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ORIGINAL ARTICLE

Efficacy and Safety of Dual Targeted Therapy for Partially or Non-responsive Inflammatory Bowel Disease: A Systematic Review of the Literature

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Abstract

Background Dual targeted therapy (DTT) has emerged as an attractive therapeutic option for select patients with active inflammatory bowel disease (IBD) who are unable to achieve remission with biologic or small molecule monotherapy. We conducted a systematic review of specific DTT combinations in patients with IBD.

Methods We conducted a systematic search of MEDLINE, EMBASE, Scopus, CINAHL Complete, Web of Science Core Collection, and Cochrane Library to identify articles related to the use of DTT for the treatment of Crohn Disease (CD) or ulcerative colitis (UC) published before February 2021.

Results Twenty-nine studies were identified comprising 288 patients started on DTT for partially or non-responsive IBD. We identified 14 studies with 113 patients receiving anti-tumor necrosis factor (TNF) and anti-integrin therapies (i.e., vedolizumab and natalizumab), 12 studies with 55 patients receiving vedolizumab and ustekinumab, nine studies with 68 patients receiving vedolizumab and tofacitinib, five studies with 24 patients receiving anti-TNF therapy and tofacitinib, six studies with 18 patients receiving anti-TNF therapy and ustekinumab, and three studies with 13 patients receiving ustekinumab and tofacitinib.

Conclusion DTT is a promising approach to improve IBD treatment for patients with incomplete responses to targeted monotherapy. Larger prospective clinical studies are needed to confirm these findings as is additional predictive modeling to identify the patient subgroups most likely to require and benefit from this approach.

Keywords Inflammatory bowel disease · Therapeutics · Combination therapy · Biologics

Abbreviations

CIs	Confidence intervals
COVID	Coronavirus
CD	Crohn's disease

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DTT	Dual targeted therapy
EIM	Extra-intestinal manifestations
IBD	Inflammatory bowel disease
IL	Interleukin
JAK	Janus kinase
NOS	Newcastle–Ottawa scale
RCTs	Randomized controlled trials
TNF	Tumor necrosis factor
UC	Ulcerative colitis

Introduction

Inflammatory bowel disease (IBD) is a chronic inflammatory condition associated with a high symptom burden, disabling complications, and frequent need for intestinal resection [1]. The older generation of therapies include non-specific broad immunosuppressive agents including corticosteroids, thiopurines, and methotrexate. More recent targeted therapies bind to specific inflammatory proteins (e.g., tumor necrosis factor (TNF) α and interleukin (IL)-23 or specific regulatory enzymes (e.g., Janus kinase (JAK) 1–3) and have increased efficacy in improving quality of life, reducing disease activity and progression, and reducing complications of IBD associated with significant morbidity [2]. Despite the development and use of targeted therapies, remission is only achieved in 50% of patients, highlighting the need for more effective therapeutics [3, 4].

Combination therapy consisting of a biologic and immunomodulator drug has helped to optimize biologic pharmacokinetics, minimize immunogenicity, and improve efficacy; however, incomplete treatment response remains commonplace, at the cost of adverse effects from broad immunosuppression [5].

In this context, there has been a growing interest in understanding whether dual targeted therapy (DTT), the combination of two or more targeted therapies, could be used to optimize treatment response. In the absence of head-to head randomized controlled trials (RCTs), we aim to compile published studies using DTT in patients with partially or non-responsive IBD in a systematic review. We aim to summarize the efficacy and safety of DTT in the treatment of partially or non-responsive IBD within the limitations of the published studies on the topic.

Methods

Study Selection and Eligibility

The goal of this review was to summarize the efficacy and safety of DTT for the treatment of IBD. Studies that reported on patients with IBD who received a combination of targeted therapies (including a biologic medication and/or targeted small molecule) for the treatment of partially or non-responsive luminal IBD were eligible for inclusion. These medications included any combination of adalimumab, certolizumab pegol, golimumab, infliximab, natalizumab, tofacitinib, ustekinumab, or vedolizumab. Randomized controlled trials (RCTs) as well as cohort studies, case series, and case reports were included. While there is a risk of bias by including studies with low quality methodology such case reports and case series, the decision was made to be "all inclusive" due to the current paucity of studies using a more rigorous methodology.

Search Strategy and Data Extraction

An experienced health sciences librarian (CS) conducted a systematic search of MEDLINE (PubMed), EMBASE (Embase.com), Scopus, CINAHL Complete (EBSCOhost), Web of Science Core Collection, and Cochrane Library to identify articles related to the use of DTT for the treatment of Crohn disease (CD) or ulcerative colitis (UC) (Supplemental Table 1). To reduce bias, no filters (including Publication Date or Language) were used and both published (i.e., peer reviewed papers) as well as unpublished (i.e., abstract of posters or oral presentations) studies were considered. ClinicalTrials.gov and the Cochrane Central Register of Controlled Trials were searched to identify ongoing trials. Findings are reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement, elaboration, and explanation and Statement for Reporting Literature Searches for Systematic Reviews [6–8]. All searches were completed by 02/04/2021.

Study Selection

Two members of the study team (EMB and JAB) independently assessed titles and abstracts for study eligibility and performed the data extraction. The full text was reviewed if study selection were discordant. Consensus on inclusion was reached by discussion between the two reviewers (EMB and JAB) with a third team member (CAS) available for adjudication of studies that could not be resolved to consensus. When possible, outcomes of interest (clinical improvement and adverse events) were considered on the patient-level rather than study level. In order to be included in our review, a study had to contain at least one patient meeting the following criteria: (1) DTT had to include medications with proven efficacy for IBD (e.g., patients on etanercept were excluded) and (2) DTT had to be initiated for an indication of active luminal IBD (e.g., patients started on DTT for an extra-intestinal manifestations (EIM) or pouchitis were excluded), which is why the numbers reported in our review may be fewer than those in the original published study. Studies involving natalizumab were included in systematic review as the authors felt that studies involving natalizumab

Table 1 Characteristics of the included studies with an anti-tumor necrosis factor combination

