y)* 2021; **17**: 406-414 [PMID: 34602905]
6 **Quiroga LC**, Sabourin AA. Review of Dual Biologics in Specialty Pharmacy Practice. *Ann Pharmacother* 2023; **57**: 1094-1110 [PMID: 36600576 DOI: 10.1177/10600280221135177]
7 **Haider M**, Lashner B. Dual Targeted Therapy for the Management of Inflammatory Bowel Disease. *J Clin Gastroenterol* 2021; **55**: 661-666 [PMID: 34238847 DOI: 10.1097/MCG.0000000000001583]
8 **Ahmed W**, Galati J, Kumar A, Christos PJ, Longman R, Lukin DJ, Scherl E, Battat R. Dual Biologic or Small Molecule Therapy for Treatment of Inflammatory Bowel Disease: A Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol* 2022; **20**: e361-e379 [PMID: 33798711 DOI: 10.1016/j.cgh.2021.03.034]
9 **Balderramo D**. Role of the combination of biologics and/or small molecules in the treatment of patients with inflammatory bowel disease. *World J Gastroenterol* 2022; **28**: 6743-6751 [PMID: 36620336 DOI: 10.3748/wjg.v28.i47.6743]
10 **Mas EB**, Calvo XC. Selecting the Best Combined Biological Therapy for Refractory Inflammatory Bowel Disease Patients. *J Clin Med* 2022; **11** [PMID: 35207347 DOI: 10.3390/jcm11041076]
11 **Privitera G**, Onali S, Pugliese D, Renna S, Savarino E, Viola A, Ribaldone DG, Buda A, Bezzio C, Fiorino G, Fantini MC, Scaldaferri F, Guidi L, Danese S, Gasbarrini A, Orlando A, Armuzzi A. Dual Targeted Therapy: a possible option for the management of refractory Inflammatory Bowel Disease. *J Crohns Colitis* 2020 [PMID: 32674156 DOI: 10.1093/ecco-jcc/jjaa149]
12 **Glassner K**, Oglat A, Duran A, Koduru P, Perry C, Wilhite A, Abraham BP. The use of combination biological or small molecule therapy in inflammatory bowel disease: A retrospective cohort study. *J Dig Dis* 2020; **21**: 264-271 [PMID: 32324969 DOI: 10.1111/1751-2980.12867]
13 **Kwapisz L**, Raffals LE, Bruining DH, Pardi DS, Tremaine WJ, Kane SV, Papadakis KA, Coelho-Prabhu N, Kisiel JB, Heron V, Faubion WA, Loftus EV Jr. Combination Biologic Therapy in Inflammatory Bowel Disease: Experience From a Tertiary Care Center. *Clin Gastroenterol Hepatol* 2021; **19**: 616-617 [PMID: 32068149 DOI: 10.1016/j.cgh.2020.02.017]
14 **Sands BE**, Kozarek R, Spainhour J, Barish CF, Becker S, Goldberg L, Katz S, Goldblum R, Harrigan R, Hilton D, Hanauer SB. Safety and tolerability of concurrent natalizumab treatment for patients with Crohn's disease not in remission while receiving infliximab. *Inflamm Bowel Dis* 2007; **13**: 2-11 [PMID: 17206633 DOI: 10.1002/ibd.20014]
15 **Yang E**, Panaccione N, Whitmire N, Dulai PS, Vande Casteele N, Singh S, Boland BS, Collins A, Sandborn WJ, Panaccione R, Battat R. Efficacy and safety of simultaneous treatment with two biologic medications in refractory Crohn's disease. *Aliment Pharmacol Ther* 2020; **51**: 1031-1038 [PMID: 32329532 DOI: 10.1111/apt.15719]
16 **Honap S**, Netter P, Danese S, Peyrin-Biroulet L. An update on the safety of long-term vedolizumab use in inflammatory bowel disease. *Expert Opin Drug Saf* 2023; **22**: 767-776 [PMID: 37610086 DOI: 10.1080/14740338.2023.2247976]
17 **Avedillo-Salas A**, Corral-Cativiela S, Fanlo-Villacampa A, Vicente-Romero J. The Efficacy and Safety of Biologic Drugs in the Treatment of Moderate-Severe Crohn's Disease: A Systematic Review. *Pharmaceuticals (Basel)* 2023; **16** [PMID: 38004446 DOI: 10.3390/ph16111581]
18 **Miyatani Y**, Choi D, Choi NK, Rubin DT. Dual-Targeted Therapy with Upadacitinib and Ustekinumab in Medically Complex Crohn's Disease. *Dig Dis Sci* 2024; **69**: 355-359 [PMID: 38112840 DOI: 10.1007/s10620-023-08182-y]

