# Real-world Pattern of Biologic Use in Patients With Inflammatory Bowel Disease: Treatment Persistence, Switching, and Importance of Concurrent Immunosuppressive Therapy

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**Background and aims:** Medication persistence, defined as the time from drug initiation to discontinuation of therapy, has been suggested as a proxy for real-world therapeutic benefit and safety. This study seeks to compare the persistence of biologic drugs among patients with inflammatory bowel disease (IBD).

**Methods:** Patients with newly diagnosed IBD were included in a retrospective study using Truven MarketScan database. Treatment persistence and switching was compared among biologic medications including infliximab, adalimumab, certolizumab, golimumab, and vedolizumab. Predictors for discontinuation and switching were evaluated using time-dependent proportional hazard regression.

**Results:** In total, 5612 patients with Crohn's disease (CD) and 3533 patients with ulcerative colitis (UC) were included in this analysis. Less than half of the patients continued using their initial biologic treatment after 1 year (48.48% in CD cohort; 44.78% in UC cohort). In the first year, adalimumab had the highest persistence and lowest switching rates for both CD (median survival time: 1.04 years) and UC (median survival time: 0.84 years). In subsequent years, infliximab users were more likely to persist in the use of biologic. Combination therapy with immunomodulators significantly decreased the risk of discontinuation, especially when immunomodulator therapy was started more than 30 days before the biologic (hazard ratio [HR], 0.22; CI, 0.16, 0.32). The major predictors for noncompliance included infection and hospitalization.

**Conclusion:** Overall, the persistence profiles of biologics suggest a high rate of dissatisfaction or adverse disease outcomes resulting in discontinuation and switching to a different agent. Early initiation of immunomodulators will substantially increase the persistence of biologic treatment.

**Key Words:** treatment persistence, switching, biologics, tumor necrosis inhibitors

## INTRODUCTION

Over the past 2 decades, the availability of biologic medications has revolutionized the therapeutic management of patients with inflammatory bowel disease (IBD).[1] Unlike traditional immunosuppressive medications, biologics are antibodies that block the inflammatory response by binding with proteins or cells that play important roles in the inflammatory cascade.[2] Medications that suppress tumor necrosis factor (TNF), a cytokine that triggers and amplifies the inflammatory process in the gut, have proven to be effective treatments for Crohn's disease (CD) and ulcerative colitis (UC).[3] The first biologic approved for IBD was infliximab, a chimeric monoclonal antibody that inhibits TNFα and induces apoptosis of macrophages and activated T lymphocytes. In addition to biologics that target TNF, other biologics with different targets and different pharmacologic and pharmaceutic properties have been approved byt the Federal Food and Drug Administration (FDA) and marketed.[4] The FDA has approved these therapies based on efficacy demonstrated in randomized clinical trials; though, in the absence of head-to-head clinical trials, the comparative effectiveness of the biologics remains controversial.[2] This information gap has left patients and physicians wondering how to best utilize these therapies in clinical practice.

Real-world assessment of effectiveness of biologic treatments is greatly needed for the several reasons. First, IBD requires long-term treatment; though somewhat surprisingly, there are a paucity of data on the benefits of long-term use of biologic treatments.[2] Second, few head-to-head randomized clinical trials (RCTs) have been conducted comparing the benefit and harm profiles of biologics.[2, 5] Third, patients enrolled in the RCTs may differ from those seen in medical practice. Studies showed that less than one-third of IBD patients were eligible to participate in the randomized clinical trials.[6] Patients

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were excluded mostly because they had stricturing or penetrating CD, were prescribed high dose steroids, or showed other comorbidities. It was also shown that these ineligible patients were more likely to have lower response rates to biologics than the patients included in the RCTs.[6] For these reasons, it is important to study the long-term outcomes of these biologics in general medical practice.

Medication persistence, defined as "the duration during which a patient remains on a prescribed therapy," is a simple indirect approach for assessing the long-term therapeutic benefit and safety profiles.[7, 8] This assumes that patients persist in using the drug as long as it reduces the symptoms and prevents relapses until they experience intolerance or lose response to the medication. This is very likely to be true for biologic medications for IBD because these drugs are indicated for long-term use to prevent disease progression. Immunogenicity is one of the most important reasons for discontinuation of biologics in practice. Immunogenicity leads to loss of response to therapy because patients develop antibodies to the drug, thereby reducing or eliminating the therapeutic effect.

Other common reasons for discontinuation of biologic treatment include adverse events such as infusion reactions, fear of side effects, health insurance plan changes, or lack of symptoms. Few studies have investigated the long-term treatment persistence of biologics and the reasons for discontinuation or switching treatments in patients with IBD. To fill this knowledge gap, we conducted a study using a large claims database aiming to compare persistence and evaluate switching patterns among market-approved biologic medications in the treatment of IBD. We also constructed prediction models for nonpersistence and switching to understand the risk factors for and reasons behind the treatment discontinuation decisions.

## METHODS

### Data Source

A retrospective study was conducted in Truven Health MarketScan data from 2008 to 2015. The study population consists of the enrollees in the Commercial Claims and Encounter databases and the Medicare Supplement database, including employees, dependents and retirees with employer-sponsored or Medicare Supplemental insurance. The 8-year analytical file contains information on diagnoses, procedures, and prescriptions for over 100 million individuals. It captures the continuum of care in all settings including physician outpatient office visits, hospital stays, retail, mail order and specialty pharmacies, and carve-out care. Individuals in the databases are covered under a variety of fee-for-services and managed care health plans.

### Patient Selection

Patients diagnosed with Crohn's disease and ulcerative colitis were identified using ICD-9-CM codes (555.* for CD and 556.* for UC) and ICD-10-CM codes (K50.* for CD and K51.* for UC) based on a previously validated algorithm and grouped into 2 mutually exclusive, inception cohorts.[9, 10] Patients were required to have at least 3 healthcare contacts for IBD on separate days within 2 years or 1 IBD-related medication exposure (aminosalicylics, budesonide, methotrexate, thiopurine, or any biologics) within 30 days after the index diagnosis. Individuals with claims for both CD and UC were assigned to the cohort based upon whichever diagnosis was made in the majority of the last 9 claims. If a determination could not be made, (eg, 8 claims only that were evenly split), then those patients were classified as IBD not otherwise specified and were excluded from the study. We only included newly diagnosed patients in this study by requiring 1-year continuous health plan enrollment before the index diagnosis, within which no prior IBD diagnosis or IBD-related biologic treatments were allowed. Furthermore, patients without pharmacy benefits were excluded from the study.

