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WORD COUNT	4116	TIME SUBMITTED	23-MAR-2023 11:49AM
		PAPER ID	97911936

Emerging role of dual biologic therapy for the treatment of inflammatory bowel disease

INTRODUCTION

Inflammatory bowel disease (IBD) comprises Crohn's disease (CD) and ulcerative colitis (UC) and is typically characterised by chronic inflammation of the gastrointestinal tract with a relapsing and remitting disease course that can lead to significant complications and morbidity[1]. Disease burden for many patients remains onerous and although some patients can achieve remission through corticosteroids or aminosalicylates, effective maintenance therapy is key to successful outcomes and reduction in life-long complications such as strictures, fistulas, abscess or surgical resection[2]. Whilst there is well established experience and national guidance for varying maintenance therapies, the use of dual biological maintenance therapy in difficult to treat and refractory disease is still a novel area with little research or published data.

The British Society of Gastroenterology consensus guidelines on the management of IBD in adults (2019)[3] provides guidance on single-agent biologic therapy in CD and UC, sequential therapy in UC following treatment failure, and combined biologic and small molecule therapies in CD. However, combinations of biologics have yet to be included in this emerging area.

In recent years, advancements in the medical management of IBD have been seen and aided by novel small molecule and biologic drugs, but observed clinical response still remains limited and sub-optimal. Treatment strategies for IBD are therefore rapidly changing to help combat ongoing disease burden and morbidity. At present, clinician experience has guided potential novel therapy combinations with most data outlined in case reports and case series in the absence of large-scale studies[4]. Dual biologic therapy (DBT) presents an attractive and potentially safe option for those who have failed

previous biologic therapies and have refractory disease. We therefore aim to outline, summarise and review the current available literature on the use of dual biological therapy for IBD, and establish whether such treatment could be beneficial in severe and/or refractory cases.

COMBINATION THERAPY

Biologic agents are commonly used as monotherapy for IBD, however only 40% of patients achieve remission within one year of therapy[5]. Consequently, the use of monoclonal antibodies which target tumour necrosis factor, TNF (infliximab, adalimumab, etanercept, and golimumab) in combination with newer agents which target interleukin (IL)-12 and IL-23 (ustekinumab, UST), a4b7-integrin (vedolizumab, VDZ) or a4-integrin (natalizumab), has become an increasing area of interest in patients with high disease burden. Patients often selected for DBT either present with refractory IBD and/or poorly controlled extra-intestinal symptoms[6].

VDZ, an anti-integrin, is a popular choice of biologic used in combination, often with anti-TNF treatment. It binds to a4b7, where T lymphocytes require a4b7 bound to mucosal addressin cell adhesion molecule 1 (MAdCAM-1) in order to migrate within the gastrointestinal tract. Inhibition therefore reduces inflammation by preventing T cells migrating to the gut mucosa[7,8]. IL-12/23 stimulates production of Interferon-g and TNF. UST has also been used in a number of cases[9-11], which inhibits IL-12 and IL-23 by binding to the p40 subunit (high levels of which are expressed in IBD), therefore preventing them from binding to receptors on T cells and natural killer (NK) cells[12].

Whilst combination therapy with a biologic and immunomodulator has previously been well studied; such as in the 2010 Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease (SONIC) trial[13]; there has been relatively little research in this area for the use of DBT in IBD. It should be noted however, that the first reports indicating safety of DBT emerged as early as 2007[14].

There have been several reports, including the aforementioned 2007 randomised controlled trial by Sands *et al*[14], retrospective studies, case studies (which make up the

majority of the reports available), and systematic reviews, which concur that dual therapy may be a safe option for treating severe IBD and extra-intestinal symptoms[4]. These are summarised in Table 1.

RANDOMISED CONTROLLED TRIAL

In 2007, Sands *et al*[14] studied the use of infliximab (IFX) in combination with natalizumab for treatment of CD in a randomised control trial, where efficacy and safety of this combination had not been previously reported. Seventy-nine patients were identified with a CD activity index (CDAI) score of 150 or more whilst on IFX; 52 of these were treated with both IFX and natalizumab, whilst 27 remained in the control group and received IFX plus a placebo. Those who received combination treatment showed an improvement in disease compared to the control; mean CDAI score was noted to be lower in those who received both IFX and natalizumab, compared to IFX alone.