References	Year	*N*	Study type	Disease	Mean age (years)	Medications (*n*)	Median duration on DTT	Response	Definition of response	Adverse reaction (*n*)
Anti-TNF and anti-integrin therapy										
Sands et al. [12]	2007	52	Randomized control trial	CD (52)	40	Infliximab + Natalizumab (52)	10 weeks	24/52 entered clinical remission at some point	Clinical remission = CDAI score of less < 150	Nasopharyngitis (5/52), URI (3/52) Headache (12/52), Fatigue (7/52), Crohn's exacerbation (7/52), Dizziness (5/52), Nausea (5/52), DNA antibody positivity (4/52), Dyspepsia (4/52), Abdominal pain (3/52), Antinuclear antibody positivity (3/52), Arthralgias (3/52), Back pain (1/52), Insomnia (3/52), Pyrexia (3/52)
Hirten et al. [13]	2015	1	Case report	CD (1)	43	Vedolizumab + Infliximab (1)	3 weeks	1/1 clinical and endoscopic improvement	Clinical and endoscopic criteria not stated	0/1 experienced an adverse event
Afzali et.al. [14]	2016	1	Case report	CD (1)	23	Vedolizumab + Adalimumab (1)	6 months	1/1 clinical, endoscopic, and inflammatory marker improvement	Clinical, and endoscopic criteria not defined	0/1 experienced an adverse event
Fischer et al. [16]	2016	1	Case report	UC (1)	33	Vedolizumab + Certolizumab (1)	21 months	1/1 clinical, endoscopic, and histological improvement	Clinical and endoscopic criteria not stated. Histological Riley score used	0/1 experienced an adverse event
Buer et al. [19]	2018	9[a]	Prospective cohort	CD (4) UC (5)	36	Vedolizumab + Infliximab (8) Vedolizumab + Adalimumab (1)	6 months	9/9 clinical and endoscopic remission	Clinical remission was defined as Harvey–Bradshaw index (HBI) ≤ 4 or partial Mayo Score ≤ 1 Endoscopic remission defined as Mayo score ≤ 1 UC and absence of ulceration in CD	URI (3/9), Tendinitis (1/9), Dyspnea (1/9), Arthritis (2/9)
Mao et al. [17]	2018	3[b]	Case series	CD (3)	"Young"	Vedolizumab + Ustekinumab (1) Vedolizumab + Golimumab (2)	17 months	3/3 clinical remission	Clinical remission not defined	*Clostridridioides Difficile* (1/3) Hand-foot-mouth (1/3), Influenza (1/3)

Table 1 (continued)

References	Year	*N*	Study type	Disease	Mean age (years)	Medications (*n*)	Median duration on DTT	Response	Definition of response	Adverse reaction (*n*)
Roblin et al. [15]	2018	1	Case report	UC (1)	48	Vedolizumab + Golimumab (1)	12 months	1/1 clinical and endoscopic remission	Clinical and endoscopic remission, not defined	0/1 experienced an adverse event
Kwapisz et al. [21]	2021	8	Case series	CD (14) UC (1) (of total case series)	36 (of total case series)	Vedolizumab + Infliximab (2) Vedolizumab + Adalimumab (2) Vedolizumab + Golimumab (3) Vedolizumab + Certolizumab (1)	6 months (of total case series)	5/8 clinical response 7/8 reduction in steroids	Clinical response measured by CD-PRO/SS and partial Mayo Score	Hospitalizations (2/8) Infections (3/8)
Glassner et al. [25]	2020	7	Retrospective cohort	CD (5) UC (2)	37 (of total cohort)	Vedolizumab + Adalimumab (3) Vedolizumab + Certolizumab (2) Vedolizumab + Golimumab (2)	8 months (of total cohort)	Unable to differentiate specific combinations. See combination section for details	Clinical remission measured by Harvey-Bradshaw index or partial Mayo score Endoscopic remission defined by simple endoscopic score for Crohn's Disease 0–2, Rutgeerts i0-i1 and Mayo endoscopic score 0	Peristomal pyoderma gangrenosum with secondary cellulitis (1/7)
Goyal et al. [20]	2020	6	Case series	CD (5) UC (1)	15.1	Vedolizumab + adalimumab (5) Vedolizumab + Infliximab (1)	39.5 weeks	2/6 remission 1/6 partial remission	Not reported	Cellulitis (1/6)
Llano et al. [22]	2021	2	Case series	UC (1) IBD-U (1)	35	Vedolizumab + Adalimumab (2)	31 weeks (of all cases)	2/2 improvement in clinical score and inflammatory markers	HBI was used for CD and indeterminate colitis (IC), and the Lichtiger score was used for UC Mayo Endoscopic Score	0/2 experienced an adverse event
Olbjørn et al. [23]	2020	8	Case series	UC (4) CD (4)	16	Vedolizumab + Infliximab (8)	9.5 months	4/8 clinical remission 3/8 normalization of biomarkers	PUCAI and weight Pediatric Crohn's Disease Activity Index (wPCDAI) used for clinical remission. Criteria for clinical and biochemical remission not stated	Elevated transaminases (1/8) Eczema (1/8)
Privitera et al. [18]	2020	2	Case series	UC (1) CD (1)	44	Vedolizumab + Adalimumab (1) Vedolizumab + Infliximab (1)	15 months	2/2 clinical improvement 1/2 discontinuation of steroids 1/1 normalization of inflammatory makers	Harvey–Bradshaw Index and partial Mayo Score for Crohn's disease and ulcerative colitis, respectively	0/2 experienced an adverse event

Table 1 (continued)

References	Year	*N*	Study type	Disease	Mean age (years)	Medications (*n*)	Median duration on DTT	Response	Definition of response	Adverse reaction (*n*)
Yang et al. [24]	2020	13[c]	Retrospective cohort	CD (13)	35 (of entire Cohort)	Vedolizumab + Adalimumab (4) Vedolizumab + Certolizumab (2) Vedolizumab + Infliximab (6) Vedolizumab + Golimumab (1)	Unknown	3/12 endoscopic remission 1/12 endoscopic improvement 4/12 clinical remission 1/12 clinical response	Endoscopic improvement during defined as either > 50% reduction in Simplified Endoscopic Score-Crohn's disease (SES-CD) or explicitly stated on the endoscopy report by an inflammatory bowel disease specialist Endoscopic remission (SES-CD < 3 or clearly stated) Clinical response (Crohn's disease–patient-reported outcome-2 score [PRO-2] reduced by 8), clinical remission (PRO2 < 8)	2/13 experienced an adverse event (Specifics not stated)
Anti-TNF and tofacitinib combination therapy										
Berinstein et al. [37]	2020	1	Case report	CD (1)	50	Infliximab + Tofacitinib (1)	24 months	1/1 control of inflammation	Not Reported	Legionnaire's disease (1/1)
Gilmore et al. [36]	2020	5	Case series	UC (5)	27	Infliximab + Tofacitinib (5)	9 months	3/5 steroid-free remission + 1/5 clinical and biochemical response + 1/5 clinical repones	Total Mayo Score	Varicella zoster (1/5)
Glassner et al. [25]	2020	9	Retrospective cohort	CD (2) UC (7)	37 (of total cohort)	Tofacitinib + Infliximab (4) Tofacitinib + Golimumab (4) Tofacitinib + Certolizumab (1)	8 months (of total cohort)	Unable to differentiate specific combinations. See combination section for details	Clinical remission measured by Harvey-Bradshaw index or partial Mayo score Endoscopic remission defined by simple endoscopic score for Crohn's Disease 0–2, Rutgeerts i0-i1 and Mayo endoscopic score 0	0/9 experienced an adverse event
Khatiwada et al. [41]	2020	7	Retrospective cohort	UC (26) CD (16) (of total cohort)	32 (of total cohort)	Tofacitinib + Infliximab (6) Tofacitinib + Certolizumab (1)	5 months (of total cohort)	Unable to differentiate specific combinations. See combination section for details	Reduction in symptoms by physician global assessment	Unable to differentiate specific combinations. See combination section for details

Table 1 (continued)