### Persistence Rate Measurement

Medications studied in this analysis include infliximab, adalimumab, certolizumab, golimumab, and vedolizumab. Biologic medications were identified using the National Drug Code (NDC) code and Healthcare Common Procedure Coding System (HCPCS) code (Appendix S1). Because infliximab and vedolizumab are administrated intravenously making "days-of-supply" data irrelevant, we used the dosing schedule recommended by the label to estimate the days-of-supply for infliximab and vedolizumab (Table 1). For example, the first dose of infliximab had a days-of-supply of 14 days, the second dose of infliximab had a days-of-supply of 28 days, and the remainder of the doses had a days-of-supply of 56 days. For adalimumab, certolizumab, and golimumab, days-of-supply in the pharmacy claims were used. Persistence was measured as the time from treatment initiation (index date) to discontinuation of index biologic medication or switching to another biologic medication. Discontinuation was defined as having a drug-free period greater than the days-of-supply of previous administration. Switching was defined as changing to a different drug before the discontinuation date. Time to switching was evaluated as a secondary outcome, in which case discontinuation of the initial drug was treated as a censored event.

### Statistical Analysis

Baseline characteristics were summarized by calculating group means and standard deviations or medians and interquartile range (IQR) for continuous variables and proportional frequencies and percentages for categorical variables. Kaplan-Meier analysis and log-rank test were used to describe the crude risk of discontinuation and switching for each biologics user group.

**TABLE 1.** Biologics Approved for Use in Patients With Inflammatory Bowel Disease

| Generic Name | Approval Date | Mechanism of Action | Route of Administration | Dosing Schedule | Refills | Days of Supply |
|---|---|---|---|---|---|---|
| Infliximab | August 1998 | TNF-α inhibitor | Intravenous | 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks. May increase dose to 10 mg/kg if patients lose their response. | 1 | 14 |
| | | | | | 2 | 28 |
| | | | | | ≥3 | 56 |
| Adalimumab | February 2007 | TNF-α inhibitor | subcutaneous | 160 mg at week 0, 80 mg at week 2, and then every 40 mg every 2 weeks. | ≥1 | 14 |
| Certolizumab | April 2008 | TNF-α inhibitor | subcutaneous | 400 mg initially and at Weeks 2 and 4. If response occurs, follow with 400 mg every four weeks. | 1, 2 | 14 |
| | | | | | ≥2 | 28 |
| Golimumab | May 2013 | TNF-α inhibitor | subcutaneous | 200 mg at Week 0, 100 mg at Week 2 and then 100 mg every 4 weeks. | 1 | 14 |
| | | | | | ≥2 | 28 |
| Vedolizumab | May 2014 | Anti-integrin | Intravenous | 300 mg at 0, 2, and 6 weeks, then every 8 weeks thereafter. | 1 | 14 |
| | | | | | 2 | 28 |
| | | | | | ≥3 | 56 |

Multivariate Cox regression was used to assess factors associated with treatment persistence of biologics. Patients who initiated vedolizumab were not included in this model because of small sample size. Baseline covariates including patient age, gender, index biologic, health plan type, region, period of treatment initiation (ie, before or after 2012), and disease duration were adjusted as time-fixed covariates. Diagnosis of heart failure, having infection within 30 days, changing diagnosis between CD and UC, having an imaging examination within 30 days, drug level test ordered within 30 days, hospitalization event, concomitant medications including aminosalicylates, steroids and immunuosuppressants (ie, azathioprine, mercaptopurine, methotrexate and tacrolimus) and biologics dose escalation over the last 30 days were adjusted as time-dependent covariates. We defined dose escalation events only during the maintenance period, which was 14 weeks after initiation of biologics. Because no dose information was directly available for intravenous biologicals, we used dosing schedule and administrative cost as proxy to estimate dose escalation. For infliximab and vedolizumab, dose escalation was defined as a dosing interval less than 6 weeks or an increase of dose by each administration, which was operationalized as more than a 50% increase of the average cost for the first 3 outpatient visits after the first 14 weeks. For other subcutaneous biologicals, dose escalation was defined as an increase above 40 mg every 2 weeks for adalimumab, an increase above 400 mg every 4 weeks for certolizumab pegol, and an increase above 200 mg every 4 weeks for golimumab.[11] Concomitant use of immunomodulators, including azathioprine, mercaptopurine, methotrexate, and tacrolimus, was collapsed into continuous treatment episodes using 45 days as an allowable gap. The variable of concomitant use of immunomodulators was defined into 4 categories: early initiation, simultaneous initiation, late initiation, and no immunomodulators. If the start date of a treatment episode is at least 30 days earlier than the initiation of biologics, then this episode of immunomodulator treatment was classified as early initiation of immunomodulators. Correspondingly, late initiation indicated the immunomodulator initiation at least 30 days after the initiation of biologics, and simultaneous initiation indicated the absolute difference between immunomodulator and biologic initiation less than 30 days. Additional analyses were conducted by stratifying patients by initial biologic treatment and age groups. All analyses were performed using SAS software, version 9.4 (SAS Institute, Inc., Cary, NC, USA). Statistical significance was based on a $P$ value <0.05, and all confidence intervals used a 95% threshold.

## RESULTS

In total, we identified 9145 biologic-naïve patients newly diagnosed with inflammatory bowel disease from 2008 to 2015, including 5612 patients (61.37%) with CD and 3533 patients (38.63%) with UC (Supplementary Fig. S1). Among patients with Crohn's disease, most initiated infliximab (47.81%) or adalimumab (46.51%), and the remainder started with certolizumab (5.20%), golimumab (0.35%), and vedolizumab (0.12%). In the UC cohort, 52.84% of the patients started on infliximab, 41.69% on adalimumab, 2.92% on certolizumab, 2.21% on golimumab, and 0.34% on vedolizumab, respectively. Table 2 and 3A summarize baseline demographic and clinical characteristics of patients with CD and UC, stratified by their index biologic medication(s). Overall, patients with CD were younger than patients with UC (mean age: 35.15 vs 40.87 years). We also observed that infliximab users were more likely to be pediatric patients (Crohn's disease: 33.36%, ulcerative colitis: 14.62%) than patients initiating other biologics. It was also noted that those who initiated certolizumab had a higher proportion of patients

