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ORIGINAL ARTICLE

Comparing Patient-Reported Outcomes Among Anti-TNF-Experienced Patients with Crohn's Disease Initiating Vedolizumab Versus Ustekinumab

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Abstract

Background Primary and secondary non-response to anti-tumor necrosis factor (TNF) therapy is common in patients with Crohn's disease (CD), yet limited research has compared the effectiveness of subsequent biological therapy.

Objective We sought to compare the effectiveness of vedolizumab and ustekinumab in anti-TNF-experienced patients with CD, focusing on patient-prioritized patient-reported outcomes (PROs).

Methods We conducted a prospective, internet-based cohort study nested within IBD Partners. We identified anti-TNF-experienced patients initiating with CD vedolizumab or ustekinumab and analyzed PROs reported approximately 6 months later (minimum 4 months, maximum 10 months). Co-primary outcomes were Patient-Reported Outcome Measurement Information System (PROMIS) domains of Fatigue and Pain Interference. Secondary outcomes included patient-reported short Crohn's disease activity index (sCDAI), treatment persistence, and corticosteroid use. Inverse probability of treatment weighting (IPTW) was used to control for a number of potential confounders and incorporated into linear and logistic regression models for continuous and categorical outcomes, respectively.

Results Overall, 141 vedolizumab and 219 ustekinumab initiators were included in our analysis. After adjustment, we found no differences between treatment groups in our primary outcomes of Pain Interference or Fatigue or the secondary outcome of sCDAI. However, vedolizumab was associated with lower treatment persistence (OR 0.4, 95% CI 0.2–0.6) and higher corticosteroid use at follow-up assessment (OR 1.7, 95% CI 1.1–2.6).

Discussion Among anti-TNF experienced patients with CD, Pain Interference or Fatigue was not significantly different 4–10 months after starting ustekinumab or vedolizumab. However, reduced steroid use and increased persistence suggest superiority of ustekinumab for non-PRO outcomes.

Keywords Crohn's disease · Comparative effectiveness · Vedolizumab · Ustekinumab · Patient-reported outcomes

Background

Crohn's disease (CD) affects approximately 500,000 individuals in the United States [1], costs over $3.6 billion annually [2], and causes substantial patient morbidity [3], missed

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work [4] and school [5], and diminished quality of life [6, 7]. Currently, anti-tumor necrosis factor (TNF) therapy is considered first-line treatment for moderate to severe disease [8–12]. Yet primary non-response occurs in up to 30% of patients, and secondary loss of response is observed in up to 80% of patients [13, 14].

When anti-TNF therapy fails, subsequent treatment options for CD include vedolizumab (antibody to $\alpha_4\beta_7$ integrin) and ustekinumab (antibody to IL-12/23). Unfortunately, anti-TNF refractory patients respond less well to subsequent treatments [15–19], underscoring the importance of selecting the most effective second-line agent. Yet there is a relative paucity of comparative effectiveness research (CER) to guide this challenging clinical decision faced by many patients and their providers [20, 21]. While a few studies published over the last three years that have suggested a potential benefit of ustekinumab over vedolizumab with regard to clinical and steroid-free remission [22–26], this benefit has not been consistently observed across studies [27, 28]. Furthermore, all studies to date have focused exclusively on patients cared for at academic health centers and none have utilized patient-reported outcomes (PROs), direct measures of how patients feel and function, to evaluate clinical effectiveness.

We sought to compare the effectiveness of vedolizumab and ustekinumab in patients with CD previously treated with anti-TNF agents, focusing on PROs prioritized by patients living with IBD. To accomplish this, we conducted a prospective, direct-to-patient, cohort study in a geographically diverse population of patients cared for in a variety of practice settings.

Methods

Study Population

IBD Partners is an internet-based cohort study of over 16,000 adult patients with IBD. Participants complete a baseline survey and receive follow-up surveys every 6 months. Participants can also update their treatment and outcome information "on demand" through a web portal. Descriptions of the methods of cohort recruitment, follow-up, and data capture have been previously published [29, 30]. For the present study, we evaluated the outcomes of a sub-cohort of IBD Partners participants with CD who reported new initiation of vedolizumab or ustekinumab following treatment with anti-TNF therapy. We supplemented enrollment through a collaboration with the Anthem and Humana health plans. These health plans reviewed claims of enrolled members on a monthly basis to identify potentially eligible participants and refer them to IBD Partners by U.S. mail, email, and telephone calls.