References	Year	*N*	Study type	Disease	Mean age (years)	Medications (*n*)	Median duration on DTT	Response	Definition of response	Adverse reaction (*n*)
Anti-TNF and ustekinumab combination therapy										
Fumery et al. [39]	2020	5[d,e]	Case series	CD (4) UC (1)	38	Ustekinumab + Adalimumab (1) Ustekinumab + Infliximab (2) Ustekinumab + Golimumab (2)	9 months	4/5 Clinical remission 5/5 Biochemical remission 4/5 endoscopic remission + 1/5 endoscopic response	Not Reported	0/5 experienced an adverse event
Dimopoulos et al. [40]	2021	1	Case report	CD (1)	24	Ustekinumab + Adalimumab (1)	5 months	NR	Not Reported	Asymptomatic SARS-CoV-2 (1/1)
Kwapisz et al. [21]	2021	2	Case series	CD (14) UC (1) (of total case series)	36 (of total case series)	Ustekinumab + Adalimumab (1) Ustekinumab + Golimumab (1)	6 months	2/2 clinical response 2/2 reduction in steroids	Clinical response measured by CD-PRO/SS and Mayo Endoscopic Score	Infection (1/2)
Olbjørn et al. [23]	2020	5	Case series	CD (5)	15	Ustekinumab + Infliximab (5)	3.6 years	3/5 clinical remission	Not Reported	Skin infection (1/5) Otitis externa (1/5)
Privitera et al. [18]	2020	2	Case series	CD (2)	33	Ustekinumab + Certolizumab (1) Ustekinumab + Infliximab (1)	5 months	1/2 clinical remission 1/2 clinical improvement 2/2 biochemical improvement	Harvey–Bradshaw Index and partial Mayo Score for Crohn's disease and ulcerative colitis, respectively	Perianal abscess (1/2)
Yang et al. [24]	2020	3	Retrospective cohort	CD (3)	35 (of entire cohort)	Ustekinumab + Adalimumab (2) Ustekinumab + Infliximab (1)	Not Reported	1/3 clinical remission + 1/3 clinical response 1/3 endoscopic remission + 1/3 endoscopic improvement	Endoscopic improvement during defined as either > 50% reduction in Simplified Endoscopic Score-Crohn's disease (SES-CD) or explicitly stated on the endoscopy report by an inflammatory bowel disease specialist Endoscopic remission (SES-CD < 3 or clearly stated) Clinical response (Crohn's disease–patient-reported outcome-2 score [PRO-2] reduced by 8), clinical remission (PRO2 < 8)	0/3 experienced an adverse event

provides important insight into other DTT combinations containing other anti-integrin therapy (i.e., vedolizumab).

Risk of Bias Assessment

A risk of bias assessment was performed independently by multiple authors (EMB, JS, JJ, and JAB). The Cochrane Risk of Bias tool was used for the quality assessment of RCTs [9]. The Newcastle–Ottawa scale (NOS) scale was used to asses quality for cohort studies [10]. Validated modified NOS criteria was used for quality assessment of case reports and case series [10, 11].

Results

Study Selection and Inclusion

A total of 5153 unique studies were identified using our search strategy (Fig. 1). Of these, 35 full text articles were reviewed. Seven studies were excluded due to overlapping publication (e.g., if both a conference abstract as well as a full-length manuscript were found) or for not having a single patient meeting our inclusion criteria. One additional article was identified from references of full text resulting in inclusion of 29 studies and 288 patients in our systematic review. Table 1 provides characteristic of included studies containing an anti-TNF combination, Table 2 provides characteristic of included studies not containing non-anti-TNF combination, and Table 3 provides characteristics of included studies with multiple different combination therapies.

Anti-TNF and Anti-integrin Combination Therapy

Fourteen studies including a combined 113 patients were treated with a combination of anti- TNF and anti-integrin therapies for the treatment of partially or non-responsive IBD. One RCT treated 52 CD patients with a combination of infliximab and natalizumab and 13 studies totaling 61 individuals were treated with a combination of anti-TNF therapy and vedolizumab for partially or non-responsive IBD (Tables 1, 3). Sands et al., presents the only RCT evaluating the safety of DTT for IBD [12]. In this exploratory multicenter, double-blind, placebo-controlled trial, 52 patients with active CD on infliximab had natalizumab added for 10 weeks [12]. The authors found no difference in adverse events. Clinical remission was achieved by 46% of patients in the DTT group, as compared to 41% in the infliximab monotherapy group, though the study was not powered to evaluate efficacy.

In one of the first case reports examining DTT, Hirten et al., presented a case of a 43- year-old man with longstanding ileocolonic CD refractory to two prior biologics

Table 1 (continued)

N total study number, *DTT* dual targeted therapy, *n* number, *CD* Crohn's disease, *UC* ulcerative colitis, *URI* upper respiratory infection, *DNA* deoxyribonucleic acid, *NR* not reported, *PICC* peripherally inserted catheter, *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2, *PRO* patient-reported outcome, *SES-CD* simplified endoscopic score-Crohn's disease, *HBI* Harvey–Bradshaw index, *IBD-U* inflammatory bowel disease—unspecified; *PUCAI* pediatric ulcerative colitis activity index, *wPCDAI* weight pediatric Crohn's disease activity index

[a]One patient was excluded for having ulcerative colitis and receiving DTT for treatment of pouchitis

[b]One patient was excluded for being on a combination that included etanercept

[c]Endoscopic data were not available for one patient

[d]Two patients were excluded for being on a combination that included ocrelizumab and etanercept

