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Immunomodulators are Commonly Used as Concomitant Therapy with Vedolizumab or Ustekinumab: TARGET-IBD Real World Cohort

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Introduction

- Newer biologics such as ustekinumab and vedolizumab have been associated with lower risk of infection than anti-tumor necrosis factor agents (anti-TNFs).
- Addition of an immunomodulator in combination therapy may limit this potential benefit, especially in those over age 65, without reducing immunogenicity.
- We aimed to evaluate the prevalence and predictors of immunomodulator use as concomitant therapy with vedolizumab or ustekinumab in patients with inflammatory bowel disease (IBD) in a large longitudinal cohort.

Methods

- TARGET-IBD is a longitudinal cohort of patients with IBD including ulcerative colitis (UC) and Crohn's disease (CD) receiving usual care at community and academic practices in the US.
- Abstractors ascertained clinical information for patients enrolled between July 2017 and November 2020 from electronic medical records and stored these data in a secured repository.
- Rates of anti-TNF, vedolizumab, and ustekinumab monotherapy and combination therapy with methotrexate, azathioprine, or mercaptopurine, at any time during the study period and at time of enrollment, were estimated.
- Analysis of rates of combination therapy was stratified by time from drug approval and previous exposure to other biologic agents.
- Patient characteristics were compared between those on monotherapy and combination therapy at enrollment using bivariate statistics.

Results

- We identified 4229 patients with IBD, 18.5% treated with vedolizumab and 13.0% treated with ustekinumab.
- Among patients with CD on vedolizumab or ustekinumab at enrollment, and patients with UC on vedolizumab at enrollment, combination therapy was used in 28.2% and 19.0% of patients, respectively (Table 1).
- The patient populations were refractory, with high rates of previous biologic exposure (the majority with 2 or more): 73.8% of patients treated with vedolizumab had previous anti-TNF exposure, and 89.6% of patients treated with ustekinumab had anti-TNF exposure, of whom 30.8% also had vedolizumab exposure.
- In patients with CD on vedolizumab or ustekinumab at enrollment, prior biologic exposure was associated with a greater likelihood of combination therapy (p=0.002 and p<0.001 for patients with CD on vedolizumab and ustekinumab, respectively).
- In patients with CD on ustekinumab at enrollment, combination therapy was more common at community sites and in patients <65 years old (p=0.03 and p=0.02, respectively).