**TABLE 2.** Demographic and Clinical Characteristics of CD Patients

| Patient Characteristics, N (%) | Infliximab (N = 2683) | Adalimumab (N = 2610) | Golimumab (N = 20) | Certolizumab (N = 292) | Vedolizumab (N = 7) | Total (N = 5612) |
|---|---|---|---|---|---|---|
| Mean age, years (SD) | 31.93 (18.78) | 38.02 (15.66) | 42.86 (15.56) | 38.35 (14.91) | 45.71 (6.32) | 35.15 (17.46) |
| Age categories | | | | | | |
| 0–18 | 895 (33.36) | 249 (9.54) | 0 (0.00) | 12 (4.11) | 0 (0.00) | 1156 (20.60) |
| 19–25 | 374 (13.94) | 450 (17.24) | 3 (15.00) | 57 (19.52) | 0 (0.00) | 884 (15.75) |
| 26–65 | 1286 (47.93) | 1822 (69.81) | 15 (75.00) | 207 (70.89) | 7 (100.00) | 3337 (59.46) |
| >65 | 128 (4.77) | 89 (3.41) | 2 (10.00) | 16 (5.48) | 0 (0.00) | 235 (4.19) |
| Median follow-up, years (IQR) | 0.65 (0.08, 1.71) | 0.71 (0.24, 1.48) | 0.55 (0.18, 1.21) | 0.47 (0.15, 1.24) | 0.31 (0.10, 0.85) | 0.67 (0.16, 1.57) |
| Male | 1315 (49.01) | 1413 (54.14) | 14 (70.00) | 161 (55.14) | 4 (57.14) | 2705 (48.20) |
| Health Plan | | | | | | |
| Comprehensive | 113 (4.21) | 91 (3.49) | 15 (5.14) | 113 (4.21) | 1 (14.29) | 221 (3.94) |
| EPO/HMO/PPO/POS | 2570 (95.79) | 2519 (96.51) | 277 (94.86) | 2570 (95.79) | 6 (85.71) | 5391 (96.06) |
| Region | | | | | | |
| North/Northeast | 1350 (50.32) | 1203 (46.09) | 9 (45.00) | 187 (64.04) | 4 (57.14) | 2664 (47.47) |
| West/South | 1301 (48.49) | 1379 (52.84) | 11 (55) | 7 (2.40) | 3 (42.86) | 2881 (51.34) |
| Median duration of disease, days (IQR) | 164 (42, 487) | 275 (83, 666) | 490 (213, 961) | 199 (68, 481) | 1757 (763, 1807) | 212 (60, 580) |
| Baseline Medication use | | | | | | |
| Steroids | 1409 (52.52) | 1436 (53.52) | 9 (45.00) | 164 (56.16) | 2 (28.57) | 3020 (53.81) |
| Immunosuppressants | 508 (18.93) | 482 (18.47) | 2 (10.00) | 52 (17.80) | 1 (14.29) | 1045 (18.62) |
| Aminosalicylates | 822 (30.64) | 711 (27.24) | 6 (30.00) | 82 (28.08) | 1 (14.29) | 1622 (28.90) |

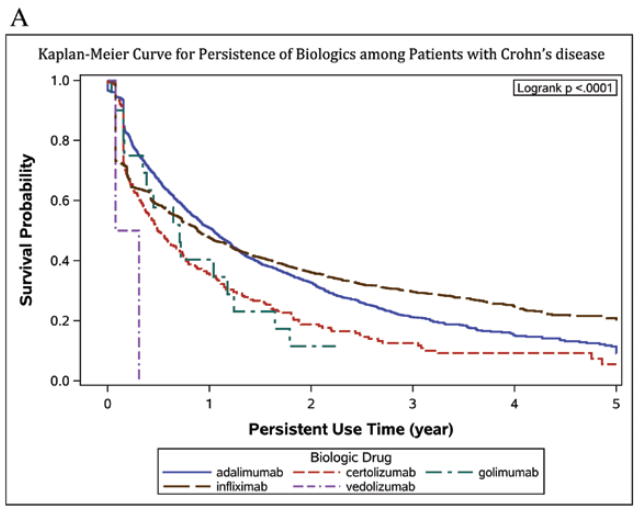
**TABLE 3A.** Demographic and Clinical Characteristics of UC Patients

| Patient Characteristics, N (%) | Infliximab (N = 1867) | Adalimumab (N = 1473) | Golimumab (N = 78) | Certolizumab (N = 103) | Vedolizumab (N = 12) | Total (N = 3533) |
|---|---|---|---|---|---|---|
| Mean age, years (SD) | 39.24 (17.81) | 42.67 (15.69) | 43.60 (16.73) | 42.36 (16.33) | 42.75 (15.00) | 40.87 (16.96) |
| Age categories | | | | | | |
| 0–18 | 273 (14.62) | 79 (5.36) | 3 (3.85) | 3 (3.85) | 1 (8.33) | 361 (10.22) |
| 19–25 | 241 (12.91) | 178 (12.08) | 11 (14.10) | 17 (16.50) | 1 (8.33) | 448 (12.68) |
| 26–65 | 1218 (65.24) | 1120 (76.04) | 58 (74.36) | 75 (72.82) | 9 (75.00) | 2480 (70.20) |
| >65 | 135 (7.23) | 96 (6.52) | 6 (7.69) | 6 (5.83) | 1 (8.33) | 244 (6.91) |
| Median follow-up, years (IQR) | 0.55 (0.08, 1.36) | 0.57 (0.23, 1.22) | 0.39, (0.16, 0.78) | 0.233 (0.15, 1.15) | 0.48 (0.21, 0.58) | 0.54 (0.17, 1.27) |
| Male | 976 (52.28) | 733 (49.76) | 39 (50.00) | 40 (38.83) | 5 (41.67) | 1795 (50.81) |
| Health Plan | | | | | | |
| Comprehensive | 96 (5.14) | 77 (5.23) | 0 (0.00) | 4 (3.88) | 1 (8.33) | 178 (5.04) |
| EPO/ HMO/PPO/POS | 1771 (94.86) | 1396 (94.77) | 78 (100.00) | 99 (96.12) | 11 (91.67) | 3355 (94.96) |
| Region | | | | | | |
| North/Northeast | 867 (46.44) | 628 (42.63) | 30 (38.46) | 43 (41.75) | 6 (50.00) | 1574 (44.55) |
| West/South | 981 (52.54) | 832 (56.48) | 46 (58.97) | 60 (58.25) | 6 (50.00) | 1925 (54.49) |
| Median duration of disease, days (IQR) | 317 (104, 637) | 468 (197, 876) | 480 (336, 966) | 245 (103, 611) | 826 (512, 1178) | 378 (146, 761) |
| Baseline Medication use | | | | | | |
| Steroids | 1224 (65.56) | 808 (54.85) | 44 (56.41) | 56 (54.37) | 5 (41.67) | 2137 (38.08) |
| Immunosuppressants | 352 (18.85) | 247 (16.77) | 7 (8.97) | 17 (16.50) | 0 (0.00) | 623 (11.10) |
| Aminosalicylates | 826 (44.24) | 501 (34.01) | 22 (28.21) | 39 (37.86) | 7 (58.33) | 1395 (24.86) |