Overall, combination therapy was deemed to be well tolerated and whilst both groups experienced adverse effects including infection, rates were similar in both groups. Other effects reported were headache, nausea and exacerbation of CD. The data suggested that treating patients with combination therapy had a greater efficacy than IFX monotherapy. Additionally, more patients developed antibodies to IFX compared to natalizumab (4% and 14%, respectively), and 5% developed hypersensitivity reactions to IFX but this was not seen in any patients secondary to natalizumab.

More recently, the VEGA study[15] assessed the use of guselkumab (an IL23 subunit antagonist) in combination with golimumab for the treatment of moderate to severe UC. Of the 214 patients in the trial, those treated with combination therapy achieved a greater response (36.6% remission) compared to patients on monotherapy of guselkumab or golimumab (21.1% and 22.2% remission, respectively). Adverse events were deemed comparable between the groups, with one case developing severe influenza and sepsis.

CASE REPORTS

In 2016, Anita and Michael[16] reported a case of CD in a 23-year-old woman with enterocolitis, who had disease recurrence following multiple immunomodulators in combination with IFX, the latter of which led to an infusion reaction. The patient was initially switched to adalimumab (ADA) with 6-mercaptopurine (6MP) in 2006 with an initial response, however had relapsed within six years. Certolizumab pegol was ineffective, and moderate colitis was noted on colonoscopy. Subsequently, she was commenced on VDZ, 6MP and prednisolone. The patient continued to be symptomatic and was unable to reduce the steroid dose, and was therefore started on ADA in combination with VDZ. The patient showed improvement symptomatically, biochemically and endoscopically after 3 mo. Steroids and 6MP were discontinued. VDZ was stopped after 6 mo, and she continued ADA alone, with no further symptoms and normal inflammatory markers noted.

Much like in 2016, anti-TNF has been used in combination with VDZ in additional case reports. A study in Germany reported successful therapy of severe chronic refractory pouchitis, and spondyloarthritis (SpA)[17]. Interestingly, VDZ monotherapy led to intestinal symptoms improving, however SpA worsened. The addition of etanercept (ETN) led to resolution of the SpA symptoms. Whilst arthralgia has been reported as a common side effect of VDZ[18], Bethge *et al*[17] concluded that as there was no statistical significance in the test group *vs* the placebo group and suggest that VDZ may not provide benefits to IBD related arthralgia, rather than causing the symptoms.

Additional reports from France[19], Norway[11,20] and the United States[21] have reported that dual therapy was safe and generally well tolerated, with clinical and endoscopic remission in both CD and UC.

Roblin and colleagues reported a case of severe UC with ankylosing spondylitis (AS) who initially received IFX and methotrexate, then ADA and methotrexate, followed by VDZ for treatment of recurrence. Despite this, the patient developed recurrence of AS symptoms and raised inflammatory markers but after one year of combined treatment

with golimumab (GOL) and VDZ, the patient was in remission both clinically and endoscopically[19].

In Norway, ten IBD patients were given DBT; nine received IFX and VDZ and one received ADA and VDZ. Eight patients were able to stop IFX; after follow-up, all were in clinical remission, whilst six were in biochemical remission and five were in endoscopic remission[20]. A later study in Norway, which looked at IBD in children found that combination therapy was well tolerated. Of the eight patients who received IFX and VDZ, four achieved clinical remission, whilst the remaining four required surgery. They noted that VDZ therapy alone led to a flare up of IBD in two of their patients. Additionally, UST alone was useful in treating skin lesions, such as psoriasis, but similarly to VDZ, monotherapy did not alleviate IBD symptoms, highlighting that combination therapy was more beneficial[11].

