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Evaluation of adverse clinical outcomes in patients with inflammatory bowel disease receiving different sequences of first- and second-line biologic treatments: findings from ROTARY

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Abstract

Background Patients with inflammatory bowel disease (IBD) are at risk of developing dysplasia and, subsequently, colorectal cancer (CRC) owing to chronic inflammation. Patients may also experience other severe disease complications, such as hospitalization and surgery. Several biologics are available for the treatment of patients with IBD and some patients require multiple lines of treatment owing to loss of response or tolerability to their prescribed biologic. Previous studies suggest that the choice of initial biologic treatment may impact the outcomes of later treatment lines. In this study, we assessed adverse clinical outcomes in patients with Crohn's disease (CD) or ulcerative colitis (UC) who received different biologic treatment sequences.

Methods ROTARY part B was a retrospective cohort study using the Optum® Clinical Database that evaluated the incidences of IBD-related hospitalization, IBD-related surgery, dysplasia, CRC, and infections in patients with CD or UC who received two biologics successively. First-line biologics included adalimumab, infliximab, ustekinumab (CD only), and vedolizumab; second-line biologics included infliximab and adalimumab.

Results In patients with CD, the treatment sequence of ustekinumab to infliximab was associated with the highest overall incidences of hospitalization (51.9%), surgery (40.7%), CRC (3.7%), and infection (37.0%). Vedolizumab followed by an anti-tumor necrosis factor alpha (anti-TNFα) treatment was associated with a significantly lower risk of experiencing an adverse medical event (hospitalization, surgery, or infection) than two successive anti-TNFα treatments (odds ratio, 1.526; 95% confidence interval, 1.004–2.320; $P < 0.05$). In patients with UC, the treatment sequence of vedolizumab to adalimumab resulted in the lowest overall incidence of adverse outcomes (20.3%, 6.3%, 0.0%, 6.3%, and 4.7% for hospitalization, surgery, CRC, dysplasia, and infection, respectively).

Conclusions We describe differences in adverse clinical outcomes associated with sequencing of biologics in patients with CD or UC and demonstrate favorable results in patients who received vedolizumab as a first-line biologic. These results provide potential guidance to clinicians choosing sequences of biologic treatments in patients with IBD.

Keywords Crohn's disease, Ulcerative colitis, Biologics

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Background

Crohn's disease (CD) is a chronic inflammatory bowel disease (IBD) that can affect any part of the gastrointestinal tract [1], while ulcerative colitis (UC) is a chronic IBD that is characterized by inflammation of the large intestine (rectum and colon) [2–4]. Both CD and UC are characterized by relapsing and remitting or progressive disease courses [1–4].

Chronic inflammation in patients with IBD increases the risk of developing dysplasia and, subsequently, colorectal cancer (CRC) [5, 6]. Additionally, patients with IBD have an increased susceptibility to infections compared with individuals without IBD [7]. Furthermore, the use of anti-tumor necrosis factor alpha (anti-TNFα) treatments is associated with an increased risk of infection compared with immunosuppressant treatments [8, 9]. IBD-related hospitalization and surgery are adverse disease-related complications experienced by patients with severe IBD [10, 11].

There are multiple biologic treatment options for patients with moderate to severe CD and UC. The anti-cytokines include adalimumab and infliximab (anti-TNFα treatments), ustekinumab (interleukin [IL]-12 and IL-23 inhibitor), and risankizumab (IL-23 inhibitor), while vedolizumab is a gut-selective anti-leukocyte trafficking α4β7 integrin inhibitor [1, 2, 12, 13]. Despite the availability of several treatment options, some patients do not adequately respond to treatment [10, 14]. Following inadequate response, loss of response, or intolerance to therapy, patients may switch from an initial biologic to a second-line biologic [11, 15].

Deciding the order in which to prescribe therapies is challenging owing to a lack of predictive therapeutic biomarkers and limited data on the clinical outcomes of patients with IBD receiving different sequences of biologic treatment. We hypothesized that sequencing of therapies may be associated with different outcomes, and here report the rates of adverse clinical outcomes, including IBD-related hospitalization, IBD-related surgery, dysplasia, CRC, and infection, associated with different sequences of biologic treatment.

Methods

Objectives

ROTARY (Real wOrld ouTcomes Across tReatment sequences in inflammatorY bowel disease patients) part B aimed to evaluate the incidence of adverse clinical outcomes in patients with CD or UC who received different biologic treatment sequences. Results for the primary objective of the ROTARY study (part A), which evaluated the persistence of first- and second-lines of biologic treatment, have been previously described [16].

Study design

ROTARY was a retrospective cohort study of electronic health record (EHR) data between January 1, 2012 and February 29, 2020. Adults with a diagnosis of CD or UC who received at least two biologics successively between January 1, 2013 and February 29, 2020 were included (Fig. 1).

The study design is depicted in Fig. 1. In brief, the start of the first line of biologic treatment was defined as the first date for prescription or administration of a qualifying biologic during the patient identification period [i.e. the index date]. The first line of biologic treatment ends at the earliest date of switching to a different biologic or the end of the study period. The date of first prescription or administration for a second qualifying biologic during the patient identification period was defined as the start of the second line of biologic treatment. The baseline period was the 12 months before the index date, while follow-up was defined as the period between the index date and, whichever came first of, the end of the second line of treatment or the end of the study period.

Data source

Data were obtained from the Optum® Clinical Database of clinical encounter data from a network of over 140,000 providers at over 700 hospitals and 7000 clinics [17]. De-identified data from the database include demographics, prescribed and administered medications, immunizations, allergies, vital signs, clinical and inpatient administrative data, and coded diagnoses and procedures.