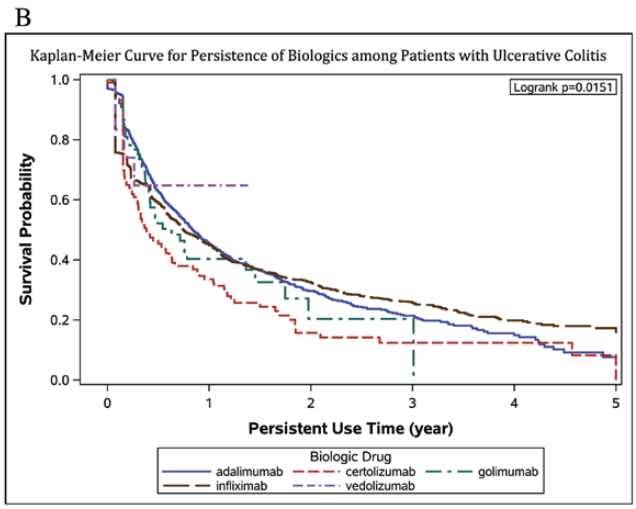
age 18 to 25 years. The CD cohort included slightly more female patients (51.80%), and the UC cohort included slightly more male patients (50.81%). A majority of patients with Crohn's disease (96.06%) and patients with ulcerative colitis (94.96%) enrolled in health plans with financial incentives, such as HMO and PPO. The duration of disease at the time of biologic initiation varied greatly among the different user groups. The median disease duration ranged from 164 days (0.44 years) for infliximab users to 1757 days (4.81 years) for vedolizumab users in patients with CD, and from 245 days (0.67 years) for certolizumab users to 826 days (2.26 years) for vedolizumab users in patients with UC. Generally, patients with CD had more concomitant baseline medication use compared with patients with UC (eg, steroids use, 53.81% vs 38.08%; immunomodulator use 18.62% vs 11.10%; and aminosalicylate use, 28.90% vs 24.86%).

The Kaplan-Meier analysis showed overall low persistence rates in both CD and UC cohorts. More than half of the patients stopped their initial biologic treatment within 1 year (Fig. 1A and B). Statistically significant differences of persistence profiles were found among the 5 biologics in both CD and UC cohorts. In patients with CD, those who started with infliximab and adalimumab generally stayed longer on their initial biologics compared with the other 3 user groups. Adalimumab seemed to have the highest persistence rate in the first year (50.89%), followed by infliximab (47.60%). However, in the following years, the patients who were the most likely to persist on their biologic treatment were infliximab users. Overall, the median treatment duration was 1.04 year for adalimumab and 0.88 years for infliximab. The persistence rates of UC cohort were slightly lower than those for the CD cohort. But the comparisons between biologics were similar to that of CD cohort, except that the difference between the biologics was smaller, and that vedolizumab and golimumab users continued their treatments longer. Nonetheless, the small sample size and short follow-up time make it difficult to draw conclusions for vedolizumab and golimumab. In sensitivity analysis by changing the gap to 2 times of the previous days-of-supply, the 1-year persistence rate increased to 61.19% for CD and 56.57% for UC, and median drug survival time increased to 1.62 years for CD and 1.30 for UC patients.

Time-to-switching analysis also indicated substantial differences among the five biologic user groups (Fig. 2A and B). Though the numbers were small, we found that vedolizumab users did not switch to other biologics during the study period. Infliximab and adalimumab users showed a very similar switching rate in both CD and UC cohorts. Patients initiating golimumab for CD were more likely to switch to another biologic product than UC patients. Table 3B showed the switching patterns among biologic treatments. For both CD and UC cohorts, infliximab users were most likely to switch to adalimumab (CD,