Mao *et al*[21] reported four cases of CD treated with DBT; one patient remained symptomatic due to CD; he was initially treated with ADA, but later developed antibodies, and was subsequently switched to VDZ with azathioprine. Endoscopically, the patient demonstrated ongoing terminal ileitis, and later developed worsening AS symptoms. He was subsequently commenced on ETN, as his AS had previously responded to anti-TNF. VDZ was switched to UST and joint pain remained controlled. The remaining three cases achieved remission of CD following treatment with VDZ and UST, VDZ, and GOL and VDZ, GOL and 6MP, respectively. All four patients tolerated dual therapy, further supporting the use of VDZ in DBT[21].

UST has also been reported in studies from 2017; Liu and Loomes[9] reported a case of severe CD and iron deficiency anaemia on UST alongside azathioprine, allopurinol, mesalazine (oral and per rectal suppository) and budesonide. Symptoms continued, faecal calprotectin (FCP) remained elevated, and magnetic resonance imaging demonstrated ongoing inflammation. Consequently, VDZ was added, with subsequent mucosal healing, reduced FCP and symptom control[9].

UST was used by a team in the United States, also for refractory CD, associated with strictures (requiring end ileostomy) and vulvo-perianal disease where UST alone was

not effective. The addition of VDZ and methotrexate starting post-proctectomy and perianal reconstruction, achieved remission endoscopically, radiologically and biochemically[10].

RETROSPECTIVE STUDIES

In 2020, Glassner *et al*[22] published a retrospective study looking at combination biologic or small molecule therapy in IBD. The study included fifty patients who had failed to respond to biologic monotherapy. Fifty percent were found to be in clinical remission, and 36% in endoscopic remission, and inflammatory markers were also found to have improved[22].

A later retrospective study including twenty-four trials of DBT in twenty-two patients, found endoscopic improvement on 43% of trials and 26% endoscopic remission (assessed *via* Simplified Endoscopic Score). Clinically; 50% had clinical response and 41% were in clinical remission (CD patient-reported outcome 2 score; PRO-2). Additionally, perianal fistulas reduced from 50% to 33%. Various biologics were used, however VDZ plus UST was found to have a higher rate of endoscopic improvement; endoscopic remission and adverse event rates were similar to other combinations of DBT[23].

An Italian study, also from 2020[24], included sixteen patients with IBD, of which, fourteen had IBD with concurrent extra-intestinal manifestations. Seven of these started dual therapy due to intestinal symptoms, whilst nine received treatment for extra-intestinal symptoms, such as psoriasis or arthritis. The patients were treated with VDZ plus anti-TNF or UST. Eight patients were receiving corticosteroids and six of these were able to withdraw them following DBT. One patient had reactivation of pouchitis, which improved with VDZ. Reactivation was thought to be due to secukinumab induction, which inhibits IL-17; as this has been reported to be associated with developing IBD or relapse and is generally advised to be used with caution in those with IBD[25].

Further data from the United States similarly demonstrates improvement in IBD with DBT; fifteen patients were treated with a combination of biologics (anti-TNF and VDZ, n = 8; anti-TNF and UST, n = 2; UST and VDZ, n = 5). Eleven patients reported improvement in symptoms, ten were able to reduce their use of corticosteroids and four demonstrated endoscopic or radiological improvement. However, three of the fifteen patients needed further surgery[26].

A 2021 European retrospective study identified 104 combinations in 98 patients; combination therapy was used for active IBD in 67% of cases, and 27% of cases were for extra-intestinal manifestations (EIM) or active immune mediated inflammatory disease (IMIM) (AS, psoriasis, rheumatoid arthritis and psoriatic arthritis). In 70% of patients, disease activity clinically improved, whilst EIM/IMIM activity improved in 81%. Worsening of symptoms was seen in 16 combinations (13 for IMID, 3 for EIM)[27].

SYSTEMATIC REVIEWS

A 2019 systematic review with pool analysis aimed to assess the effectiveness and safety of DBT with anti-TNF, VDZ or UST. Seven studies were included, comprising of a total of eighteen patients (fifteen were treated with anti-TNF plus VDZ, whilst the remaining three were treated with VDZ and UST). Overall, all patients were found to have clinical improvement, whilst 93% of patients showed endoscopic improvement, and no serious adverse events were noted[28].