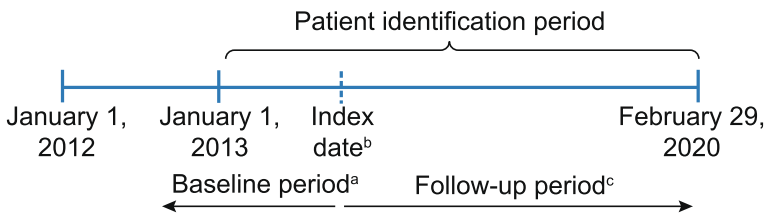

Fig. 1 ROTARY study design. [a]The baseline period was defined as the 12 months before the index date. [b]The index date was defined as the first date for prescription or administration of a qualifying biologic during the patient identification period. [c]Follow-up was defined as the period between the index date and whichever came first of the end of the second line of treatment or the end of the study period. The date of first prescription or administration for a second qualifying biologic during the patient identification period was defined as the start of the second line of biologic treatment

Study population

Adult patients were eligible for inclusion if they met the following criteria: at least one prescription or administration of adalimumab, infliximab, vedolizumab, or ustekinumab during the patient identification period; only one qualifying therapy on the index date; a minimum of 12 months of EHR activity before the index date; at least 18 years old on the index date with valid demographic information; at least two diagnoses of CD or UC during the baseline period and one diagnosis during follow-up identified using International Classification of Diseases, 9th or 10th edition codes; and at least one prescription or administration of adalimumab, infliximab, vedolizumab, or ustekinumab following the first line of biologic treatment.

Patients were excluded from the analysis if they met any of the following criteria: prescription or administration of adalimumab, infliximab, vedolizumab, or ustekinumab during the baseline period; and diagnosis of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, plaque psoriasis, hidradenitis suppurativa, or non-infectious uveitis in the 6 months before the index date.

For the CD cohort, only patients who had received adalimumab, infliximab, ustekinumab, or vedolizumab as first-line biologics followed by infliximab or adalimumab as second-line biologics were included in the analyses. Risankizumab was not included because its date of regulatory approval in the US was after the end of the patient identification period. For UC, only patients who had received adalimumab, infliximab, or vedolizumab as first-line biologics followed by infliximab or adalimumab as second-line biologics were included in the analyses. Since use of anti-TNFα treatments as first-line biologics is well established [10, 11], the scope of the study was limited to include only anti-TNFα treatments as second-line biologics.

Variables

Baseline variables were captured using data recorded on the closest date to the index date (not inclusive) or the entire baseline period, depending on the variable. Demographics included age, sex, race/ethnicity, and insurance type. Clinical characteristics included Charlson Comorbidity Index (CCI) score [18]. Comorbid conditions, disease characteristics (CD only), disease location (CD only), disease extent (UC only), smoking status, body mass index, all-cause hospitalization, duration of conventional therapy, and extraintestinal manifestations.

Endpoints

The incidence of adverse clinical outcomes was evaluated during each line of treatment individually and for both lines of treatment overall. Adverse clinical outcomes included IBD-related hospitalization, IBD-related surgery (elective and emergency), dysplasia, CRC, and infection. IBD-related hospitalizations were identified based on the existence of a primary diagnosis of UC or CD on at least one of the hospitalization events. IBD-related surgeries were identified using procedure codes (abscess drainage, colectomy, endoscopic dilation, fistulectomy/fistulotomy, proctectomy, proctocolectomy, seton placement, small bowel resection, and strictureplasty). Infections, dysplasia, and CRC were identified based on diagnosis codes in the EHRs. Dysplasia rates were calculated using the entire CD or UC cohort as the denominator. Infections included complicated intra-abdominal infections, pneumonia, blood stream infections, *Clostridioides difficile* colitis, and tuberculosis for CD, and viral, fungal, and bacterial infections for UC. For the adjusted analyses, hospitalization, surgery, or infection were combined, owing to low event numbers, to form the composite outcome 'adverse medical event'.

Statistical analysis

The CD and UC cohorts were analyzed separately. Demographics and clinical characteristics of patients were stratified by treatment sequence. Means, standard deviations, and percentiles were calculated, as appropriate, for continuous variables. For categorical variables, the number and proportion of patients were recorded. Descriptive statistics were used to describe the incidence of adverse clinical outcomes during each line of treatment individually and for both lines of treatment overall. A logistic regression model, adjusted for age, sex, race/ethnicity, body mass index, baseline smoking, baseline disease extent (UC only), baseline CD-related conditions (CD only), baseline disease location (CD only), baseline extraintestinal manifestations, baseline all-cause hospitalization, baseline CCI score, baseline mental disorder, baseline concomitant therapy, and index year, was used to determine the odds of experiencing an adverse medical event. Statistical analyses were performed as exploratory analyses with no *a priori* hypotheses using SAS v9.4 or later. A significance level of 0.05 on a two-tailed test was used to determine statistical significance.

Results

Baseline demographics and clinical characteristics

A total of 1273 patients with CD and 779 patients with UC met the eligibility criteria and were included in the analyses (Supplementary Tables 1 and 2). Baseline demographics and characteristics stratified by treatment sequence are summarized in Tables 1 and 2.