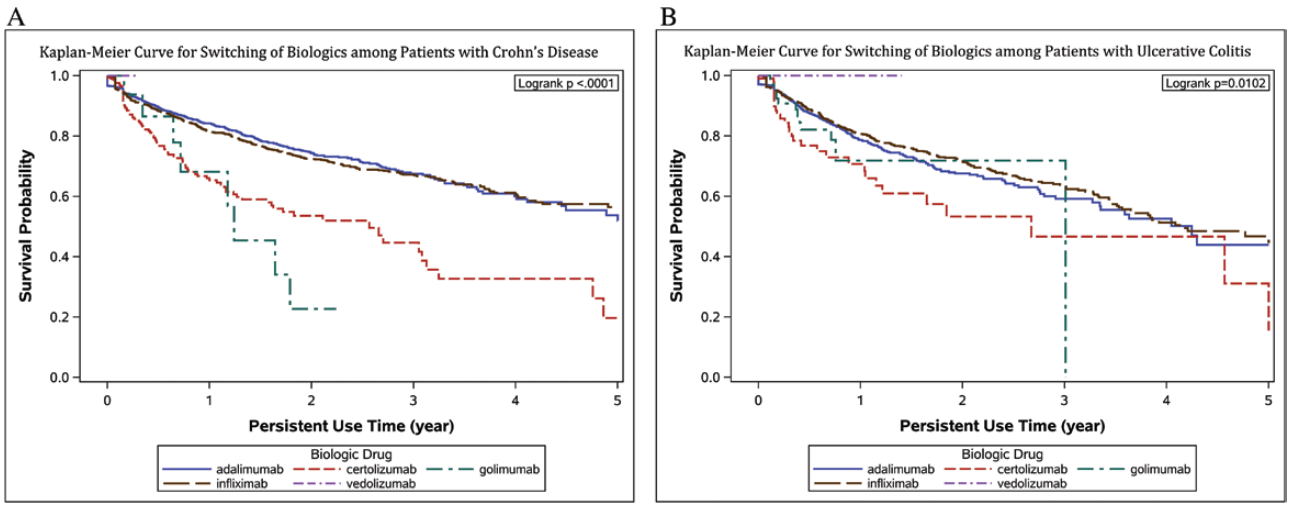



| | Survivial Rate (%) | | | | | Median survival time (95% CI) |
|---|---|---|---|---|---|---|
| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | |
| Infliximab | 47.60 | 36.03 | 39.5 | 24.43 | 20.04 | 0.88 (0.81, 0.98) |
| Adalimumab | 50.89 | 32.49 | 21.09 | 14.93 | 9.13 | 1.04 (0.93, 1.10) |
| Certolizumab | 35.34 | 18.18 | 12.56 | 11.73 | 5.53 | 0.49 (0.38, 0.67) |
| Golimumab | 34.62 | 11.54 | - | - | - | 0.71 (0.16, 1.24) |
| Vedolizumab | - | - | - | - | - | 0.19 (0.08, 0.30) |
| Overall | 48.48 | 33.53 | 24.87 | 19.46 | 15.50 | 0.92 (0.88, 0.99) |




| | Survivial Rate (%) | | | | | Median survival time (95% CI) |
|---|---|---|---|---|---|---|
| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | |
| Infliximab | 44.91 | 32.53 | 25.68 | 19.52 | 15.65 | 0.74 (0.69, 0.88) |
| Adalimumab | 45.36 | 29.52 | 21.10 | 14.26 | 7.68 | 0.84 (0.76, 0.92) |
| Certolizumab | 32.46 | 14.20 | 12.43 | 12.43 | 0.00 | 0.38 (0.30, 0.63) |
| Golimumab | 40.36 | 20.38 | 0.00 | - | - | 0.63 (0.41, 1.36) |
| Vedolizumab | 64.84 | - | - | - | - | - |
| Overall | 44.78 | 30.78 | 23.61 | 17.61 | 13.18 | 0.78 (0.73, 0.85) |

FIGURE 1. Kaplan-Meier curve for persistence of biologics among patients with (A) Crohn's disease and (B) ulcerative colitis. If event rate is higher than 50%, the median survival or its confidence interval cannot be calculated.




| | Survivial Rate (%) | | | | | Median survival time (95% CI) |
|---|---|---|---|---|---|---|
| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | |
| Infliximab | 81.47 | 72.26 | 66.98 | 60.18 | 56.43 | - |
| Adalimumab | 84.17 | 74.14 | 67.08 | 59.09 | 51.94 | - |
| Certolizumab | 65.31 | 51.95 | 41.66 | 26.18 | 19.64 | 2.56 (1.61, 3.13) |
| Golimumab | 56.79 | 22.72 | - | - | - | 1.24 (0.64, - ) |
| Vedolizumab | - | - | - | - | - | - |
| Overall | 81.89 | 72.04 | 66.00 | 58.69 | 52.34 | - |

| | Survivial Rate (%) | | | | | Median survival time (95% CI) |
|---|---|---|---|---|---|---|
| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | |
| Infliximab | 80.49 | 71.29 | 62.39 | 50.41 | 44.49 | 4.13 (3.65, -) |
| Adalimumab | 78.49 | 67.15 | 57.94 | 50.16 | 43.89 | 4.24 (3.55, -) |
| Certolizumab | 68.32 | 53.29 | 46.64 | 46.64 | 15.54 | 2.67 (1.15, 5.00) |
| Golimumab | 71.84 | 71.84 | 0.00 | - | - | 3.01 (-, -) |
| Vedolizumab | 100.00 | - | - | - | - | - |
| Overall | 79.25 | 69.14 | 60.85 | 50.32 | 42.97 | 4.08 (3.63, 5.02) |

FIGURE 2. (A) Kaplan-Meier curve for switching of biologics among patients with Crohn's disease. If event rate is lower than 50%, the median survival or its confidence interval cannot be calculated. (B) Kaplan-Meier curve for switching of biologics among patients with ulcerative colitis. If event rate is lower than 50%, the median survival or its confidence interval cannot be calculated.

**TABLE 3B.** Switching Patterns Among Biologic Treatments

| | Secondary Treatment, N (%) | Infliximab (N = 4550) | Adalimumab (N = 4083) | Certolizumab (N = 395) | Golimumab (N = 98) | Vedolizumab (N = 19) |
|---|---|---|---|---|---|---|
| Crohn's Disease | Infliximab | — | 250 (57.08) | 45 (45.45) | 5 (55.56) | 0.00 |
| | Adalimumab | 420 (77.21) | — | 50 (50.51) | 3 (33.33) | 0.00 |
| | Certolizumab | 68 (12.50) | 122 (27.85) | — | 0 (0.00) | 0.00 |
| | Golimumab | 24 (4.41) | 24 (5.48) | 2 (2.02) | — | 0.00 |
| | Vedolizumab | 32 (5.88) | 42 (9.59) | 2 (2.02) | 1 (11.11) | — |
| | Total switch cases | 544 | 438 | 99 | 9 | 0 |
| Ulcerative Colitis | Infliximab | — | 169 (58.08) | 12 (34.29) | 6 (42.86) | 0.00 |
| | Adalimumab | 290 (76.92) | — | 19 (54.29) | 7 (50.00) | 0.00 |
| | Certolizumab | 29 (7.69) | 43 (14.78) | — | 1 (7.14) | 0.00 |
| | Golimumab | 28 (7.43) | 46 (15.81) | 1 (2.86) | — | 0.00 |
| | Vedolizumab | 30 (7.96) | 33 (11.34) | 3 (8.57) | 0 (0.00) | — |
| | Total switch cases | 377 | 291 | 35 | 14 | 0 |

77.21%; UC, 76.92%). On the other hand, a lower percentage of adalimumab initiators switched to infliximab (CD, 57.08%; UC, 58.08%). It is noted that among patients with Crohn's disease, more than one-fourth of the adalimumab users who switched off therapy were prescribed certolizumab as their secondary treatment. Although, golimumab as a second treatment choice accounts for a much larger proportion in the UC cohort than in the CD cohort.

