

# Patient-Preferences Favoring Treatment Discontinuation Are Reduced With Vedolizumab and Ustekinumab Compared With TNF Antagonists in Inflammatory Bowel Disease

Anand Kumar, MD,\* Emilie S. Kim, BS,\*† Philip Kozan, MD,‡ Vinita Jacob, MD,\* Randy S. Longman, MD, PhD,\* Ellen J. Scherl, MD,\* Robert J. Battat, MD,\* and Dana J. Lukin, MD, PhD\*<sup>○</sup>

**Background:** Nonadherence to biologic therapy in inflammatory bowel disease (IBD) is associated with risk of relapse, immunogenicity, and disease complications. Significant nonadherence prevalence is reported with tumor necrosis factor (TNF) antagonists but the risk of nonadherence with newer biologics with better safety profiles is unknown. This study aimed to investigate if IBD patient-preferences favoring biologic discontinuation vary by biologic class and analyze factors associated with such preferences.

**Methods:** A convenience sample of 200 adults with IBD on biologic therapy treated at an academic outpatient center was surveyed using a 22-point questionnaire. Patient-preference favoring treatment discontinuation between TNF-antagonist and non-TNF-antagonist biologics [vedolizumab (VDZ)/ustekinumab (UST)] was compared using  $\chi^2$  test. Risk factors associated with a preference to discontinue biologic therapy were evaluated using univariable and multivariable logistic regression, and Spearman rank correlation analyses.

**Results:** A total of 190 questionnaires were analyzed that contained data on preferences regarding biologic discontinuation (median age 36 years, 62% were females; 63% had Crohn disease; 56% were receiving a TNF antagonist, 31% VDZ, and 14% UST). Overall, 32% patients reported a preference to discontinue biologic treatment with a higher proportion among those receiving a TNF antagonist compared with VDZ/UST (39.6% vs 21.4%;  $P < 0.01$ ). Current VDZ/UST use was independently associated with a reduced odds of patient-preference favoring biologic discontinuation [adjusted odds ratio: 2.67 (1.42–5.01);  $P < 0.01$ ]. The most concerning factor to patients was the perceived risk of side effects. Patients on VDZ/UST perceived their therapy to be safer than those receiving a TNF antagonist ( $r = 0.2$ ,  $P = 0.04$ ).

**Conclusions:** Patient-preference favoring treatment discontinuation is improved with VDZ/UST compared with TNF-antagonist biologic therapy.

## Lay Summary

Despite several benefits of biologic therapy in inflammatory bowel disease patients, high rates of nonadherence and discontinuation have been reported. This study demonstrates that a significantly lower proportion of patients receiving vedolizumab or ustekinumab compared with tumor necrosis factor-antagonist therapy preferred to discontinue therapy.

**Key Words:** inflammatory bowel disease, nonadherence, biologic therapy, patient preference, vedolizumab, ustekinumab, TNF antagonist

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\*Division of Gastroenterology, Jill Roberts Center for Inflammatory Bowel Disease, Weill Cornell Medical College, New York, New York, USA; †New Jersey Medical School—Rutgers University, New Brunswick, New Jersey, USA; ‡Department of Medicine, University of California, Los Angeles, Los Angeles, California, USA

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Address correspondence to: Dana J. Lukin, MD, PhD, 1315 York Avenue, Mezzanine SM1A15, New York, NY 10021 ([dj9010@med.cornell.edu](mailto:dj9010@med.cornell.edu)).

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## INTRODUCTION

Inflammatory bowel diseases (IBD), including Crohn disease (CD) and ulcerative colitis (UC), are chronic idiopathic diseases of the digestive tract. Current treatment targets include controlling symptoms and achieving mucosal healing.<sup>1</sup> Biologic agents are recommended as a first-line of therapy to achieve these treatment targets in patients with moderately to severely active IBD. Infliximab (IFX), a tumor necrosis factor- $\alpha$  (TNF $\alpha$ ) antagonist, was the first biologic agent to be approved by the Food and Drug Administration (FDA) for the treatment of CD and UC. Subsequently, other TNF antagonists, anti-interleukin-12/23 (ustekinumab, UST), and anti-integrin therapies (vedolizumab, VDZ) have also shown efficacy in achieving and maintaining clinical and endoscopic remission, reducing need for steroids, complications, hospitalization, and surgery, and in improving patients' quality of life (QOL).<sup>2-6</sup> However, TNF antagonists have been associated with the risk of adverse effects including opportunistic infections, skin cancers, and lymphoma.<sup>7,8</sup> Although the newly approved biologics such as VDZ and UST have not yet demonstrated the risk of serious infections or malignancy,<sup>7,9-12</sup> concern among patients and providers still exists when initiating these agents.

In addition to patient and provider preferences of biologic medication safety, other limitations of existing therapies include significant rates of primary nonresponse and secondary loss of response, medication cost, healthcare access, and time commitment.<sup>2,13,14</sup> Patient's perceptions of their disease state and need for therapy are also driven by culture, belief systems, psychological state, educational level, income, insurance coverage, and their interactions with providers and healthcare systems.<sup>15-17</sup> As patients have different perceptions of acceptable risks and benefits, individual patient preferences must be included in the shared decision-making process.