Patients with CD

The mean ages of all patients with CD ranged between 39.9 and 44.7 years. Across the six treatment sequences investigated in patients with CD, 38.2–51.9% of patients were male. The majority of patients with CD had commercial insurance coverage (55.6–71.4%) and were white or Caucasian (70.4–94.6%), although more patients who received ustekinumab to infliximab were black or African American (22.2%) than those receiving any other treatment sequence (5.4–9.7%). Clinical characteristics were generally similar across treatment sequences; however, notably, the proportion of patients with ileocolonic disease was greater for individuals who had received ustekinumab as a first-line biologic (51.9–63.6%) than for those who had received adalimumab (33.8%), infliximab (34.1%), or vedolizumab (33.9–38.2%) as first-line biologics. In addition, perianal disease and abscesses were absent at baseline in patients who received vedolizumab to adalimumab or ustekinumab to infliximab but present

Table 1 Baseline demographics and clinical characteristics stratified by treatment sequence in patients with Crohn's disease

	ADA to IFX ***n*** **= 637**	**IFX to ADA** ***n*** **= 454**	**VDZ to ADA** ***n*** **= 55**	**VDZ to IFX** ***n*** **= 56**	**UST to ADA** ***n*** **= 44**	**UST to IFX** ***n*** **= 27**
Baseline demographics						
Age, years, mean [SD]	40.6 [15.3]	39.9 [14.7]	44.7 [13.4]	40.8 [14.8]	40.8 [14.9]	43.2 [15.5]
Male, %	41.3	45.6	38.2	41.1	47.7	51.9
Race/ethnicity, %						
Asian	0.6	0.7	0.0	0.0	0.0	3.7
Black or African American	8.0	9.7	5.5	5.4	6.8	22.2
White or Caucasian	88.4	86.1	90.9	94.6	90.9	70.4
Unknown or other	3.0	3.5	3.6	0.0	2.3	3.7
Commercial insurance, %	60.0	58.8	61.8	71.4	68.2	55.6
Baseline clinical characteristics						
Conditions in the pre-index period,[a] %						
Mental disorder	26.1	23.6	16.4	30.4	25.0	18.5
Cardiovascular disease	24.0	21.4	25.5	21.4	22.7	11.1
Chronic pulmonary disease	16.3	16.5	20.0	7.1	13.6	14.8
Liver disease	6.0	6.8	10.9	10.7	6.8	3.7
Diabetes mellitus	7.5	4.9	1.8	1.8	0.0	0.0
CCI score, mean [SD]	0.5 [1.0]	0.5 [1.0]	0.8 [1.2]	0.6 [0.9]	0.8 [1.3]	0.5 [0.9]
Body mass index, kg/m^2, mean [SD]	27.4 [6.8]	26.6 [6.8]	26.4 [6.4]	24.7 [5.5]	25.9 [5.5]	26.2 [7.5]
Smoking, %	23.4	23.8	14.6	21.4	29.6	11.1
Disease characteristics, %						
Perianal disease	4.1	6.4	0.0	3.6	4.6	0.0
Fistula	12.1	15.0	3.6	10.7	13.6	11.1
Abscess	4.1	6.4	0.0	3.6	4.6	0.0
Stricture	0.2	0.4	0.0	0.0	0.0	0.0
Disease location, %						
Ileum–colon	33.8	34.1	38.2	33.9	63.6	51.9
Colon	24.7	26.0	29.1	28.6	11.4	11.1
Ileum	21.0	18.9	16.4	19.6	20.5	25.9
Unspecified	20.6	20.9	16.4	17.9	4.6	11.1
Duration of conventional therapy, %						
0 days	23.1	22.0	25.5	23.2	25.0	25.9
1–30 days	12.1	13.4	0.0	16.1	20.5	7.4
31–60 days	12.9	18.7	14.6	10.7	22.7	22.2
61–90 days	9.6	9.5	20.0	10.7	6.8	7.4
≥ 91 days	42.4	36.3	40.0	39.3	25.0	37.0

ADA Adalimumab, *CCI* Charlson Comorbidity Index, *IFX* Infliximab, *SD* Standard deviation, *UST* Ustekinumab, *VDZ* Vedolizumab

[a] Five most prevalent conditions in the total Crohn's disease cohort

Table 2 Baseline demographics and clinical characteristics stratified by treatment sequence in patients with ulcerative colitis

	ADA to IFX *n* = 330	IFX to ADA *n* = 266	VDZ to ADA *n* = 64	VDZ to IFX *n* = 119
Baseline demographic				
Age, years, mean [SD]	41.8 [15.8]	41.8 [15.2]	47.1 [16.1]	47.2 [18.5]
Male, %	50.9	47.0	54.7	53.8
Race/ethnicity, %				
Asian	1.5	1.5	3.1	2.5
Black or African American	6.4	8.3	3.1	5.0
White or Caucasian	88.8	85.0	85.9	89.1
Unknown or other	3.3	5.3	7.8	3.4
Commercial insurance, %	66.1	66.2	56.3	53.8
Baseline clinical characteristics				
Conditions in the pre-index period,[a] %				
Cardiovascular disease	22.1	28.2	21.9	27.7
Mental disorder	16.1	24.1	18.8	14.3
Chronic pulmonary disease	10.9	15.4	12.5	15.1
Diabetes mellitus	7.3	5.6	4.7	10.1
Liver disease	8.2	6.4	4.7	6.7
CCI score, mean [SD]	0.4 [0.9]	0.5 [1.0]	0.8 [1.2]	0.8 [1.3]
Body mass index, kg/m^2, mean [SD]	27.8 [6.5]	27.2 [6.8]	26.1 [5.3]	27.4 [5.6]
Smoking, %	18.5	17.7	10.9	14.3
Disease extent, %				
Pancolitis	47.3	44.7	45.3	53.8
Left sided	8.8	11.7	12.5	5.9
Proctosigmoiditis	8.5	2.6	9.4	8.4
Proctitis, other, and unspecified	35.5	41.0	32.8	31.9
Duration of conventional therapy, %				
0 days	8.8	10.5	7.8	20.2
1–30 days	11.5	12.4	3.1	14.3
31–60 days	11.2	13.5	15.6	8.4
61–90 days	11.2	7.9	7.8	9.2
≥ 91 days	57.3	55.6	65.6	47.9

ADA Adalimumab, *CCI* Charlson Comorbidity Index, *IFX* Infliximab, *SD* Standard deviation, *VDZ* Vedolizumab

[a] Five most prevalent conditions in the total ulcerative colitis cohort

in a small proportion of patients in other treatment groups (3.6–6.4% for both).

