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Dual Biological Therapy with Anti-TNF, Vedolizumab or Ustekinumab in Inflammatory Bowel Disease: A Systematic Review with Pool Analysis

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Abstract

Background: Inflammatory bowel diseases patients eligible for biological therapy represent a group with considerable disease burden and biologics only achieve 40% clinical remission rates in responders after 1 year of therapy.

Aims: To collect all the published data about patients treated with dual biological therapy with an Anti-TNF, vedolizumab or ustekinumab, for a period of at least 3 months and to pool the data about the effectiveness and safety.

Methods: A MEDLINE, and Web of Science search of all studies published in English until January 1, 2019 was conducted.

Results: We included 7 studies with a total of 18 patients. Fifteen patients were treated with a combination of an anti-TNF and vedolizumab, 3 patients were treated with vedolizumab and ustekinumab. Fifty-six percent of patients were affected by Crohn's disease and 50% of patients were treated with an immunosuppressant drug or steroid too. A clinical improvement was obtained in 100% of patients, and an endoscopic improvement in 93% of patients. No serious adverse events were reported.

Conclusions: The use of dual biological therapy is an attractive therapeutic option and may be an opportunity to better tailor and personalize the therapies for patients. Further studies, as randomized control trials, to provide comparative efficacy and safety endpoints of combination therapies, and to clarify potential advantages of combined biological therapies, are needed.

Key Words: Anti-integrin; Biologics; Crohn's disease; Inflammatory bowel disease; Ulcerative colitis

1 Introduction:

Inflammatory bowel diseases (IBD) patients eligible for biological therapy represent a group with considerable disease burden who have failed conventional medication such as corticosteroids and thiopurines and therefore are at high risk of surgical intervention. In these patients, biologic agents only achieve approximately 40% of clinical remission rates in responders after 1 year of therapy [1].

Given the extensive redundancy of the inflammatory network, concomitant use of two different biologics may combine different mechanisms of action.

Most of the experience in Crohn's disease (CD) and ulcerative colitis (UC) have relied on the combination of targeted biologics with immunomodulators [2], but there is a lack of information regarding the effects of long-term combination of biological therapies in IBD.

A recent narrative review [3] included no studies about patients with active IBD treated with a combination of two among an Anti-TNF effective in IBD, vedolizumab or ustekinumab for a period of at least 3 months.

The aim of this systematic review is to collect all the published data about patients treated with a combination of two among an Anti-TNF effective in IBD (i.e. we excluded etanercept), vedolizumab or ustekinumab for a period of at least 3 months and to pool the data regarding the effectiveness and safety of this therapeutic strategy.

2 Materials and methods:

Articles published in English, about the use of dual biological therapy in IBD, were identified through PubMed and Web of Science ("All databases") searches using the terms "infliximab[Title] AND vedolizumab[Title]", "infliximab[Title] AND ustekinumab[Title]", "adalimumab[Title] AND vedolizumab[Title]", "adalimumab[Title]

AND ustekinumab[Title]", "certolizumab[Title] AND vedolizumab[Title]", "certolizumab[Title] AND ustekinumab[Title]", "golimumab[Title] AND vedolizumab[Title]", "golimumab[Title] AND ustekinumab[Title]", "anti-TNF[Title] AND vedolizumab[Title]", "Anti-TNF[Title] AND Ustekinumab[Title]", "vedolizumab[Title] AND ustekinumab[Title]". The final date of the search was January 1, 2019.

Reference lists from published articles were also employed, such as citing articles on PubMed Central. Titles of these publications and their abstracts were scanned in order to eliminate duplicates and irrelevant articles.

The inclusion criteria were:

- a) original studies;
- b) active IBD;
- c) combination treatment with an Anti-TNF, vedolizumab or ustekinumab;
- d) duration of co-treatment: at least three months;
- e) data about clinical or endoscopic IBD improvement.

The inclusion criteria were:

- a) combination treatment with etanercept.

There was no restriction for the study design type or the sample size.

