# Adalimumab Persistence for Inflammatory Bowel Disease in Veteran and Insured Cohorts

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## ABSTRACT

**OBJECTIVES:** Identify predictors of persistence with adalimumab (ADA) among veterans and privately insured patients with inflammatory bowel disease (IBD) in the United States.

**STUDY DESIGN:** Retrospective cohort study.

**METHODS:** Patients with IBD taking ADA as their first biologic were identified from the Veterans Health Administration (VHA) database from 2009 to 2013 and the Truven Health MarketScan database from 2009 to 2012 with a 12-month follow-up. Persistence was defined as continued use 1 year after initiation. Adherence was assessed by calculating a medication possession ratio, which was dichotomized as greater than 0.86 or less than or equal to 0.86. Multivariable logistic regression was used to evaluate predictors of persistence.

**RESULTS:** There were 1030 patients in the VHA population compared with 3264 patients in the privately insured (MarketScan) cohort. In MarketScan, 1800 patients (55%) remained on ADA compared with 755 (73%) in the VHA cohort. In multivariable analysis, male sex (odds ratio [OR], 1.38; 95% CI, 1.16-1.63; *P* <.01), Crohn disease (OR, 1.27; 95% CI, 1.02-1.57; *P* = .03), greater adherence (OR, 1.83; 95% CI, 1.45-2.30; *P* <.01), and dose escalation (OR, 1.82; 95% CI, 1.42-2.33; *P* <.01) were associated with higher ADA persistence in the MarketScan cohort; narcotic use (OR, 0.71; 95% CI, 0.58-0.88; *P* <.01) and hospitalization or new steroid use after initiation (OR, 0.04; 95% CI, 0.03-0.05; *P* <.01) were associated with lower persistence. In the VHA cohort, only a hospitalization or new steroid use (OR, 0.50; 95% CI, 0.36-0.70; *P* <.01) was associated with lower persistence.

**CONCLUSIONS:** Despite being older and having more comorbidities, patients in the VHA, which is an integrated healthcare system, appear to be more likely to remain on ADA at 1 year than patients in the MarketScan database. Further studies of system differences are needed to understand the reasons behind this discrepancy.

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Inflammatory bowel disease (IBD) is a chronic relapsing and remitting idiopathic disorder of the gastrointestinal tract. There are approximately 1.5 million Americans with IBD,[1] and among these, 70,000 are veterans.[2] For those patients with moderate to severe IBD, treatment with monoclonal antibodies targeting tumor necrosis factor alpha (TNF), such as adalimumab (ADA), has been shown to reduce corticosteroid use and improve quality of life.[3] Concomitant therapy with thiopurines further increases the chance of steroid-free remission.[4] Despite the superior efficacy of anti-TNFs and thiopurines, approximately one-third of patients who initially respond to these medications lose response over the course of time, requiring a change in therapy, dose escalation, and/or reinitiation of corticosteroids.[5] Loss of response often occurs due to the development of antibodies to the drug, which can lead to increased clearance of the drug. Nonadherence to or intermittent use of biologics has been linked to a higher risk of antibody formation,[6] which can therefore lead to reduced persistence.



Prior studies of persistence with biologics for IBD have identified that approximately 20% of patients have stopped the drug within 6 months.[7] Another study of persistence with ADA for all indications in Israel found that 52% stopped the drug within the follow-up period (mean = 3 years).[8] Predictors of higher persistence from both studies include concomitant immunomodulator use, Crohn disease, and concomitant steroid use. Among patients with Crohn disease, those with the small and large intestines affected—this disease location is typically more aggressive and more likely to lead to surgery[9]—have been identified as being more likely to be persistent.[7] In other disease states, patients with more comorbidities were less likely to be persistent with biologics.[10] Patients with rheumatoid arthritis with higher persistence were noted to have higher overall health costs, but nonpharmacy costs were lower among patients who were persistent.[11] Patient support programs have been found to improve adherence and persistence among patients taking biologics for a broad spectrum of diseases.[12]

The aim of our study was to describe the patterns and predictors of persistence with the most commonly used anti-TNF, ADA, in a nationwide cohort of privately insured patients and a

veteran population. We evaluated the effects of predictors of disease severity—including concomitant medications such as immunomodulators and narcotics, dose escalation of ADA, and hospitalizations or corticosteroid use—other comorbidities, and adherence to ADA on persistence.