Table 1. Participant Characteristics at Enrollment

	Vedolizumab -Crohn's Disease			Ustekinumab-Crohn's Disease			Vedolizumab-Ulcerative colitis		
Summary	**Combination Therapy (N=72)**	**Mono-therapy (N=209)**	**P-value**	**Combination Therapy (N=113)**	**Mono-therapy (N=263)**	**P-value**	**Combination Therapy (N=42)**	**Mono-therapy (N=179)**	**P-value**
Age at Study Entry by Category, n (%)									
<65	60 (83.3)	176 (84.2)	0.86	111 (98.2)	242 (92.0)	**0.02**	40 (95.2)	157 (87.7)	0.16
>=65	12 (16.7)	33 (15.8)		2 (1.8)	21 (8.0)		2 (4.8)	22 (12.3)	
Sex, n (%)									
Female	42 (58.3)	124 (59.3)	0.88	71 (62.8)	149 (56.7)	0.27	20 (47.6)	94 (52.5)	0.57
Male	30 (41.7)	85 (40.7)		42 (37.2)	114 (43.3)		22 (52.4)	85 (47.5)	
Race, n (%)									
White	61 (84.7)	186 (89.0)		94 (83.2)	213 (81.0)		38 (90.5)	146 (81.6)	
Nonwhite	6 (8.3)	19 (9.1)	0.13	16 (14.2)	38 (14.4)	0.68	2 (4.8)	26 (14.5)	0.23
Not Reported	5 (6.9)	4 (1.9)		3 (2.7)	12 (4.6)		2 (4.8)	7 (3.9)	
BMI (kg/m^2)									
Median (n)	26.0 (72)	27.0 (206)	0.55	26.0 (110)	27.0 (252)	0.55	26.0 (41)	27.0 (176)	0.70
Min - Max	16 - 54	15 - 53		18 - 44	13 - 56		19 - 38	17 - 52	
Tobacco Use, n (%)									
Current smoker	6 (8.3)	25 (12.0)	0.40	8 (7.1)	31 (11.8)	0.17	1 (2.4)	4 (2.2)	0.95
Non current smoker	66 (91.7)	184 (88.0)		105 (92.9)	232 (88.2)		41 (97.6)	175 (97.8)	
Duration of Disease (years)									
Median (n)	16.0 (66)	14.0 (191)	0.30	13.0 (110)	12.0 (245)	0.40	8.0 (39)	6.5 (172)	0.54
Min - Max	2 - 54	0 - 58		1 - 56	0 - 49		1 - 31	0 - 37	
Any Previous Biologic Exposure, n (%)[1]									
No	6 (8.3)	53 (25.4)	**0.002**	1 (0.9)	39 (14.8)	**<0.001**	12 (28.6)	72 (40.2)	0.16
Yes	66 (91.7)	156 (74.6)		112 (99.1)	224 (85.2)		30 (71.4)	107 (59.8)	
Number of Previous Biologic Exposures, n (%)									
0	6 (8.3)	53 (25.4)		1 (0.9)	39 (14.8)		12 (28.6)	72 (40.2)	
1	20 (27.8)	57 (27.3)	**0.02**	23 (20.4)	58 (22.1)	**<0.001**	15 (35.7)	73 (40.8)	0.09
2	28 (38.9)	56 (26.8)		36 (31.9)	79 (30.0)		12 (28.6)	30 (16.8)	
3 or more	18 (25.0)	43 (20.6)		53 (46.9)	87 (33.1)		3 (7.1)	4 (2.2)	
Steroid Use at Enrollment, n (%)									
No	49 (68.1)	159 (76.1)	0.18	69 (61.1)	185 (70.3)	0.09	27 (64.3)	111 (62.0)	0.78
Yes	23 (31.9)	50 (23.9)		44 (38.9)	78 (29.7)		15 (35.7)	68 (38.0)	
History of IBD Surgery, n (%)[2]									
No	33 (45.8)	112 (53.6)	0.26	53 (46.9)	141 (53.6)	0.23			
Yes	39 (54.2)	97 (46.4)		60 (53.1)	122 (46.4)				
Location of Crohn's Disease, n (%)									
Colon	10 (13.9)	39 (18.7)		15 (13.3)	41 (15.6)				
Ileocolon	34 (47.2)	87 (41.6)	0.74	71 (62.8)	135 (51.3)	0.08			
Ileum	20 (27.8)	56 (26.8)		18 (15.9)	71 (27.0)				
Not Reported	8 (11.1)	27 (12.9)		9 (8.0)	16 (6.1)				
History of Perianal Disease, n (%)[3]									
No	45 (62.5)	142 (67.9)	0.40	69 (61.1)	160 (60.8)	0.97			
Yes	27 (37.5)	67 (32.1)		44 (38.9)	103 (39.2)				

Note: p-values for categorical variables are from the Cochran-Mantel-Haenszel general association test, and p-values for continuous variables are from the Kruskal-Wallis test. [1]Previous biologic and steroid use include use prior to the start of the vedolizumab or ustekinumab. [2]History of IBD surgery includes: Small intestinal resection, Ileocaecal resection, Colectomy, Colectomy total, Ileocolectomy, Proctocolectomy, Ileostomy, Jejunostomy, Colorectostomy, Colostomy, Enterostomy, Ileocolostomy, Rectal fistula repair, Anal fistula excision, Anal fistula, Anal fistula repair, Colon fistula repair, Gastrointestinal fistula repair, Intestinal fistula repair, Abscess drainage, Abscess management, Perirectal abscess. [3]History of Perianal Disease is based on physical exam, IBD Status, or imaging.