Two authors (D.G.R. and G.P.C.) independently reviewed titles and abstracts of references retrieved from the literature search and selected potentially relevant studies. The full-text versions of selected studies were then assessed by the two authors to determine whether the inclusion criteria were satisfied. Differences in opinion were solved by discussion until consensus was reached. If an agreement failed to be reached, a third author (A.M.) was consulted.

Since only case series and case reports are available in literature, all the studies in agreement with the inclusion criteria were included in the systematic review and in the pool analysis, without a quality analysis of each study.

2.1 Statistical analysis

The number of patients, their sex, the disease (UC or CD), the biologic drugs, the indication for dual biological therapy, the additional treatment with immunomodulator or prednisone, the duration of combination therapy, the onset of side effects during co-treatment, the clinical improvement and the endoscopic improvement were collected in a datasheet and pool analyzed.

Data were tested for normality using the D'Agostino-Pearson test. If the data were not normally distributed, the median (range) was reported, otherwise the mean (95% confident interval (CI)) was reported. Categorical variables were reported as number (%).

Statistical analyses were conducted using Med Calc® version 14.8.1 software.

3 Results:

The flow diagram about the studies' identification, screening, eligibility and the number of the included studies is reported in **Figure 1**.

Figure 1.

3.1 Anti-TNF and vedolizumab

The first data about the effectiveness of dual biological therapy in IBD have been presented by Afzali et al. at the "American College of Gastroenterology" 2016 meeting [4]. It was a case report of a 23-year-old female with ileo-colonic and perianal CD previously treated with prednisone, infliximab, adalimumab, certolizumab. Despite ongoing treatment with vedolizumab and mercaptopurine, she was unable to taper the steroids, with a severe colonic disease at endoscopy, so

adalimumab was added. A clinical and endoscopic improvement was obtained. She stopped the steroids and mercaptopurine. Vedolizumab was discontinued after 6 months and clinical remission persisted until the end of follow-up. No side effects were reported (**Table 1**).

Table 1.

The first case of UC treated with two biologics was presented by Fischer et al. in 2017 [5]. The patient was a 33-year-old man with therapy (azathioprine, cyclosporine, adalimumab, infliximab, golimumab)-refractory UC. Proctocolectomy was refused by the patient. Sigmoidoscopy showed signs of severe inflammation. Vedolizumab was started, without endoscopic improvement at week 8. Since the patient developed spondyloarthritis, certolizumab was added. The spondyloarthritis completely resolved and the underlying colitis activity continuously improved with occurrence of clinical remission at week 16. Sigmoidoscopy was performed 21 months after initiation of the ongoing combination therapy with vedolizumab and certolizumab: mucosal healing was revealed. During the whole-treatment period no therapy-associated side effects occurred.

Roblin et al. [6] reported the first case of an IBD patient co-treated with golimumab and vedolizumab. A 48-year-old female was affected by a severe, extensive, UC and ankylosing spondylitis despite previous treatment with infliximab and adalimumab. Disabling symptoms of ankylosing spondylitis re-emerged after 10 weeks of vedolizumab therapy so, given the good initial improvement of UC' activity to vedolizumab, golimumab was added to vedolizumab and induced resolution of intestinal and axial symptoms. After 1 year of combined vedolizumab-golimumab treatment the patient was in clinical and endoscopic remission with no clinical activity

of spondyloarthritis. No adverse effects, nor infection events occurred throughout the year of treatment.