Withdrawal of TNF antagonist therapy has been associated with a significant risk of relapse approaching 50% at 1 year and above 70% beyond 7 years.<sup>18-20</sup> In addition, nonadherence to biologic therapy is associated with increased risk of immunogenicity, loss of response, disease-related complications, reduced QOL, and increased healthcare cost.<sup>21-24</sup> Despite this, studies have reported nonadherence rates of 38%–77% for biologic therapy.<sup>25,26</sup> Risk of nonadherence with newer classes of biologics and factors that shape a patient's preference to discontinue biologic therapy in IBD are not well understood. Few studies have retrospectively examined potential risk factors of nonadherence in patients who discontinued biologic therapy.<sup>23,24</sup> Identifying IBD patients at risk of biologic discontinuation prior to actual discontinuation would provide opportunities to intervene in a timely fashion, and potentially prevent negative outcomes resulting from unsupervised withdrawal of biologic therapy.

The advent of multiple new biologic drug classes further complicates the identification of patients at risk for biologic treatment cessation. Despite clear differences in safety

profiles of TNF antagonists and newer biologic therapies, it is unclear if this information is adequately relayed to the patients. Therefore, this study aimed to determine if IBD patient-preferences favoring biologic discontinuation, while still on therapy, vary by biologic class and analyze factors associated with such preferences.

## METHODS

### Study Design and Participants

Survey data were prospectively collected from August 2019 to October 2019 on a convenience sample of 200 adult ( $\geq 18$  years) patients with IBD presenting for routine visits at a large outpatient IBD center affiliated with a tertiary academic institution. Included patients were English-speaking and receiving a single approved biologic therapy [IFX, adalimumab (ADA), certolizumab pegol (CZP), golimumab (GOL), VDZ, or UST]. Patients were excluded if a response for the primary variable of interest, ie, need for biologic discontinuation (Survey question #17) was not provided. Additional clinical data were obtained through medical chart review.

### Survey Instrument

For the survey, we designed a 22-item questionnaire consisting of multiple-choice questions for patients to select a single response (Fig. 1). Included items were selected based upon existing data on factors associated with treatment nonadherence and their clinical relevance.<sup>23,27</sup> A team of IBD specialists and trainees developed the initial questionnaire which was pilot-tested on 10 patients. After 2 iterations that included shortening to fit within a 2-sided page and simplifying the language to allow for self-administration, the final version was distributed to eligible participants.

The questionnaire consisted of 4 sections (Fig. 1). The first section included questions on patient demographics, educational status, insurance status, and annual household income. The second section pertained to IBD diagnosis, medications, smoking status, and history of anxiety or depressive disorder. The third section consisted of a series of questions on a Likert scale regarding patient perceptions about QOL, literacy of IBD and biologics, safety of biologic therapy, and preferences about the need for continuation or discontinuation of current biologic therapy. The fourth section assessed factors important in considering continuation or discontinuation of biologic therapy, and acceptable risk of flare and willingness for follow-ups among those considering treatment cessation. Details regarding the IBD type (UC or CD) and disease activity indices were completed by the physician. Clinical disease activity in UC was defined using partial Mayo score (PMS; remission: 0–1, mildly active: 2–4, moderately active: 5–6, severely active: 7–9) and in CD using the Harvey Bradshaw Index (HBI; remission: <5, mildly active: 5–7, moderately active: 8–16, severely active: >16).