Table 2. Combination Therapy by Biologic Type

	Ulcerative Colitis (N=1620)	Crohn's Disease (N=2609)	All Participants (N=4229)
Total Count of Anti-TNF Users[1], n	666	1581	2247
Anti-TNF combination therapy[2], n (%)			
No	405 (60.8%)	931 (58.9%)	1336 (59.5%)
Yes	261 (39.2%)	650 (41.1%)	911 (40.5%)
Total Count of Vedolizumab Users[1], n	328	455	783
Vedolizumab combination therapy[2], n (%)			
No	239 (72.9%)	301 (66.2%)	540 (69.0%)
Yes	89 (27.1%)	154 (33.8%)	243 (31.0%)
Total Count of Ustekinumab Users[1], n	17	531	548
Ustekinumab combination therapy[2], n (%)			
No	13 (76.5%)	334 (62.9%)	347 (63.3%)
Yes	4 (23.5%)	197 (37.1%)	201 (36.7%)

[1] Includes treatment use at any time during the retrospective or prospective periods. [2] Includes treatment use in combination with methotrexate, azathioprine, or mercaptopurine. Note: Participants may be users of more than one of anti-TNF, vedolizumab, or ustekinumab.

Table 3. Combination Therapy by Start Date

	Ulcerative Colitis		Crohn's Disease		Crohn's Disease	
Summary	**Vedo started 2014-2016 (N=77)**	**Vedo started 2017-2020 (N=249)**	**Vedo started 2014-2016 (N=182)**	**Vedo started 2017-2020 (N=271)**	**Ustek started 2016-2018 (N=370)**	**Ustek started 2019-2020 (N=140)**
Treatment type, n (%)[1]						
n	77	249	182	271	370	140
Monotherapy	48 (62.3%)	189 (75.9%)	106 (58.2%)	194 (71.6%)	223 (60.3%)	104 (74.3%)
Combination therapy with methotrexate	5 (6.5%)	14 (5.6%)	30 (16.5%)	36 (13.3%)	70 (18.9%)	18 (12.9%)
Combination therapy with azathioprine	12 (15.6%)	33 (13.3%)	27 (14.8%)	31 (11.4%)	57 (15.4%)	14 (10.0%)
Combination therapy with mercaptopurine	14 (18.2%)	14 (5.6%)	25 (13.7%)	17 (6.3%)	30 (8.1%)	4 (2.9%)

Note: Start year is based on earliest therapy start date recorded. Participants may have also had prior use of ustekinumab of vedolizumab.
[1]Combination therapy includes the use of vedolizumab or ustekinumab concurrently with methotrexate, azathioprine, or mercaptopurine, at any point during the retrospective or prospective periods. The three combination therapy groups are not mutually exclusive.
Note: Ustekinumab start year is based on earliest ustekinumab start date recorded in IBD Treatment Exposures. Participants may have also had prior ustekinumab use.
Note: 5 and 12 ulcerative colitis participants had ustekinumab start years from 2016-2018 and 2019-2020, respectively (data not shown in table).

Results (continued)

- No difference in rates of combination therapy for patients treated with ustekinumab as compared to anti-TNFs (p=0.10), (Table 2).
- Vedolizumab not used as frequently in combination therapy as anti-TNFs (p<0.01).
- Vedolizumab was more commonly used in combination therapy in CD as compared to UC (p=0.045).
- No statically significant difference in rates of combination therapy with vedolizumab as compared to ustekinumab in CD (p=.29).
- Rates of combination therapy decreased with time from drug approval (Table 3).

Conclusions

- **Combination therapy with vedolizumab or ustekinumab was common, with ustekinumab used as frequently with an immunomodulator as anti-TNFs.**
  - **Use of vedolizumab combination therapy was additionally common, especially in Crohn's disease.**
- **Use of combination therapy in CD was associated with greater exposure to other biologics.**
  - **For patients with CD treated with ustekinumab, combination therapy was lower in those over age 65.**
- **Use of combination therapy decreased with time from drug approval.**
- **Further data are needed on efficacy and safety of combination therapy in patients initiating vedolizumab or ustekinumab for IBD to avoid unnecessary risk with otherwise generally safe therapies.**

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