Patients with UC

The mean ages of all patients with UC ranged between 41.8 and 47.2 years. Patients who had received vedolizumab as a first-line biologic were on average older than those who received an anti-TNFα treatment. Mean ages ranged from 47.1 to 47.2 years for patients treated with vedolizumab as a first-line biologic, and was 41.8 years for those who received an anti-TNFα treatment as a first-line biologic. Across the four treatment sequences investigated in patients with UC, 47.0–54.7% of patients were male. Similar to the CD cohort, the majority of patients with UC were white or Caucasian (85.0–89.1%) and had commercial insurance coverage (53.8–66.2%). Patients who had received vedolizumab as a first-line biologic had a higher mean CCI score (0.8) than those who had received an anti-TNFα treatment as a first-line biologic (0.4–0.5). The proportion of patients who did not receive conventional therapy was higher for those who were treated with vedolizumab followed by infliximab (20.2%) than for any other treatment sequence (7.8–10.5%).

Overall incidence of adverse clinical outcomes

Patients with CD

In patients with CD, overall incidences of hospitalization for first and second lines of biologic treatment were in the range of 30.9–51.9% for all treatment sequences. Incidence of hospitalization was higher for those treated with either adalimumab or infliximab as first-line biologics (44.0–48.5%) than for those treated with vedolizumab as a first-line biologic followed by either adalimumab or infliximab (30.9–37.5%) (Fig. 2A).

The overall incidences of both hospitalization and surgery were greatest in those treated with ustekinumab followed by infliximab (51.9% and 40.7% for hospitalization and surgery, respectively). Overall incidence of surgery was 14.6–40.7%, with similar rates observed for those treated with either adalimumab (22.1%) or infliximab (27.1%) as first-line biologics. The lowest overall incidence of surgery was observed for those receiving vedolizumab followed by adalimumab (14.6%).

Overall incidence of dysplasia was less than 9% for all treatment sequences. The highest incidence of dysplasia was observed for those who received an anti-TNFα treatment as a first-line biologic (8.6% for adalimumab and 7.7% for infliximab as first-line biologics). Overall incidence of CRC was less than 4% for all treatment sequences.

For those who received an anti-TNFα treatment (adalimumab or infliximab) as a first-line biologic, overall incidence of infection (24.0–25.3%) was higher than for those treated with vedolizumab as a first-line biologic followed by either adalimumab or infliximab (16.4–17.9%). The incidence of infection was highest in patients treated with ustekinumab followed by infliximab (37.0%).

Similar trends to the overall incidence of adverse clinical outcomes were observed during the first line of biologic treatment in patients with CD (Fig. 2B).

Patients with UC

In patients with UC, the overall incidence of hospitalization was 20.3–43.0% for all treatment sequences (Fig. 3A). The overall incidence of hospitalization was lowest in those treated with vedolizumab followed by adalimumab (20.3%). The overall incidence of surgery was 6.3–26.1% and was lowest in those who received vedolizumab followed by adalimumab. Overall incidence of dysplasia was 6.3–12.7%, while only two patients in total had CRC across all treatment sequences.

Receiving two anti-TNFα treatments in succession, or receiving vedolizumab followed by infliximab, resulted in a similar overall incidence of infection (13.0–16.8%), while the lowest incidence of infection was observed for the vedolizumab to adalimumab treatment sequence (4.7%).

Similar trends to the overall incidence of adverse clinical outcomes were observed during the first line of biologic treatment in patients with UC (Fig. 3B).

Incidence of adverse clinical outcomes during the second line of biologic treatment

Patients with CD

In patients with CD, the incidence of surgery during the second line of biologic treatment was lowest in patients who received vedolizumab followed by adalimumab (9.1%), and in patients who received ustekinumab followed by adalimumab (9.1%). No incidences of dysplasia were reported during the second line of biologic treatment in patients who received vedolizumab followed by adalimumab, or ustekinumab followed by infliximab. Similarly, no incidences of CRC were reported in patients who received vedolizumab followed by adalimumab, ustekinumab followed by adalimumab, or ustekinumab followed by infliximab, with incidences of CRC below 2.0% for all treatment sequences (Fig. 2C).

During the second line of biologic treatment, the incidence of hospitalization was lower in patients with CD who had received vedolizumab as a first-line biologic followed by adalimumab (20.0%) or infliximab (25.0%) than in those who had received adalimumab followed by infliximab (27.3%) or infliximab followed by adalimumab (30.8%). The incidence of hospitalization during the second line of biologic treatment was lowest in those who received ustekinumab followed by adalimumab (18.2%). Similarly, the incidence of infection during the second line of biologic treatment was lower in patients with CD who had received vedolizumab as a first-line biologic followed by adalimumab (9.1%) or infliximab (8.9%) than those who had received adalimumab followed by infliximab (11.5%) or infliximab followed by adalimumab (12.6%). The incidence of infection was lowest in those who received ustekinumab followed by adalimumab (6.8%), and highest in those receiving ustekinumab followed by infliximab (18.5%) (Fig. 2C).

Patients with UC

In patients with UC, the incidences of dysplasia, hospitalization, and surgery during the second line of biologic treatment were lowest in patients who received vedolizumab followed by adalimumab. The incidence of CRC was below 1.0% for all treatment sequences, with no incidences of CRC in patients who received adalimumab followed by infliximab or in patients who received vedolizumab followed by adalimumab (Fig. 3C).

