No Benefit of Concomitant Immunomodulator Therapy on Efficacy of Biologics That are Not Tumor Necrosis Factor Antagonists in Patients With Inflammatory Bowel Diseases: a Meta-Analysis

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Word count: Abstract – 285 ; Manuscript - 3130
References: 57
Tables and Figures: 2 and 2
Supplementary Table and Figure : 2 and 13

Financial support: None

Potential competing interests:

SS: Research grants from AbbVie and Janssen
MF : Abbvie, Ferring, MSD, Janssen, Takeda, Tillots, Pfizer, Gilead, Celgene, Biogen, Boehringer.
No conflict to declare for other authors

Guarantor of the article: Mathurin Fumery, MD, PhD

Specific author contributions:
Collection of data: CY, MF
Interpretation of data: CY, MF, FB, SS, JM, MD
Drafting of the manuscript: CY, MF
Critical revision of the manuscript: All
Approval of the final version of the manuscript: All

Abbreviations: Inflammatory bowel disease (IBD), Crohn's disease (CD), ulcerative colitis (UC)

Abstract

Background & Aims: There is debate over whether patients with inflammatory bowel diseases (IBD) treated with biologics that are not tumor necrosis factor antagonists (such as vedolizumab or ustekinumab) should receive concomitant treatment with immunomodulators. We conducted a meta-analysis to compare the efficacy and safety of concomitant immunomodulator therapy vs vedolizumab or ustekinumab monotherapy.

Methods: In a systematic search of publications, through July 31, 2019, we identified 33 studies (6 randomized controlled trials and 27 cohort studies) of patients with IBD treated with vedolizumab or ustekinumab. The primary outcome was clinical benefit, including clinical remission, clinical response, or physician global assessment in patients who did vs did not receive combination therapy with an immunomodulator. Secondary outcomes were endoscopic improvement and safety. We performed random-effects meta-analysis and estimated odds ratio (OR) and 95% CIs.

Results: Overall, combination therapy was not associated with better clinical outcomes in patients receiving vedolizumab (16 studies: OR, 0.84; 95% CI, 0.68–1.05; I2=13.9%; Q test P=.17) or ustekinumab (15 studies: OR, 1.1; 95% CI, 0.87–1.38; I2=11%; Q test P=.28). Results were consistent in subgroup analyses, with no difference in clinical remission or response in induction vs maintenance studies or in patients with Crohn's disease vs ulcerative colitis in studies of vedolizumab. Combination therapy was not associated with better endoscopic outcomes in patients receiving vedolizumab (3 studies: OR, 1.13; 95% CI, 0.48–2.68; I2=0; Q test P=.96) or ustekinumab (2 studies: OR, 0.58; 95% CI, 0.21–1.16; I2=47%; Q test P=.17). Combination therapy was not associated with an increase in adverse events during vedolizumab therapy (4 studies: OR, 1.17; 95% CI, 0.75–1.84; I2=0; Q test P=.110).

Conclusions: In a meta-analysis of data from studies of patients with IBD, we found that combining vedolizumab or ustekinumab with an immunomodulator is no more effective than monotherapy in induction or maintenance of remission.

KEY WORDS: integrin inhibitor, interleukin, anti-IL12-23, CD, UC

Introduction

Since 2000, biologics have revolutionized the therapeutic strategies for inflammatory bowel diseases (IBD). For many years, the available biological therapies were restricted to anti-tumor necrosis factor (anti-TNF) agents. Anti-TNF and immunomodulator combination therapy were identified early as the gold standard, with clinical trial data demonstrating that combination therapy was superior to monotherapy (1-3). Combination therapy was associated with improved anti-TNF drug pharmacokinetics (higher median trough serum concentrations) and lower immunogenicity, identified as one of the main causes of loss of response (1, 2, 4).

Over the past decade, vedolizumab (anti-integrin α4β7) and then ustekinumab (anti-interleukin 12/23) were successively approved for treatment of Crohn's disease (CD) and Ulcerative Colitis (UC) (5-8). The current evidence and clinical experience with anti-TNF agents raised the idea that all biologics may optimally be used in combination with immunomodulators. However, the evidence supporting the use of combination therapy with these new biologics are limited and conflicting. These drugs are less immunogenic and it is not certain that adding an immunomodulator improves their efficacy (5,6, 9-11). On the other hand, the addition of an immunomodulator may be deleterious due to increased risk of serious and opportunistic infections (12, 13).