**TAKEAWAY POINTS**

Among veterans with inflammatory bowel disease in the United States taking adalimumab (ADA), 73% were still taking the medication 1 year after initiation, whereas just 55% of privately insured patients remained on the drug.

- Men, patients with Crohn disease, and patients who were more adherent to ADA were more likely to remain on the drug among the privately insured patients.
- Those less likely to remain persistent among the privately insured cohort were patients who took narcotics and, among veterans, only those who were hospitalized after initiation.
- Unmeasured factors in the Veterans Health Administration, such as improved provider communication, appear to improve persistence.

# METHODS

## Study Design

We conducted a retrospective cohort study of administrative claims for patients with IBD in a privately insured cohort and in the Veterans Health Administration (VHA). The University of Michigan Institutional Review Board reviewed and approved this study.

## Data Sources

We studied administrative claims of patients identified to have IBD from the Truven Health MarketScan Commercial Claims and Encounters database from 2009 to 2012 with follow-up into 2013. MarketScan is a large administrative claims database derived from insurance claims of enrollees who are covered by large private employers in the United States. The database includes inpatient, outpatient, and pharmacy claims for approximately 50 million people.

A comparable cohort was selected from the national VHA to conduct a retrospective cohort study of patients with IBD receiving anti-TNFs from 2009 to 2013 with follow-up into 2014. An extra year of data was included in the VHA analysis to expand the cohort size. The VHA's Corporate Data Warehouse contains data extracted from electronic health records, including pharmacy fills, inpatient records, and outpatient records, for all veterans receiving care through VHA facilities and programs across the United States. The VHA is one of the largest integrated healthcare systems in the world, caring for approximately 9 million veterans.[13]

## Sample Selection

Individuals were identified as having IBD in the MarketScan cohort based on the presence of a single inpatient encounter or 2 outpatient claims on different days with an *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) code of Crohn disease (555.X) or ulcerative colitis (UC) (556.X) between 2009 and 2012. Patients were excluded if they did not have at least 12 months of continuous coverage with pharmacy benefits and 12 months of follow-up after initiation of ADA. Patients' data were therefore included until the conclusion of 2013. When patients had multiple periods of coverage, only the most recent coverage period was examined to ensure that relevant outcomes were captured. There is no validated method to classify patients into a particular IBD phenotype (Crohn disease or UC) in this large administrative cohort. We therefore elected to use a method previously studied in other large insurance data sets,[14] where the diagnosis of Crohn disease or UC was assigned based on the majority of the 9 most recent *ICD-9-CM* codes. Patients with equivalent numbers of codes for Crohn disease and UC were classified as having indeterminate colitis. Patients were included if ADA was the first anti-TNF prescribed during the time period studied and if they had 3 months of coverage prior to ADA initiation with no other anti-TNF prescriptions during that time. This 3-month window was created to ensure that patients were less likely to be on an anti-TNF prior to acquiring coverage in the VHA or MarketScan cohorts.

Patients with IBD in the VHA were identified using previously validated algorithms based on a combination of inpatient and outpatient *ICD-9-CM* codes for Crohn disease (555.X) and UC (556.X) between 2002 and 2014.[15] Patients were required to have at least 2 encounters with a diagnosis of IBD, with at least 1 encounter as an outpatient. In this administrative cohort, this classification method for Crohn disease and UC has been studied and validated.[16] Patients were classified as having Crohn disease if all *ICD-9-CM* codes were 555.X, UC if all codes were 556.X, and indeterminate colitis in the remainder. This approach has positive predictive values of 0.84 for Crohn disease and 0.91 for UC in the VHA.[16] To be consistent with the date range of available data in MarketScan, only patients with their first prescribed anti-TNF between 2009 and 2013 were considered for inclusion, with follow-up until the conclusion of 2014. Due to a 75% smaller sample in the VHA, we included 1 extra year of data.