When comparing sequences of anti-TNFα treatments, incidences of hospitalization (23.6% vs 19.2%), surgery (14.2% vs 7.1%), dysplasia (8.2% vs 7.1%), and infections

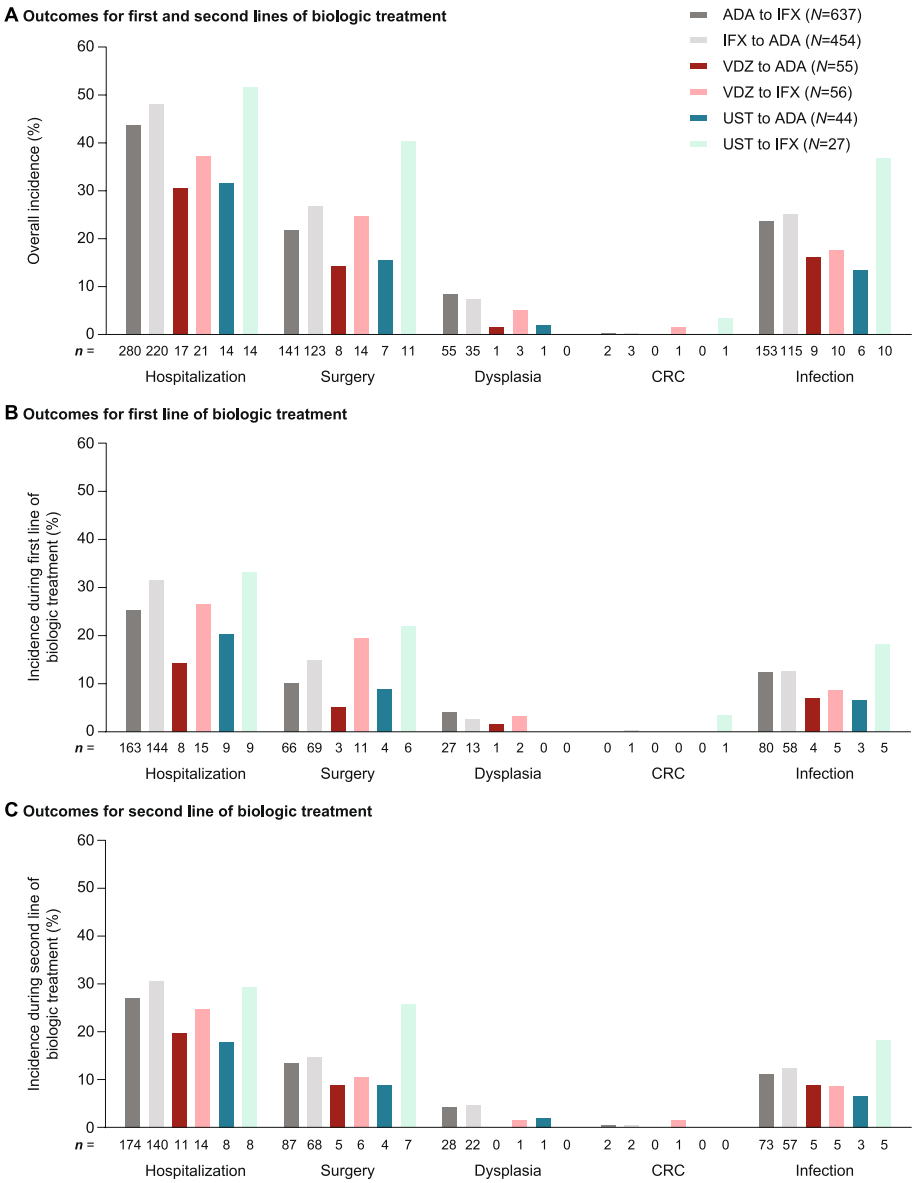

Fig. 2 Incidence of adverse clinical outcomes in patients with CD. For hospitalization and surgery, patients with events occurring during both first and second lines of biologic treatment were counted individually for each line of treatment. Overall totals count only the first event and therefore do not equal the sum of patients with events during first and second lines of biologic treatment. Dysplasia, CRC, and infection were counted for the line of treatment incident with the event onset; therefore, overall totals equal the sum of patients with events in the first and second lines of biologic treatment. ADA, adalimumab; CD, Crohn's disease; CRC, colorectal cancer; IFX, infliximab; UST, ustekinumab; VDZ, vedolizumab

(6.1% vs 3.8%) on the second line of biologic treatment were lower in patients with UC receiving infliximab followed by adalimumab than in patients receiving adalimumab followed by infliximab (Fig. 3C).

Adjusted odds of experiencing an adverse medical event

Patients with CD

Adjusted for baseline demographics and clinical characteristics, results of the logistic regression model suggest that the overall odds of experiencing an adverse medical event during the first and second lines of biologic treatment were 52.6% higher for patients with CD who received two anti-TNFα treatments successively than for those who received vedolizumab followed by an anti-TNFα treatment (odds ratio [OR], 1.526; 95% confidence interval [CI], 1.004–2.320; $P<0.05$) (Fig. 4A). There was no significant difference between treatment with ustekinumab followed by an anti-TNFα treatment

