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Combination therapy is not associated with improved rates of clinical or endoscopic remission in patients with inflammatory bowel disease treated with ustekinumab or vedolizumab: a retrospective study

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Abstract

Background Management of inflammatory bowel disease (IBD) involves biological agents, often in combination with thiopurines or methotrexate. The aim of our study was to compare clinical and endoscopic outcomes in IBD patients treated with vedolizumab or ustekinumab, as monotherapy or in combination with thiopurines or methotrexate.

Methods We conducted a retrospective cohort study of all patients aged ≥18 years with a diagnosis of ulcerative colitis or Crohn's disease, commenced on vedolizumab or ustekinumab between October 2015 and March 2022. Primary outcome was clinical remission or response calculated by partial Mayo score (remission: <3; response: improvement >1) for ulcerative colitis or Harvey-Bradshaw index (<5, >2 respectively) for Crohn's disease over 1 year. Secondary endpoints were treatment failure, relapse, endoscopic remission at 1 year. Statistical analysis was done using 2-sample Student's *t* and chi-square tests.

Results A total of 159 IBD patients were included in the study, 85 (53%) on vedolizumab and 74 (47%) on ustekinumab. For those on vedolizumab, 61 (72%) patients had ulcerative colitis, and 24 (28%) has Crohn's disease. All patients on ustekinumab had Crohn's disease. Mean disease duration in was 9.4 and 13.5 years respectively. There was no difference in clinical response or remission for vedolizumab or ustekinumab monotherapy compared to combination therapy at 1 year. There was also no difference in treatment failure, relapse or endoscopic remission.

Conclusion Combining vedolizumab or ustekinumab with an immunomodulator is not superior to monotherapy in terms of clinical response or endoscopic remission up to 1 year in IBD.

Keywords Ulcerative colitis, Crohn's disease, biologics, thiopurines

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Introduction

Treatment options for patients with inflammatory bowel disease (IBD), which includes ulcerative colitis (UC) and Crohn's disease (CD), have been growing over the last decade. Steroids, immunomodulators such as thiopurines and methotrexate, and tumor necrosis factor (TNF)-α inhibitors such as infliximab (IFX) and adalimumab (ADA) have been the mainstay of treatment for the past decade [1-3]. There are now newer biologic monoclonal agents that target their own distinct immunological pathway, notably the anti-integrin antibody vedolizumab (VDZ) and the interleukin 12/23 antibody ustekinumab (UST).

Immunomodulators have commonly been used in combination with an anti-TNF-α to provide a synergistic effect from treatment, as well as to prevent immunogenicity of the biologic agent. The rate of immunogenicity and loss of response is quite variable amongst studies, with an estimated risk of around 13% per patient-year for IFX [4-6]. Subsequently, the

use of combination therapy with immunomodulators and IFX to reduce rates of immunogenicity has been demonstrated in the SONIC and UC-SUCCESS trials [7,8]. The benefit of combination treatment for ADA is less clear, with mixed results in the literature [9,10]. It is now considered standard practice to use combination therapy with anti-TNF-α agents, in particular with IFX [11]. It is less clear whether combination therapy confers any benefit with the newer agents, including VDZ and UST, given that they work on a different immunological pathway. VDZ has a significantly lower rate of immunogenicity than IFX, at around 4% [12], while UST is around 4.6% [13].

Evidence for VDZ combination therapy is mixed, with one study of 164 patients showing treatment failure at 1 year in 9.3% of UC patients on combination therapy, compared to 26.3% for VDZ monotherapy [14]. Another multicenter cohort study of 136 patients found better clinical response and remission in CD patients on combination therapy, with an odds ratio (OR) of 2.71 (95% confidence interval [CI] 1.11-6.57), but not for UC (OR 0.22, 95%CI 0.05-0.88) [15]. This contrasted with a *post hoc* analysis in the GEMINI trial, along with a real-world cohort study showing no difference in outcome for combination therapy for both UC and CD compared to VDZ monotherapy [16,17].

There are also mixed results with UST. A study of 122 anti-TNF-α refectory CD patients demonstrated that immunomodulator use in combination with UST was a predictive factor for clinical efficacy at 3 months (OR 5.43, 95%CI 1.14-25.77; P=0.03) [18], whereas 3 other studies found no difference in clinical outcomes [13,17,19].