Ahmed *et al*[29] published a later systematic review with meta-analysis which identified 30 studies with 288 trials of dual biologic or small molecule therapy in 279 patients; 48% were treated with anti-TNF plus VDZ, 19% were treated with UST and VDZ and 7% were treated with anti-TNF plus UST. Pooled rate of clinical remission was 59%, whilst endoscopic remission was 34%, with 12% needing surgical intervention. Overall, combination therapy showed better response in patients with extra-intestinal manifestations compared to those with refractory IBD alone.

The most recent available systematic review with meta-analysis (2022) also suggested that DBT and small molecule combined with biologic therapy (SBT) was a safe and

effective therapeutic option with the caveat that evidence is still limited[30]. 13 studies were included, comprising a total of 273 patients undergoing 279 trials; seven patients (eight trials) were excluded due to being on biologics/small molecule therapy that was not approved by the FDA. Patients on VDZ and anti-TNF achieved 77.9% clinical response and 55.1% clinical remission. Those on VDZ plus tofacitinib (a Janus kinase, JAK inhibitor) showed clinical response of 59.9% and clinical remission of 47.8%. Patients administered VDZ plus UST had a pooled clinical response of 83.9% and remission 47.0%.

ADVERSE EFFECTS

Wheat *et al*[31] concluded in their meta-analysis that therapies used in the treatment for IBD were not linked to increased risk of serious infection. Furthermore, no specific treatment combination demonstrated a higher risk of serious infection compared to others. However, due to the small number of studies included for specific therapies, confidence intervals were subsequently wide, and therefore a significant increase cannot be excluded. Patients on a combination of biologics and immunomodulators did not show an increased risk compared to those on biologic monotherapy.

A systematic review by Bonovas *et al*[32] found that the use of biologics increased the risk of infection (odds ratio, OR 1.19), and these drugs also posed a significant increase in the risk of opportunistic infections (OR 1.90). Similar to Wheat *et al*[31], risk of serious infection was not found to be higher in patients on biologics (OR 0.89), and in fact showed to reduce this risk. Furthermore, they found that biologics did not increase the risk of malignancy, however data on this area remains insufficient.

In 2019, Borren *et al*[33] also carried out a systematic review with meta-analysis to establish the safety of biologic therapy in older patients. Fourteen studies identified that older patients were at higher risk of malignancy (OR 3.07) compared to younger patients, and infection (OR 3.60) compared to those who did not use biologics. Interestingly, comparison of older patients who used biologics to older patients not on biologics did not show higher odds of malignancy (OR 0.54). It concluded that older age

is a recognized risk factor for malignancy, however biologics themselves do not appear to be linked to a higher risk of cancer.

Nevertheless, it is important to note that these analyses were based on studies on patients on either biologic monotherapy, or a combination of biologics with immunomodulators. Data on infection risk and long-term effects in DBT remains limited and therefore it is difficult to ascertain whether these risks apply to patients on DBT.

From review of the literature, whilst adverse events include arthralgia, IBD flare up and skin lesions (including eczema and psoriasis), infections appear to be the most common issue reported, which are summarised in Table 2.

DISCUSSION

Although Sands *et al*[14] established that natalizumab was able to lead to improvement in disease burden in patients with CD, clinicians have subsequently opted for alternative biologics with a safer profile. Natalizumab binds to the a4 subunit of integrin to prevent interaction with MAdCAM-1. Similar to the more specific VDZ, natalizumab prevents migration of lymphocytes into the mucosa, thus reducing T cell mediated inflammation[34]. Whilst this has been approved in the United States for CD, its associated risk with developing progressive leukoencephalopathy due to the John Cunningham virus has led to a lack of widespread use[35].

VDZ was a prevalent choice in many of the cases examined, however it was noted that in some patients, it did not control extra-intestinal manifestations when used alone. For example, patients reported arthralgia[17,20], and in some cases they developed severe and disabling symptoms of concurrent arthropathy, which subsequently improved on administering an anti-TNF agent[19,21]. In a paediatric study, lack of IFX led to a flare of IBD in one patient, another also experienced an IBD flare and rheumatoid arthritis, whilst one developed a perianal fistula[11]. As a result, it has been suggested that the use of DBT may be helpful as a form of bridging therapy until a patient is in remission[24]. Furthermore, the use of VDZ or UST is an attractive possibility due to their favourable

safety profile[23] combining biologics with different mechanisms of action may be safer and more effective. Although current data is encouraging in terms of the use of DBT, it is still unclear which combination works best; many favour the use of anti-TNF plus VDZ or UST but anti-TNF is not always an option, especially for patients in which this is contra-indicated or not tolerated[36].