[e]Indication for addition of ustekinumab was anti-TNF induced psoriasis

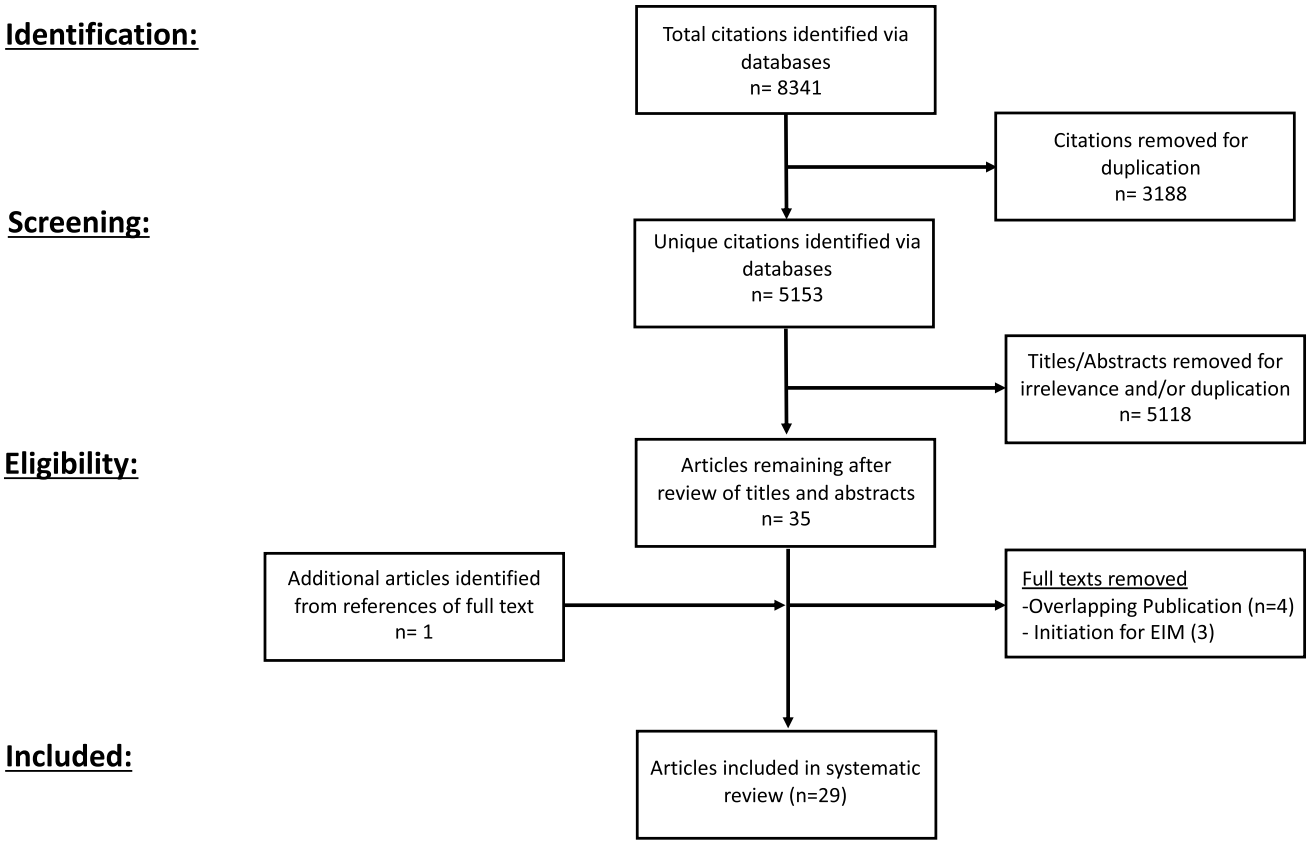

Fig. 1 Included and excluded studies

and immunosuppressive therapy. The patient lost response to infliximab 5 mg/kg administered every 8 weeks after 4 years and was switched to vedolizumab [13]. Unfortunately, he developed erythema nodosum (EN) after infliximab withdrawal which the authors suggested "highlighted the limitations of the gut specific therapy". With the re-initiation of infliximab and withdrawal of vedolizumab the patient's EN rapidly improved at the expense of his colonic disease worsening. While the patient was only on DTT for several weeks, the authors argued that their experience demonstrated the "superiority of combination therapy, with infliximab controlling the patient's systemic disease and vedolizumab allowing for further mucosal healing". Following Hirten et al.,'s experience, several small case reports and small cohort studies involving seven patients with refractory disease (three UC and four CD) demonstrated 100% clinical improvement with combination vedolizumab and anti-TNF therapy [14–18]. Adverse events reported in this group included one patient who developed both hand-foot-mouth disease (that resolved without treatment) and influenza despite having received an influenza vaccination [17].

Subsequently, larger cohort studies were reported [19–24]. Buer et al., performed a cohort study including the first ten patients started on combination treatment with anti-TNF therapy and vedolizumab from November 2015 to July 2016 at their center. At the end of follow-up, all patients were reported to be in clinical remission, six out of eight patients were in biochemical remission, and 5 patients were in endoscopic remission. Eight patients were able to discontinue anti-TNF treatment and receive vedolizumab monotherapy. Two of the patients with CD required combination treatment throughout follow-up to obtain sustained remission. In these 2 patients, treatment with anti-TNF was initially discontinued due to clinical and biochemical remission after 6 and 12 months respectively, however, anti-TNF was reintroduced due to recurrence of disease. Adverse events were mild and limited to URI in three patients, tendinitis in one patient, dyspnea in one patient, and arthritis in two patients [19]. Goyal et al., presented six patients who received vedolizumab in combination with adalimumab for a mean of nine months with a reported clinical response in 50% of individuals and one case of cellulitis [20]. Kwapisz et al., reported on eight patients that were treated with vedolizumab and an anti-TNF resulting in five patients experiencing a clinical response, seven patients able to reduce steroids, two requiring surgery, and three patients requiring hospitalization and antibiotics [21]. Llano et al., reported 100% clinical improvement in three patients treated with

Table 2 Characteristics of the included studies with non-anti-tumor necrosis factor combinations

References	Year	*N*	Study type	Disease	Mean age (years)	Medications (*n*)	Median duration on DTT	Response	Definition of response	Adverse reaction (*n*)
Vedolizumab and ustekinumab combination therapy										
Biscaglia et al. [30]	2020	2	Case report	CD (1) UC (1)	51	Vedolizumab + Ustekinumab (2)	22 months	1/1 CD patient (1): clinical remission 1/1 UC patient (1): clinical and endoscopic remission	HBI score and total Mayo score used for the CD and UC patient, respectively	0/2 experienced an adverse event
Elmoursi et al. [29]	2020	1	Case report	CD (1)	35	Vedolizumab + Ustekinumab (1)	8 months	1/1 clinical, endoscopic, and histological remission	Not reported	0/1 experienced an adverse event
Huff-Hardy et al. [27]	2017	1	Case report	CD (1)	22	Vedolizumab + Ustekinumab (1)	12 months	1/1 clinical, endoscopic, biochemical, and histological remission	Not reported	Rotavirus (1/1)
Liu et al. [28]	2017	1	Case report	CD (1)	27	Vedolizumab + Ustekinumab (1)	6 months	1/1 clinical, endoscopic, and biochemical improvement	Not reported	0/1 experienced an adverse event
Dolinger et al. [26]	2020	4	Case series	CD (3) UC (1)	< 18	Vedolizumab + Ustekinumab (4)	6 months	3/4 steroid-free remission	wPCDAI ≤ 12.5 for CD or partial Mayo Score < 2 for UC/IBD-U, and no form of corticosteroids for at least 4 weeks	0/4 experienced an adverse event
Glassner et al. [25]	2020	25	Retrospective cohort	CD (23) UC (1) IBD-U (1)	37 (of total cohort)	Vedolizumab + Ustekinumab (25)	8 months (of total cohort)	Unable to differentiate specific combinations. See combination section for details	Clinical remission measured by Harvey-Bradshaw index or partial Mayo score Endoscopic remission defined by simple endoscopic score for Crohn's Disease 0–2, Rutgeerts i0-i1 and Mayo endoscopic score 0	Bacterial enteric infection (1/25) Peripherally inserted central catheter infection (2/25) *Clostridridioides Difficile* with sigmoid perforation (1/25)
Goyal et al. [20]	2020	2	Case series	CD (2)	16	Vedolizumab + Ustekinumab (2)	51.5 weeks	1/2 remission + 1/2 partial response	Not Reported	Anastomotic bleeding (1/2)
Llano et al. [22]	2021	3	Case series	CD (2) UC (1)	29.3	Vedolizumab + Ustekinumab (3)	31 weeks (of all cases)	3/3 clinical remission and improvement in inflammatory markers	HBI was used for CD and indeterminate colitis (IC), and the Lichtiger score was used for UC Mayo Endoscopic Score	Rotavirus infection (1/3)

Table 2 (continued)