The larger case series about combining Anti-TNF- α and Vedolizumab has been published by a Norwegian group [7]. All patients showed some effect of anti-TNF treatment, but they still had disease activity assessed by clinical symptoms or endoscopy. Six UC patients treated with infliximab and vedolizumab and 4 CD patients (3 patients treated with infliximab and vedolizumab and 1 patient treated with adalimumab and vedolizumab) were included. Three CD and 1 UC patients received immunomodulators at baseline and 1 UC patient received systemic corticosteroids at the time of inclusion. Throughout the 17 months (median) of follow-up 8 patients stopped anti-TNF therapy after a median of 6 months of combination therapy: all these patients were in clinical remission and 5 in endoscopic remission. Two CD patients carried on the combination treatment with vedolizumab and anti-TNF after 20 and 19 months, respectively. In these 2 patients, treatment with anti-TNF was discontinued due to clinical remission after 6 and 12 months. However, anti-TNF was reintroduced after 4 months and 6 weeks due to the recurrence of gastrointestinal symptoms/arthritis in the first patient and to the recurrence of gastrointestinal symptoms in the second patient. At the end of the follow-up, none of the patients received corticosteroids. In UC patients, endoscopic evaluation was performed at a median of 10 months after the start of combination treatment. Three patients showed endoscopic remission and 3 patients showed significant endoscopic improvement. In CD patients, endoscopic evaluation was performed at a median of 14 months after the start of combination treatment. Two patients showed endoscopic remission and 1 patient showed significant endoscopic improvement. The fourth patient stopped infliximab therapy after 12 months on combination treatment when in clinical and biochemical remission but experienced a sudden and severe flare at 4 weeks before

the planned endoscopy; in this patient, no endoscopic improvement was observed. Regarding side effects, three patients received antibiotics for upper airway infection during follow-up. One UC patient experienced dyspnea 5 months after starting combination treatment, but clinical examination, spirometry, and pulmonary high-resolution computed tomography revealed no pathology. The symptoms resolved without any treatment.

Finally, Mao et al. [8] presented two additional cases of patients with CD treated with golimumab and vedolizumab.

The first case was about a young man with stricturing ileocolonic and perianal CD, previously treated with azathioprine, infliximab, adalimumab, certolizumab, ustekinumab. At the age of 23 he required a second resection with end-ileostomy. Postoperatively vedolizumab was started, but he experienced disease recurrence 1 year after initiation. Magnetic resonance enterography demonstrated inflammatory changes and narrowing in two segments of small bowel. At the age of 26 the patient was admitted to the hospital with a partial small bowel obstruction requiring intravenous corticosteroids despite vedolizumab therapy. In addition, golimumab was added to his regimen given his reluctance to pursue further surgery. During 8 months of dual biological therapy he developed one flare of partial small bowel obstruction requiring hospitalization and corticosteroids. He has successfully tapered off corticosteroids and considered himself in clinical remission. He didn't experience infectious complications.

The second case was a young woman with stricturing ileocolonic and perianal CD, previously treated with infliximab, adalimumab, certolizumab. She underwent to ileocolic resection and postoperatively she achieved clinical remission on natalizumab but developed antibodies to the John Cunningham virus and the drug was stopped. She failed ustekinumab and she required a second ileal resection with

diverting loop ileostomy for severe perianal disease, which was complicated by postoperative recurrence only 8 weeks after surgery, confirmed by ileoscopy demonstrating distal ileal and stomal ulcerations. She was treated with tocilizumab and then with tofacitinib, with a temporary response to the latter drug. Given prior response to natalizumab, vedolizumab was initiated after ileostomy takedown. Tofacitinib was subsequently discontinued and switched to golimumab as the patient desired conception. She achieved clinical remission on this regimen, though this has not been confirmed endoscopically. Her first pregnancy was uncomplicated and the baby was delivered at term on golimumab, vedolizumab and mercaptopurine. Her second pregnancy, on the same medical regimen, was complicated by subchorionic hemorrhage and single umbilical artery, hand-foot-mouth disease that self-resolved and influenza despite vaccination. She delivered another normal baby at term.

3.2 Vedolizumab and ustekinumab

In 2017 Huff-Hardy et al. [9] presented the first IBD patients treated with vedolizumab and ustekinumab dual therapy. A 22-year-old woman was affected by a refractory CD, with severe colonic involvement and multiple strictures eventually requiring subtotal colectomy and end ileostomy. Moreover, she also developed aggressive penetrating disease with enterocutaneous perianal fistulas. Over the course of her disease, she was treated with infliximab, adalimumab, certolizumab, natalizumab, and vedolizumab combined with immunomodulators with poor responses, and in some instances, poorly tolerated side effects including infections. Ustekinumab was initiated because of progressive and unresponsive disease affecting her small bowel and rectal stump with development of perianal fistulas and severe vulvar disease. However, there was little subjective change in her gastrointestinal complaints and her vulvo-perianal disease continued to progress. Because of the unresponsive nature of

the disease, vedolizumab, ineffective as monotherapy in the past, was added to the ustekinumab and methotrexate regimen. At her 8-week follow-up the vulvo-perianal disease improved dramatically. She subsequently underwent completion proctectomy with perineal reconstruction. This patient experienced a combination therapy with vedolizumab, ustekinumab, and methotrexate for over 1 year and achieved deep remission. During the follow-up period she underwent to an episode of self-limited rotavirus infection.