BIOLOGIC THERAPY SURVEY		
<b>Patient Name:</b> DOB: _____ Age (years): _____ Sex: Male <input type="checkbox"/>   Female <input type="checkbox"/>	<b>What is your race?</b> White <input type="checkbox"/>   Black <input type="checkbox"/>   Asian/Pacific Islander <input type="checkbox"/>   Indian/Pakistani/Bengali <input type="checkbox"/>   Other? _____	<b>What is your ethnicity?</b> Hispanic <input type="checkbox"/>   non-Hispanic <input type="checkbox"/>   other <input type="checkbox"/>
<b>Highest level of education:</b> High school or less <input type="checkbox"/>   Some college, no degree <input type="checkbox"/>   College graduate <input type="checkbox"/>   Advanced degree <input type="checkbox"/>	<b>What kind of insurance do you have?</b> Commercial <input type="checkbox"/>   None <input type="checkbox"/>   Medicaid <input type="checkbox"/>   Medicare <input type="checkbox"/>   Government (VA) <input type="checkbox"/>	<b>What is your annual household income (optional)?</b> 0-\$9,999 <input type="checkbox"/>   \$10,000-24,999 <input type="checkbox"/>   \$25,000-49,999 <input type="checkbox"/>   \$50,000-99,999 <input type="checkbox"/>   >\$100,000 <input type="checkbox"/>
1. Inflammatory Bowel Disease (IBD) type: Crohn's disease <input type="checkbox"/> Ulcerative colitis <input type="checkbox"/>		
2. Age at IBD diagnosis (years): _____ Duration of IBD (years): _____		
3. Which of the following treatments are you currently receiving? (Select one or more) Infliximab (Remicade) <input type="checkbox"/> Adalimumab (Humira) <input type="checkbox"/> Certolizumab (Cimzia) <input type="checkbox"/> Golimumab (Simponi) <input type="checkbox"/> Ustekinumab (Stelara) <input type="checkbox"/> Vedolizumab (Entyvio) <input type="checkbox"/> Natalizumab (Tysabri) <input type="checkbox"/> Tofacitinib (Xeljanz) <input type="checkbox"/>		
4. Duration of present biologic therapy (years): _____		
5. Which of the other IBD medications are you currently receiving? (Select all that apply) Mesalamine (Pentasa, Asacol, Lialda, Apriso, Delzicol, Canasa, Rowasa) <input type="checkbox"/> Sulfasalazine (Azulfidine, Sulfazine) <input type="checkbox"/> Balsalazide (Colazal) <input type="checkbox"/> Olsalazine (Dipentum) <input type="checkbox"/> Prednisone <input type="checkbox"/> Hydrocortisone (Cortef, Anusol) <input type="checkbox"/> Methylprednisolone (Medrol) <input type="checkbox"/> Budesonide (Uceris, Entocort) <input type="checkbox"/> Azathioprine (Imuran) <input type="checkbox"/> Mercaptopurine <input type="checkbox"/> Methotrexate (Rheumatrex, Trexall) <input type="checkbox"/>		
6. History of surgery for IBD? Yes <input type="checkbox"/>   No <input type="checkbox"/>	7. History of anxiety/depression? Yes <input type="checkbox"/>   No <input type="checkbox"/>	8. Smoking Status: Never <input type="checkbox"/>   Current <input type="checkbox"/>   Former <input type="checkbox"/>
For the following questions, please select the most appropriate choice:		
9. What is your perceived quality of life currently? Poor <input type="checkbox"/>   Fair <input type="checkbox"/>   Good <input type="checkbox"/>   Excellent <input type="checkbox"/>		
10. What is your perceived quality of life now compared to before immunosuppressive therapy? Same <input type="checkbox"/>   Improved <input type="checkbox"/>   Decreased <input type="checkbox"/>		
11. How would you characterize your knowledge on IBD? None <input type="checkbox"/>   Minimal <input type="checkbox"/>   Moderate <input type="checkbox"/>   Excellent <input type="checkbox"/>		
12. How would you characterize your knowledge of biologic therapies used to treat IBD? None <input type="checkbox"/>   Minimal <input type="checkbox"/>   Moderate <input type="checkbox"/>   Excellent <input type="checkbox"/>		
13. How severe would you characterize your disease: Severe <input type="checkbox"/>   Moderate <input type="checkbox"/>   Mild <input type="checkbox"/>   Remission <input type="checkbox"/>		
14. How safe do you consider your current biologic therapy? Not safe <input type="checkbox"/>   Minimally safe <input type="checkbox"/>   Moderately safe <input type="checkbox"/>   Very safe <input type="checkbox"/>		
15. What is your perceived need for continuation of biologic therapy on a scale of 1 to 10? (1 = no need, 10 = very important): _____		
16. For how many years do you think you need to remain on immunosuppressive therapy: <1 <input type="checkbox"/>   1-2 <input type="checkbox"/>   3-5 <input type="checkbox"/>   5-10 <input type="checkbox"/>   >10 (indefinitely) <input type="checkbox"/>		
17. Do you wish to stop your biologic therapy? Yes <input type="checkbox"/>   No <input type="checkbox"/>		
18. What is important to you when considering the continuation of immunosuppressive therapy? 10a. Select one or more: Avoid symptoms/flare <input type="checkbox"/>   Avoid complication/need for surgery <input type="checkbox"/>   Remaining in remission/Disease control <input type="checkbox"/>   Avoid steroid use <input type="checkbox"/>   Improving/maintaining quality of life <input type="checkbox"/>   Other: _____ 10b. Which of the above is the most important? (select one): _____		
19. Which of the following would cause you to stop biologic therapy? 11a. Select one or more: Lack/loss of response <input type="checkbox"/>   Safety/side effects <input type="checkbox"/>   Time (appointments/infusion therapy) <input type="checkbox"/>   Cost <input type="checkbox"/>   Being in prolonged remission <input type="checkbox"/>   Inconvenience of taking medication (infusion, injection, taking pills) <input type="checkbox"/>   Had surgery for IBD <input type="checkbox"/>   Other: _____ 11b. Which of the above is the most important? (select one): _____		
20. Which of these potential adverse effects is most concerning to you? 12a. Select one or more: Infection <input type="checkbox"/>   Lymphoma <input type="checkbox"/>   Skin cancer <input type="checkbox"/>   Demyelinating conditions (nerve problems) <input type="checkbox"/>   Worsening of heart failure <input type="checkbox"/>   Infusion reactions <input type="checkbox"/>   Rash <input type="checkbox"/>   Headache <input type="checkbox"/>   Liver injury <input type="checkbox"/>   Low blood counts <input type="checkbox"/> 12b. Which of the above is the most important? (select one): _____		
21. How much risk of disease flare is acceptable to you? 0% <input type="checkbox"/>   <10% <input type="checkbox"/>   11-25% <input type="checkbox"/>   26-50% <input type="checkbox"/>   >50% <input type="checkbox"/>		
22. If you stopped therapy, would you be willing to be followed for signs of recurrence? Yes <input type="checkbox"/>   No <input type="checkbox"/>   Maybe <input type="checkbox"/>		
14a. Get blood work 2+ times per year? Yes <input type="checkbox"/>   No <input type="checkbox"/>   Maybe <input type="checkbox"/>		
14b. Get stool studies 2+times per year? Yes <input type="checkbox"/>   No <input type="checkbox"/>   Maybe <input type="checkbox"/>		
14c. Get an MRI every 1-2 years? Yes <input type="checkbox"/>   No <input type="checkbox"/>   Maybe <input type="checkbox"/>		
14d. Get periodic colonoscopy? Yes <input type="checkbox"/>   No <input type="checkbox"/>   Maybe <input type="checkbox"/>		