## Selected Predictors

Pharmaceutical claims for each cohort were analyzed for dispenses of ADA. Erroneous claims, identified as those indicating that a quantity of 0 or less was dispensed, were excluded from analysis. Claims data indicating that unusual quantities of medication were dispensed were also deleted, based on the following criteria. For ADA, we expected to find no more than 6 syringes dispensed in 14 days during induction (ratio of 2.33 days/injection) and no less than 2 syringes dispensed in 30 days for maintenance (ratio of 15 days/injection). Any patients with ADA dispensing ratios of less than 2.33 days per injection or more than 15 days per injection were removed from the data set. Patients with fewer than 3 fills of the medication in the study period were also removed.

A medication possession ratio (MPR) was used to assess adherence for the first year during the maintenance dosing after the first

**TABLE 1.** Characteristics of Patients Using ADA for Inflammatory Bowel Disease at Baseline

| | MarketScan (n = 3264) | VHA (n = 1030) |
|---|---|---|
| Age in years, mean (SD) | 41.1 (15.3) | 47.7 (15.6) |
| Male, n (%) | 1513 (46.4) | 919 (89.2) |
| Crohn disease, n (%) | 2646 (81.1) | 561 (54.5) |
| UC, n (%) | 600 (18.4) | 232 (22.5) |
| Indeterminate colitis, n (%) | 18 (0.6) | 237 (23.0) |
| CCI score, mean (SD) | 0.2 (0.5) | 0.73 (1.2) |
| Cumulative MPR, mean (SD) | 0.96 (0.11) | 0.90 (0.16) |
| Dose escalation within 1 year of ADA start, n (%) | 500 (15.3) | 139 (13.5) |
| Hospitalization or new steroid prescription after ADA start, n (%) | 829 (25.4) | 262 (25.4) |
| Steroid user at ADA start, n (%) | 1278 (39.2) | 265 (25.7) |
| Narcotic user at ADA start, n (%) | 662 (20.3) | 283 (27.5) |
| Immunomodulator user at ADA start, n (%) | 747 (22.9) | 319 (31.0) |

ADA indicates adalimumab; CCI, Charlson Comorbidity Index; MPR, medication possession ratio; UC, ulcerative colitis; VHA, Veterans Health Administration.

month's induction period. The MPR was calculated by summing the days of medication supplied and dividing by the sum of the days in the total refill intervals. Patients with an MPR above the 99th percentile (MPR >1.2) were deleted because those patient records were suspected to contain erroneous claims data. The MPR was therefore capped at 1.2. Based on prior studies that indicated an MPR for ADA of 0.86 was ideal to avoid complications, we classified patients as adherent if their MPR was over this value.[17] We elected to include MPRs over 1 to allow capture of early refill data.[17]

We identified dose escalation of ADA by comparing prescriptions from the beginning of maintenance to the last prescription within the first year and identified any increase in the ratio of pens dispensed to days supplied. Concurrent medication usage (corticosteroids and immunomodulators) at study initiation was assessed by determining if there was use of either of these medications in the 90 days before or 30 days after starting ADA. The immunomodulators evaluated included thiopurines and methotrexate. Concurrent narcotic use at initiation was defined as a prescription in the 30 days prior to or 30 days post ADA initiation. A complete detailed list of concomitant medications evaluated is located in **eAppendix Table 1** (eAppendix available at **ajmc.com**). The effect of a disease flare on persistence was addressed by determining if a patient had a hospitalization or new corticosteroid prescription after starting ADA. In order to account for the effect of comorbidities on medication persistence, we calculated Charlson Comorbidity Index (CCI) scores during the 1 year prior to ADA initiation.[18]

### Outcome

The outcome measure of persistence was defined as continued filled prescription of ADA 1 year after initiation without an interruption of greater than 4 months. An interruption of 4 months was chosen due to the half-life of ADA, which is estimated at 10 to 20 days,[19] and the fact that the medication is typically stopped perioperatively for lengthy periods of time.