Eligibility Criteria

Overall, IBD Partners inclusion criteria include age $\geq$ 18 years, a self-reported diagnosis of IBD, internet access, and the ability to complete surveys in English. A prior validation study of IBD Partners participants indicated that self-reported diagnoses of IBD were highly accurate, with 97% of participants having their diagnosis confirmed by their treating physicians [31]. For this sub-cohort, additional inclusion criteria included (1) initiation of ustekinumab or vedolizumab), (2) prior use of 1 or more anti-TNF agents, and (3) a reported diagnosis of CD at or immediately prior to date of ustekinumab or vedolizumab initiation. As ustekinumab received FDA approval for CD in September 2016, we only considered participants who initiated vedolizumab or ustekinumab after January 1, 2017 in order to maximize equal comparisons. For participants who initiated both vedolizumab and ustekinumab, only the first biologic following anti-TNF therapy was considered.

Primary Comparison

We compared new initiators of vedolizumab versus ustekinumab. The first of these medications used following anti-TNF was assigned as the index treatment. The date of first reported use was assigned as the index date.

Follow-Up

Participants were followed until the outcome assessment date, defined as the survey date closest to 6 months following the index date (no earlier than 4 months and no later than 10 months following index date). This timeframe was selected a priori based on our clinical judgment that responders to either treatment should have achieved steroid-free clinical remission by this point. We encouraged follow-up with patient-centered messaging developed by our patient co-investigators regarding the importance of the research question and provided a $25 incentive for completing the 6-month follow-up survey.

Outcomes

Prespecified, co-primary outcomes included NIH Patient-Reported Outcome Measurement and Information System (PROMIS) measures of Fatigue and Pain Interference. These domains were selected based on (1) prioritization by two patient co-investigators (JB and JD) and the broader IBD Partners Patient Governance Committee following review of multiple potential PRO measures and (2) prior evidence demonstrating construct validity and responsiveness

to changes over time in the short Crohn's disease index (sCDAI) and the short IBD questionnaire, a disease-specific quality of life measure [32]. In addition, a recent study of over 400 patients with CD concluded that Fatigue was the symptom that had the highest impact on the lives of patients with CD based upon symptom prevalence and average impact, whereas Pain also featured prominently on the symptoms that most significantly affect patients with CD [33]. PROMIS scales are continuous measures, calibrated using a *T* score metric to the US general population with a mean of 50 and standard deviation of 10. Minimal important differences (MIDs) have been reported to be in the range of 2 to 6 [34]. Secondary outcomes measured at the same time point included patient-reported sCDAI [35], PRO-2 [36], the PROMIS domain of Social Satisfaction, continued use of the index medication (persistence), corticosteroid use, narcotic use, and abdominal surgery..

Covariates

We assessed age, sex, race, Hispanic ethnicity, and years from IBD diagnosis using data collected from each participant's baseline IBD Partners survey. Current smoking status and body mass index (BMI) were ascertained at the index date or the prior recorded survey whereas baseline measures of sCDAI, and PROMIS domains of Pain Interference, Fatigue, Social Satisfaction, Sleep Disturbance, Anxiety, and Depression were ascertained at the index date or in the 6 months prior to the index date. The number of prior anti-TNF agents, use of prior medications [immunomodulators (6-mercaptopurine, azathioprine, and methotrexate), calcineurin inhibitors (tacrolimus and cyclosporine) and corticosteroids], and prior hospitalization and surgery were evaluated based on all IBD Partners data recorded prior to the index date. Concomitant use of immunomodulators was defined as any use reported after the index date and at or prior to follow-up assessment.

Sample Size

To detect a clinically relevant effect size (difference in PROMIS *T* scores ≥ 5 with a standard deviation of 10), we estimated that a total of 180 participants would be needed to achieve 80% power with a two-sided α of 0.05, assuming no more than a 2:1 imbalance in treatment group size and no more than 20% loss to follow-up. However, rather than limiting participants to this number, we planned to follow as many participants as possible with an index date prior to December 31, 2020, based upon pre-set project milestones, under the assumption that exceeding the minimum sample size would provide additional precision for subgroup analyses.

Statistical Analysis

We used standard descriptive and bivariate statistics to summarize the study population and compare demographic and baseline characteristics between users of the two treatments. We also compared the characteristics of retained participants versus those lost to follow-up within each treatment group. We then conducted unadjusted analyses for primary and secondary outcomes using two-sample *t* tests for continuous variables and χ^2 tests for categorical variables. As prespecified in our study protocol, our primary analyses utilized outcome data collected at follow-up, regardless of whether or not patients continued on their index treatment at the time of follow-up. We used an intention-to-treat (ITT) analysis because this comparative effectiveness study aimed to evaluate the compare the effectiveness of initiating vedolizumab versus ustekinumab rather than compare the biological efficacy of the medications themselves.