FIGURE 1. Study questionnaire.

### Statistical Analysis

The primary objective was to compare rates of patient-preference favoring treatment discontinuation (primary outcome) between those receiving TNF-antagonist and non-TNF antagonist biologic medications (VDZ and UST). Other potential risk factors associated with patients' preference to discontinue biologic therapy were also analyzed. We used  $\chi^2$  test to compare categorical variables and student *t* test for continuous variables. Logistic regression analysis was employed for estimates of effect sizes. Patient Likert responses were dichotomized and univariable logistic regression was performed for each potential risk factor and the primary outcome. Independent associations were then calculated using a multivariable logistic regression model including covariates with *P*-value <0.1 in the univariable analysis. The secondary objectives were to describe patient-reported factors responsible for their preference favoring biologic discontinuation. Additional relationships between Likert response scales and the primary outcome variable were explored using Spearman rank correlation. All statistical analyses were performed using IBM SPSS Version 25.0 (IBM Corp., Armonk, NY). The study was reviewed and approved by the Weill Cornell Medicine Institutional Review Board.

### RESULTS

Of the 263 eligible patients who were given the questionnaire, 200 responded and returned the survey (response rate 76%). Of this, 190 patients provided data on preferences for biologic medication discontinuation and were therefore included for analysis. The median response rate per question was 98% [interquartile range (IQR) 96%–100%]. Median age of the respondents was 36 (IQR 29–51) years, 62% (N = 117) were females; 77% (N = 141) patients had either an advanced or college degree, 71% (N = 129) had commercial health insurance, 60% (N = 84) had an annual household income of >100,000 USD (Table 1). A total of 63% and 37% of patients had CD and UC, respectively and 66% of CD and 54% of UC patients were in clinical remission. Overall, 56% (N = 106) were receiving a TNF antagonist, 31% (N = 58) VDZ, and 14% (N = 26) UST. The median duration on the current biologic therapy was 2 (IQR 2–3) years and 40% had received another biologic previously. Additionally, 16% of patients were receiving concurrent treatment with corticosteroids (oral or rectal), 24% with aminosallylates (oral or rectal) and 6% were on combination therapy with a thiopurine or methotrexate. Twenty-six percent (N = 49) of patients reported to have undergone an IBD-related