### Statistical Analysis

Descriptive statistics were used to compare the VHA and MarketScan populations. Two-sample *t* tests were used for continuous variables, and $\chi^2$ tests were used for categorical variables. The relationship of concomitant medication use, adherence, and demographic predictors with persistence was assessed within the 2 cohorts using multivariable logistic regression. The effect of adherence was assessed by classifying MPR as a binary variable using the 0.86 threshold for adherence, and odds ratios (ORs) for age were calculated per decade due to small effect size. Model parameters were assessed by type III $\chi^2$ tests, and *P* values and 95% CIs for ORs were constructed using Wald test specifications. Sensitivity analyses were conducted to determine if a standardized definition of IBD phenotype (Crohn disease vs UC) between the 2 cohorts had an effect on outcomes and if there was an interaction between dose escalation and immunomodulator use. All statistics were performed using SAS 9.4 (SAS Institute Inc; Cary, North Carolina).

## RESULTS

### MarketScan Cohort

From 2009 to 2012, we identified 15,606 patients with IBD who were prescribed ADA. After applying exclusion criteria, 4252 were prescribed ADA as their only anti-TNF, and 3264 of those patients were given at least 3 months' supply without other erroneous fill data and at least 1 year of follow-up.

### VHA Cohort

In the VHA, 1900 patients were found to have IBD with a prescription for ADA, and 1765 were prescribed only ADA. After applying exclusion criteria, 1030 patients of the 1765 had at least 3 valid prescriptions of ADA in the study period with no other erroneous fill data and at least 1 year of follow-up from the date of anti-TNF initiation.

### Cohort Comparisons

**Table 1** outlines the different characteristics of the patients in each cohort. The VHA cohort included mostly men, and the mean (SD) age in this cohort was higher than that seen in MarketScan: 47.7 (15.6) years versus 41.1 (15.3) years, respectively. There was also a difference in the IBD phenotypes between the 2 cohorts. The VHA cohort had fewer patients with Crohn disease (VHA, 54.5% vs MarketScan, 81.1%) and more patients classified as having indeterminate colitis (VHA, 23% vs MarketScan, 0.6%), likely due to differences in classification of IBD phenotype. The VHA classification determines phenotype based on all the codes being consistent for that phenotype; it is indeterminate if there are any discrepancies. In a sensitivity analysis that used this VHA method as a unified diagnosis classification for the IBD phenotype between the 2 cohorts, there remained a

difference in the diagnosis makeup of the cohort (**eAppendix Table 2**), primarily in the classification of patients with UC versus indeterminate colitis. The mean (SD) CCI score was higher among veterans than the MarketScan population: 0.7 (1.2) versus 0.2 (0.5), respectively. When examining the concomitant medications, veterans were less likely to be taking steroids (VHA, 25.7% vs MarketScan, 39.2%), but more likely to be using immunomodulators (VHA, 31% vs MarketScan, 22.9%) and narcotics (VHA, 27.5% vs MarketScan, 20.3%), at the time of ADA initiation.

The mean (SD) adherence, as calculated by cumulative MPR, was high in both the VHA and MarketScan cohorts, at 0.90 (0.16) and 0.96 (0.11), respectively. Despite the MarketScan population's higher adherence, the rates of dose escalation within 1 year and hospitalization or new steroid prescription were similar between the 2 populations (Table 1).

**Table 2** shows that the percentage of patients who were persistent on ADA at 1 year without a significant interruption was lower among the MarketScan population (MarketScan, 1800 [55.2%] vs VHA, 755 [73.3%]). Concomitant steroid use remained higher in the MarketScan population at the 1-year time point (MarketScan, 10.3% vs VHA, 3.8%), whereas concomitant narcotic use and immunomodulator use were similar in the 2 populations at 1 year.