19 **Feagan BG**, Sands BE, Sandborn WJ, Germinaro M, Vetter M, Shao J, Sheng S, Johanns J, Panés J; VEGA Study Group. Guselkumab plus golimumab combination therapy versus guselkumab or golimumab monotherapy in patients with ulcerative colitis (VEGA): a randomised, double-blind, controlled, phase 2, proof-of-concept trial. *Lancet Gastroenterol Hepatol* 2023; **8**: 307-320 [PMID: 36738762 DOI: 10.1016/S2468-1253(22)00427-7]

20 **Goessens L**, Colombel JF, Outtier A, Ferrante M, Sabino J, Judge C, Saeidi R, Rabbitt L, Armuzzi A, Domenech E, Michalopoulos G, Cremer A, García-Alonso FJ, Molnar T, Karmiris K, Gecse K, Van Oostrom J, Löwenberg M, Farkas K, Atreya R, Ribaldone DG, Selinger C, Hoentjen F, Bihin B, Sebastian S; European COMBIO study group, Rahier JF. Safety and efficacy of combining biologics or small molecules for inflammatory bowel disease or immune-mediated inflammatory diseases: A European retrospective observational study. *United European Gastroenterol J* 2021; **9**: 1136-1147 [PMID: 34694746 DOI: 10.1002/ueg2.12170]

21 **Macaluso FS**, Orlando A. Anti-TNF combination therapy in inflammatory bowel disease: de novo or selective? *Minerva Gastroenterol Dietol* 2019; **65**: 291-297 [PMID: 31602970 DOI: 10.23736/S1121-421X.19.02617-5]

22 **Han B**, Tang D, Lv X, Li S, Fan J, Xu X, Zhang J, Xu S, Ye W, Huang Z, Zhan L. Comparative efficacy and safety of combination therapy with infliximab for Crohn's disease: a systematic review and network meta-analysis. *Int J Colorectal Dis* 2023; **38**: 82 [PMID: 36971914 DOI: 10.1007/s00384-023-04378-w]

23 **Panaccione R**, Ghosh S, Middleton S, Márquez JR, Scott BB, Flint L, van Hoogstraten HJ, Chen AC, Zheng H, Danese S, Rutgeerts P. Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis. *Gastroenterology* 2014; **146**: 392-400.e3 [PMID: 24512909 DOI: 10.1053/j.gastro.2013.10.052]

24 **Colombel JF**, Reinisch W, Mantzaris GJ, Kornbluth A, Rutgeerts P, Tang KL, Oortwijn A, Bevelander GS, Cornillie FJ, Sandborn WJ. Randomised clinical trial: deep remission in biologic and immunomodulator naïve patients with Crohn's disease - a SONIC post hoc analysis. *Aliment Pharmacol Ther* 2015; **41**: 734-746 [PMID: 25728587 DOI: 10.1111/apt.13139]

25 **Roblin X**, Boschetti G, Williet N, Nancey S, Marotte H, Berger A, Phelip JM, Peyrin-Biroulet L, Colombel JF, Del Tedesco E, Paul S, Flourie B. Azathioprine dose reduction in inflammatory bowel disease patients on combination therapy: an open-label, prospective and randomised clinical trial. *Aliment Pharmacol Ther* 2017; **46**: 142-149 [PMID: 28449228 DOI: 10.1111/apt.14106]

26 **Feagan BG**, McDonald JW, Panaccione R, Enns RA, Bernstein CN, Ponich TP, Bourdages R, Macintosh DG, Dallaire C, Cohen A, Fedorak RN, Paré P, Bitton A, Saibil F, Anderson F, Donner A, Wong CJ, Zou G, Vandervoort MK, Hopkins M, Greenberg GR. Methotrexate in combination with infliximab is no more effective than infliximab alone in patients with Crohn's disease. *Gastroenterology* 2014; **146**: 681-688.e1 [PMID: 24269926 DOI: 10.1053/j.gastro.2013.11.024]

27 **Singh S**, Stitt LW, Zou G, Khanna R, Dulai PS, Sandborn WJ, Feagan BG, Jairath V. Early combined immunosuppression may be effective and safe in older patients with Crohn's disease: post hoc analysis of REACT. *Aliment Pharmacol Ther* 2019; **49**: 1188-1194 [PMID: 30891808 DOI: 10.1111/apt.15214]

28 **Colombel JF**, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D, Lichtiger S, D'Haens G, Diamond RH, Broussard DL, Tang KL, van der Woude CJ, Rutgeerts P; SONIC Study Group. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med* 2010; **362**: 1383-1395 [PMID: 20393175 DOI: 10.1056/NEJMoa0904492]