References	Year	*N*	Study type	Disease	Mean age (years)	Medications (*n*)	Median duration on DTT	Response	Definition of response	Adverse reaction (*n*)
Privitera et al. [18]	2020	2	Case series	CD (2)	33.3	Vedolizumab + Ustekinumab (2)	8.3 months	2/2 clinical improvement 1/2 normalization of inflammatory biomarkers 1/1 discontinuation of steroids	Harvey–Bradshaw Index and partial Mayo Score for Crohn's disease and ulcerative colitis, respectively	0/2 experienced an adverse event
Yang et al.' [24]	2020	8	Retrospective cohort	CD (8)	35 (of entire cohort)	Vedolizumab + Ustekinumab (8)	Not Reported	2/8 endoscopic remission 5/8 endoscopic improvement 4/7 clinical remission[a] 5/7 clinical response[a]	Endoscopic improvement during defined as either > 50% reduction in Simplified Endoscopic Score-Crohn's disease (SES-CD) or explicitly stated on the endoscopy report by an inflammatory bowel disease specialist Endoscopic remission (SES-CD < 3 or clearly stated) Clinical response (Crohn's disease–patient-reported outcome-2 score [PRO-2] reduced by 8), clinical remission (PRO2 < 8)	2/13 experienced an adverse event (Specifics not stated)
Kwapisz et al. [21]	2021	5	Case series	CD (14) UC (1) (of total case series)	36 (of total case series)	Vedolizumab + Ustekinumab (5)	6 months (of total case series)	4/5 clinical response 2/5 reduction in steroid	Clinical response measured by CD-PRO/SS and Mayo Endoscopic Score	Hospitalization (1/5)
Vedolizumab and tofacitinib combination therapy										
Kuehbacher et al. [34]	2019	3[b]	Case series	UC (3)	NR	Vedolizumab + Tofacitinib (3)	14 weeks	3/3 clinical, endoscopic, and biochemical response	PRO-2, and total Mayo Score used. CRP and fecal calprotectin were assessed at all visits. Sigmoidoscopy preformed at baseline and at week 14	0/3 experienced an adverse event
Le Berre et al. [31]	2019	1	Case report	UC (1)	67	Vedolizumab + Tofacitinib (1)	3 months	1/1 clinical remission	Clinical remission criteria not reported	0/1 experienced an adverse event

Table 2 (continued)

References	Year	*N*	Study type	Disease	Mean age (years)	Medications (*n*)	Median duration on DTT	Response	Definition of response	Adverse reaction (*n*)
Lee et al. [32]	2020	1	Case report	UC (1)	55	Vedolizumab + Tofacitinib (1)	6 months	1/1 clinical, endoscopic, and biochemical remission	Not Reported	0/1 experienced an adverse event
Scheinberg et al. [35]	2020	9	Retrospective cohort	CD (1) UC (8)	48	Vedolizumab + Tofacitinib (9)	6 months	5/9 clinical response 2/4 reduction in steroids	Not Reported	0/9 experienced an adverse event
Taberner Bonastre et al. [33]	2021	1	Case report	UC (1)	48	Vedolizumab + Tofacitinib (1)	3 months	1/1 clinical remission and biochemical improvement	Not Reported	0/1 experienced an adverse event
Dolinger et al. [26]	2020	9	Case series	CD (4) UC (4) IBD-U (1)	< 18	Vedolizumab + Tofacitinib (9)	6 months	7/9 steroid-free remission	wPCDAI ≤ 12.5 for CD or pMS < 2 for UC/IBD-U, and no form of corticosteroids for at least 4 weeks	1/9 septic arthritis 1/9 deep vein thrombosis
Glassner et al. [25]	2020	8	Retrospective cohort	UC (8)	37 (of total cohort)	Vedolizumab + Tofacitinib (8)	8 months (of total cohort)	Unable to differentiate specific combinations. See combination section for details	Clinical remission measured by Harvey-Bradshaw index or partial Mayo score Endoscopic remission defined by simple endoscopic score for Crohn's Disease 0–2, Rutgeerts i0-i1 and Mayo endoscopic score 0	0/8 experienced an adverse event
Khatiwada et al. [41]	2020	27	Retrospective cohort	UC (26) CD (16) (of total cohort)	32 (of total cohort)	Vedolizumab + Tofacitinib (27)	5 months (of total cohort)	Unable to differentiate specific combinations. See combination section for details	Reduction in symptoms by physician global assessment	Unable to differentiate specific combinations. See combination section for details
Llano et al. [22]	2021	9	Case series	UC (8) CD (1)	44	Vedolizumab + Tofacitinib (9)	31 weeks (of all cases)	5/6 clinical improvement 5/6 biochemical improvement 3/3 endoscopic improvement	Harvey–Bradshaw index (HBI) was used for CD and indeterminate colitis (IBD-U), and the Lichtiger score was used for UC Mayo Endoscopic Score	1/9 pneumonia

Table 2 (continued)

References	Year	*N*	Study type	Disease	Mean age (years)	Medications (*n*)	Median duration on DTT	Response	Definition of response	Adverse reaction (*n*)
Ustekinumab and tofacitinib combination therapy										
Dolinger et al. [26]	2020	3	Case series	UC (2)	< 18	Ustekinumab + Tofacitinib (3)	12 months	2/3 steroid-free remission	Weight Pediatric Crohn's Disease Activity Index) wPCDAI ≤ 12.5 for CD or Partial Mayo Score < 2 for UC/ IBD-U, and no form of corticosteroids for at least 4 weeks	0/3 experienced an adverse event

N total study number, *DTT* dual targeted therapy, *n* number, *CD* Crohn's disease, *UC* ulcerative colitis, *URI* upper respiratory infection, *DNA* deoxyribonucleic acid, *NR* not reported, *UTI* urinary tract infection, *PRO* patient-reported outcome, *SES-CD* simplified endoscopic score-Crohn's disease, *HBI* Harvey–Bradshaw index, *IBD-U* inflammatory bowel disease—unspecified, weight pediatric Crohn's Disease Activity Index wPCDAI

[a]Clinical response and remission were unable to be calculated due to presence of an ostomy

[b]Two patients were removed due the indication for adding a second agent being extra-intestinal manifestations

this combination without any reported infections [22]. Olbjørn et al., treated eight pediatric patients with a combination of vedolizumab and infliximab for a mean duration of 6.5 months due to only a partial response to infliximab alone. Clinical remission was achieved in four patients, whereas the other four patients underwent colectomy. No infections or serious adverse events associated with the dual therapy were noted [23]. Privitera, et al., presented four patients treated with vedolizumab and either adalimumab or infliximab. There were no adverse events reported and all four had clinical improvement, two of which achieved clinical remission [18]. In a multi-center cohort study of 12 patients on infliximab and vedolizumab by Yang et al., only five patients experienced clinical improvement and two patients experienced infection. The adverse events reported are not attributable to a specific DTT combination, however reported adverse events included drug-induced lupus (attributed to a combination containing adalimumab), pneumonia, and the combination of basal cell skin cancer, recurrent *Clostridioides difficile* infection, and Acinetobacter bacteremia in a patient with a recurrent history of all three diseases prior to initiation of DTT [24].