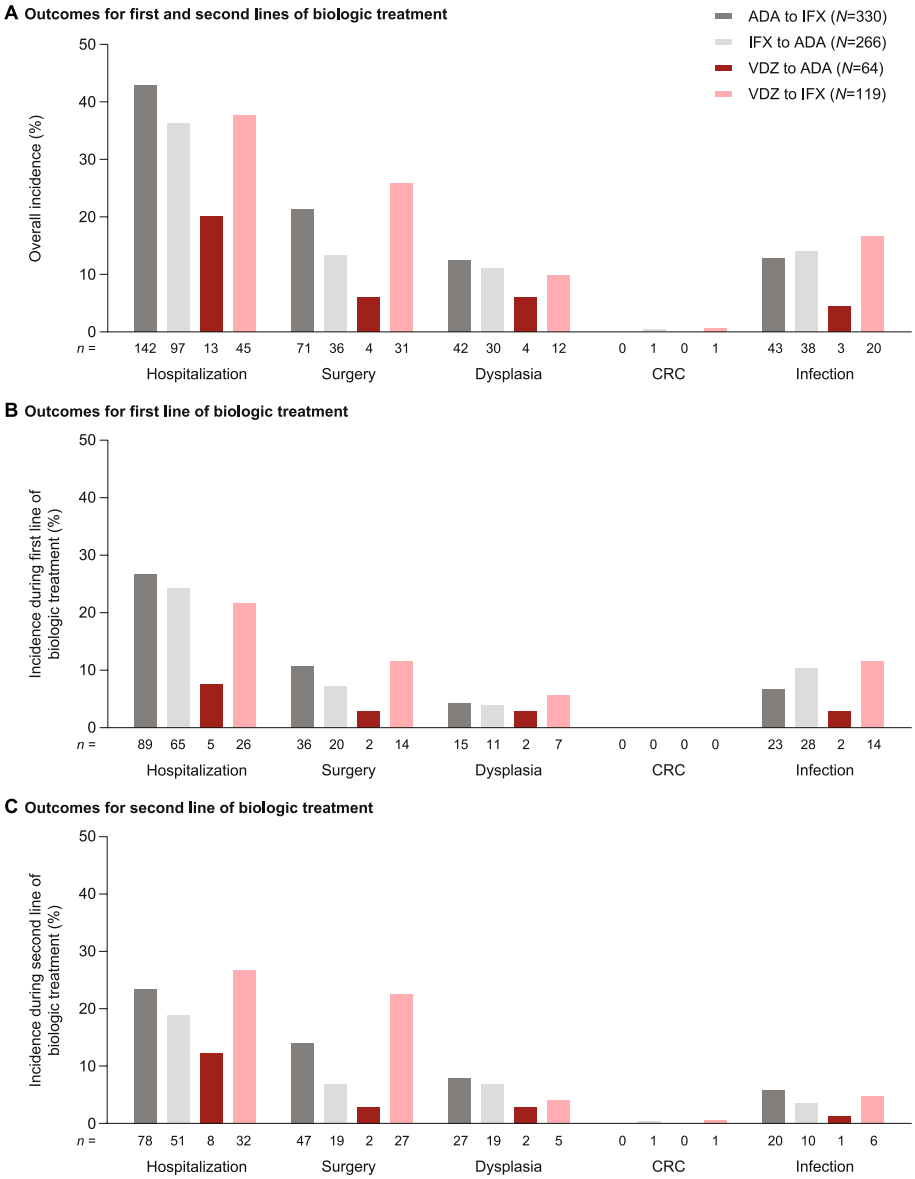

Fig. 3 Incidence of adverse clinical outcomes in patients with UC. For hospitalization and surgery, patients with events occurring during both first and second lines of biologic treatment were counted individually for each line of treatment. Overall totals count only the first event and therefore do not equal the sum of patients with events during first and second lines of biologic treatment. Dysplasia, CRC, and infection were counted for the line of treatment incident with the event onset; therefore, overall totals equal the sum of patients with events during first and second lines of biologic treatment. ADA, adalimumab; CRC, colorectal cancer; IFX, infliximab; UC, ulcerative colitis; VDZ, vedolizumab

and vedolizumab followed by an anti-TNFα treatment (OR, 1.596; 95% CI, 0.833–3.059; $P=0.159$). In patients with CD, one to two and three or more hospitalization events were associated with higher odds of experiencing an adverse medical event than no hospitalization events (OR, 1.700; 95% CI, 1.307–2.211; $P<0.001$ for one to two hospitalization events, and OR, 4.298; 95% CI, 2.352–7.855; $P<0.001$ for three or more hospitalization events). Initiating biologic treatment in 2017, 2018, and 2019/20 was associated respectively with a 34.9% (OR, 0.651; 95% CI, 0.425–0.996; $P=0.048$), 55.4% (OR, 0.446; 95% CI, 0.276–0.720; $P<0.001$), and 61.9% (OR, 0.381; 95% CI, 0.216–0.673; $P<0.001$) lower odds of experiencing an adverse medical event than in 2013.

Patients with UC

Adjusted for baseline demographics and clinical characteristics, results of the logistic regression model suggest