29 **Louis E**, Resche-Rigon M, Laharie D, Satsangi J, Ding N, Siegmund B, D'Haens G, Picon L, Bossuyt P, Vuitton L, Irving P, Viennot S, Lamb CA, Pollok R, Baert F, Nachury M, Fumery M, Gilletta C, Almer S, Ben-Horin S, Bouhnik Y, Colombel JF, Hertervig E; GETAID and the SPARE-Biocycle research group. Withdrawal of infliximab or concomitant immunosuppressant therapy in patients with Crohn's disease on combination therapy (SPARE): a multicentre, open-label, randomised controlled trial. *Lancet Gastroenterol Hepatol* 2023; **8**: 215-227 [PMID: 36640794 DOI: 10.1016/S2468-1253(22)00385-5]

30 **Roblin X**, Williet N, Boschetti G, Phelip JM, Del Tedesco E, Berger AE, Vedrines P, Duru G, Peyrin-Biroulet L, Nancey S, Flourie B, Paul S. Addition of azathioprine to the switch of anti-TNF in patients with IBD in clinical relapse with undetectable anti-TNF trough levels and antidrug antibodies: a prospective randomised trial. *Gut* 2020; **69**: 1206-1212 [PMID: 31980448 DOI: 10.1136/gutjnl-2019-319758]

31 **Lambrescak E**, Vaysse T, Allez M, Ungar B, Gleizes A, Hacein-Bey S, Chowers Y, Roblin X, Kopylov U, Rachas A, Carbonnel F. Duration of combination therapy and risk of treatment failure in patients with inflammatory bowel disease. *Clin Res Hepatol Gastroenterol* 2021; **45**: 101503 [PMID: 32893176 DOI: 10.1016/j.clinre.2020.07.008]

32 **D'Haens G**, Reinisch W, Schreiber S, Cummings F, Irving PM, Ye BD, Kim DH, Yoon S, Ben-Horin S. Subcutaneous Infliximab Monotherapy Versus Combination Therapy with Immunosuppressants in Inflammatory Bowel Disease: A Post Hoc Analysis of a Randomised Clinical Trial. *Clin Drug Investig* 2023; **43**: 277-288 [PMID: 37004656 DOI: 10.1007/s40261-023-01252-z]

33 **Hisamatsu T**, Kato S, Kunisaki R, Matsuura M, Nagahori M, Motoya S, Esaki M, Fukata N, Inoue S, Sugaya T, Sakuraba H, Hirai F, Watanabe K, Kanai T, Naganuma M, Nakase H, Suzuki Y, Watanabe M, Hibi T, Nojima M, Matsumoto T; DIAMOND2 Study Group. Withdrawal of thiopurines in Crohn's disease treated with scheduled adalimumab maintenance: a prospective randomised clinical trial (DIAMOND2). *J Gastroenterol* 2019; **54**: 860-870 [PMID: 31041545 DOI: 10.1007/s00535-019-01582-w]

34 **Matsumoto T**, Motoya S, Watanabe K, Hisamatsu T, Nakase H, Yoshimura N, Ishida T, Kato S, Nakagawa T, Esaki M, Nagahori M, Matsui T, Naito Y, Kanai T, Suzuki Y, Nojima M, Watanabe M, Hibi T; DIAMOND study group. Adalimumab Monotherapy and a Combination with Azathioprine for Crohn's Disease: A Prospective, Randomized Trial. *J Crohns Colitis* 2016; **10**: 1259-1266 [PMID: 27566367 DOI: 10.1093/ecco-jcc/jjw152]

35 **Dai C**, Huang YH, Jiang M. Combination therapy in inflammatory bowel disease: Current evidence and perspectives. *Int Immunopharmacol* 2023; **114**: 109545 [PMID: 36508920 DOI: 10.1016/j.intimp.2022.109545]

36 **Christensen B**, Gibson PR, Micic D, Colman RJ, Goeppinger SR, Kassim O, Yarur A, Weber CR, Cohen RD, Rubin DT. Safety and Efficacy of Combination Treatment With Calcineurin Inhibitors and Vedolizumab in Patients With Refractory Inflammatory Bowel Disease. *Clin Gastroenterol Hepatol* 2019; **17**: 486-493 [PMID: 29751166 DOI: 10.1016/j.cgh.2018.04.060]

37 **Sands BE**, Van Assche G, Tudor D, Akhundova-Unadkat G, Curtis RI, Tan T. Vedolizumab in Combination With Corticosteroids for Induction Therapy in Crohn's Disease: A Post Hoc Analysis of GEMINI 2 and 3. *Inflamm Bowel Dis* 2019; **25**: 1375-1382 [PMID: 30615117 DOI: 10.1093/ibd/izy384]