**TABLE 1.** Baseline Characteristics of the Survey Population

Respondent Characteristics		Total Patients (N = 190)	Patients on TNF Antagonist (N = 106)	Patients on VDZ/UST (N = 84)	P*	
		N (%) or Median (IQR)	N (%) or Median (IQR)	N (%) or Median (IQR)		
Age categories	<40 years	107 (56.3)	63 (59.4)	44 (52.4)	0.03	
	≥40 years	83 (43.7)	43 (40.6)	40 (47.6)		
Gender	Females	117 (61.6)	64 (60.4)	53 (63.1)	0.12	
	Males	73 (38.4)	42 (39.6)	31 (36.9)		
Race <sup>†</sup>	Caucasian	135 (73.8)	72 (70.6)	63 (77.8)	0.27	
	Non-Caucasian	48 (26.2)	30 (29.4)	18 (22.2)		
Ethnicity <sup>†</sup>	Non-Hispanic	159 (86.9)	91 (89.2)	68 (84)	0.22	
	Hispanic	23 (12.6)	10 (9.8)	13 (16)		
Educational status <sup>†</sup>	Advanced degree	72 (39.1)	38 (37.2)	34 (41.5)	0.85	
	College graduate with degree	69 (37.5)	41 (40.2)	28 (34.1)		
	Some college, no degree	30 (15.8)	16 (15.7)	14 (16.7)		
	High school or less	12 (6.5)	7 (6.9)	5 (6.1)		
Health insurance <sup>†</sup>	Commercial	129 (70.9)	69 (68.3)	60 (74.1)	0.10	
	Other (Medicare/Medicaid/ government/none)	53 (29.1)	32 (31.7)	21 (25.9)		
Annual household income <sup>†</sup>	>\$100,000	84 (60.0)	45 (56.2)	39 (65)	0.26	
	≤\$100,000	56 (40.0)	35 (43.8)	21 (35)		
Smoking status	Never smoker	164 (86.3)	93 (87.8)	71 (84.5)	0.75	
	Current smoker	9 (4.7)	5 (4.7)	4 (4.8)		
	Former smoker	17 (8.9)	8 (7.5)	9 (10.7)		
History of anxiety/depression		28 (14.7)	14 (13.2)	14 (16.7)	0.53	
IBD type	UC	70 (36.8)	40 (37.7)	30 (35.8)	0.14	
	CD	120 (63.2)	66 (62.3)	54 (64.2)		
Age at diagnosis	<40 years	111 (58.4)	64 (60.3)	47 (56)	0.05	
	>40 years	79 (41.6)	42 (39.6)	37 (44)		
Duration of IBD (years), median (IQR)		10 (6–17)	10 (5–15.25)	12 (6.25–20)	0.16	
HBI categories <sup>‡</sup>	Remission (<5)	79 (65.8)	42 (63.6)	37 (68.5)	0.92	
	Mild (5–7)	16 (13.3)	9 (13.6)	7 (13)		
	Moderate (8–16)	19 (15.8)	11 (16.7)	8 (14.8)		
	Severe (>16)	6 (5)	4 (6.1)	2 (3.7)		
PMS categories <sup>§</sup>	Remission (0–1)	38 (54.3)	21 (52.5)	17 (56.7)	0.21	
	Mild (2–4)	16 (22.9)	9 (22.5)	7 (23.3)		
	Moderate (5–6)	6 (8.6)	7 (17.5)	2 (6.7)		
	Severe (7–9)	7 (10.0)	3 (7.5)	4 (13.3)		
Current biologic therapy	TNF antagonist	Infliximab	82 (43.2)	82 (77.4)	—	
		ADA	17 (8.9)	17 (16)	—	
		CZP	6 (3.2)	6 (5.7)	—	
		GOL	1 (0.5)	1 (0.9)	—	
	Non-TNF antagonist	VDZ	58 (30.5)	—	58 (69)	
	UST	26 (13.7)	—	26 (31)		
Duration of current biologic therapy (years), median (IQR)		2 (1–3)	2 (1–3.25)	1.75 (0.5–3.5)	0.08	
Concurrent steroids		31 (16.3)	18 (17)	13 (15.5)	0.29	
Concurrent aminosalicilate		46 (24.2)	23 (21.7)	23 (27.4)	0.39	

TABLE 1. Continued

Respondent Characteristics	Total Patients (N = 190)	Patients on TNF Antagonist (N = 106)	Patients on VDZ/UST (N = 84)	P*
	N (%) or Median (IQR)	N (%) or Median (IQR)	N (%) or Median (IQR)	
Concurrent immunomodulator	12 (6.3)	8 (7.5)	4 (4.8)	0.43
Prior biologic therapy	None	72 (67.9)	43 (51.2)	0.02
	1	18 (17.0)	19 (22.6)	
	≥2	16 (15.1)	22 (26.2)	
Prior IBD-related surgery	49 (25.8)	26 (24.5)	23 (27.4)	0.37

\*Comparing TNF antagonist vs VDZ/UST groups using Pearson  $\chi^2$  test or *t* test.

†Missing values: race: 7, ethnicity: 8, educational status: 7, health insurance: 8, annual household income: 50.

‡Percentages represent out of CD patients.

§Percentages represent out of UC patients.

surgery previously. Patients receiving TNF antagonists and non-TNF antagonist (VDZ/UST) biologic therapy had similar baseline characteristics except higher proportion of patients over the age of 40 years and with prior biologic use among those on VDZ/UST (Table 1). QOL was reported as either good or excellent in 72% of patients and 77% reported their QOL to have improved after being on biologic treatment. The majority of patients perceived their literacy of IBD and biologic therapy to be moderate (55% and 58%, respectively). Fifty-eight percent perceived the safety of their current biologic therapy as either moderately safe or very safe (Table 2).

### Patient-Preference Favoring Discontinuation of Therapy Across Biologic Classes

Overall, 31.6% (N = 60) patients perceived a need to discontinue biologic treatment. A higher proportion of patients receiving TNF-antagonist (39.6%, n = 42) favored treatment discontinuation compared with patients receiving non-TNF antagonist biologics (VDZ/UST) (21.4%, n = 18,  $P = 0.01$ , Fig. 2A). In univariable regression analysis, compared with TNF-antagonist therapy, non-TNF antagonist use was associated with reduced odds of the perceived need for biologic discontinuation [odds ratio (OR): 0.42 (95% confidence interval: 0.22–0.80);  $P < 0.01$ ] and this remained significant on multivariable analysis [adjusted OR (aOR): 0.23 (0.09–0.58);  $P < 0.01$ ] (after adjusting for age, sex, race, educational level, perceived knowledge of biologics and their safety, duration of biologic therapy, concurrent steroid use, smoking status, and history of anxiety/depression; Table 3).