Hence, we aimed to evaluate the comparative effectiveness and safety of using vedolizumab or ustekinumab monotherapy vs. in combination with an immunomodulator in patients with IBD through a systematic-review and meta-analysis.

Methods

This systematic review followed the preferred reporting items for systematic reviews and meta-analysis (PRISMA) standards, and followed an a priori protocol.

Selection Criteria

Studies meeting the following criteria were included: randomized controlled trials, observational cohort in (b) adult patients (c) with a diagnosis of IBD, CD or UC (d) treated with vedolizumab or ustekinumab (e) reporting the rate of clinical response or remission, endoscopic response or remission, or safety, (f) in patients treated with and without combination therapy with an immunomodulator including thiopurines or methotrexate. We excluded studies that did not report clearly outcomes stratified by mono or combination therapy, or that did not provide adequate information to allow estimation of difference in outcomes. When multiple studies from the same cohort were reported, then the most comprehensive report providing information of interest was included.

Search Strategy

We conducted a comprehensive search of multiple electronic databases through, July 2019, with no language restrictions using the following search terms: (“IBD” OR “UC” OR “CD”) AND (“vedolizumab” OR “ustekinumab”). The databases included: Ovid Medline, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, and Scopus. The search strategy was designed and conducted by an experienced medical librarian with input from the study investigators, using controlled vocabulary supplemented with keywords. In addition, conference abstracts (Digestive Disease

Week, United European Gastroenterology Week, and European Crohn's and Colitis Organization annual meeting) from 2014 to 2019, as well as bibliography of the selected articles and review articles on the topic were manually searched for additional studies, with no language restrictions. Two reviewers (CY and MF) independently assessed the title and abstract of studies identified in the primary search for inclusion (Level 1 screen), and the full text of remaining articles were examined to determine whether they met inclusion criteria (Level 2 screen). Any discrepancy in article selection was resolved by consensus and in discussion with a third reviewer (FB). A reviewer (MF) contacted the primary study authors as needed for additional data or missing information.

Data Abstraction and Quality Assessment

Two authors (CY and MF) independently extracted data on a standardized data collection form: (a) study characteristics: primary author, study period/year of publication, country of the study population, population source, number of patients, duration of follow-up; induction or maintenance study; (b) population characteristics: type of IBD; previous failure to immunomodulators or anti-TNFs; number of patients treated by combination as well as monotherapy, if available type of immunomodulator; (c) Outcome: clinical benefit / endoscopic improvement / safety: definition, timepoint of evaluation. For each outcome were collected Odds Ratio (OR), Relative Risk (RR), rate ratios for combination and monotherapy group (comparator), together with their 95% confidence intervals (CI), were recorded. When several adjustment models were reported, the most adjusted estimates were used in the analysis. When only raw event rates were reported, the numbers of events in the groups compared were extracted. Any discrepancies were addressed by a joint re-

evaluation of the original article. A quality assessment for observational studies was conducted for studies included in the meta-analysis using the NewCastle Ottawa Scale. For RCTs, risk of bias assessment was conducted using the tool developed by the UK's National Institute for Health and Care Excellence (NICE; https://www.nice.org.uk/process/pmg24/chapter/clinical-effectiveness).

Outcomes Assessed

The primary effectiveness outcome was the clinical benefit including clinical remission, clinical response or global physician judgement (as defined in individual studies) in IBD patients with combination therapy as compared to those who were not. We then evaluated each of these outcomes individually. Secondary outcomes measures were endoscopic improvement as defined by endoscopic remission, response or histologic remission. Primary safety outcome was defined by the risk of adverse events as defined in individual studies. Sub-group analyses were performed by type of IBD (UC / CD), by induction / maintenance treatment, by study design (randomized controlled trial vs observational studies, and prospective vs retrospective studies), as for serious infection.

Statistical Analysis

Assuming inherent heterogeneity between studies, we used the random-effects model described by DerSimonian and Laird to calculate pooled OR (and 95% CI) of study endpoints (14). We assessed heterogeneity between study-specific estimates using the inconsistency index (I2), with cut-offs of <30%, 30%–59%, 60%–75% and >75% to suggest low, moderate, substantial and considerable heterogeneity, respectively (15). A p value < 0.10 was considered to indicate statistically significant

heterogeneity using Cochran's Q test. Small study effects were assessed qualitatively using funnel plot asymmetry and quantitatively using Egger's regression test (16). All statistical analyses were performed with R-Studio software (Version 1.0.143).