Examining predictors of persistence at the 1-year time point in the MarketScan population, we found that men (OR, 1.38; 95% CI, 1.16-1.63; $P$ <.01), patients with Crohn disease (vs UC) (OR, 1.27; 95% CI, 1.02-1.57; $P$ = .03), patients who were adherent (OR, 1.83; 95% CI, 1.45-2.30; $P$ <.01), and those who had a dose escalation (OR, 1.82; 95% CI, 1.42-2.33; $P$ <.01) were more likely to remain on the drug at 1 year in multivariable analysis (**Table 3**). Patients who were on narcotics around the time of anti-TNF initiation (OR, 0.71; 95% CI, 0.58-0.88; $P$ <.01) or those who had a hospitalization or new steroid use (OR, 0.04; 95% CI, 0.03-0.05; $P$ <.01) were conversely less likely to be on the drug at the 1-year time point. Age, CCI score, immunomodulator use, and corticosteroid use at ADA initiation did not influence the continued use of ADA at the 1-year time point. In a sensitivity analysis using a consistent IBD phenotype definition with the VHA cohort, Crohn disease (vs UC) had a similar effect on persistence but was no longer a significant predictor of persistence due to sample size limitation (**eAppendix Table 3**). Altering the IBD phenotype category did not significantly change the effect of other predictors in the multivariable model.

Examining persistence through multivariable analysis with the same predictors in the VHA population, we found no effect for male gender (OR, 1.16; 95% CI, 0.74-1.81; $P$ = .52), a comparable beneficial trend for patients with Crohn disease (vs UC) (OR, 1.34; 95% CI, 0.95-1.90; $P$ = .22), but no benefit for those who had a dose escalation (OR, 1.04; 95% CI, 0.69-1.58; $P$ = .85) (Table 3). No effect was observed for patients who were on narcotics (OR, 1.02; 95% CI, 0.74-1.40; $P$ = .91), whereas a negative but not significant trend was seen for patients who were on steroids at ADA initiation (OR, 0.76; 95% CI, 0.55-1.06; $P$ = .11). However, a significant negative effect was seen in those who had a hospitalization or new steroid use

**TABLE 2.** ADA Persistence in the MarketScan and VHA Populations Over a 12-Month Follow-up

| | MarketScan (n = 3264) | VHA (n = 1030) |
|---|---|---|
| Persistence, n (%) | 1800 (55.2) | 755 (73.3) |
| Immunomodulators and ADA 1 year later, n (%)[a] | 282 (15.7) | 128 (17.0) |
| Narcotics and ADA 1 year later, n (%)[a] | 332 (18.4) | 138 (18.3) |
| Steroids and ADA 1 year later, n (%)[a] | 186 (10.3) | 29 (3.8) |

ADA indicates adalimumab; TNF, tumor necrosis factor; VHA, Veterans Health Administration.

[a]Denominator includes only those patients on anti-TNF therapy at 1 year (n = 1800 for MarketScan; n = 755 for VHA).