Vedolizumab and Ustekinumab Combination Therapy

Twelve studies including a combined 55 patients were treated with a combination of vedolizumab with ustekinumab for the treatment of partially or non-responsive IBD (Tables 2, 3). Two retrospective cohort studies from 2020 evaluated the use of vedolizumab in combination with ustekinumab in patients with partially or non-responsive IBD. In the first, Yang et al., followed eight patients with refractory CD [24]. Five of these patients showed endoscopic improvement (two with endoscopic remission) and five showed clinical response (four with clinical remission). One of these eight patients experienced an adverse event, which was not further described. The second retrospective cohort study by Glassner et al., included 53 patients on DTT [25]. Twenty-five of these patients were on combination vedolizumab and ustekinumab. Overall, patients on DTT did show clinical, biochemical, and endoscopic improvement; however, results were not further categorized by medication subtype. While the vedolizumab in combination with ustekinumab patients made up the largest proportion of DTT evaluated in the study, it remains unclear if this group alone had a clinically significant response to therapy. Importantly, four adverse events were reported in the vedolizumab and ustekinumab group, including a rectosigmoid fistula with presacral abscess, postoperative abdominal wall abscess, *Clostridioides difficile* infection with sigmoid perforation and abscess, and coagulation negative Staphylococcus bacteremia associated with a peripherally inserted central catheter

Table 3 Characteristics of the included studies with multiple different combination therapies

Studies with multiple different combination therapies										
References	Year	N	Study type	Disease	Mean age (years)	Medications (n)	Median duration on DTT	Response	Definition of response	Adverse reaction (n)
Dolinger et al. [26]	2020	16	Case series	CD (7) UC (8) IBD-U (3)	16[a]	Vedolizumab + Tofacitinib (9) Vedolizumab + Ustekinumab (4) Ustekinumab + Tofacitinib (3)	12 months	12/16 steroid-free remission	Weight Pediatric Crohn's Disease Activity Index (wPCDAI) ≤ 12.5 for CD or pMS < 2 for UC/IBD-U, and no form of corticosteroids for at least 4 weeks	Septic arthritis (1/16) Deep vein thrombosis (1/16)
Glassner et al. [25][b]	2020	50[c]	Retrospective cohort study	CD (31) UC (18) IBD-U (1)	37	Vedolizumab + Tofacitinib (8) Vedolizumab + Ustekinumab (25) Vedolizumab + Adalimumab (3) Vedolizumab + Certolizumab (2) Vedolizumab + Golimumab (2) Tofacitinib + Infliximab (4) Tofacitinib + Golimumab (4) Tofacitinib + Ustekinumab (2)	2 months	13/33 clinical remission 9/30 endoscopic remission 19/29 discontinued steroids	Clinical remission measured by Harvey-Bradshaw index or partial Mayo score Endoscopic remission defined by simple endoscopic score for Crohn's Disease 0–2, Rutgeerts i0-i1 and Mayo endoscopic score 0	Bacterial enteric infections (3/37), *C. difficile* infection (3/37), Viral enteritis (1/37), URI (1/37), Acute bronchitis (2/37), Sinusitis (3/37), Strep throat (1/37), Peristomal cellulitis(1/37), Abdominal wall abscesses (2/37), Viral warts (1/37), UTI (1/37), Pelvic abscesses (2/37), PICC line infection(1/37), Sepsis event secondary to PICC line infection and perianal abscess (1/37)
Goyal et al. [20]	2020	8[d]	Case series	CD (7) UC (1)	15	Vedolizumab + Adalimumab (5) Vedolizumab + Ustekinumab (2) Vedolizumab + Infliximab (1)	10 months	3/8 remission + 3/8 partial response	Not Reported	Cellulitis (1/15), Bleeding (1/15)
Khatiwada et al. [41]	2020	42	Retrospective cohort study	CD (16) UC (26)	32[a]	Vedolizumab + Tofacitinib (27) Tofacitinib + Infliximab (6) Tofacitinib + Certolizumab (1) Ustekinumab + Tofacitinib (8)	5 months	3/42 clinical remission + 26/42 clinical response	Reduction in symptoms by physician global assessment	Candida esophagitis (1/42) Headache (2/42) Rash (1/42)

Table 3 (continued)

Studies with multiple different combination therapies										
References	Year	N	Study type	Disease	Mean age (years)	Medications (n)	Median duration on DTT	Response	Definition of response	Adverse reaction (n)
Llano et al. [22]	2021	14	Case series	CD (10) UC (3) IBD-U (1)	38	Vedolizumab + Ustekinumab (3) Vedolizumab + Tofacitinib (9) Vedolizumab + Adalimumab (2)	31 weeks [e]	5/9 clinical remission 3/3 improvement of Mayo Endoscopic Score 4/6 discontinuation of steroids 5/9 normalization of inflammatory markers	Harvey–Bradshaw index (HBI) was used for CD and indeterminate colitis (IBD-U), and the Lichtiger score was used for UC Mayo Endoscopic Score	Clostridium Difficile (1/14), rotavirus (1/14), Pneumonia (1/14), URI (1/14), Flare requiring hospitalization (1/14), surgery (1/14), rash (1/14), paresthesia (1/14)
Olbjørn et al. [23][f]	2020	13	Case series	CD (9) UC (4)	16	Ustekinumab + Infliximab (5) Vedolizumab + Infliximab (8)	22 months	4/8 clinical remission 3/8 normalization of biomarkers	Pediatric Ulcerative Colitis Activity Index (PUCAI) and weight Pediatric Crohn's Disease Activity Index (wPCDAI) used for clinical remission. Criteria for clinical and biochemical remission not stated	Skin infection (1/16) Otitis externa (1/16) Elevated LFTs (1/16) Eczema (1/16) Pustulosis psoriatic (1/16)
Privitera et al. [18][g]	2020	6	Case series	CD (1) UC (5)	36	Ustekinumab + Certolizumab (1) Ustekinumab + Infliximab (1) Vedolizumab + Adalimumab (1) Vedolizumab + Infliximab (1) Vedolizumab + Ustekinumab (2)	7 months	1/6 clinical remission 5/6 clinical response 5/6 normalization of inflammatory markers 4/5 discontinuation of steroids	Harvey–Bradshaw Index and partial Mayo Score for Crohn's disease and ulcerative colitis, respectively	Perianal abscess (1/6)

Table 3 (continued)