Based on the current literature, it is unclear whether combination therapy for VDZ or UST is associated with better clinical and endoscopic outcomes for UC and CD, in terms of either a synergistic effect from treatment or the prevention of immunogenicity by the biologic agent. Thiopurines and methotrexate also have several adverse effects, with particular concerns being an increased risk of infection and malignancy, including lymphoma [20]. Avoiding their use would improve the safety outcomes for patients with IBD. The aim of this retrospective cohort study was to determine whether there was a difference in clinical or endoscopic outcomes for UST or VDZ as monotherapy, compared to their combination with thiopurines or methotrexate.

Patients and methods

Study design and setting

Data were prospectively collected from a tertiary IBD center in Australia between October 2015 to March 2022. This study was approved by the Quality Improvement Committee of Royal Perth Hospital and the East Metropolitan Health Service.

Study population

Patients were included if they were over the age of 18, had an endoscopic diagnosis of UC or CD, and were commenced on either VDZ or UST over the trial period. Patients were excluded if they had not completed a full induction regimen and had not subsequently transitioned onto maintenance treatment. Patients on regular VDZ or UST maintenance who did not have at least one Harvey-Bradshaw index (HBI) score for CD or a partial Mayo score for UC available were also excluded.

Study outcomes

The primary outcome was a composite endpoint of clinical remission or response. For UC this was calculated using the partial Mayo score, with remission defined as a score less than 3, and response defined as an improvement in the score greater than 1. For CD this was calculated using the HBI, with remission defined as a score less than 5, and response defined as an improvement in the score greater than 2. Scores were calculated at week 14, 26 and 52. Secondary endpoints were defined as treatment failure at 52 weeks, and endoscopic remission at 52 weeks. Treatment failure or relapse was a combination endpoint consisting of need for dose escalation, reinduction, ceasing biologic medication, and/or IBD-related hospital admission or surgery.

Data collection

Characteristics of both groups were collected, including baseline sex, age at diagnosis, previous surgery and type of IBD, including the Montreal classification for CD. Baseline HBI or partial Mayo score prior to commencement of treatment was determined. Details on treatment were also collected, including time from diagnosis until starting UST or VDZ, previous thiopurine use and previous biologic exposures. During the study period, HBI and partial Mayo were calculated at weeks 14, 26, and 52.

Statistical analysis

Statistical analysis was undertaken using the SPSS statistics software package. Comparisons between groups were made using the 2-sample Student's *t*-test for continuous variables and the chi-square test for categorical variables. Significance was defined as a P-value less than 0.05.

Results

A total of 159 patients were included in the study. Of these, 85 (53%) of patients received treatment with VDZ and

74 (47%) with UST. In the VDZ group, 61 (72%) patients were diagnosed with UC and 24 (28%) with CD. In the UST group, all patients (100%) were diagnosed with CD. The characteristics of the VDZ and UST groups are detailed in Tables 1 and 2, respectively.

In the VDZ group, 56 (66%) were on VDZ monotherapy, with the remainder (33%) on combination therapy. The median age was higher in the VDZ monotherapy group, at 33±11.0 years, compared to 26±13.0 years in the combination group (P=0.03). Disease duration prior to starting VDZ was similar in both groups (9.4±9.1 years and 9.9±9.0 years for VDZ monotherapy and combination therapy, respectively; P=0.79). Steroid use at the time of induction did not differ significantly between the groups: 15 (27%) for VDZ monotherapy and 5 (17%) for combination therapy (P=0.30). For those on VDZ monotherapy, 44 (79%) had previously used a thiopurine and 6 (11%) had used methotrexate. For those on combination therapy 26 (90%) were being treated with a thiopurine, compared to 3 (10%) on methotrexate. There was no difference in previous exposure to anti-TNF-α agents: 31 (55%) and 19 (66%) for VDZ monotherapy and combination therapy, respectively (P=0.55). Only 24 (43%) of the VDZ monotherapy and 10 (35%) of the combination therapy patients were biologic naïve prior to starting VDZ (P=0.86). Baseline mean HBI

Table 1 Characteristics of patients with inflammatory bowel disease on vedolizumab monotherapy or in combination with another immunomodulator