Results

Vedolizumab

Of 794 unique studies identified using our search strategy, 17 studies were included (17-25, 27-33). In addition, we identified one abstract from conference proceedings, and two studies could be included after contacting the authors (34-35) and hence, included a total of 20 studies for quantitative synthesis (26) (**Figure S1**). The characteristics of these studies are summarized in **Table 1**. Three of these studies were randomized controlled trial (25,28,33). Among the 17 cohort studies, eight were prospective and two population-based. Two studies included only CD patients, one only UC patients. Finally, respectively 1890 and 4392 patients with combination therapy and monotherapy were included. Only five studies have reported the number of patients previously exposed / failed immunomodulator. The mean number of anti-TNF exposed patients was 80% (range, 0-98%). The range of quality assessment score for observational studies and post hoc analyses included in the meta-analyzed study was 6-8 (of maximum score of 8), indicating a high quality of the included studies (**Table S1**). The three RCTs included in the meta-analysis also were of relatively high quality (**Table S2**).

Clinical benefit

Sixteen studies including 2,053 CD patients and 1,260 UC were analyzed. Respectively 933 and 2378 patients with combination therapy and monotherapy (17-30, 34-35) were included. On meta-analysis, combination therapy was not associated with better clinical benefit as compared with monotherapy (OR 0.84; 95% CI 0.68-1.05) with low heterogeneity (I2 = 14%, Q test-pvalue=0.17) (**Figure 1**). No benefit in term of clinical remission (6 studies - OR 0.87; 95% CI, 0.57-1.31 – I2 = 29%, Q test-

p=0.26), clinical response (5 studies - OR 0.60; 95% CI, 0.31-1.15 – I2 = 29%, Q test-p=0.18), global physician judgment (4 studies - OR 0.96; 95% CI, 0.70-1.31 – I2 = 19%, Q test-p=0.25) were observed **(Figure S2, S3 and S4)**. Overall results were consistent in subgroup analysis with no difference in terms of clinical benefit in UC (7 studies - OR 0.92; 95% CI, 0.60-1.41 – I2 = 21%, Q test-p=0.23) or CD (9 studies - OR 0.84; 95% CI, 0.53-1.33 - I2 = 49%, Q test-p = 0.46) (**Figures S5 and S6**), and in both induction (11 studies - OR 0.84; 95% CI, 0.61-1.16 – I2 = 31%, Q test-p=0.06) and maintenance (9 studies - OR 0.80; 95% CI, 0.64-1.01 – I2 = 5.2%, Q test-p=0.62) studies (**Figures S7 and S8**). Also similar results were observed in subgroups analysis including both cohorts studies (14 studies - OR 0.82; 95% CI, 0.67-1.02 – I2 = 4.5%, Q test-p=0.29) and randomized controlled trial (2 studies - OR 0.81; 95% CI, 0.18-3.55 – I2 = 77%, Q test-p=0.03), and both prospective (8 studies - OR 0.82; 95% CI, 0.58-1.15 – I2 = 35%, Q test-p=0.14) and retrospective studies (9 studies - OR 0.95; 95% CI, 0.72-1.25 – I2 = 0%, Q test-p=0.28). The symmetrical distribution of the studies on the funnel plot suggested that no publication bias was observed (p = 0.3372) (**Figures S9**).

Endoscopic remission

Three studies including a total of 589 patients were analyzed (29,31,35). On meta-analysis combination therapy was not associated with better endoscopic outcome as compared with monotherapy (OR 1.13; 95% CI, 0.48-2.68) with no heterogeneity (I2 = 0%, Q test-p=0.96).

Safety

Four studies with 1,527 patients treated with vedolizumab in combination therapy, and 2,891 in monotherapy reported the numbers of adverse event (18, 19, 32, 33).

On meta-analysis combination therapy was not associated with higher risk of adverse event (OR 1.17; 95% CI, 0.75-1.84) with no heterogeneity (I2 = 0%, Q test-p=0.110). No increased risk of serious infections was observed (3 studies - OR 1.29; 95% CI, 0.75-2.21 – I2 = 0%, Q test-p=0.11).

Ustekinumab

Of 417 unique studies identified using our search strategy, 13 studies were included (36-48). Two studies could be included after contacting the authors (49-50) (**Figure S10**). **Table 2** shows their main characteristics. Three of these studies were randomized controlled trial. Among the twelve cohort studies, all came from referral centers, four were prospective and eight multicenter. Only six studies have reported the number of patients previously exposed / failed immunomodulator, with a rate ranging from 60 to 100%. The mean number of anti-TNF exposed patients was 90% (range, 50-100%). The range of quality assessment score for observational studies and post hoc analyses included in the meta-analyzed study was 6-8, indicating a high quality of the included studies (**Table S1**). The thee RCTs included in the meta-analysis also were of relatively high quality (**Table S2**).