In addition to DBT, other agents such as JAK inhibitors are also increasing in use. JAK inhibitors are a class of small molecule drugs which have proven useful in the treatment of a range of inflammatory conditions such as rheumatoid arthritis, psoriasis, dermatitis, and IBD. Le Berre *et al*[36] published the first case report involving a JAK inhibitor; a 67-year-old woman with UC, associated with HLA B27 positive SpA. The patient developed multiple mononeuropathies secondary to IFX, which then resolved on discontinuation. As a result, further anti-TNF therapy was deemed a contraindication in this patient. She was subsequently treated with VDZ and methotrexate but went on to develop arthralgia and flare up of her IBD. Methotrexate was replaced with tofacitinib, with clinical remission of symptoms within three months.

Tofacitinib has been approved for use in moderate to severe UC, where treatment with anti-TNF has failed. Unlike biologics, which are given intravenously and can have a slow onset of action, JAK inhibitors can be administered orally, with a rapid onset of action, short half-life and does not trigger an immune response[37]. Whilst other studies have found that the use of anti-TNF may help with extra-intestinal manifestations, this study also highlights an alternative option for managing these symptoms.

JAK inhibitors should, however, be used with caution, as they have been associated with an increased risk of developing Herpes zoster infection, thus highlighting the need to consider vaccination in high-risk patients[38]. Additionally, JAK inhibitors are thought to also increase the risk of cardiac event, malignancy, venous thromboembolism and gastrointestinal perforation[37,39]. Although, these events occur in higher numbers in patients who are at higher risk (for example, active UC is deemed a hypercoagulable state), suggesting that there is no significant difference in the risks due to JAK inhibitors compared to biologics[40].

From the data that is currently available, DBT in IBD may be a suitable option for managing severe refractory cases with or without extra-intestinal symptoms. Whilst rates of remission may vary, it is important to note that the population included in these studies are already high risk and difficult to treat. As a result, worsening of symptoms and/or requiring surgical intervention should come as no surprise, particularly in those with strictures or perianal disease. These cases could instead, be deemed as a failure to respond to medical therapy, rather than a true complication of combined biologic therapy[27].

In terms of adverse events, Goessens *et al*[27] reported that 42% of patients experienced 42 significant adverse events in total, particularly infections. Furthermore, Alayo *et al*[30] reported that the most common adverse event from their systematic review and meta-analysis was increased infection, making up approximately 75% of all events. This risk may be reduced by considering discontinuation of immunomodulators prior to starting DBT[22]. Interestingly, the use of biologics has been shown to increase the risk of opportunistic infections but reduce the risk of serious infections in some meta-analyses[31,32]. Although increased infections have been noted in many of the cases reported so far, it is important to consider whether this was somewhat inevitable due to being on a biological agent, or, if these are a direct consequence of being on dual therapy. The former hypothesis is supported by the VEGA study, which found comparable rates on infection in patients on dual therapy and monotherapy with biologics. More importantly, when considering long term effects of these agents, they did not report any cases of malignancy, tuberculosis or deaths[15].

Additionally, a prospective observational study by CLARITY IBD found that patients on infliximab treatment were more prone to breakthrough infection due to SARS-CoV-2 (despite three doses of appropriate vaccination) compared to those on vedolizumab, highlighting the importance of booster doses[41].

At present, one of the main limitations when evaluating the safety and efficacy of the use of DBT is the lack of further randomised controlled trials. Thus, short- and long-term safety profiles of biologic combinations in IBD is yet to be investigated in detail.

Randomised controlled trials in other inflammatory conditions highlight some serious adverse effects, particularly in patients being treated with anti-TNF[5]. To combat this, IBD has gut specific options available in the form of VDZ and UST, and the combination of these two agents has shown some encouraging results[9,10].