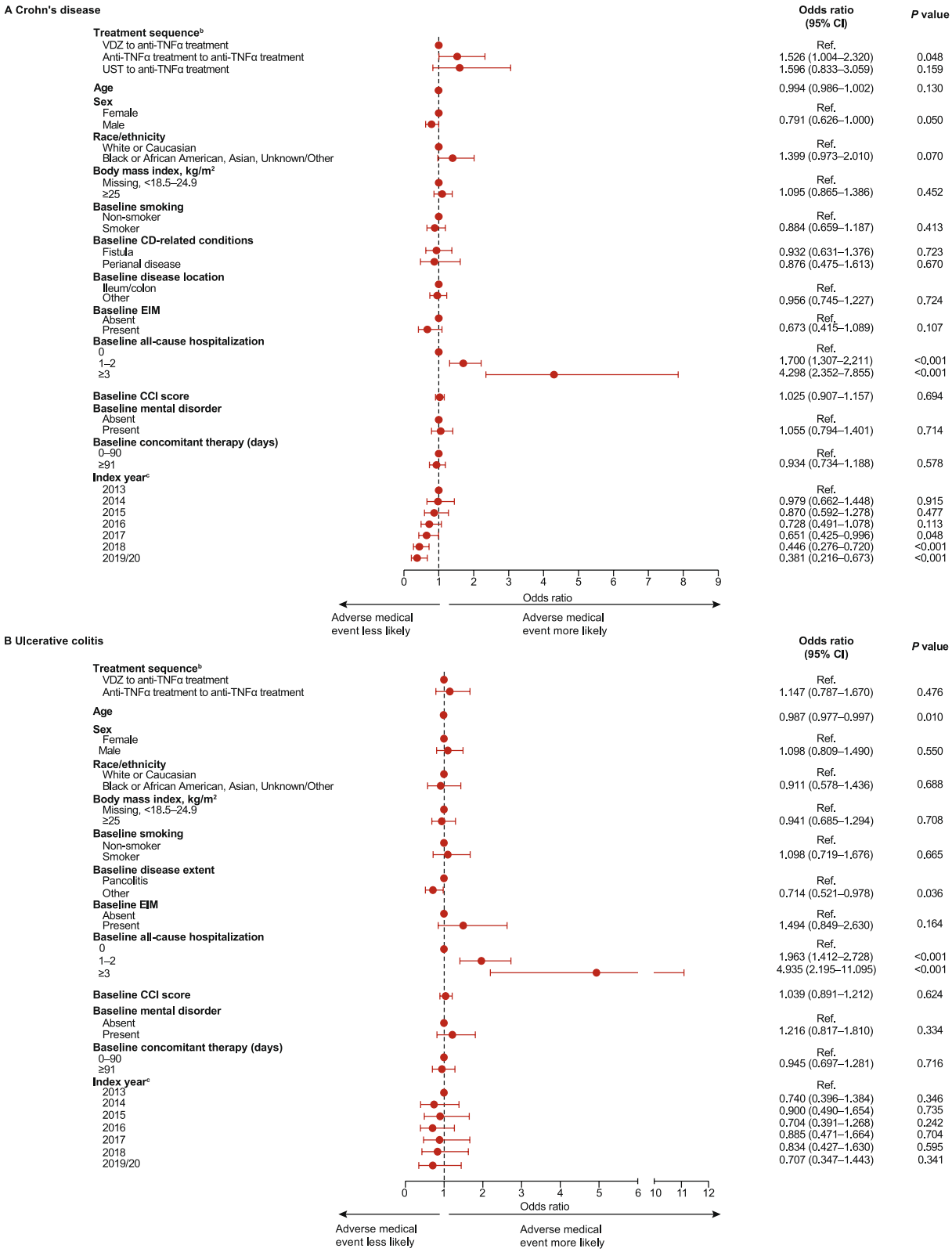

Fig. 4 Adjusted odds of experiencing an adverse medical event. [a]An adverse medical event was any incidence of hospitalization, surgery, or infection. [b]Anti-TNFα treatments were adalimumab and infliximab. [c]Index year was the year of first prescription of biologic treatment. CD, Crohn's disease; CCI, Charlson Comorbidity Index; CI, confidence interval; EIM, extraintestinal manifestation; Ref., reference; TNFα, tumor necrosis factor alpha; UST, ustekinumab; VDZ, vedolizumab

that the overall odds of experiencing an adverse medical event during first and second lines of biologic treatment were not significantly different between patients with UC who received two anti-TNFα treatments successively and those who received vedolizumab followed by an anti-TNFα treatment (OR, 1.147; 95% CI, 0.787–1.670; $P=0.476$) (Fig. 4B).

In patients with UC, one to two and three or more hospitalization events were associated with higher odds of experiencing an adverse medical event than no hospitalization events (OR, 1.963; 95% CI, 1.412–2.728; $P<0.001$ for one to two hospitalization events, and OR, 4.935; 95% CI, 2.195–11.095; $P<0.001$ for three or more hospitalization events). Less extensive disease than pancolitis was associated with lower odds of experiencing an adverse medical event in patients with UC (OR, 0.714; CI, 0.521–0.978; $P=0.036$). Each year increase in age was associated with lower odds of experiencing an adverse medical event in patients with UC (OR, 0.987; 95% CI, 0.977–0.997; $P=0.010$).

Discussion

Sequencing of therapies in patients with IBD has become a pressing clinical need as more therapies have become available, with evidence suggesting that the choice of initial treatment may impact the outcomes of later lines of treatment [19]. Studies have suggested that response rates to biologics may be greater for patients who are anti-TNFα treatment-naïve than for those who have previously received an anti-TNFα treatment [20–23]. There are limited data available from clinical trials comparing outcomes for patients with IBD receiving sequences of biologics [19]. This retrospective, real-world study of adult patients with IBD aimed to provide further insight into the impact of sequencing of various biologics within a treatment sequence on adverse clinical outcomes.

In our study, the vedolizumab to adalimumab treatment sequence had the lowest unadjusted overall incidences of hospitalization and surgery among patients with CD and UC, which may result from the first-line biologic effectiveness of vedolizumab [24]. We observed that in patients with CD who were unsuccessfully treated with either vedolizumab or ustekinumab as a first-line biologic, treatment with infliximab resulted in higher overall unadjusted incidences of hospitalization and surgery than treatment with adalimumab. However, treatment with infliximab followed by adalimumab resulted in higher overall unadjusted incidences of hospitalization and surgery than vedolizumab to infliximab, but not than ustekinumab to infliximab.

In patients with UC who received two anti-TNFα treatments in succession, during the second line of biologic treatment, treatment with adalimumab as a second-line biologic was associated with lower incidences of hospitalization, surgery, dysplasia, and infections than infliximab. Overall, incidence of infection in patients with UC was lowest for those treated with vedolizumab followed by adalimumab, although it was highest for those who received infliximab as a second-line biologic after treatment with vedolizumab. We observed higher rates of infection in patients treated with adalimumab followed by infliximab than in those treated with vedolizumab followed by adalimumab. These results are similar to those of the head-to-head VARSITY trial, which demonstrated that, in patients with moderate to severe UC, those who received vedolizumab had fewer infections than those who received adalimumab [22]. The majority of patients included in VARSITY were anti-TNFα treatment-naïve and had not previously received vedolizumab, although some patients had previously received an anti-TNFα treatment other than adalimumab.

Overall unadjusted incidences of dysplasia and CRC were relatively low in both CD and UC cohorts, and thus limited conclusions may be drawn from these data. In line with our findings, a previous meta-analysis of patients with CD, UC, or both, showed that the cumulative risk of CRC is less than 1% in those with a disease duration of less than 10 years [25].