In the same year, Liu et al. presented a second case of a refractory ileocolonic CD in a 27-year-old female [10]. She underwent a right hemicolectomy at the age of 17, followed by small bowel resections at the age of 20 and 21 for medically refractory disease. She was previously treated with azathioprine, prednisone, infliximab, adalimumab, and ustekinumab, and she joined clinical trials testing tofacitinib and mongersen. She was assessed for ongoing severe CD receiving a retreat of infliximab with the addition of methotrexate combination therapy. Colonoscopy showed ongoing deep serpiginous ileal ulcers, colonic aphthous ulceration, and worsening deep rectal ulceration. As her previous ustekinumab therapy didn't included intravenous loading, infliximab combo therapy was stopped, and she restarted ustekinumab with induction dosing and then subcutaneously, in combination with azathioprine. Despite this, symptoms continued: magnetic resonance enterography showed ongoing evidence of inflammation five months post initiation of ustekinumab; so vedolizumab was added. Five months after adding vedolizumab to ustekinumab abdominal pain and nausea began to improve. Colonoscopy 6 months after dual biological therapy showed mucosal healing of the ileum and colon. No side effects from her medical therapy have arisen thus far.

The most recent case of vedolizumab and ustekinumab combination therapy was presented by Mao et al [8]. A young man diagnosed with colonic and perianal CD,

previously treated with infliximab, had a secondary loss of response despite co-treatment with methotrexate and infliximab dose optimization. Colonoscopy demonstrated colitis to the hepatic flexure. Infliximab was switched to ustekinumab. Initially the patient demonstrated a clinical response to ustekinumab, but he continued to experience bloody diarrhea and nocturnal symptoms, requiring concurrent high-dose prednisone taper. Given his partial response to ustekinumab and prior mechanistic failure of anti-TNF, vedolizumab was added to ustekinumab. After 2 months of dual biological therapy he achieved steroid-free clinical remission. During 5 months of dual biological therapy he experienced two episodes of *Clostridium difficile* infection: he was treated with 2-week courses of vancomycin.

3.3 Pool analysis

A total of 18 patients have been treated with dual biological therapy. Their clinical characteristics are reported in **Table 2**.

Table 2.

The geometric mean duration of dual biological therapy has been 14 months (range = 5-37 months). Nine out of the 18 patients (50%) were also treated with corticosteroids or immunosuppressants **Figure 2**.

Figure 2.

A clinical improvement was obtained in 18 out of the 18 patients (100%), an endoscopic improvement in 14 out of the 15 patients in which this data was available (93%). **Figure 3**.

Figure 3.

Seven out of the 18 patients experienced a side effect (38.9%): 3 cases of upper respiratory tract infections, 1 case of dyspnea, 1 case of rotavirus infection, 1 case of recurrent *Clostridium difficile* infection, 1 case of self-limited viral illnesses (hand-foot-mouth disease and influenza despite vaccination) **Figure 4.**

Figure 4.

4 Discussion:

Despite the introduction of new biological therapies many patients with IBD remain refractory to available treatments [11].

This study represents the first systematic review with pool analysis about the effectiveness and safety of dual biological therapy in active IBD.

Unlike the recent narrative review of Hirten et al. [3], that included no study about patients with active IBD treated with a combination of an Anti-TNF effective in IBD, vedolizumab or ustekinumab for a period of at least 3 months, we included 7 studies with a total of 18 patients. We excluded patients treated with etanercept, a fusion protein that blocks the TNF receptor without inducing lymphocyte apoptosis, since its ineffectiveness in the treatment of IBD; moreover it's the drug most frequently implicated in this immunologic toxicity [12]. We excluded patients treated with natalizumab as this drug is associated with progressive multifocal leukoencephalopathy and is not approved for IBD in the European Union [13].