38 **Kato K**, Ohkusa T, Terao S, Chiba T, Murakami K, Yanaka A, Uehara T, Ishii Y, Soma M, Tajiri H. Adjunct antibiotic combination therapy for steroid-refractory or -dependent ulcerative colitis: an open-label multicentre study. *Aliment Pharmacol Ther* 2014; **39**: 949-956 [PMID: 24628398 DOI: 10.1111/apt.12688]

39 **Koido S**, Ohkusa T, Kajiura T, Shinozaki J, Suzuki M, Saito K, Takakura K, Tsukinaga S, Odahara S, Yukawa T, Mitobe J, Kajihara M, Uchiyama K, Arakawa H, Tajiri H. Long-term alteration of intestinal microbiota in patients with ulcerative colitis by antibiotic combination therapy. *PLoS One* 2014; **9**: e86702 [PMID: 24489770 DOI: 10.1371/journal.pone.0086702]

40 **Mishra S**, Mandavdhare HS, Singh H, Choudhury A, Shah J, Ram S, Kalsi D, Samanta J, Prasad KK, Sharma AK, Dutta U, Sharma V. Adjuvant use of combination of antibiotics in acute severe ulcerative colitis: A placebo controlled randomized trial. *Expert Rev Anti Infect Ther* 2021; **19**: 949-955 [PMID: 33245002 DOI: 10.1080/14787210.2021.1856656]

41 **Rhodes JM**, Subramanian S, Flanagan PK, Horgan GW, Martin K, Mansfield J, Parkes M, Hart A, Dallal H, Iqbal T, Butterworth J, Culshaw K, Probert C. Randomized Trial of Ciprofloxacin Doxycycline and Hydroxychloroquine Versus Budesonide in Active Crohn's Disease. *Dig Dis Sci* 2021; **66**: 2700-2711 [PMID: 32681228 DOI: 10.1007/s10620-020-06477-y]

42 **Ben-Horin S**, Har-Noy O, Katsanos KH, Roblin X, Chen M, Gao X, Schwartz D, Cheon JH, Cesarini M, Bojic D, Protic M, Theodoropoulou A, Abu-Kaf H, Engel T, Tang J, Veyrard P, Lin X, Mao R, Christodoulou D, Karmiris K, Knezevic-Ivanovski T; ComboMesa investigators. Corticosteroids and Mesalamine Versus Corticosteroids for Acute Severe Ulcerative Colitis: A Randomized Controlled Trial. *Clin Gastroenterol Hepatol* 2022; **20**: 2868-2875.e1 [PMID: 35272029 DOI: 10.1016/j.cgh.2022.02.055]

43 **Probert CS**, Dignass AU, Lindgren S, Oudkerk Pool M, Marteau P. Combined oral and rectal mesalazine for the treatment of mild-to-moderately active ulcerative colitis: rapid symptom resolution and improvements in quality of life. *J Crohns Colitis* 2014; **8**: 200-207 [PMID: 24012063 DOI: 10.1016/j.crohns.2013.08.007]

44 **Travis S**, Silverberg MS, Danese S, Gionchetti P, Löwenberg M, Jairath V, Feagan BG, Bressler B, Ferrante M, Hart A, Lindner D, Escher A, Jones S, Shen B; EARNEST Study Group. Vedolizumab for the Treatment of Chronic Pouchitis. *N Engl J Med* 2023; **388**: 1191-1200 [PMID: 36988594 DOI: 10.1056/NEJMoa2208450]

45 **Dewint P**, Hansen BE, Verhey E, Oldenburg B, Hommes DW, Pierik M, Ponsioen CI, van Dullemen HM, Russel M, van Bodegraven AA, van der Woude CJ. Adalimumab combined with ciprofloxacin is superior to adalimumab monotherapy in perianal fistula closure in Crohn's disease: a randomised, double-blind, placebo controlled trial (ADAFI). *Gut* 2014; **63**: 292-299 [PMID: 23525574 DOI: 10.1136/gutjnl-2013-304488]

46 **Ribaldone DG**, Pellicano R, Vernero M, Caviglia GP, Saracco GM, Morino M, Astegiano M. Dual biological therapy with anti-TNF, vedolizumab or ustekinumab in inflammatory bowel disease: a systematic review with pool analysis. *Scand J Gastroenterol* 2019; **54**: 407-413 [PMID: 30945576 DOI: 10.1080/00365521.2019.1597159]