Clinical benefit

Fifteen studies including a total of 2,786 patients were included (36-50). Two studies were included with UC (37,46), and finally a total of respectively 2,458 and 328 CD and UC patients included. Overall, respectively 856 and 1,926 patients with combination therapy and monotherapy were included.

On meta-analysis, ustekinumab combination therapy was not associated with better clinical outcomes compared to ustekinumab monotherapy (OR 1.1; 95% CI 0.87-1.38) with low heterogeneity (I2 = 10.96%, Q test-p= 0.285) (**Figure 2**). The symmetrical distribution of the studies on the funnel plot suggested that no publication bias was observed (p = 0.3) (**Figure S11**). No benefit in term of clinical remission (7 studies - OR 1.1; 95% CI, 0.76-1.57 – I2 = 0%, Q test-p=0.446), clinical response (5 studies - OR 1.1; 95% CI, 0.69-1.60 – I2 = 35%, Q test-p=0.212), global physician judgment (3 studies - OR 1.4; 95% CI, 0.40-4.54 – I2 = 58%, Q test-p=0.098) were observed (**Figure S9, S10 and S11)**.

Consistent results were observed in both induction (8 studies - OR 1.1; 95% CI, 0.81-1.49 – I2 = 26%, Q test-p=0.210) and maintenance studies (11 studies - OR 1.1; 95% CI, 0.89-1.47– I2 = 0%, Q test-p=0.712) (**Figure S12 and S13**).

Also similar results were observed in subgroups analysis including both cohorts studies (12 studies - OR 1.0; 95% CI, 0.80-1.36 – I2 = 0%, Q test-p=0.58) and randomized controlled trial (3 studies - OR 1.30; 95% CI, 0.95-1.66 – I2 = 29%, Q test-p=0.24), and both prospective (7 studies - OR 1.20; 95% CI, 0.94-1.49 – I2 = 15%, Q test-p=0.353) and retrospective studies (8 studies - OR 1.10; 95% CI, 0.79-1.52 – I2 = 0%, Q test-p=0.36).

Endoscopic remission

Two studies including a total of 229 patients with CD were analyzed (39,40). On meta-analysis, combination therapy was not associated with better endoscopic outcome as compared with monotherapy (OR 0.58; 95% CI, 0.21-1.16) with moderate heterogeneity (I2 = 47%, Q test-p=0.167).

Safety

None of the studies had reported safety outcomes in patients with and without combination therapy with ustekinumab.

Discussion

This meta-analysis assesses the clinically relevant and controversial question of whether to combine an immunomodulator when initiating non anti-TNF biologics in patients with IBD. We observed that combination therapy with an immunomodulator was not associated with better clinical outcome whether in induction or maintenance, or better endoscopic outcome.

For many years, the only available biological therapies were anti-TNF agents. In CD and UC, there was general consensus that concomitant azathioprine or methotrexate with anti-TNFs is the most effective therapy and appropriate, except in special populations (1-4). In naïve patients, the SONIC trial demonstrated the superiority of the combination of infliximab and azathioprine over monotherapy to obtain corticosteroid-free clinical remission in CD (1) and the SUCCESS trial (2) showed similar results in UC with 40% of corticosteroid-free remission at week 16 for patients receiving combination therapy, compared with 22% for patients receiving infliximab alone. Data are more conflicting for patients previously exposed to immunomodulators. On the basis of a meta-analysis of randomized controlled trial, continued use of immunomodulator therapy after starting anti-TNF therapy is no more effective than anti-TNF monotherapy in inducing or maintaining response or remission (51). Also, the benefit of combination therapy in non-infliximab anti-TNF is subject to debate. Recently, the DIAMOND study observed that the clinical efficacy of a combination of adalimumab and azathioprine did not differ from that of adalimumab monotherapy in CD naïve to both medications, despite a significant higher rate of endoscopic improvement in the combination group (52).