Most of the patients were treated with a combination of an anti-TNF and vedolizumab (15 out of the 18 patients), while 3 patients were treated with

vedolizumab and ustekinumab. In literature the data about a dual biological therapy with an anti-TNF and ustekinumab report the efficacy only regarding dermatological associated diseases and about safety (good), but not about the efficacy on an active IBD [14].

Regarding the epidemiological characteristics of the patients treated so far, sex and category of IBD are almost equally distribute (56% of female, 56% of CD).

Despite the dual biological therapy, 50% of patients were treated also with an immunosuppressant drug or steroid, because of the extreme difficult-to-treat diseases: the addition of a second biological drugs, an off-label strategy, seemed to be the only therapeutic chance for these patients. For example, in patients with numerous previous surgical interventions, at risk for short bowel syndrome, dual biological therapy could be considered as a surgery-sparing strategy.

Considering the type of patients treated, often with a history of non-response or loss of response to all currently available drugs, a 100% rate of clinical improvement and a 93% rate of endoscopic improvement are more than flattering rates.

The patients in our systematic review have been treated with dual biological therapy for almost 14 months, without an excess risk of serious adverse events (3 cases of upper respiratory tract infections, 1 case of dyspnea, 1 case of rotavirus infection, 1 case of recurrent *Clostridium difficile* infection, 1 case of self-limited viral illnesses). The possibility of achieving clinical benefit outweighed potential adverse effects of dual biological therapy, especially with the favorable safety profiles of vedolizumab and ustekinumab. However, to confirm the data about the safety, further studies with larger sample sizes are warranted.

A gut-specific anti-integrin therapy like vedolizumab has the benefit of being potentially safer than systemic therapies and could be the ideal drugs to be associated with other target therapies. Given its mechanism of action, it seems

reasonable to postulate that vedolizumab could be safely combined with other biological agents, without substantially increasing the risk of serious infections.

In addition to outcomes consideration, economic cost will likely play an increasing role in the real-world application of this therapeutic strategy. Although dual biological agents are more expensive than immunomodulator combinations, we must consider that the failure of sustained clinical remission during medical therapy implies an increased risk of surgery, hospitalization, colorectal cancer, work disability, and reduced quality of life [15]. Furthermore, the possible savings associated with of biosimilars may offset the cost.

In this light, a short coinduction with dual biologic agents and then transitioning to monotherapy could be the more suitable strategy. The onset of vedolizumab activity typically occurs more slowly than the activity of Anti-TNF, even several months after the induction of the therapy [16]. Consequently, in patients with only a partial improvement to Anti-TNF, a combination of Anti-TNF and vedolizumab may act as a bridge until the expected vedolizumab effect occurs, thereby avoiding the use of additional corticosteroids, which is associated with serious and sometimes irreversible side effects [17]. This is supported by the findings of Buer et al. [7]: 3 out of 10 patients received corticosteroids at some point during the combination treatment. According to clinical experience, more frequent use of long-term corticosteroids might be necessary without the combination of anti-TNF and vedolizumab. Furthermore, all of the UC patients could successfully stop anti-TNF therapy and continue with vedolizumab in monotherapy, whereas 2 out of the 4 CD patients were still on combination treatment at the end of the follow-up [7]. This finding suggests that CD patients could more often require the synergistic effect of combination therapy. Thus, combination treatment with anti-TNF and vedolizumab could represent a long-term option in selected CD patients.