Studies with multiple different combination therapies										
References	Year	N	Study type	Disease	Mean age (years)	Medications (n)	Median duration on DTT	Response	Definition of response	Adverse reaction (n)
Yang et al. [24]	2020	24[h]	Retrospective Cohort	CD (22)	35	Ustekinumab + Adalimumab (2) Ustekinumab + Infliximab (1) Vedolizumab + Adalimumab (4) Vedolizumab + Certolizumab (2) Vedolizumab + Infliximab (6) Vedolizumab + Golimumab (1) Vedolizumab + Ustekinumab (8)	8 months	9/22 clinical remission + 2/22 clinical response 6/23 endoscopic remission + 4/23 endoscopic improvement	Endoscopic improvement during defined as either > 50% reduction in Simplified Endoscopic Score-Crohn's disease (SES-CD) or explicitly stated on the endoscopy report by an inflammatory bowel disease specialist Endoscopic remission (SES-CD < 3 or clearly stated) Clinical response (Crohn's disease–patient-reported outcome-2 score [PRO-2] reduced by 8), clinical remission (PRO2 < 8)	Pneumonia (1/22) Clostridium Difficile (1/22) Acinetobacter bacteria (1/22) Drug-induced lupus (1/22) Basel Cell Carcinoma (1/22)
Kwapisz et al. [21]	2021	15	Case series	CD (14) UC (1)	36	Ustekinumab + Adalimumab (1) Ustekinumab + Golimumab (1) Vedolizumab + Infliximab (2) Vedolizumab + Adalimumab (2) Vedolizumab + Golimumab (3) Vedolizumab + Certolizumab (1) Vedolizumab + Ustekinumab (5)	6 months	11/15(73%) symptomatic improvement 10/15 (67%) reduction in corticosteroids 4/15(44%) endoscopic or radiologic improvement	Clinical response measured by CD-Patient-Reported Outcome/Signs and Symptoms (PRO/SS) Score and Mayo Endoscopic Score	Hospitalizations (3/15) Salmonella gastroenteritis (1/15) Clostridium difficile (1/15) Malnutrition (1/15) Infections requiring antibiotics (4/15) Arthralgias (1/15)

N total study number, *DTT* dual targeted therapy, *n* number, *CD* Crohn's disease, *UC* ulcerative colitis, *URI* upper respiratory infection, *UTI* urinary tract infection, *PICC* peripherally inserted catheter, *LDL* low density lipoprotein, *LFTs* liver function tests, *PRO* patient-reported outcome, *SES-CD* simplified endoscopic score-Crohn's disease; *HBI* Harvey–Bradshaw index, *IBD-U* inflammatory bowel disease—unspecified; PUCAI pediatric ulcerative colitis activity index, *wPCDAI* weight pediatric Crohn's disease activity index

[a]Age is reported as a median

[b]Patients excluded if in clinical or endoscopic remission before initiation of DTT

[c]Study initially included 50 patients on 53 combinations. Three combinations were excluded due the indication for adding a second agent being extra-intestinal manifestations

[d]One patient was excluded for being on a combination that included anakinra

[e]Duration of DTT is reported as a median

[f]Indication for addition of ustekinumab was anti-TNF induced psoriasis

[g]Nine patients were removed due the indication of a second agent being extra-intestinal manifestations and one patient was excluded for being on a combination including secukinumab

[h]22 patients received 24 therapeutic trials of DTT

and perianal abscess. Two of these patients with adverse events were also on immunomodulator therapy with methotrexate or azathioprine.

The remaining data available for vedolizumab and ustekinumab combination therapy comes from several case series and case reports. In the largest of these case series, Kwapisz et al., followed five IBD patients treated with vedolizumab and ustekinumab for a median duration of 24 months [21]. Of these five patients, four showed clinical improvement, two were able to reduce corticosteroids, and one required hospitalization and surgery. No infections or other adverse events were reported in this group. In another large case series of pediatric patients by Dolinger et al., four patients on combination vedolizumab and ustekinumab were followed [26]. Three of these four patients achieved steroid-free remission at 6 months and one developed worsening symptoms requiring hospitalization and diverting loop ileostomy. No other infections or adverse reactions were reported. Llano et al. followed three patients (two CD, one UC) treated with vedolizumab and ustekinumab [22]. All three patients demonstrated clinical remission based on the Harvey-Bradshaw Index (CD) or Lichtiger score (UC). The only adverse event reported was one self-limited rotavirus infection. Finally, Privitera et al., included two CD patients treated with vedolizumab and ustekinumab combination therapy [18]. Both patients had reported clinical improvement without any reported infections. The remaining case reports included eight patients (seven CD and one UC) treated with vedolizumab and ustekinumab combination therapy. Two patients showed endoscopic improvement with resolution of a perianal fistula [20]. The remaining six patients were able to achieve steroid-free remission on combination therapy with vedolizumab and ustekinumab [17, 27–30]. Adverse events reported in this group include *Clostridioides difficile* infection with a single recurrence [17], anastomotic bleeding [20], and rotavirus infection [28].

Vedolizumab and Tofacitinib Combination Therapy

Nine studies totaling 68 patients were treated with a combination of vedolizumab and tofacitinib for the treatment of partially or non-responsive IBD (Tables 2, 3). Several small case reports and case series of vedolizumab and tofacitinib included six UC patients treated for refractory disease and demonstrated 100% clinical improvement without any reported infections [31–34]. In the case presented by Lee et al., vedolizumab monotherapy was started in a patient not responsive and intolerant to anti-TNF therapy. Initially vedolizumab monotherapy produced clinical response without remission despite every five-week dosing and adequate drug levels. Tofacitinib 5 mg twice daily was added and achieved steroid-free remission as well as an endoscopically normal colon at six months. Withdrawal of vedolizumab was attempted with re-emergence of symptoms 11 weeks after last vedolizumab infusion, however, remission was restored after re-initiation of vedolizumab as DTT [32].

In a larger cohort study, Dolinger, et al., reported on sixteen pediatric patients who transitioned to DTT after failing at least two biologic agents. Four CD patients and five UC/IBD-unspecified patients were trialed on a combination of vedolizumab and tofacitinib. Seven of these patients achieved the primary outcome of steroid-free remission of six months. Only one patient-reported an adverse event which was a patient who developed septic arthritis of the knee two months after initiation of DTT. After incision and drainage, and a prolonged course of intravenous antibiotics, the child also developed a deep vein thrombosis. Despite decreasing the patient's tofacitinib dose to 5 mg twice daily the patient achieved mucosal healing and steroid-free remission. After remission was achieved, the patient was transitioned to vedolizumab monotherapy and maintained deep remission. Notably, all patients on tofacitinib underwent lipid monitoring and no patient developed hypercholesterolemia or hypertriglyceridemia [26]. Llano et al., presented a case series of 14 patients of which nine (eight UC and one CD) were placed on vedolizumab and tofacitinib with incomplete intestinal disease despite use of a targeted monotherapy. All patients experienced a partial clinical response, however one patient still had evidence of endoscopic disease [22]. Scheinberg et al., reported a study of nine patients (eight UC and one CD) who started vedolizumab and tofacitinib DTT after failing at least two targeted monotherapies previously. In the UC group, 62.5% of patients experienced clinical response based on patient-reported improvement in symptoms and 50% had reduction in steroid use without any hospitalizations or adverse events reported. The CD patient did not respond to DTT, had no reduction in steroid use, and was ultimately admitted for a flare and underwent colectomy [35].

Anti-TNF and Tofacitinib Combination Therapy

Four small studies totaling 21 individuals were treated with a combination of anti-TNF therapy with tofacitinib for partially or non-responsive IBD (Tables 1, 3). The first reported case of combining anti-TNF with tofacitinib included five patients treated with infliximab in combination with tofacitinib for a minimum of 90 days [36]. All five patients demonstrated a partial response to intensified infliximab dosing following a median total of eight months. After 90 days of treatment with tofacitinib which was added to infliximab, all five patients experienced clinical, endoscopic, and

biochemical improvement. Zoster developed in one patient who then responded to oral valacyclovir. This was followed by a single case report of a 50-year-old male with high-risk fistulizing and stricturing CD with upper GI involvement and multiple small bowel resections. Tofacitinib was added to infliximab after an incomplete response to infliximab monotherapy. The patient had done "remarkably" well with a reported significant clinical improvement, however he unfortunately developed disseminated legionella including meningitis which lead to permanent residual neurologic deficits [37].