47 **Alayo QA**, Fenster M, Altayar O, Glassner KL, Llano E, Clark-Snustad K, Patel A, Kwapisz L, Yarur AJ, Cohen BL, Ciorba MA, Thomas D, Lee SD, Loftus EV Jr, Fudman DI, Abraham BP, Colombel JF, Deepak P. Systematic Review With Meta-analysis: Safety and Effectiveness of Combining Biologics and Small Molecules in Inflammatory Bowel Disease. *Crohns Colitis 360* 2022; **4**: otac002 [PMID: 35310082 DOI: 10.1093/crocol/otac002]

48 **Berinstein EM**, Sheehan JL, Jacob J, Steiner CA, Stidham RW, Shannon C, Bishu S, Levine J, Cohen-Mekelburg SA, Waljee AK, Higgins PDR, Berinstein JA. Efficacy and Safety of Dual Targeted Therapy for Partially or Non-responsive Inflammatory Bowel Disease: A Systematic Review of the Literature. *Dig Dis Sci* 2023; **68**: 2604-2623 [PMID: 36807832 DOI: 10.1007/s10620-023-07837-0]

49 **Barberio B**, Gracie DJ, Black CJ, Ford AC. Efficacy of biological therapies and small molecules in induction and maintenance of remission in luminal Crohn's disease: systematic review and network meta-analysis. *Gut* 2023; **72**: 264-274 [PMID: 35907636 DOI: 10.1136/gutjnl-2022-328052]

50 **Buer LCT**, Høivik ML, Warren DJ, Medhus AW, Moum BA. Combining Anti-TNF-α and Vedolizumab in the Treatment of Inflammatory Bowel Disease: A Case Series. *Inflamm Bowel Dis* 2018; **24**: 997-1004 [PMID: 29668901 DOI: 10.1093/ibd/izx110]

51 **Biscaglia G**, Piazzolla M, Cocomazzi F, Melchionda G, De Cata A, Bossa F, Palmieri O, Andriulli A. Landmarks for dual biological therapy in inflammatory bowel disease: lesson from two case reports of vedolizumab in combination with ustekinumab. *Eur J Gastroenterol Hepatol* 2020; **32**: 1579-1582 [PMID: 32947419 DOI: 10.1097/MEG.0000000000001919]

52 **Mao EJ**, Lewin S, Terdiman JP, Beck K. Safety of dual biological therapy in Crohn's disease: a case series of vedolizumab in combination with other biologics. *BMJ Open Gastroenterol* 2018; **5**: e000243 [PMID: 30538822 DOI: 10.1136/bmjgast-2018-000243]

53 **Bethge J**, Meffert S, Ellrichmann M, Conrad C, Nikolaus S, Schreiber S. Combination therapy with vedolizumab and etanercept in a patient with pouchitis and spondylarthritis. *BMJ Open Gastroenterol* 2017; **4**: e000127 [PMID: 28243458 DOI: 10.1136/bmjgast-2016-000127]

54 **Roblin X**, Paul S, Ben-Horin S. Co-treatment With Golimumab and Vedolizumab to Treat Severe UC and Associated Spondyloarthropathy. *J Crohns Colitis* 2018; **12**: 379-380 [PMID: 29088342 DOI: 10.1093/ecco-jcc/jjx142]

55 **Liu EY**, Loomes DE. Ustekinumab and Vedolizumab Dual Biologic Therapy in the Treatment of Crohn's Disease. *Case Rep Med* 2017; **2017**: 5264216 [PMID: 29250117 DOI: 10.1155/2017/5264216]

56 **Huff-Hardy K**, Bedair M, Vazquez R, Burstein E. Efficacy of Combination Vedolizumab and Ustekinumab for Refractory Crohn's Disease. *Inflamm Bowel Dis* 2017; **23**: E49 [PMID: 28858074 DOI: 10.1097/MIB.0000000000001232]

57 **Eronen H**, Kolehmainen S, Koffert J, Koskinen I, Oksanen P, Jussila A, Huhtala H, Sipponen T, Ilus T. Combining biological therapies in patients with inflammatory bowel disease: a Finnish multi-centre study. *Scand J Gastroenterol* 2022; **57**: 936-941 [PMID: 35238727 DOI: 10.1080/00365521.2022.2045350]

58 **Triantafillidis JK**, Papalois AE, Parasi A, Anagnostakis E, Burnazos S, Gikas A, Merikas EG, Douzinas E, Karagianni M, Sotiriou H. Favorable response to subcutaneous administration of infliximab in rats with experimental colitis. *World J Gastroenterol* 2005; **11**: 6843-6847 [PMID: 16425394 DOI: 10.3748/wjg.v11.i43.6843]

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