Characteristics	Combination	Monotherapy	P-value
Total number of patients (n=85)	29	56	
Age at diagnosis (mean±SD)	26±11	33±13	0.03
Disease duration prior to starting vedolizumab (years, mean±SD)	9.9±9.0	9.4±9.1	0.79
Type of IBD			0.55
UC	22 (76%)	39 (70%)	
CD	7 (24%)	17 (30%)	
Male sex (n, %)	14 (48%)	28 (50%)	0.88
Location (CD)			0.13
L1	0 (0%)	2 (12%)	
L2	4 (57%)	3 (18%)	
L3	3 (43%)	12 (71%)	
L4	0 (0%)	0 (0%)	
Behavior (CD)			0.47
B1	4 (57%)	9 (53%)	
B2	3 (43%)	5 (29%)	
B3	0 (0%)	3 (18%)	
Perianal disease (CD) (yes, %)	3 (43%)	5 (29%)	0.52
Previous surgery (yes, %)	3 (10%)	12 (21%)	0.23
Steroid use at time of treatment (yes, %) at induction	5 (17%)	15 (27%)	0.30
Thiopurine use			<0.001
Never used	2 (7%)	12 (21%)	
Previously used	1 (3%)	44 (79%)	
Currently using	26 (90%)	0 (0%)	
Methotrexate use			0.01
Never used	26 (90%)	50 (89%)	
Previously used	0 (0%)	6 (11%)	
Currently using	3 (10%)	0 (0%)	
Number of previous biologic exposures			0.86
0	10 (35%)	24 (43%)	
1	14 (14%)	25 (44%)	
2	4 (14%)	6 (11%)	
3	1 (3%)	1 (2%)	
Previous anti-TNF (yes, %)	19 (66%)	31 (55%)	0.55
Baseline HBI (CD) (mean±SD)	5.8±2.0	7.6±5.0	0.29
Baseline partial Mayo (UC) (mean±SD)	3.9±2.1	3.9±1.8	0.79

SD, standard deviation; yrs, years; IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; anti-TNF, tumor necrosis factor α inhibitors; HBI, Harvey-Bradshaw Index

Table 2 Characteristics of patients with inflammatory bowel disease on ustekinumab monotherapy or in combination with another Immunomodulator

Characteristics	Combination	Monotherapy	P-value
Total number of patients (74)	21	53	
Age at diagnosis (mean±SD)	34±19	32±15	0.69
Disease duration prior to starting vedolizumab (years, mean±SD)	13.5±9.5	12.3±11.0	0.67
Male sex (n, %)	10 (48%)	21 (40%)	0.53
Smoking status (yes, %)	3 (14%)	13 (24%)	0.33
Location (CD)			0.40
L1	5 (24%)	15 (28%)	
L2	7 (33%)	9 (17%)	
L3	9 (43%)	27 (51%)	
L4	0 (0%)	2 (4%)	
Behavior (CD)			0.40
B1	12 (57%)	22 (42%)	
B2	6 (29%)	17 (32%)	
B3	3 (14%)	14 (26%)	
Perianal disease (CD) (yes, %)	5 (24%)	17 (32%)	0.48
Previous surgery (yes, %)	11 (52%)	32 (60%)	0.53
Steroid use at time of treatment (yes, %)	5 (24%)	9 (17%)	0.50
Thiopurine use			<0.001
Never used	3 (14%)	15 (28%)	
Previously used	2 (10%)	38 (72%)	
Currently using	16 (76%)	0 (0%)	
Methotrexate use			<0.001
Never used	16 (76%)	47 (89%)	
Previously used	0 (0%)	6 (11%)	
Currently using	5 (24%)	0 (0%)	
Number of previous biologic exposures			0.39
0	5 (24%)	16 (30%)	
1	9 (43%)	25 (47%)	
2	6 (29%)	12 (23%)	
3	1 (4%)	0 (0%)	
Previous anti-TNF (yes, %)	16 (76%)	36 (68%)	0.48
Baseline HBI (CD) (mean±SD)	6.8±3.8	4.9±3.2	0.04

SD, standard deviation; yrs, years; IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; anti-TNF, tumor necrosis factor α inhibitors; HBI, Harvey-Bradshaw Index

and Mayo scores were similar between the groups for VDZ monotherapy (HBI 7.6±5.0, partial Mayo 3.9±1.8; P=0.29) and combination therapy (HBI 5.8±2.0, partial Mayo 3.9±2.1; P=0.79).