There was no significant difference in the preference for treatment discontinuation when categorized by route of administration, ie, intravenous (IFX/VDZ, 34.3%, n = 48) vs subcutaneous (ADA/CZP/GOL/UST, n = 12, 24.0%),

$P = 0.18$ ] (Fig. 2B). Additionally, within the 2 biologic classes, there was no statistical difference in patient preference for treatment cessation based on prior biologic use (Supplementary Table 3).

Patients on VDZ/UST perceived their therapy to be safer than those receiving a TNF antagonist [correlation coefficient ( $r$ ) = 0.2,  $P = 0.04$ ]. The factor most concerning to patients in contemplating biologic cessation was the perceived risk of side effects (44%, N = 83), followed by the risk of loss of response (26%, N = 50) and being in prolonged remission (13%, N = 24). Of the patients who considered discontinuation of biologic therapy, 53% would accept <10% hypothetical risk of flare after stopping therapy and none was willing to accept >50% risk of flare (Supplementary Table 1).

### Additional Factors Associated With Patient Preference for Discontinuation of Biologic Therapy

In multivariate regression analysis, male sex [aOR: 3.65 (1.53–8.74)], age <40 years [aOR 2.9 (1.09–7.70)], concurrent corticosteroid therapy [aOR 3.38 (1.26–10.8)], and a history of anxiety/depressive disorder [aOR 3.51 (1.01–12.11)] were associated with an increased odds of patient-preference favoring biologic discontinuation. Conversely, factors associated with a reduced odds of such preference included having an advanced educational degree [aOR 0.45 (0.18–0.91)], perceived excellent literacy of biologics [aOR 0.27 (0.08–0.92)], and a moderate-to-high perceived safety of biologic therapy [aOR 0.24 (0.13–0.56)] (Table 3). Additionally, in univariable analysis, non-Caucasian race, annual household income ≤\$100,000 and current smoking status were associated with the higher odds of patient-preference favoring biologic discontinuation. Detailed results of univariate analysis are described in Supplementary Table 2.

**TABLE 2.** Patient-Perceived QOL, Literacy of IBD/Biologics and Safety of Biologic Therapy

Patient Perception		All Patients (N = 190)	Patients on TNF Antagonist (N = 106)	Patients on VDZ/UST (N = 84)	P*
		N (%)			
QOL <sup>†</sup>	Poor	10 (5.4)	6 (5.7)	4 (5)	0.86
	Fair	41 (22.2)	21 (20)	20 (25)	
	Good	69 (37.3)	40 (38.1)	29 (36.3)	
	Excellent	65 (35.1)	38 (36.2)	27 (33.8)	
QOL after starting biologic <sup>†</sup>	Same	26 (14.1)	13 (12.6)	13 (15.9)	0.83
	Improved	142 (77.2)	80 (78.4)	62 (75.6)	
	Worsened	16 (8.7)	9 (8.8)	7 (8.5)	
Literacy of IBD <sup>†</sup>	None-Minimal	15 (7.9)	10 (9.5)	5 (6)	0.48
	Moderate	104 (55.0)	59 (56.2)	45 (53.6)	
	Excellent	69 (36.5)	35 (33.3)	34 (40.5)	
Literacy of biologic agents <sup>†</sup>	None-Minimal	38 (20.1)	23 (21.9)	15 (17.9)	0.63
	Moderate	109 (57.7)	61 (58.1)	48 (57.1)	
	Excellent	42 (22.2)	21 (20)	21 (25)	
Perceived disease severity <sup>†</sup>	Remission	70 (37.4)	35 (34)	35 (41.7)	0.84
	Mild	31 (16.6)	18 (17.6)	13 (15.5)	
	Moderate	53 (28.3)	29 (28.4)	24 (28.6)	
	Severe	33 (17.6)	19 (18.6)	14 (16.7)	
Perceived safety of biologic therapy <sup>†</sup>	Not safe	17 (9.6)	10 (10.4)	7 (8.6)	0.22
	Minimally safe	35 (19.8)	24 (25)	11 (13.6)	
	Moderately safe	58 (32.8)	31 (32.3)	30 (37.0)	
	Very safe	45 (25.4)	21 (21.9)	24 (29.6)	
	Not sure	22 (12.4)	10 (10.4)	9 (11.1)	

\*Comparing TNF antagonist vs VDZ/UST using Pearson  $\chi^2$  test.

<sup>†</sup>Missing values: QOL: 5, QOL after biologic: 6, literacy of IBD: 2, literacy of biologic: 1, perceived disease severity: 3, perceived safety of biologic therapy: 13.