Figure 3 summarizes the risk factors associated with nonpersistence of the biologic medication. By adjusting for other demographic and clinical factors, adalimumab users seemed to have a lower risk for nonpersistence than infliximab users (hazard ratio [HR], 0.88; 95% confidence interval [CI], 0.83–0.93), whereas certolizumab users had a higher nonpersistence risk (HR, 1.18; CI, 1.05–1.33). We also found that demographic factors including female gender, age above 65, age between 18 to 25, and location in south or west region were significantly associated with increased risk of nonpersistence. The analysis also suggested that patients with UC had slightly increased risk of stopping initial biologic treatment than patients with CD (HR, 1.07; CI, 1.01–1.13). Figure 3 also shows other clinical factors that may increase the risk of nonpersistence, including having infection diagnosis in the past 30 days (HR, 1.45; CI, 1.23–1.70), changing diagnosis between CD and UC (HR, 1.06; CI, 1.00–1.13), treated with steroids (HR, 1.63; CI, 1.51–1.75), and hospitalization (HR, 4.23; CI, 3.82–4.68). Hospitalization, steroids use, and infection diagnosis are among the strongest predictors, suggesting treatment side effects and worsening disease are likely to be the major reason for discontinuation of treatment. We further investigated in our sensitivity analysis the subtype of infections. The results suggest septicaemia and *Clostridium difficile* infections were significant risk factors for both nonpersistence and switching, whereas pneumonia only predicted nonpersistence but not switching. However, it might

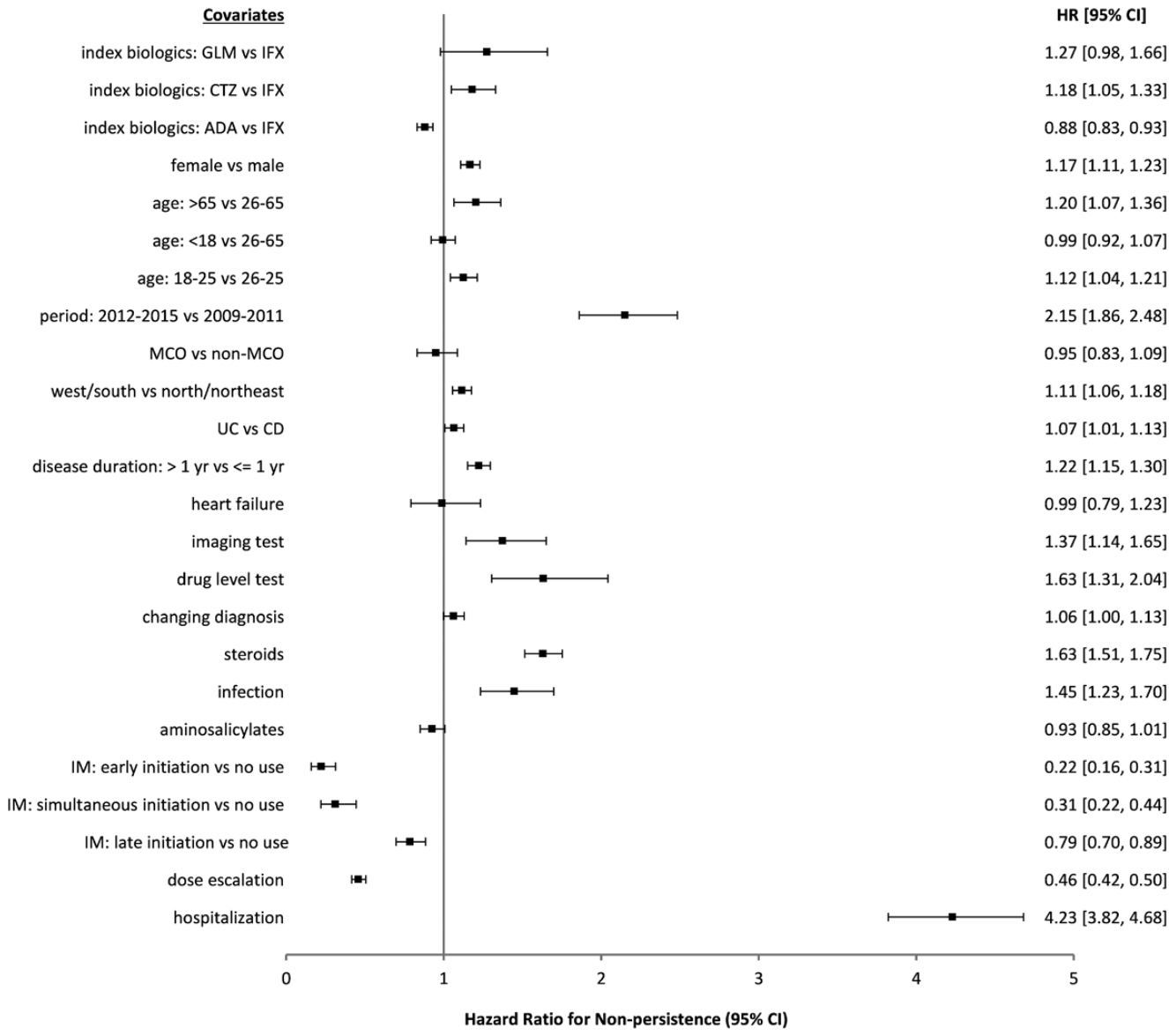



FIGURE 3. Forest plot of predictors for nonpersistence. Abbreviations: GLM, golimumab; IFX, infliximab; CTZ, certolizumab; ADA, adalimumab; MCO, manage care organization; IM, immunosuppressants.