In the UST group, 53 (72%) were on UST monotherapy and 21 (28%) on combination therapy. The median age was similar, 32 years and 34 years for UST monotherapy and combination group, respectively (P=0.69), as was disease duration prior to starting UST: 12.3±11.0 years and 13.5±9.5 years (P=0.67). Steroid use at the time of induction did not differ significantly between the groups: 9 (17%) for UST monotherapy and 5 (24%) for combination therapy (P=0.50). For those on UST monotherapy, 38 (72%) had previously used a thiopurine and 6 (11%) had used methotrexate. Among those on combination therapy, 16 (76%) were being treated with a thiopurine, compared to 5 (24%) on methotrexate. There was no difference in the previous rate of anti-TNF-α agents: 36 (68%) and 16 (76%) for VDZ monotherapy and combination therapy, respectively (P=0.48). A smaller proportion of patients were biologic naïve compared to the VDZ group, with 16 (30%) on UST monotherapy and 5 (24%) on combination therapy (P=0.39). Baseline mean HBI scores differed significantly between the groups: 4.9±3.2 for UST monotherapy and 6.8±3.8 for combination treatment (P=0.04).

There was no difference in the primary endpoint of clinical response or remission for VDZ monotherapy compared to combination therapy (Table 3) at week 12 (80% vs. 70%; P=0.38), week 26 (82% vs. 80%; P=0.83) and week 52 (82% vs. 91%; P=0.32). Twenty-five of the 56 (45%) patients on VDZ

monotherapy and 18 of the 29 (62%) on combination therapy had a 1-year colonoscopy, with no difference in endoscopic remission (66% vs. 78%; P=0.36). Similarly, there was no difference in the rate of treatment failure or relapse (23% vs. 19%; P=0.80).

In the UST group (Table 4), there was also no difference in clinical response or remission for UST monotherapy compared to combination therapy at week 12 (78% vs. 93%; P=0.21), week 26 (86% vs. 89%; P=0.74) and week 52 (97% vs. 88%; P=0.23). Twenty of the 53 (38%) patients on VDZ monotherapy and 18 of the 29 (62%) on combination therapy had a 1-year colonoscopy, with no difference in endoscopic remission (70% vs. 63%; P=0.70). There was also no difference in the rate of treatment failure or relapse (21% vs. 24%; P=0.17).

Discussion

VDZ and UST are safe and effective treatment options for the treatment of both CD and UC. This study demonstrated similar rates of clinical response and remission, as well as endoscopic remission, in those treated with monotherapy compared with combination therapy. There were no differences in the rate of treatment failure or relapse between those on monotherapy and those on combination therapy.

Importantly, when the VDZ and UST combination and monotherapy cohorts were compared the groups were relatively well matched, with no major differences. It is noteworthy that, while a proportion of the patients were on steroids during induction for monotherapy and combination therapy with VDZ and UST, there was no statistical difference between these groups. Similarly, previous biologic exposure did not differ significantly among all groups. Given that these groups were similar with regard to both steroid and previous biologic use, we would not expect these variables to affect our findings. There were also varied reasons for treatment failure or relapse, spread among the subgroups of dose escalation, reinduction, change in agent, IBD-related surgery, or IBD-related hospitalization.

This study supports the existing evidence suggesting that there is no benefit from combination therapy for VDZ or UST. Notably, this has been shown in a *post hoc* analysis for a small

Table 3 Outcomes for patients with inflammatory bowel disease on vedolizumab monotherapy or in combination with another Immunomodulator

Outcome	No. of Patients	Combination (%)	No. of Patients	Monotherapy (%)	P-value
Clinical response or remission	29		56		
Week 12	27	19 (70%)	44	35 (80%)	0.38
Week 26	25	20 (80%)	50	41 (82%)	0.83
Week 52	23	21 (91%)	51	42 (82%)	0.32
Endoscopic remission	18	14 (78%)	35	23 (66%)	0.36
Treatment failure or relapse	29	5 (19%)	56	13 (23%)	0.80
Dose escalation		2 (8%)		3 (5%)	
reinduction		1 (4%)		3 (5%)	
Agent ceased or changed		0 (0%)		3 (5%)	
IBD-related surgery		2 (8%)		3 (5%)	
IBD-related hospitalization		0 (0%)		1 (2%)	