## DISCUSSION

Limited data exist on factors associated with biologic therapy discontinuation in patients with IBD and further knowledge gaps are present in identifying these elements while patients are still receiving therapy which might enable preventative interventions prior to self-discontinuation. This large study prospectively surveyed preferences favoring biologic discontinuation in 200 IBD patients and demonstrated higher rates favoring discontinuation in patients receiving TNF antagonist compared to non-TNF antagonist biologic medications. Additionally, overall rates of preference favoring treatment cessation were similar to known nonadherence rates of biologic therapies.<sup>26,27</sup>

Previous research has been focused on understanding the prevalence and predictors of treatment nonadherence in patients who withdraw therapy. Estimates of nonadherence prevalence have been extremely varied. A systematic review 41 studies reported nonadherence to biologics in 38%–77% of patients with 7%–65% patients discontinuing by 12 months.<sup>26</sup> Higher rates of adherence are reported with biologic therapies compared with nonbiologic therapies.<sup>28</sup> Among those on

biologics, a higher adherence prevalence is reported in those on VDZ than anti-TNFs,<sup>27,29</sup> which is consistent with the current study. While few studies have reported higher nonadherence risk in patients on subcutaneously administered biologic (vs intravenous),<sup>24,30</sup> we found no significant difference. Although IFX is a highly effective therapy and often the preferred agent to treat severely active IBD and fistulizing disease, the non-TNF-antagonist biologics including VDZ and UST offer potential advantages such as improved safety profile and minimal risk of immunogenicity.<sup>7,9,12,31</sup>

Our findings suggest that male sex, younger age, non-Caucasian race, and lower educational and income status are associated with a preference favoring biologic discontinuation. Additionally, active smoking and history of anxiety or depression were associated with an attitude favoring biologic discontinuation. These factors have previously been studied for treatment nonadherence with nonbiologic and TNF antagonist therapies.<sup>28,32–35</sup> In a systematic review, female sex, smoking, anxiety, and psychological distress were found to predict nonadherence to TNF antagonists.<sup>23</sup> Consistent with our results, 2 observational studies that included patients receiving

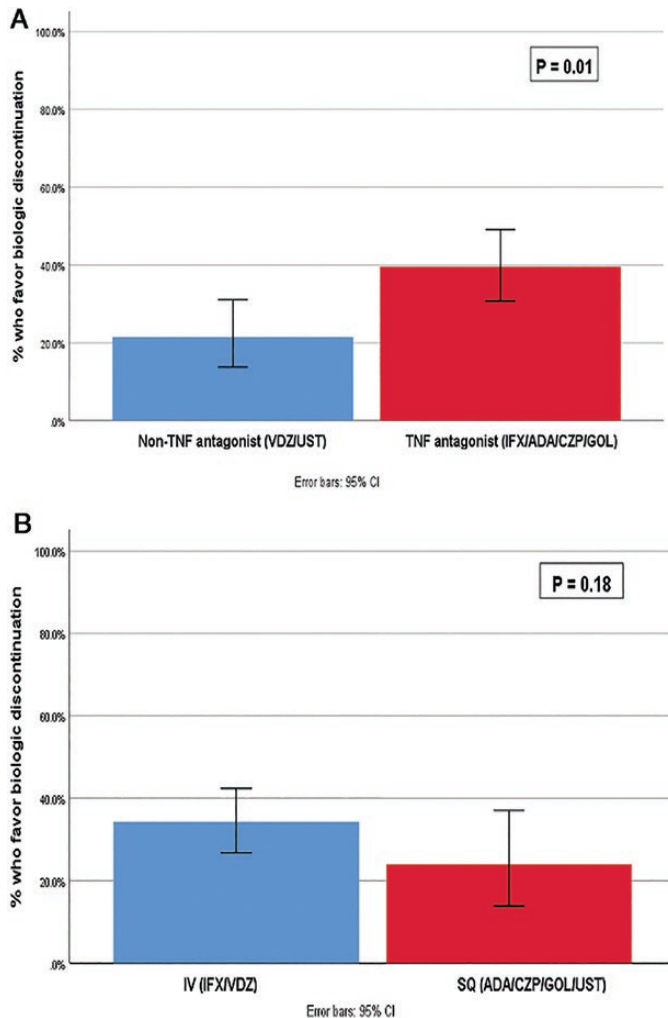


FIGURE 2. Patient-preference favoring biologic discontinuation based on: (A) Biologic class: non-TNF antagonist vs TNF antagonist. (B) Route of administered: intravenous vs subcutaneous. ADA (N = 17); CZP (N = 6); GOL (N = 1); IFX (N = 82); IV, intravenously administered; SQ, subcutaneously administered; UST (N = 26); VDZ (N = 58).