Only a small number of patients were treated with a dual biological therapy: this is the major limitation of our systematic review, but these data are of paramount importance for a topic of potentially increasing interest in the coming years. The definition of clinical improvement is a weak outcome, but the extreme difficult-to-treat population and the correlation with a rate of 93% of endoscopic improvement give strength to these efficacy data. Given the small sample size sub-analyses about the specific biologic in use are not feasible. Despite the short-term safety seems promising, data deriving from a long-term follow-up, even after the dual biological therapy stopping, are needed. We didn't consider in our pool analysis the adverse events occurred after discontinuing one of the two biologics, i.e., on biologic monotherapy. In particular, Anti-TNF is an effective treatment for extraintestinal manifestations associated with IBD, including musculoskeletal and cutaneous manifestations [18]. It is therefore reasonable to assume that flare of extraintestinal manifestations might occur in patients who discontinue Anti-TNF therapy, and it could be an argument for long-lasting combination treatment in selected patients.

Increasing attention to the use of combination biological agents and the possible incorporation of future small molecule therapies hold great promise in closing the remaining therapeutic gap that exists in IBD. Furthermore, an efficacious combination of biological therapies would not only provide a significant therapeutic advance but would also offer further insights into the underlying pathogenesis of IBD.

5 Conclusions:

In conclusion, the use of dual biological therapy in IBD is an attractive therapeutic option: with different target-specific biologics now available and improved immunological understanding of IBD, there may be an opportunity to better tailor and personalize our therapies for patients.

Further studies in IBD should be developed, as randomized control trials, to provide comparative efficacy and safety endpoints of combination therapies, and to clarify potential advantages of combined biological therapies. Since the potentially dire consequences of untreated severe disease, patients at high risk for progression or affected by severe disease would likely benefit most from this early aggressive approach and would be an ideal initial study population.

Conflicts of Interest Statement

None to declare.

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Table 1. Studies about dual biological therapy in inflammatory bowel disease (IBD)

Author	Year	Type of study	Disease	Indication	Drugs	Immunomodulator or prednisone	Clinical improvement	Endoscopic improvement	Months of dual therapy	Side effects
Afzali et al. [4]	2016	Case report	CD	Active IBD	Ada-Ved	Yes	Yes	Yes	6	No
Fischer et al. [5]	2017	Case report	UC	Active IBD and spondyloarthritis	Cer-Ved	No	Yes	Yes	21	No
Roblin et al. [6]	2018	Case report	UC	IBD and active ankylosing spondylitis	Gol-Ved	No	Yes	Yes	12	No
Buer et		Case	6 UC	Active IBD	9 Ixx-Ved	5 Yes	Yes	9 Yes	>6	3 U.A.I.

al. [7]	series	4 CD		1 Ada-Ved	5 No		1 No		1 Dysp.
Huff- Hardy et al. [9]	Case report	CD	Active luminal and vulvar IBD	Ved-Ust	Yes	Yes	Yes	12	Rot.
Liu et al. [10]	Case report	CD	Active luminal and perianal	Ved-Ust	Yes	Yes	Yes	6	No
Mao et al. [8]	Case series	CD	Active IBD	1 Ved-Ust 2 Gol-Ved	1 No 2 Yes	Yes	N/A	5-37	1 CDI 1 SLVI

CD = Crohn's disease; Ada = adalimumab; Ved = vedolizumab; Cer = certolizumab; Gol = golimumab; lfx = infliximab; U.A.I. = upper airway infection; Dysp. = dyspnea; Ust. = Ustekinumab; Rot. = rotavirus infection; CDI = *Clostridium difficile* infection; N/A = not available; SLVI = self-limited viral illnesses

Table 2. Clinical characteristics of all patients treated with dual biological therapy

Sex	Disease	Drugs
(n; %)	(n; %)	(n; %)
		Ada-Ved: 2; 11.1
M: 8; 44	CD: 10; 56	Cer-Ved: 1; 5.6
F: 10; 56	UC: 8; 44	Gol-Ved: 3; 16.7
		Ifx-Ved: 9; 50
		Ved-Ust: 3; 16.7

M = male; F = female; CD = Crohn's disease;

UC = ulcerative colitis; Ada = adalimumab;

Ved = vedolizumab; Cer = certolizumab;

Gol = golimumab; Ifx = infliximab;

Ust. = Ustekinumab

Figure 1. Flow diagram of the study

Figure 2. Co-treatment with immunosuppressant drugs or steroids

Figure 3. Endoscopic improvement

Figure 4. Rate of side effects