Whereas an abundant literature is available for anti-TNF and combination therapy, there is a knowledge gap with regard to new biologics. No trials have specifically compared vedolizumab, or ustekinumab with immunomodulators vs monotherapy. There also are limited data on the comparative efficacy of combination therapy over monotherapy from cohort studies. None of them had specifically addressed this question, whereas a significant proportion of the patients included in these studies were treated with immunomodulators. Finally, the few data available are conflicting. Recently the AGA guidelines chose to rate the quality of evidence supporting vedolizumab, or ustekinumab with immunomodulator over vedolizumab, or ustekinumab monotherapy as low quality (53). In the recent ECCO guidelines on therapeutics in CD, while the authors suggest against the combination of adalimumab and thiopurines over adalimumab alone, they did not state about combination therapy with non-anti-TNF biologics (54). Through this meta-analysis, combination therapy was not associated with improved clinical and endoscopic outcome during both vedolizumab or ustekinumab therapies. Results were consistent in subgroup analysis, with the same results observed in induction and maintenance therapy, as in CD and UC, in randomized controlled trial and cohort studies as well as in prospective and retrospective studies.

Several controversial mechanisms have been proposed to explain the superiority of combination therapy over monotherapy. Combination therapy has a protective effect against anti-drug antibody development and lower trough levels, which were identified as one of the main drivers of primary non-response and loss of response during anti-TNF therapy (1,2). Post-hoc analyses of the SONIC trial suggested that the primary benefit of azathioprine was on pharmacokinetics of infliximab (55), whereas the PANTS study showed that concomitant immunomodulator use in

infliximab-treated patients was associated with higher remission at week 54 compared with no immunomodulator use, and this independently of drug concentration or immunogenicity status, suggesting that the addition of immunosuppression to anti-TNF therapy might have additional benefits (56).

As for anti-TNF, association between vedolizumab or ustekinumab concentration and clinical efficacy has been reported. However, unlike anti-TNF, prospective studies as well as post-hoc analysis of randomized controlled trial consistently reported a low immunogenicity. For vedolizumab, the LOVE study reported detectable drug antibodies in 1% to 4% of patients at different time points, that are transient in most cases without impacting VDZ serum concentrations (57). During the IM-UNITI long term follow-up, rates of antibodies to ustekinumab through week 156 was only 4.6%. Also, all the prospective studies available to date have shown no impact of immunomodulator on the trough serum level of vedolizumab (35, 58) or ustekinumab (59,60). The association of immunomodulator with biologics may also be deleterious. Combination with anti TNF is associated with an increased risk of serious, opportunistic infections and lymphoma (12,13). On meta-analysis including 4 studies with 1,527 patients treated with vedolizumab in combination therapy, and 2,891 with vedolizumab monotherapy, combination therapy was not associated with an increased risk of adverse event. Similar data were not available for ustekinumab.

This study presents several limitations. Firstly, differences in the definition of clinical outcomes were observed, with studies reporting clinical remission and other clinical response, with their own definition. However, in subgroups analysis, we did not detect any benefit of combination therapy in studies evaluating clinical remission as in those evaluating clinical response. For endoscopic improvement, only two studies

could be included on meta-analysis, thus limiting the interpretation of the results. Secondly, our study does not address the question of the interest of combination therapy in patients who had been previously exposed to (and failed) immunomodulator and those who had not because exposure rates were available in a too limited number of studies. Third, we must recognize that patients treated with combination therapy in the included studies could be more severe. This could influence our results. Also, were not able to evaluate separately the impact of thiopurines and methotrexate. Finally, we were unable to study the impact of immunomodulators on the biologics serum levels with the data currently available in the literature. On the other hand, this first meta-analysis evaluating the interest of combination therapy with the new biologics was not associated with significant heterogeneity across the analyses and no publication biases were observed. The results were consistent in all subgroups analysis performed, thus promoting the applicability of the results.

In conclusion, this meta-analysis found that overall the use of combination therapy in patients treated with vedolizumab or ustekinumab was not associated with a clinical benefit in comparison with the use of monotherapy. In subgroups analyses, consistent results were observed during induction and maintenance therapy for both drugs as well as for CD and UC for vedolizumab.