Next, we conducted adjusted analyses (linear regression for PROMIS measures and sCDAI and logistic regression for persistence and corticosteroid use) using inverse probability treatment weights (IPTW) to assess average treatment effects while accounting for potential baseline differences and clinical characteristics between the two treatment groups. The logistic regression model for the IPTW considered the following covariates: age, sex, race, ethnicity, BMI, smoking status, number of prior anti-TNF therapies, and previous medications. The test statistics were then weighed by the IPTW, calculated by inverse the predicted probability derived from the logistic regression model. We reported weighted mean differences between the treatment groups if the outcome is continuous and odds ratios (ORs) for binary outcomes, with 95% confidence intervals (CIs) and Wald-type *p* values. We used multiple imputations to handle missing covariates, as long as the proportion of participants with missing data was less than 20%. As baseline sCDAI and PROMIS measures were missing in many participants since not all participants completed surveys immediately prior to treatment initiation, we planned a priori to include those variables only if they differed significantly between the two treatment groups with a *p* value of less than 0.05.

Subgroup and Sensitivity Analyses

We conducted a number of prespecified subgroup analyses with stratification based on age group, sex, the number of prior anti-TNF agents (1 vs. more than 1), and concomitant immunomodulator therapy. Due to the smaller sample size among subgroups and the consistency between unadjusted and adjusted results in our overall analyses, we only performed unadjusted subgroup analyses.

In addition, as treatment persistence differed between vedolizumab and ustekinumab initiators, we performed a

few post hoc analyses. First, as an alternative to our prespecified ITT analysis, we performed an alternative analysis for our primary outcomes using the first observation carried forward for patients who did not continue their index therapy through follow-up assessment. In addition, we compared outcomes of Pain Interference, Fatigue, Social Satisfaction, and sCDAI between patients who persisted in their index treatment versus those who discontinued prior to follow-up assessment.

All statistical analyses were conducted using SAS 9.4 (Cary, NC). The study protocol was approved by the Institutional Review Board at the University of North Carolina at Chapel Hill.

Results

Study Population

Overall, 219 vedolizumab initiators and 363 ustekinumab initiators met the eligibility criteria, and 141 (64%) and 219 (60%) had follow-up data available. Standardized mean differences (SMDs) in the demographic and clinical characteristics of vedolizumab and ustekinumab users before and after IPTW are shown in Table 1. The mean age of both groups was 46. Females represented 71% of vedolizumab and 76% of ustekinumab users. The study sample was composed of primarily non-Hispanic whites and non-smokers. More than half of the population reported prior use of 2 or more anti-TNF agents. sCDAI and PROMIS scores did not differ significantly between vedolizumab and ustekinumab initiators. Other baseline characteristics are summarized in Table 1. After IPTW, treatment groups were generally well balanced.

Considering the relatively high loss-to-follow-up (36% of vedolizumab users and 40% of ustekinumab users), we compared the baseline characteristics of participants retained versus lost within treatment groups (Supplemental Table 1). Demographic and utilization of prior treatments did not differ between participants retained versus those lost to follow-up in either treatment group. Among ustekinumab users, baseline Anxiety and Depression scores were slightly higher in participants lost to follow-up versus those retained.

Main Findings

Our unadjusted results are shown in Table 2. Our co-primary endpoints of Pain Interference and Fatigue at 6 months did not differ between vedolizumab and ustekinumab treated patients [mean *T* scores 51.2 versus 51.6 ($p = 0.75$) and 54.7 versus 54.4 ($p = 0.78$), respectively]. Regarding secondary outcomes, we observed a higher persistence among ustekinumab users than vedolizumab users (93% versus 84%, $p = 0.01$). There were no significant differences in corticosteroid use, narcotic use, surgery, Social Satisfaction, sCDAI, or PRO-2 at follow-up.

We also evaluated change from baseline in the subgroup of participants with available baseline data. As shown in Supplemental Table 2, measures of Pain Interference, Fatigue, Social Satisfaction, and sCDAI were all slightly improved (below the threshold of minimally important clinical difference) after initiation of both treatments, with no observed differences between treatment groups.