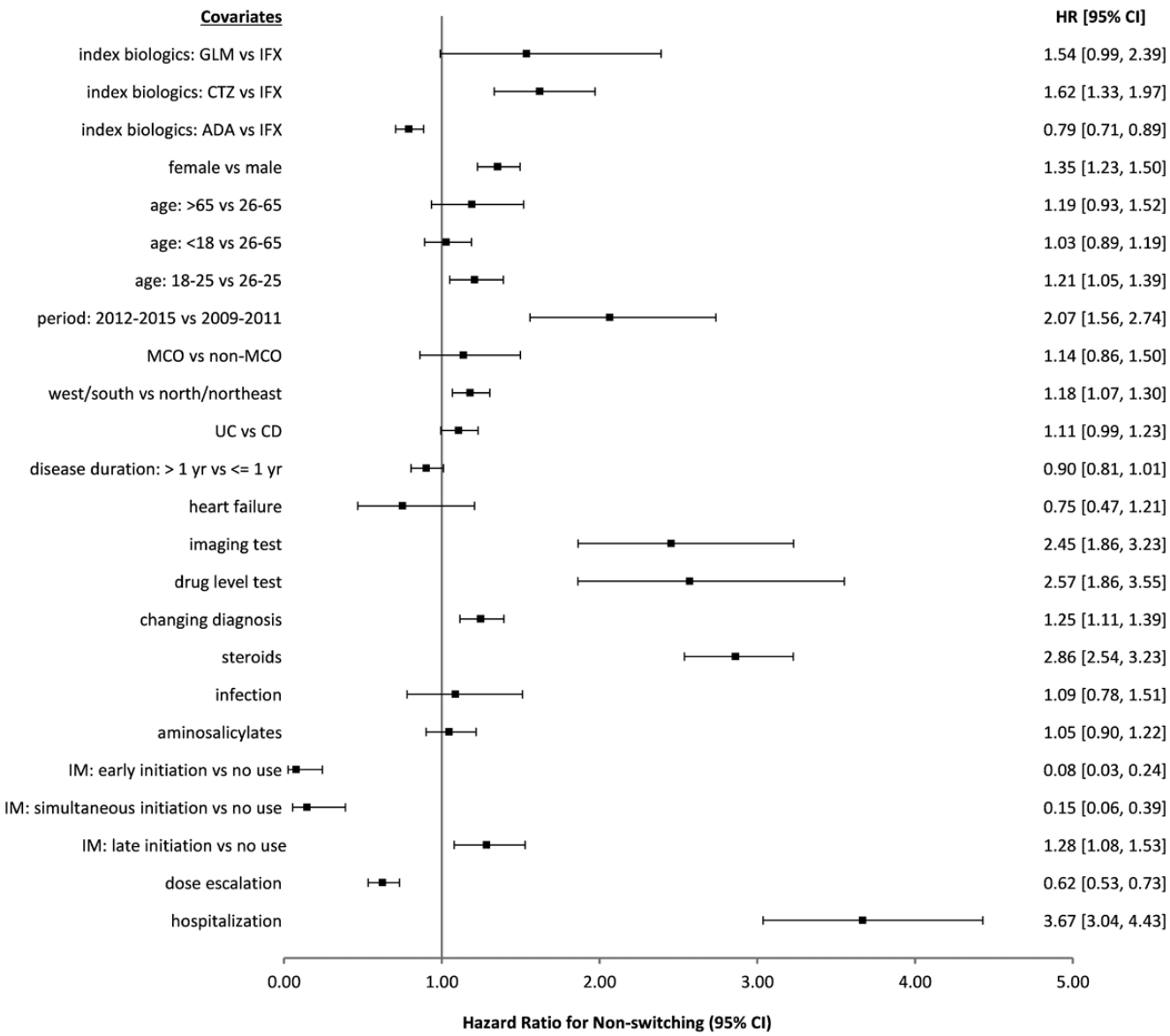



FIGURE 4. Forest plot of predictors for switching. Abbreviations: GLM, golimumab; IFX, infliximab; CTZ, certolizumab; ADA, adalimumab; MCO, manage care organization; IM, immunosuppressants.

also be due to the insufficient statistical power, as there were limited switching events in the dataset. Having imaging examination (HR, 1.85; CI, 1.54–2.22) and drug level test ordered (HR, 1.71; CI, 1.36–2.14) also predicted the stopping the initial biologic treatment in 30 days. In addition, it has been found that the persistence rate decreased significantly from 2012 to 2015 compared with that from 2009 to 2011 (HR, 2.15; CI, 1.86–2.48). Interestingly, we found that combination therapy with immunomodulators significantly decreased the risk of nonpersistence. Particularly, the beneficial effect was most pronounced when the immunomodulatory was started more than 30 days before the biologic (early initiation subgroup; HR, 0.22; CI, 0.16–0.32), followed by simultaneous initiation group (HR, 0.32; CI, 0.22–0.45) and the least in the late initiation group (started more than 30 days after the biologic; HR, 0.80; CI, 0.71–0.91). Escalation of biologic dose also reduced the risk of nonpersistence by 55% over the following 30 days (HR, 0.45; CI, 0.41–0.50). The predictors for switching had a very similar pattern, except factors including being over 65 and disease duration at time of biologic initiation became insignificant, and late initiation of immunosuppressant changed to a significant risk factor for switching (Fig. 4).

The subgroup analyses stratifying by initial biologic treatment and patient age group yielded very similar results,

although the effects of some of the predictors cannot be calculated due to insufficient sample size. To investigate the reasons for discontinuation and switching, we performed the same analyses separately in patients initiating infliximab and adalimumab (Supplementary Figs. S2–S5). Patients initiating other biologics were not analyzed because of small sample size. The results were consistent with the main analyses, in that hospitalization events, steroids use and infection diagnosis were the main risk factors, and early initiation of immunomodulators and dose escalation were major protective factors. When stratifying by age group, the main results remained consistent (Supplementary Fig. S6). We further investigated the effect of types of infection on the persistence and switching of biologic use. The results showed septicaemia and *Clostridium difficile* infection are the major contributors to the discontinuation (Supplementary Fig. S7), and only *Clostridium difficile* infection seemed to be a significant predictor for switching (Supplementary Fig. S8).

## DISCUSSIONS

The availability of biologic medications has revolutionized the treatment of inflammatory bowel disease. Despite the clear clinical efficacy of these medications to reduce and maintain remission of IBD, the high treatment cost, risk of immunogenicity, and serious side effects including cancer and infection make their benefit-and-risk profiles controversial. Evidence from clinical trials is not robust enough to support all the clinical decisions because of the lack of head-to-head comparisons, the relative short follow-up period, and limited generalizability. Therefore, clinicians often have to make critical treatment decisions case by case. Using real-world evidence from a large claims database, our study was able to provide important information on utilization of biologic medications, head-to-head comparison of the biologics, and factors affecting the decision to discontinue or switch treatment.

Although medication persistence of biologics has been substantially evaluated for other autoimmune diseases such as rheumatoid arthritis and ankylosing spondylitis, the persistence profiles of biologics in the treatment of IBD are less well studied. A systematic review of 52 studies found persistence rates ranged between 32.0% and 90.9% after 1 year among patients with rheumatoid arthritis.[12] In Japan, this rate was reported to be 86% among patients with rheumatoid arthritis and even as high as 96% for biologic-naïve patients.[13] In ankylosing spondylitis, the 1-year persistence rate has been reported as 79.0%.[14] In these studies, persistence rates of biologics varied by country, indication, and drug.[12–15] By contrast, our study showed that the persistence rate ranged from 34.6% to 50.9% for CD and 32.5% to 64.8% for UC. Our persistence rates are less than a Canadian population-based study that noted a 60% 1-year persistence rate for patients with IBD.[16] The reason for the difference is unknown but may relate to the differences in health care insurance and utilization in the 2 countries. A recent claim-based study in Brazil comparing the persistence of infliximab, adalimumab, and etanercept for rheumatoid arthritis treatment showed that etanercept has the best survival profile (median survival year: 3.7), followed by infliximab (median survival year: 3.7), and adalimumab (median survival year: 3.3).[15] However, in our study, the median survival time for all user groups was less than 1 year. We also found the persistence rate dropped by about 20% in the first 3 months, which was not observed in other studies. The reason for this observation may be because the primary loss-of-response rate or the side-effect rate is higher among patients with IBD than other diseases. These comparisons suggest biologic medications may not work as well in the treatment of IBD as in other autoimmune diseases.