After adjusting for baseline demographics and clinical characteristics, vedolizumab as a first-line biologic followed by an anti-TNFα treatment (adalimumab or infliximab) was associated with significantly lower odds of experiencing an adverse medical event (hospitalization, surgery, or infection) than sequences of two successive anti-TNFα treatments in patients with CD. These results are in line with observations of other retrospective studies evaluating first-line biologics in patients with CD or UC, in which receiving vedolizumab was demonstrated to result in lower incidences of surgery (in patients with CD), infection, and other adverse events than receiving an anti-TNFα treatment [24, 26].

In patients with UC, no significant difference was observed in the odds of experiencing an adverse medical event between those who received two successive anti-TNFα treatments and those who received vedolizumab followed by an anti-TNFα treatment.

This retrospective, observational study has some limitations. We were unable to adjust for clinical characteristics that were not available in the EHR database, such as disease activity, behavior, duration, and severity. In addition, the definition of infection differed between patients with CD and patients with UC, with different infections included for these two cohorts of patients. However, the present study does not draw comparisons between patients with CD and UC, so the different infections

included for these patients does not affect the conclusions drawn from these analyses, which compared the rates of infections between patients who received different treatment sequences. The use of diagnostic, procedural, and pharmacy codes from EHR data may result in inaccuracies because the presence of a certain code does not guarantee that the patient has received that diagnosis, treatment, or procedure. Conversely, events related to CD or UC without a concurrent diagnosis of CD or UC would have been missed. In addition to on-site administration records, use of medications was imputed from prescription orders, which may be incomplete or contain errors, particularly those which are self-administered. However, owing to the requirement for multiple records to define treatment sequences, we expect this to have had a limited impact on our longitudinal study. Data on additional treatment sequences than those reported here were collected; however, only the most common treatment sequences were included in the analysis in order to optimize the statistical robustness of the regression model by comparing fewer treatment sequences. Related to this, the smaller numbers of available patients with treatment sequences including vedolizumab or ustekinumab as first-line biologics means that these estimates may be associated with larger errors than those where anti-TNFα treatments were used as first-line biologics. However, we believe the numbers included for sequences with vedolizumab or ustekinumab as first-line biologics were sufficiently large to draw meaningful conclusions. It is also important to note that the present study included data collected between January 1, 2013 and February 29, 2020 and includes biologic treatment sequences that were commonly used during that period. As newer advanced therapies were introduced both during and after this period, treatment sequences used may have evolved and further analysis would be needed to address how these sequences including newer advanced therapies would impact the outcomes measured here.

Conclusions

In conclusion, in this real-world study of treatment sequences in IBD, we observed differences in the incidence of adverse clinical outcomes, generally favoring treatment with vedolizumab as a first-line biologic followed by adalimumab over anti-TNFα treatments or ustekinumab as first-line biologics followed by an anti-TNFα treatment. Whether these findings are related to the treatments or to the disease in patients who need multiple successive therapies is not known, but the possibility that the mechanisms of action of these therapies affect the biology of inflammation in these patients should be explored further. In the meantime, these data provide important insights into the impact of different sequences of biologic treatments on adverse clinical outcomes in IBD and provide guidance to clinicians when choosing sequences of biologics for treating patients with moderate to severe CD or UC.

Abbreviations

CCI	Charlson Comorbidity Index
CD	Crohn's disease
CI	Confidence interval
CRC	Colorectal cancer
EHR	Electronic health record
IBD	Inflammatory bowel disease
IL	Interleukin
OR	Odds ratio
TNFα	Tumor necrosis factor alpha
UC	Ulcerative colitis

Supplementary Information

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Supplementary Material 1.

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Authors' contributions
Study design and concept: SG, NC, TF, KU, DTR. Data acquisition and analysis: BC, TB. Data interpretation: NKC, SG, NC, TF, KU, DTR. Drafting and critical revisions of the manuscript: NKC, SG, BC, TB, NC, TF, KU, DTR.

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Availability of data and materials
The data underlying the results presented in the study include administrative medical and pharmacy claims from data available from Optum and cannot be broadly disclosed or made publicly available at this time. The disclosure of these data to third party clients assumes certain data security and privacy protocols are in place and that the third-party client has executed a standard license agreement which includes restrictive covenants governing the use of the data. Please see https://www.optum.com/content/dam/optum/resources/productSheets/Clinformatics_for_Data_Mart.pdf for more information about licensing these data from Optum.

Data availability
Data are not publicly available.

Declarations

Ethics approval and consent to participate
This study was conducted in accordance with the Guidelines for Good Pharmacoepidemiology Practice published by the International Society for Pharmacoepidemiology. This study used de-identified retrospective electronic health record data from the Optum® Research Database, therefore no specific ethical approval was required.

Consent for publication
Not applicable.

Competing interests
Noa Krugliak Cleveland served as a consultant for Arena Pharmaceuticals, Bristol Myers Squibb, and Takeda Pharmaceuticals U.S.A., Inc. Benjamin Chastek and Tim Bancroft are employees of Optum. Sabyasachi Ghosh is a former employee of Takeda Pharmaceuticals U.S.A, Inc. and has stock or stock options. Ninfa Candela and Tao Fan are employees of Takeda Pharmaceuticals U.S.A., Inc. and hold stock or stock options. Kandavadivu Umashankar is an employee of University of Illinois, Chicago, IL, USA, who was supported by a Takeda Pharmaceuticals U.S.A., Inc. fellowship at the time of the study. David T. Rubin received grant support from Takeda Pharmaceuticals U.S.A., Inc. and has served as a consultant for AbbVie, AltruBio, Arena Pharmaceuticals, Bristol Myers Squibb, Genentech/Roche, Gilead Sciences, Iterative Scopes, Janssen Pharmaceuticals, Lilly, Pfizer, Prometheus Biosciences, Takeda, and TechLab Inc.

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