In adjusted analyses, we found no differences in our primary outcomes of Pain Interference or Fatigue between initiators of vedolizumab versus ustekinumab (Table 3). Similarly, Social Satisfaction and sCDAI did not differ between the two groups. However, vedolizumab was associated with lower treatment persistence (OR 0.36, 95% CI 0.22–0.60) and higher corticosteroid use at follow-up assessment (OR 1.69, 95% CI 1.13–2.56).

Subgroup and Sensitivity Analyses

We conducted a number of prespecified subgroup analyses with stratification based on age group, sex, the number of prior anti-TNF agents (1 vs. more than 1), and concomitant immunomodulator therapy. Results for our primary outcomes of Pain Interference and Fatigue were not significant in any subgroup. Generally speaking, the direction and magnitude of the effect in subgroups mirrored that in the population as a whole (Supplemental Table 3), with treatment persistence remaining statistically significant in many but not all subgroups.

We also conducted a post hoc sensitivity analysis using the first observation carried forward for patients who did not continue their index treatment through full follow-up. Unadjusted analyses showed no differences in primary outcomes of Pain Interference (52.8 versus 52.5, $p = 0.77$) or Fatigue (mean *T* score 56.0 versus 54.4, $p = 0.21$) among vedolizumab versus ustekinumab initiators. To further explore the difference in persistence between vedolizumab and ustekinumab users, we did a post hoc analysis to compare outcomes of Pain Interference, Fatigue, Social Satisfaction, and sCDAI between patients who persisted on treatment versus those discontinued prior to follow-up. Patients in both treatment groups who discontinued the index medication prior to the follow-up visit reported higher levels of Pain Interference and Fatigue and lower amounts of Social Satisfaction at follow-up than those who persisted in therapy. Similarly, those who discontinued treatment reported a higher symptom burden, as measured by sCDAI (Supplemental Table 4). Yet no differences in any measured outcomes were observed in a subgroup analysis comparing only treatment-persistent participants.

Table 1 Demographic and baseline characteristics of patients with Crohn's disease initiating treatment with vedolizumab versus ustekinumab following anti-TNF therapy

	Vedolizumab $n=141$		Ustekinumab $n=219$		SMD	SMD after IPTW
	N/mean	%/SD	*N*/mean	%/SD		
Index year (*N*, %)					0.331	0.003
2017	55	39%	45	21%		
2018	31	22%	56	26%		
2019	26	18%	65	30%		
2020	29	21%	53	24%		
Age (mean, SD)	46.4	15.46	46.0	14.98	0.024	0.001
Sex (*N*, %)					0.121	0.009
Male	41	29%	52	24%		
Female	100	71%	167	76%		
Race/ethnicity (*N*, %)					0.173	0.008
Hispanic	3	2%	3	1%		
Non-Hispanic White	129	91%	193	88%		
Non-Hispanic Black	2	1%	2	1%		
Other/unknown	7	5%	21	10%		
Years from diagnosis (mean, SD)	19.6	14.17	18.0	12.00	0.119	0.009
Number of prior anti-TNF (*N*, %)						
1	70	50%	97	44%	0.105	0.008
2	51	36%	87	40%		
3+	20	14%	35	16%		
Smoking status (*N*, %)					0.023	0.002
Nonsmoker	97	69%	153	70%		
Former smoker	41	29%	58	26%		
Current smoker	3	2%	8	4%		
BMI prior to index (mean, SD)	25.3	6.45	25.4	5.85	0.018	0.016
Prior hospitalization (*N*, %)	97	75%	144	75%	0.018	0.005
Prior surgery (*N*, %)	71	55%	114	60%	0.103	0.013
Prior use of steroids (pred, bud) (*N*, %)	127	98%	187	98%	0.018	0.007
Prior use of 6MP/AZA (*N*, %)	103	79%	147	77%	0.022	0.009
Prior use of MTX (*N*, %)	40	31%	58	30%	0.036	0.011
Prior use of tacrolimus/cyclosporine (*N*, %)	7	5%	6	3%	0.002	0.004
Baseline sCDAI (mean, SD)*	186	105.2	172	90.0	0.147	0.144
Baseline PROMIS (mean, SD)*						
Anxiety	52.1	10.49	50.7	8.70	0.151	0.140
Depression	49.4	9.94	48.5	8.29	0.102	0.112
Fatigue	56.3	11.52	55.0	10.74	0.118	0.125
Sleep	51.4	8.86	50.0	7.69	0.169	0.138
Pain	53.1	10.11	52.8	9.71	0.029	0.021
Social	48.5	10.57	49.3	8.90	0.084	0.125