Another potential reason for the lower persistence rate in IBD is that our analysis used a slightly different definition of a gap in treatment. Previous studies used a fixed time window (eg, 30 days, 60 days, or 120 days) to define a gap in therapy; whereas in our study the gap, was defined as the length of previous days-of-supply. Because the biologics included in our study have very different and complex dosing schedules, the comparisons would not be equitable if we used a fixed time window for all the drugs across the treatment periods. Furthermore, in our sensitivity analysis we changed the gap to 2 times of the previous days-of-supply; the results were still consistently lower than the persistence in the treatment of rheumatoid arthritis or ankylosing spondylitis. Although our analysis showed adalimumab seemed to have a higher 1-year persistence rate and median drug survival time than infliximab, we also found infliximab showed a better long-term persistence rate. It might be because infliximab requires intravenous administration at an outpatient visit, while adalimumab can be subcutaneously injected by patients themselves. After the 1-year treatment period, those infliximab users might be more committed to the fixed outpatient visit schedule and having more contact with health professionals compared with adalimumab users.

Our study also showed high switch rates among patients using biologics to treat IBD. About 20% of the patients initiating infliximab or adalimumab switched to another biologic in the first year. These 2 groups of patients had different preferences for their secondary biologics. More than three-fourths of the infliximab users switched to adalimumab, whereas only half of the adalimumab users chose infliximab. Notably, although vedolizumab was generally not used as the first biologic treatment, it was often considered as a secondary choice comparable to certolizumab and golimumab. It should also be noted that certolizumab was only approved for CD; and golimumab was only approved for UC in the United States, which may explain the differences of utilization and switching in the 2 cohorts.

We used treatment persistence as a proxy for the benefit-and-harm profile of biologic medications, assuming that most patients discontinue their biologic treatment because of loss of response or side effects. Although in practice, other reasons may cause patients to stop their treatment such as health insurance plan restrictions and higher co-pays. However, in our

multivariate regression model, health plan was not a significant predictor for nonpersistence or switching. However, diagnosis of an infection and evidence of worsening disease activity (eg, imaging examination, therapeutic drug level monitoring test, initiation of steroids, and hospitalization events) seemed to be strong predictors for nonpersistence and switching. This suggests that disease progression, loss of response, and infection event remain the most important reasons for treatment discontinuation. Heart failure, as a contraindication for anti-TNF medications, was not a significant predictor in our analysis, which may be due to low event rate. Another important and unique finding is that patients between 18 to 25 years old were at higher risk of discontinuing their treatment. These patients may make decisions based on desire for or actual pregnancy or could have their care compromised by the transition from pediatric care to adult care. The change in lifestyle and insurance status when they move to college or start a new job may increase the likelihood of treatment persistence. We also observed that the treatment persistence rate was greatly reduced after 2011. This was consistent with previous findings in the use of biologics among patients with rheumatoid arthritis.[16] The possible reasons might be more treatment options and more ambitious treatment targets.[16]

A very enlightening finding of our study is that in real-world experience, combination therapy using immunomodulators can increase the persistence of biologic treatments. More importantly, our analysis demonstrated a clear temporal relationship that earlier patients receiving immunomodulators stayed longer on biologic therapy. This is consistent with findings in rheumatoid arthritis that combination use of disease-modifying drugs (DMARDS) will increase the persistence of biologics treatment among patients with rheumatoid arthritis.[17] The potential reasons could be that immunomodulators can add anti-inflammatory effects and can decrease the formation of antibodies to biologic medications. It is also possible that patients receiving combination therapy had more severe disease and as a result were more likely to adhere to therapy.

This study has several methodological strengths. First, our study took into consideration the complex dosing schedule of biologics in the treatment of IBD. Using a fixed gap definition could result in unfair comparison between biologics, possibly overestimating effects during induction period or underestimating effects during the maintenance period. Second, we used time-dependent Cox proportional hazard model to account for the potential violation of the proportionality assumption due to the covariate change during the follow-up. This approach may also help to illustrate factors influencing discontinuation in the real-world setting. Thirdly, this study employed a large sample size by using a nationwide commercial administrative claim database. Additionally, as IBD can occur at any age and mostly affects patients in their 30s to 40s, the study is representative of the target patient group. We limited our study to newly diagnosed patients so as to eliminate the confounding factors associated with multiple prior therapies.

Several study limitations should also be noted. First, because the claim database does not contain days of supply information for injectable drugs (eg, infliximab and vedolizumab), we used the sequence of outpatient visits to determine the next dosing time, which may lead to misclassification. Second, the study lacks laboratory results (eg, complete blood counts, C-reactive protein, serum level of biologics, and antibodies) to further investigate the association between disease progression, formation of drug antibodies, and treatment discontinuation decisions. Also, we used an arbitrary definition for the persistence gap, which is the same length as the assumed days-of-supply, which could misclassify the dose delay to nonpersistence. In addition, medication use during hospitalization period may not be captured in a claims dataset because of bundled payment, which can also introduce misclassification. However, sensitivity analysis changing the gap definition to incorporate the scenarios such as dose delay or treatment during hospitalization did not alter the main conclusion. Furthermore, even if dose delay was misclassified as nonpersistence, as it is still an inferior treatment outcome that could lead to disease relapses, the risk factors identified in our model were also important findings for clinical practice.

## CONCLUSIONS

Overall, the persistence profiles of biologics suggest a high rate of dissatisfaction with the drugs resulting in discontinuation and switching to a different biologic. Less than half of the patients stayed on their initial biologics for 1 year. The reasons for nonpersistence are likely to be worsening disease activity, or complications such as infection; age, gender, and geographic reasons also may exist. Initiating immunomodulatory therapy before biologics will increase the persistence of biologic treatment.

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