VDZ or UST reported younger age, noncommercial insurance, psychiatric history, and smoking, among others, as risk factors of nonadherence.<sup>27,36</sup> Given the high prevalence of depression and anxiety within the IBD population, further studies are required to assess if screening tools such as the Patient Health Questionnaire (PHQ-9) and Generalized Anxiety Disorder (GAD-7) questionnaires may screen for those at risk of nonadherence to biologic treatment. While corticosteroids are potent anti-inflammatory agents, they are associated with serious adverse effects. Consistent with a previous study, we found concurrent steroid therapy to be associated with attitude favoring biologic discontinuation.<sup>37</sup>

Concern for the risk of side effects was the primary factor in considering discontinuation of biologic medications in this

study. This supports our hypothesis for the observed differences in the perceived need to withdraw therapy among biologic classes and demonstrates concordance between patient preference of non-TNF antagonist biologics and clinical trial data.<sup>9,11,12</sup> Furthermore, excellent literacy of biologic therapy and preferences of medication safety were associated with lower desire to discontinue therapy. This underscores the importance of educating patients and using a shared decision-making process after a thorough discussion of risks, benefits, and alternatives of available therapies and individual factors that could impact adherence. We found that a high proportion of patients who desired biologic discontinuation were willing to undergo regular follow-ups for objective disease activity assessments. Supervised de-escalation of biologics therapy may be an option in IBD patients in prolonged deep remission when implemented in conjunction with periodic clinical, biochemical, and endoscopic monitoring.<sup>38,39</sup> However, further research on identifying low-risk individuals and the long-term outcomes of this strategy are needed before such an approach can be widely adopted.

Studies have used various questionnaire tools to study medication adherence in IBD.<sup>21,24</sup> However, no specific tool is available to examine patient preferences of biologics in IBD. Generic tools devised for chronic conditions such as the Illness Preference Questionnaire and the Beliefs About Medicine Questionnaire did not apply to our research question. Therefore, we devised a questionnaire tool to conduct a detailed evaluation of prevalence and risk factors of patient preferences toward biologics. Strengths of the current study included a large sample size, high response rates on the survey questions, and inclusion of patients with major classes of currently approved biologics in IBD. Study limitations included the use of self-reported measures which may be subject to recall and/or reporting biases and a ceiling effect due to social desirability of perfect responses.<sup>40</sup> Given that we recruited patients from a tertiary referral center using convenience sampling and a majority of participants were well-educated, further data are needed to understand application of these findings to other practice settings. Some of the validated yet elaborate QOL questionnaires such as the IBD questionnaire (IBDQ) and short IBDQ were not be incorporated to limit the total number of questions. Additionally, validation of the current questionnaire is required.

In summary, the current study demonstrates that patient-preference favoring treatment discontinuation is improved with VDZ and UST compared to TNF antagonists among patients currently receiving biologic. Identifying individuals at risk of biologic discontinuation or nonadherence will provide opportunities to intervene and prevent risks associated with unplanned withdrawal of biologic therapy. Further studies are required to identify the relationship between preferences favoring discontinuation while undergoing therapy and subsequent nonadherence, as well as whether interventions based on patient-preference influence outcomes.

**TABLE 3.** Multivariable Stepwise Logistic Regression Analysis of the Factors Associated With Patient-Preference Favoring Biologic Discontinuation<sup>†</sup>

Variable	Unadjusted OR (95% CI)	aOR (95% CI)	Multivariate P
Biologic: non-TNF antagonist vs TNF antagonist	0.42 (0.22–0.80)	0.23 (0.09–0.58)	<0.01*
Gender: males vs females	2.67 (1.42–5.01)	3.65 (1.53–8.74)	<0.01*
Age: <40 vs >40 years	2.31 (1.19–4.46)	2.9 (1.09–7.70)	0.03*
Race: non-Caucasian vs Caucasian	3.61 (1.84–7.09)	2.78 (0.96–8.17)	0.08
Level of education: advanced vs other <sup>a</sup>	0.44 (0.22–0.85)	0.45 (0.18–0.91)	0.04*
Perceived knowledge of IBD: excellent vs other <sup>b</sup>	0.48 (0.25–0.94)	1.77 (0.68–4.65)	0.24
Perceived knowledge of biologic: excellent vs other <sup>b</sup>	0.23 (0.08–0.62)	0.27 (0.08–0.92)	0.04*
Perceived safety of biologic: moderate-to-very safe vs other <sup>c</sup>	0.17 (0.07–0.41)	0.24 (0.13–0.56)	<0.001*
Duration of therapy (continuous)	0.97 (0.93–1.00)	1.00 (0.96–1.05)	0.88
Concurrent corticosteroid therapy	4.28 (1.86–9.86)	3.38 (1.26–10.8)	0.03*
Smoking status			
Current vs never	7.76 (1.51–39.85)	4.97 (0.46–53.3)	0.19
Former vs never	2.3 (0.84–6.32)	1.45 (0.33–6.42)	0.62
History of anxiety/depression	2.14 (0.94–4.71)	3.51 (1.01–12.11)	0.047*

\*Significant P-value (<0.05) on multivariable analysis.

<sup>†</sup>Multivariable model included variables from univariable analysis with P < 0.1. Annual household income was excluded from multivariable analysis given 50 missing values.

“Other” defined as: a: college graduate with degree, some college without degree, high school or less; b: none, minimal, moderate; c: not safe, minimally safe. CI, confidence interval.

## SUPPLEMENTARY MATERIAL

Supplementary data are available at *Crohn's & Colitis 360* online.

## DATA AVAILABILITY

Data for this study are not publicly available. Any requests should be addressed to the corresponding author.

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