*Baseline measures of short Crohn's disease index (sCDAI) and Patient-Reported Outcome Measurement Information System (PROMIS) measures were evaluated in the 6 months prior to index date. The number of participants with non-missing data ranged from 84 to 91 for vedolizumab initiators and from 126 to 144 for ustekinumab initiators

Discussion

We conducted a geographically diverse, prospective, direct-to-patient cohort study to compare patient-reported and patient-prioritized outcomes among anti-TNF experienced patients with CD initiating treatment with either vedolizumab or ustekinumab. At 6 months, co-primary outcome measures of Fatigue and Pain Interference did not differ between treatments. The estimated treatment persistence at 6 months, a secondary study outcome, was higher among ustekinumab initiators (93% versus 84%). Additionally, corticosteroid use at follow-up was lower among ustekinumab

Table 2 Unadjusted outcomes at 6-months among patients with Crohn's disease initiating treatment with vedolizumab versus ustekinumab following anti-TNF therapy

	Vedolizumab $n=141$		Ustekinumab $n=219$		p value
	N/mean	%/SD	*N*/mean	%/SD	
Primary outcomes					
PROMIS Fatigue* (Mean, SD)	54.7	11.73	54.4	12.31	0.778
PROMIS Pain interference* (mean, SD)	51.2	10.17	51.6	9.94	0.751
Secondary outcomes					
Index medication persistence (*N*, %)	119	84%	203	93%	0.012
Corticosteroid use at follow-up (*N*, %)	27	19%	28	13%	0.103
Narcotic use at follow-up (*N*, %)	18	13%	19	9%	0.214
Recent surgery	16	12%	26	12%	0.088
Short Crohn's disease activity index	147	89.6	144	85.8	0.785
PRO-2	9.1	7.93	8.6	7.31	0.564
PROMIS social satisfaction (mean, SD)* (mean, SD)	49.1	10.59	49.3	10.06	0.887

*Patient-Reported Measurement Information System

Table 3 Average treatment effects (adjusted) at 6 months among patients with Crohn's disease initiating treatment with vedolizumab versus ustekinumab following anti-TNF therapy

	Estimate (95% confidence intervals)*	p value
Primary outcomes		
Fatigue	0.6 (−1.9.0 to 3.0)	0.657
Pain Interference	−0.2 (−2.3 to 1.9)	0.824
Secondary outcomes		
Index medication persistence	0.36 (0.22 to 0.60)	<0.001
Corticosteroid use	1.69 (1.13 to 2.56)	0.010
sCDAI	6.0 (−13.36 to 25.36)	0.688
Social satisfaction	−0.9 (−3.0 to 1.3)	0.435

*Estimates for Patient-Reported Measurement Information System (PROMIS) measures of Fatigue, Pain Interference, and Social Satisfaction and the Short Crohn's Disease Activity Index (sCDAI) represent adjusted mean differences comparing treatment with vedolizumab versus ustekinumab. Estimates for persistence and corticosteroid use represent adjusted odds ratios for treatment for vedolizumab versus ustekinumab

users (13% versus 19%). However, outcomes for other PROs including patient-reported sCDAI and Social Satisfaction did not differ between treatments. Taken together, these findings suggest that patients with CD who have been previously treated with anti-TNF feel and function similarly regardless of whether they decide upon treatment with vedolizumab or ustekinumab. Hence, other factors such as patient preference regarding route of administration, cost, and/or data regarding other outcomes, including direct measures of mucosal inflammation, must be considered when making decisions about subsequent treatment options.

Our study complements the growing literature comparing vedolizumab to ustekinumab in this patient population [22–27]. In a recent meta-analysis, Parrot et al. concluded that both treatments were equally effective in the induction of remission, but ustekinumab was associated with more favorable 1-year outcomes including clinical remission, steroid-free remission, and biological remission (normalization of C-reactive protein and fecal calprotectin) [24]. In contrast, a multi-center French cohort reported no difference in 52-week clinical remission [27], and an Italian study found that vedolizumab was associated with higher rates of clinical and steroid-free remission at week 52, albeit no differences were observed in objective markers such as endoscopy, small bowel ultrasound, or radiologic imaging. In our study, we observed lower corticosteroid use and higher persistence with ustekinumab as compared to vedolizumab, a finding that is relatively consistent across studies [22–24, 26]. Our study expands prior work in at least two important ways. First, we focus on PROs that have been prioritized by patient stakeholders and reflect important domains of how patients feel and function. Second, while prior studies have been conducted at centers of excellence across Europe, our study included patients cared for in a variety of practice settings across the U.S. As both treatments yield roughly comparable effectiveness across a broad array of PROs, we hope these findings will help to ease the high decisional burden faced by this patient population. At the same time, a relatively consistent finding between our studies and most prior studies was the higher persistence among ustekinumab initiators, a surrogate of treatment effectiveness, and/or tolerability that requires further exploration. Possible drivers may include differences in clinical or biological endpoints as have been suggested by some studies along with potential differences in access, cost, and patient preference. Ultimately, treatment decisions for patients refractory or intolerant to anti-TNF therapy will require the balancing of many factors.