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Study	Study design	Source	Country	Time period	Diseases (Crohn / UC), n	Medications		Outcome (definition)	Timepoint
						Vedolizumab combo, n	Vedolizumab mono, n		
Shelton et al., 2015	Multicenter retrospective cohort	Referral center	USA, Boston	2014-2015	107 / 59	51	121	Clinical response (decrease in HBI ≥3 and SCCAI≥ 3 or physician assessment of clinical response)	W14
Eriksson et al., 2017	Multicenter prospective cohort	Population-based	Sweden	2014-2015	147 / 92	92	152	Clinical response (drug discontinuation, because of lack of or loss of response) and safety	End of follow-up
Lenti et al. 2018	Multicenter retrospective, UK	Referral center	UK	2014-2018	135 / 68	101	102	Clinical response (partial, though significant, improvement) and safety	W14 / W52
Kopylov et al. 2018	Multicenter, retrospective, Europe	Referral center	Europe	2015-2017	50 /134	40	148	Clinical response (Improvement of at least 1 severity score (HBI, CDAI, Lichtiger score, SCCAI, PMS)	W14
Shmidt et al. 2018 Messerve et al. 2019	Multicenter retrospective cohort	Referral center	USA, VICTORY	2014-2016	264 /195 650/437	190 417	262 670	Loss of response (recurrence or worsening of IBD-related symptoms that required surgery, a change in treatment, or VDZ intensification)	W26 / W52
								Serious adverse event	End of follow-up
Macaluso et al. 2018	Multicenter retrospective cohort	Population-based	Italy	2016-2017	84 / 79	13	150	Clinical response (absence of steroid-free remission, but reduction of HBI≥3 or MPS ≥ 2 with a concomitant reduction of CS dosage at W10, and discontinuation at W22)	W12 / W22
Christensen et al. 2018	Monocenter prospective cohort	Referral center	USA, Chicago	2014-2015	94 / 42	51	85	CS free clinical remission (HBI ≤ 4 or SCCAI ≤ 2)	W52
Samaan et al. 2017	Multicenter, retrospective cohort	Referral center	UK	2014-2015	27 /23	21	29	Clinical response (reduction ≥ three or more in HBI or SCCAI)	W14
Allegretti et al. 2017	Retrospective multicenter cohort	Referral center	USA, Boston	/	96 / 40	44	92	Clinical response (decrease in HBI ≥ 3 or SCCAI ≥ 3 or by physician assessment) or Clinical remission (HBI ≤ 4 or SCCAI ≤ 2 or by physician assessment)	W54
Sands et al. 2014	RCT	Referral center	International	2010-2012	209 / 0	71	138	Clinical remission (CDAI ≤ 150)	W10

Parisi et al. 2017	Monocenter retrospective cohort	Referral center	UK	2015-2016	28 / 31	/	/	Clinical response (reduction of HBI ≥ 3 points or a reduction of PMS ≥ 2points).	Induction
Stallmach et al. 2016	Multicenter prospective cohort	Referral center	Germany	2014-2015	67 / 0	15	112	Clinical remission (HBI ≤ 4)	W54
Watanabe et al. 2020	RCT	Referral center	Japan	2014-2017	79 / 0	39	30	Clinical remission (CDAI ≤ 150)	W10
Kotze et al. 2018	Monocenter retrospective cohort	Referral center	Canada, Calgary	2012-2017	122 /100	39	183	Clinical remission (complete absence of symptoms without CS in CD or PMS ≤2, as well as the resolution of rectal bleeding without CS in UC and endoscopic remission (complete mucosal normalization or complete normalization of inflammatory parameters on cross-sectional imaging in CD or endoscopic Mayo= 0 in UC	W52
Biemans et al. 2019	Multicenter prospective cohort	Referral center	Netherlands	/	192 / 119	59	251	Corticosteroid-free clinical remission (HBI ≤ 4 or SCCAI ≤ 2)	W12 / W54
Pouillon et al. 2019	Monocenter retrospective cohort	Referral center	France, Nancy	2014-2018	0 / 31	7	24	Histological healing	End of follow-up
Colombel et al. 2014	RCT	Referral center	International	2008-2012	1770 / 1114	917	1967	Adverse event according to medra classification	End of follow-up
Amiot et al. 2019	Multicenter prospective cohort	Referral center	France	2014	173 / 121	70	224	Clinical remission (HBI ≤4 for CD patients and a partial Mayo Clinic score <3 with a combined stool frequency and rectal bleeding subscore of ≤1 for UC)	W14/W54
Vertsock et al. 2019	Unicenter prospective cohort	Referral center	Belgium	2015-2018	179 / 157	37	299	Clinical remission (PGA), endoscopic remission (Crohn, the complete absence of ulcerations; UC, Mayo endoscopic sub-score ≤1)	W14 /W22

Table 1: Vedolizumab - Characteristics of studies included in the analysis. RCT, Randomized Controlled trial ; W, Week ; HBI, Harvey-Bradshaw Index ; CDAI, Crohn's disease activity index ; CD, Crohn's disease ; UC, Ulcerative colitis ; PMS, Partial Mayo Score ; SCCAI, Simple Clinical Colitis Activity Index ; CS, Corticosteroids ; PGA, Physician global assessment.