As DBT does not demonstrate 100% efficacy and potentially increases the risk of some adverse events, it is important to explain both risks and intended benefits of treatment to patients using joint decision-making processes and discuss cases using a multi-disciplinary team approach[42].

CONCLUSION

The increasing use of dual biologics, alongside small molecule therapies, particularly in earlier disease, may help to improve cost effectiveness and reduce morbidity experienced by patients with IBD. However, further dedicated research is still needed in this area particularly looking into efficacy and short- and long-term safety profiles of DBT, but reported data, albeit small in number, remains promising at this stage.

Table 1 Summary of trials, case reports and retrospective studies on dual biological therapy for inflammatory bowel disease

Ref.	Study type	No. of patients	Disease	Treatment used
Sands *et al*[14], 2007	RCT	79	CD	IFX + natalizumab
Anita and Michael[16], 2016	CR	1	CD	VDZ + ADA
Bethge *et al*[17], 2017	CR	1	UC	VDZ + ETN
Liu and Loomes[9],	CR	1	CD	UST + VDZ

2017				
Huff-Hardy *et al*[10], 2017	CR	1	CD	UST + VDZ
Roblin *et al*[19], 2018	CR	1	UC	GOL + VDZ
Buer *et al*[20], 2018	CS	10	4 × CD, 6 × UC	Anti-TNF + VDZ
Mao *et al*[21], 2018	CS	4	CD	VDZ + UST/GOL
Olbjørn *et al*[11], 2020	CS	13	9 × CD, 4 × UC	IFX + UST/VDZ
Glassner *et al*[22], 2020	Retrospective	50	CD + UC	UST + ANTI-TNF/VDZ, tofacitinib + VDZ/UST/anti-TNF, Cyclosporin, rituximab, SEC, leflunomide, tacrolimus
Yang *et al*[23], 2020	Retrospective	22	CD	VDZ + UST/anti-TNF, UST + anti-TNF
Privitera *et al*[24], 2020	Retrospective	16	11 × CD, 5 × UC	UST + CZP/IFX/ADA/VDZ, VDZ + ADA/SEC/IFX/CZP/aprelimast
Kwapisz *et al*[26], 2021	Retrospective	15	14 × CD, 1 × UC	VDZ + anti-TNF/UST, UST + anti-TNF/VDZ
Goessens *et al*[27], 2021	Retrospective	98	58 × CD, 40 × UC	ADA + VDZ/UST, VDZ + INF + azathioprine, VDZ + UST + azathioprine, UST + ETN, IFX + VDZ + methotrexate, CZP + VDZ + methotrexate

No author listed[15], 2022	RCT	214	UC	GOL + guselkumab	

ADA: Adalimumab; CD: Crohn's disease; CR: Case report; CS: Case series; CZP: Certolizumab; ETN: Etanercept; GOL: Golimumab; IBD: Inflammatory bowel disease; IFX: Infliximab; RCT: Randomised controlled trial; SEC: Secukinumab; TNF: Tumour necrosis factor; UC: Ulcerative colitis; UST: Ustekinumab; VDZ: Vedolizumab.

Table 2 Summary of infections reported in randomised controlled trial and case studies of patients on dual biologic therapy for inflammatory bowel disease

Ref.	Infections documented
Sands *et al*[14], 2007	Nasopharyngitis
Buer *et al*[20], 2018	Tonsillitis × 2
	Sinusitis × 1
Olbjørn *et al*[11], 2020	Skin infection
Mao *et al*[21], 2018	Clostridium difficile × 2
	Hand, foot and mouth disease
	Influenza
Yang *et al*[23], 2020	Pneumonia
	Clostridium difficile
	Actinetobacter bacteraemia
Privitera *et al*[24], 2020	Perianal abscess
Kwapisz *et al*[26], 2021	Salmonella
	Clostridium difficile
	4 × patients needing antibiotics
Goessens *et al*[27], 2021	Osteomyelitis
	Enterocutaneous fistula infection
	Perianal abscess
	Viral URTI
	Campylobacter
	Pneumonia
	Herpetic meningoencephalitis
	Oesophageal candidiasis
	Influenza

URTI: Upper respiratory tract infections.

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