Strengths of this study include the patient-centered design and implementation achieved by strong patient engagement

across all phases of our study. Indeed, we far surpassed our recruitment goals and experienced far higher retention than most direct-to-patient studies. In addition, we focused on highly relevant and patient-prioritized PROs, capturing not only traditional gastrointestinal symptoms but also non-traditional symptoms such as fatigue and social satisfaction that are central drivers of patient well-being. The geographic diversity of participants cared for in many practice settings is another strength of our study. We also note a number of limitations. First, we include patients with self-reported rather than physician-confirmed CD and acknowledge the potential for misclassification of IBD status or type (CD vs. UC). However, a prior validation study within IBD Partners has demonstrated the high validity of self-reported diagnoses in the overall cohort [31], and we anticipate even greater validity in this sub-cohort of treatment-experienced individuals who have reported prior anti-TNF therapy as well as current treatment with either vedolizumab or ustekinumab. In addition, loss to follow-up in IBD Partners and other internet-based cohorts is relatively high given the lack of direct participant engagement and may not have occurred at random, thus, introducing a potential source of bias. We also acknowledge that our study population is a convenience sample rather than a representative sample and is not fully generalizable to the broader US population of patients with CD. Indeed, our cohort overrepresents well-educated patients and females and lacks robust participation from minority populations frequently underrepresented in health research. We also acknowledge the possibility of confounding, including unmeasured confounding, in this observational study. In addition, we did not collect data on reason for prior TNF discontinuation or on dose, interval, or changes/optimization for ustekinumab or vedolizumab. Finally, while the focus of this manuscript is on PROs, we lack data on clinical, laboratory, and endoscopic measures and, therefore, are unable to adjust for or compare these parameters. However, we were able to adjust for prior hospitalization and prior CD-related surgery as more objective parameters of CD severity.

In conclusion, this first-of-its-kind comparative effectiveness study of anti-TNF-experienced patients with CD initiating vedolizumab or ustekinumab showed similar effectiveness of both agents at 6 months, as measured by a broad panel of patient-centered outcomes, although we did observe higher persistence and lower corticosteroid use among ustekinumab users. In the absence of clear medical superiority of either option, we advocate for a strong role for patient preference and the importance of individualized decision making.

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Data availability Study data will be made available to qualified investigators on a case-by-case basis as consistent with the IBD Partners ancillary studies processes described at https://cgibd.med.unc.edu/ccfapartners/researchers/.

Declarations

Conflict of interest MDK has consulted for Abbvie, Janssen, Pfizer, Takeda, and Lilly, is a shareholder in Johnson & Johnson, and has received research support from Pfizer, Takeda, Janssen, AbbVie, Lilly, Genentech, Boehringer Ingelheim, Bristol Myers Squibb, Celtrion, and Arenapharm. JDL has served as a consultant for Janssen Pharmaceuticals, Samsung Bioepis, Bristol-Myers Squibb, Merck, Celgene, AbbVie, Entasis Therapeutics, and Bridge Biotherapeutics. JDL has served as a paid member of a data-monitoring committee for Pfizer, UCB, Gilead, Arena Pharmaceuticals, Protagonist Therapeutics, and Amgen. JDL has received research funding from Janssen Pharmaceuticals, AbbVie, and Takeda Pharmaceuticals. JDL has received educational grant funding from Takeda Pharmaceuticals. XZ, FL, LW, WC, JB, VN, AK, AD report no conflicts of interest. JD is a shareholder in Pfizer. LP is employed by HealthCore/Anthem. KH was employed by Anthem at the time of the research and is currently an employee of Janssen Research & Development. ML consulting for AbbVie, Janssen, Pfizer, Takeda, Lilly, BMS, Prometheus, Target Pharmasolutions, Calibr, Roche, Genentech, Theravance, Research support Takeda, Pfizer.

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