Study	Study design	Source	Country	Time period	Diseases (Crohn / UC), n	Medications		Outcome (definition)	Timepoint
						Ustekinumab combo, n	Ustekinumab ab mono, n		
Miyazaki et al. 2020	Monocenter retrospective cohort	Referral center	Japan	2017-2018	47 / 0	18	29	Clinical remission (CDAI < 150 points)	W8 / W24
Iborra et al. 2019	Multicenter retrospective cohort	Referral center	Spain, ENEIDA	/	305 / 0	122	183	Clinical remission (HBI score ≤ 4 points)	W14
Biemans et al. 2020	Multicenter prospective cohort	Referral center	Netherland, ICC registry	2016-2019	221 / 0	44	177	CS free clinical remission (HBI ≤ 4 points)	W12 / W 24 / W52
Pugliese et al. 2019	Multicenter, retrospective cohort	Referral center	Italy	2012-2017	64 / 6	11	59	Clinical remission (HBI ≤ 4 or PMS ≤ 2 with no subscore > 1)	Last follow up
Liefferinckx et al. 2019	Multicenter retrospective cohort	Referral center	Belgium	2016-2017	152 / 0	25	127	Clinical remission (HBI ≤4 points)	W52
Battat et al. 2017	Multicenter prospective cohort	Referral center	Canada, Montreal	2014-2015	62 / 0	16	46	Clinical response (reduction HBI ≥ 3) Endoscopic response (SES-CD reduced by 50% or more or SES-CD ≤2)	W 26
Ma et al. 2017	Multicenter retrospective cohort	Referral center	Canada	2011-2016	167 / 0	73	94	Clinical response (improvement in disease symptoms by either PGA or decrease in HBI ≥3 points and complete tapering of steroids). Endoscopic response: improvement in mucosal inflammation compared to baseline with at minimum, resolution of deep ulcerations	W26
Feagan et al. 2016	RCT	Referral center	International	2011-2015	931 / 0	320	607	Clinical response (decrease from baseline in CDAI ≥ 100 points or a total CDAI score ≤ 100), Clinical remission (CDAI <150 points)	W6 W44
Khorrami et al. 2016	Multicenter Retrospective cohort	Referral center	Spain	2010-2014	116 / 0	42	74	Clinical benefit defined as clinical remission (HBI ≤4), or response (decrease in HBI ≥ 3)	Between W8 and W12
Kopylov et al. 2014	Monocenter retrospective cohort	Referral center	Canada, Montreal	2011-2013	40 / 0	4	36	Clinical response (improvement in the patient's symptoms coupled with the decision to continue ustekinumab treatment)	End of follow up

Sandborn et al. 2012	RCT	Referral center	International	2008-2010	131 / 0	35	96	Clinical response (≥100-point decrease from the baseline CDAI score) Clinical remission (CDAI ≤ 150)	W6 W 22
Wils et al. 2016	Multicenter retrospective cohort	Referral center	France and Swiss	2011-2014	122 / 0	19	103	Clinical benefit (significant improvement in CD-related clinical symptoms and laboratory tests assessed by the patient's physician leading to continued ustekinumab treatment, associated with complete weaning from steroids if they were being taken at inclusion, without surgery, or immunosuppressant introduction)	-
Sands et al. 2019	RCT	Referral center	International	2015-2018	0 / 322	89	233	Clinical remission (total Mayo score of ≤2 and no subscore >1)	W8 and 44
Soufflet et a. 2019	Multicenter prospective study	Referral center	France	/	51 / 0	6	45	Clinical remission (HBI ≤ 4 points)	W16
Painchart et al. 2019	Monocenter prospective cohort	Referral center	France	2015-2017	49 / 0	32	17	Clinical response (three-point HBI reduction or by the PGA if the HBI was not applicable)	W28