IBD, inflammatory bowel disease

Table 4 Outcomes for IBD patients on ustekinumab monotherapy or in combination with another immunomodulator

Outcomes	No. of Patients	Combination (%)	No. of Patients	Monotherapy (%)	P-value
Clinical response or remission	21		53		
Week 12	14	13 (93%)	45	35 (78%)	0.21
Week 26	18	16 (89%)	42	36 (86%)	0.74
Week 52	16	14 (88%)	30	29 (97%)	0.23
Endoscopic remission	8	5 (63%)	20	14 (70%)	0.70
Treatment failure or relapse	21	5 (24%)	53	11 (21%)	0.17
Dose escalation		0 90%)		5 (9%)	
Reinduction		1 (5%)		0 (0%)	
Agent ceased or changed		2 (10%)		1 (2%)	
IBD-related surgery		2 (10%)		3 (6%)	
IBD-related Hospitalization		0 (0%)		2 (4%)	

IBD, inflammatory bowel disease

subgroup of the GEMINI trial, and a larger cohort study of patients in the United States, Canada and France, which both showed no difference in the outcomes of combination therapy for both UC and CD compared to VDZ monotherapy [16,17]. The latter study found that, for VDZ, there was no difference in clinical response or remission with combination therapy compared to monotherapy at week 54 (78.3% vs. 72.9%; P=0.33). For UST, the difference at week 54 was similar (62.1% vs. 67.0%; P=0.52).

The mechanism for immunomodulators in the prevention of immunogenicity is still slightly unclear. It is thought that the addition of immunomodulators to biologic therapy (monoclonal therapy in particular) causes the immune system to be suppressed, which then results in a decrease in antibody formation. Therefore, the addition of thiopurines or methotrexate to biologic therapy could prevent the activation of immune cells and reduce the number of anti-drug antibodies [21]. As the risk of immunogenicity is much lower for VDZ (around 4%) and UST (around 4.6%), it may be that any benefit that could be realized from the addition of an immunomodulator is non-significant [12,13].

Furthermore, there are significant drawbacks to the use of immunomodulators [20]. These include quite significant nausea and leukopenia, as well as an increased risk of serious infection or cancer, and lymphoma in particular. The issue of serious infection is compounded when these drugs are used in addition to biologic therapy.

There are some limitations to this study. It was a retrospective study and there may have been an underlying bias in the selection of patients with more severe disease for combination therapy. For VDZ there was no statistical difference between baseline HBI or partial Mayo scores between the groups; however, in the UST group those on combination therapy had a higher baseline HBI. The study was also limited by the data available from our cohorts, with limited numbers in some subgroups. In addition, as this was a retrospective trial, some variables were incomplete for each time period assessed and were not included in the analysis. Similarly, additional variables, including drug levels and anti-drug antibodies, C-reactive protein and fecal calprotectin, were not included because of missing data. Future research could include a structured prospective study, which would allow for more regular and systematic collection of biomarkers and drug levels, as well as removing any inherent bias in the patient selection.

In conclusion, patients with IBD commencing either VDZ or UST have similar rates of clinical and endoscopic efficacy whether the drug is used as a monotherapy or as part of a combination therapy. There is conflicting evidence for monotherapy in the literature, and this paper adds to the growing evidence that combination VDZ or UST therapy does not lead to better outcomes. Combination therapy with an immunomodulator (thiopurine or methotrexate) can be avoided, which reduces the risks associated with these agents.

Summary Box

What is already known:

- Combination therapy with immunomodulators and infliximab in inflammatory bowel disease to reduce rates of immunogenicity has been demonstrated previously
- Vedolizumab or ustekinumab is often given in combination with an immunomodulator
- It is unclear whether combination therapy for vedolizumab or ustekinumab is associated with better clinical and endoscopic outcomes
- Thiopurines and methotrexate also have several adverse effects, with concerns about infection and malignancy, including lymphoma

What the new findings are:

- Vedolizumab or ustekinumab had similar rates of clinical and endoscopic efficacy if used as a monotherapy compared to combination therapy at 1 year
- This paper adds to the growing evidence that combination therapy does not lead to better outcomes
- Combination therapy with an immunomodulator can be avoided, which reduces the risks associated with these agents

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