Anti-TNF and Ustekinumab Combination Therapy

Six studies totaling 18 patients were treated with combination anti-TNF therapy and ustekinumab (Tables 1, 3). In the first reported study looking at anti-TNF therapy in combination with ustekinumab, Kwapisz et al., reported on two patients who either received a combination of ustekinumab in combination with adalimumab or golimumab for a mean duration of five months [38]. In this study all patients had a clinical response. One patient had an infection requiring antibiotics but not hospitalization (type of infection not reported). Oljørn et al., presented a study of five pediatric patients on maintenance therapy with infliximab for a median of two years, who were switched to ustekinumab when they developed a severe paradoxical psoriasis resistant to topical treatment [23]. While their psoriasis improved, they all experienced a flare of their CD requiring re-initiation of infliximab. Interestingly, all five patients improved with DTT, however, two experienced a relapse after de-escalation to monotherapy. No adverse events were reported in any of these patients. Fumery et al., presented their institution's experience with five patients treated with ustekinumab in combination with either adalimumab, infliximab, or golimumab [39]. In this report three of five patients experienced clinical improvement with three of them achieving deep remission and one patient experiencing endoscopic improvement. There were no adverse events among any participant after mean of nine months of DTT. Yang et al., presented a retrospective cohort study of 23 patients treated with DTT, of which three were treated with ustekinumab in combination with either adalimumab and infliximab [24]. They reported that one of the three, experienced clinical response and endoscopic improvement without infections among all three patients treated with this combination. However, they did report that one patient on a DTT combination which included adalimumab developed drug-induced lupus. Dimopoulos, et al., reported on one patient who received combination ustekinumab and adalimumab for 5 months and developed SARS-CoV-2 but remained asymptomatic [40]. Privitera, et al., presented two cases of patients treated with ustekinumab in combination with either adalimumab or golimumab among nine Italian IBD referral centers for a mean of five months [18]. Both patients developed a clinical response, however one patient treated with this combination developed a perianal abscess.

Ustekinumab and Tofacitinib Combination Therapy

One study included three individuals who were treated with a combination of ustekinumab and tofacitinib (Tables 2, 3) [26]. In this study two of patients experienced clinical improvement without any reported adverse event among this DTT combination.

Studies with Several Unattributable Combinations

Two studies could not be subgrouped due to our inability to differentiate which DTT combination was attributable to our outcome of interest (Table 3) [25, 41]. Glassner, et al., presented a retrospective cohort study of 50 patients on 53 combinations of DTT from 2015 to 2019 of which the most prevalent combination was vedolizumab and ustekinumab ($n=25$) followed by vedolizumab and tofacitinib ($n=8$). While three DTT trials were initiated due to EIMs, these could not be excluded from their analysis. Of the 50 patients treated with DTT there were significantly more patients in clinical (50% vs 14%, $p=0.001$) and endoscopic remission (34% vs 6%, $P=0.0039$) compared to baseline. Eight serious adverse events were reported including one bacterial enteric infection, two abdominal wall abscesses, one peristomal cellulitis, two pelvic abscesses, one peripherally inserted catheter (PICC) line infection and one episode of sepsis secondary to PICC line infection and perianal abscess [25]. Khatiwada, et al., presented a retrospective study of 35 IBD patients who were on tofacitinib and either vedolizumab (six CD and 21 UC), ustekinumab (eight CD), infliximab (one CD and five UC) and certolizumab pegol (one CD). Seventeen patients were on concomitant steroids and three patients on an immunomodulator at the start of combination therapy. After eight or sixteen weeks of DTT, 26 patients (66.7%) had achieved clinical response with three (7.1%) in clinical remission. Thirty patients (33.3%) had no response. There was no significant difference in endoscopic response or biochemical improvement. Adverse events were reported in four patients (one CD and three UC), including headaches, itchiness, rash, and candida esophagitis.

Risk of Bias Assessment and Sensitivity Analysis

The randomized control trial conducted my Sands et al. was at low risk of bias, however all of the 28 included cohort, case series, or case report studies scored < 7 on the NOS, indicating greater risk for bias and potentially lower-quality studies [10, 11]. (Supplemental Table 2–4).

Discussion

We present a large and comprehensive systematic review of patients receiving dual targeted therapy for the treatment of partially or non-responsive IBD. Based on available data, it appears that DTT is promising for the treatment of IBD who fail to achieve remission on targeted monotherapy, with a moderate proportion of infectious complications. The patients included in our review consisted entirely of patients who previously failed and were unable to achieve clinical remission on targeted monotherapy. These patients have a high predicted risk of IBD exacerbations, complications, and surgery and are less likely to respond to additional targeted monotherapies.

There is an urgent need to better optimize therapy in the context of shifting treatment targets to achieve endoscopic remission, which remains unachievable in distressingly large numbers of high-risk patients with conventional therapy. Further high quality prospective randomized trials are needed to further evaluate the efficacy and safety of DTT for the treatment of IBD, and to determine the optimal combination, dose, frequency, and duration of DTT to achieve our desired outcomes. The gut-selective nature of IBD-specific therapies, such as vedolizumab, may make DTT less of a safety risk as compared to other autoimmune conditions. In addition, predictive modeling studies are needed to identify the patients most likely to require and benefit from DDT.

The costs and value of such approach need to be thoroughly evaluated. In the future, the costs of a DTT approach may be offset by reductions in emergency service utilization and complications related to not achieving remission, especially when utilized for a limited course, which may be further enhanced when the combination includes a biosimilar [42].

There are several major limitations to this study, which must be considered when interpreting our findings. The majority of the studies included in our review are low quality case reports and case series. Inclusion of these studies increase the risk of publication bias favoring extreme results [43]. In addition, several DTT combinations had a paucity of studies and participants. It should also be noted that our endpoint of clinical improvement was defined extremely heterogeneously among the included studies. This high degree of heterogeneity highlights the need for more rigorous endpoint reporting (including objective markers of improvement/remission) in future studies in this area.

The strength of this review is the number of patients included across many combinations of DTT. Previous reviews included significantly fewer participants [23, 42, 44]. DTT is a promising approach to improve IBD treatment for patients with incomplete responses to targeted monotherapy. More rigorous randomized control trials are needed to build on this current analysis and to better understand DTT efficacy, safety, heterogeneity of treatment effects and costs of this approach.

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Declarations

Conflict of interest PDRH received consulting fees from AbbVie, Amgen, Genentech, and Pfizer. RWS received consulting fees from AbbVie, Janssen, Takeda, Merck, Gilead, Eli Lily, Exact Science, Evergreen Pharmaceuticals, Corrona LLC. JAB received consulting fees from BUHLMANN Diagnostics Corp. All other authors report no relevant disclosures.

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