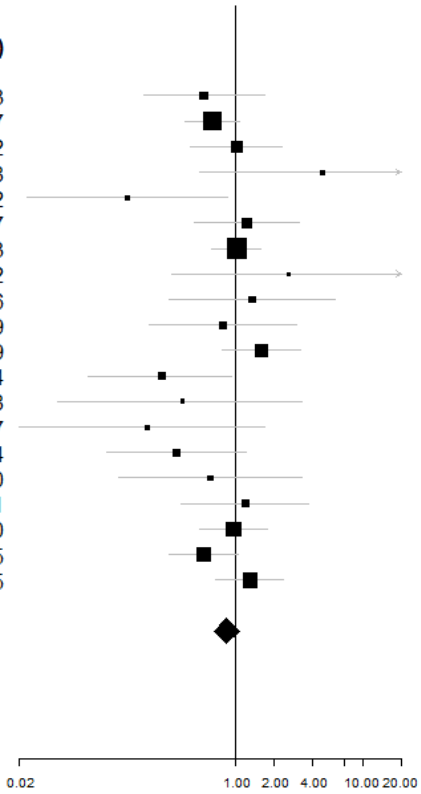
Table 2: Ustekinumab - Characteristics of studies included in the analysis. RCT, Randomized Controlled trial ; W, Week ; HBI, Harvey-Bradshaw Index ; CDAI, Crohn's disease activity index ; CD, Crohn's disease ; UC, Ulcerative colitis ; PMS, Partial Mayo Score ; CS, Corticosteroids ; PGA : Physician Global assessment ; SES-CD, Simple endoscopic score-Crohn's disease.

Figure 1: Vedolizumab - Comparative Clinical Efficacy of Combination Therapy And Monotherapy In Inflammatory Bowel Diseases. OR, Odds Ratio ; CI, Confidence Interval.

Figure 2: Ustekinumab - Comparative Clinical Efficacy of Combination Therapy And Monotherapy In Inflammatory Bowel Diseases. OR, Odds Ratio ; CI, Confidence Interval.

Author	Population	Year	OR	95% CI	Weight (%)
Shelton E	IBD	2015	0.56	0.19- 1.66	3.73
Eriksson	IBD	2017	0.65	0.40- 1.05	13.57
Lenti	CD	2018	1.01	0.44- 2.29	6.02
Lenti	UC	2018	4.69	0.52-42.48	0.98
Kopylov	CD	2018	0.14	0.02- 0.86	1.42
Kopylov	UC	2018	1.21	0.47- 3.10	4.77
Shmidt	IBD	2018	1.01	0.64- 1.57	14.93
Macaluso	IBD	2018	2.58	0.31-53.68	0.72
Christensen	UC	2018	1.33	0.30- 5.96	2.06
Samaan	IBD	2017	0.79	0.21- 2.97	2.59
Sands	CD	2014	1.57	0.78- 3.19	7.79
Parisi	IBD	2017	0.26	0.07- 0.91	2.74
Stallmach	CD	2016	0.38	0.04- 3.25	0.98
Stallmach	UC	2016	0.20	0.02- 1.66	0.97
Watanabe	CD	2019	0.34	0.10- 1.21	2.84
Kotze	CD	2018	0.63	0.12- 3.26	1.70
Kotze	UC	2018	1.18	0.37- 3.75	3.31
Biemans	IBD	2019	0.95	0.51- 1.77	9.60
Amiot	IBD	2019	0.56	0.30- 1.03	9.65
Verstockt	IBD	2019	1.28	0.69- 2.37	9.65
Summary			**0.84**	**0.68 - 1.05**	

Q(df=19)=24.66
p=0.1719
I2=13.9%



Authors	Year	OR	95% CI	Weight (%)
Miyazaki T	2020	1.50	0.23-10.4	1.5
Iborra M	2019	1.37	0.8- 2.3	14.2
Biemans VBC	2020	1.00	0.41- 2.5	6.0
Pugliese D	2019	0.40	0.08- 1.9	2.1
Liefferinckx C	2019	0.90	0.38- 2.2	6.3
Battat R	2017	1.00	0.32- 3.1	3.9
Ma C	2017	0.98	0.51- 1.9	10.5
Feagan BG-UNITI1 et 2	2016	1.85	1.03- 3.3	12.3
Feagan BG-UNITI1 et 2	2016	0.69	0.39- 1.2	12.5
Khorrami S	2016	0.58	0.19- 1.7	4.1
Kopylov U	2014	0.44	0.05- 3.5	1.2
Sandborn WJ	2012	1.02	0.46- 2.2	7.5
Wils P	2016	5.21	1.09-24.9	2.1
Sands BE	2019	1.43	0.75- 2.7	10.6
Soufflet	2019	0.25	0.04- 1.5	1.6
Painchart	2019	1.57	0.49- 5.1	3.7
Summary		**1.1**	**0.87 - 1.38**	

Q(df=15)=17.59
p=0.2850
I2=10.96%