**TABLE 3.** Multivariable ORs of ADA Persistence at 1 Year in the MarketScan and VHA Populations

| | OR (95% CI) | P |
|---|---|---|
| **MarketScan Population (n = 3264)** | | |
| Age (per decade) | 1.02 (0.96-1.08) | .55 |
| Men (vs women) | 1.38 (1.16-1.63) | <.01 |
| Diagnosis | | |
| Crohn disease (vs UC) | 1.27 (1.02-1.57) | .03 |
| Indeterminate colitis (vs UC) | 0.48 (0.16-1.41) | .12 |
| MPR >0.86 (vs ≤0.86) | 1.83 (1.45-2.30) | <.01 |
| Immunomodulator use around ADA start | 1.11 (0.90-1.35) | .33 |
| Narcotic use around ADA start | 0.71 (0.58-0.88) | <.01 |
| Steroid use around ADA start | 0.88 (0.74-1.05) | .14 |
| Dose escalation during initial year | 1.82 (1.42-2.33) | <.01 |
| Hospitalization or new steroid use during year following ADA initiation | 0.04 (0.03-0.05) | <.01 |
| CCI score (per 1-unit change) | 0.97 (0.82-1.16) | .77 |
| **VHA Population (n = 1030)** | | |
| Age (per decade) | 1.04 (0.94-1.15) | .43 |
| Men (vs women) | 1.16 (0.74-1.81) | .52 |
| Diagnosis | | |
| Crohn disease (vs UC) | 1.34 (0.95-1.90) | .22 |
| Indeterminate colitis (vs UC) | 1.31 (0.87-1.97) | .19 |
| MPR >0.86 (vs ≤0.86) | 1.17 (0.86-1.60) | .31 |
| Immunomodulator use around ADA start | 1.09 (0.80-1.49) | .58 |
| Narcotic use around ADA start | 1.02 (0.74-1.40) | .91 |
| Steroid use around ADA start | 0.76 (0.55-1.06) | .11 |
| Dose escalation during initial year | 1.04 (0.69-1.58) | .85 |
| Hospitalization or new steroid use during year following ADA initiation | 0.50 (0.36-0.70) | <.01 |
| CCI score (per 1-unit change) | 0.98 (0.87-1.11) | .76 |

ADA indicates adalimumab; CCI, Charlson Comorbidity Index; MPR, medication possession ratio; OR, odds ratio; UC, ulcerative colitis; VHA, Veterans Health Administration.

(OR, 0.50; 95% CI, 0.36-0.70; $P < .01$); these patients were 50% less likely to be on the drug at the 1-year time point. Age, CCI score, adherence, immunomodulator use, and corticosteroid use at ADA initiation did not influence the continued use of ADA at the 1-year time point in the VHA population.

# DISCUSSION

In this analysis of anti-TNF persistence in 2 large administrative databases, we found that patients with IBD initiated on ADA had an approximately 60% likelihood of remaining on the drug at 1 year without an interruption of more than 4 months. The persistence rate among the veteran population was higher at 73% versus 55% in the privately insured cohort. We found expected differences in demographics between the MarketScan and the veteran population but also found differences in concomitant medications at ADA initiation. We also identified that patients who were on narcotics or had a flare (assessed through a hospitalization or new steroid use) in the MarketScan cohort were significantly less likely to remain on ADA 1 year later. Although we could not assess for ADA drug levels, we did identify that patients who underwent dose escalation or were more adherent were also more likely to be persistent in the MarketScan cohort.

Unexpectedly, we did not find a relationship between concomitant immunomodulator use and persistence. In a cohort study by Targownik et al of Canadian patients with IBD started on anti-TNFs, 60% of patients remained on the anti-TNF at the 1-year mark.[20] In another cohort study, of veterans taking anti-TNFs in the United States, 24% were no longer taking the medication at the 6-month time point.[7] In both of these studies, concurrent immunomodulator use was found to be a predictor of continued drug use. Concurrent immunomodulator use has been shown to lead to beneficial outcomes in clinical trials and clinical practice,[4,21] and it is hypothesized that persistence is improved due to reduced levels of antidrug antibodies and/or increased drug levels.[22] In our much larger study, although results showed that concurrent immunomodulator use did not influence continued anti-TNF use, we found that anti-TNF dose escalation was in fact associated with persistence in the MarketScan cohort. We speculate that immunomodulator use was not associated with ADA persistence here either due to insufficient dosing of the immunomodulator or poor adherence to the immunomodulator. The effect of an interaction term between escalation of ADA and immunomodulator use was found to be not significant when added to the model, and the estimated effect of immunomodulator use did not change when escalation was dropped from the model as a sensitivity analysis. Overall, we can conclude in our study that immunomodulator use did not affect persistence.

Despite higher ADA persistence in the VHA cohort, we saw similar rates of hospitalization and steroid use within 1 year between the 2 cohorts. This finding is more remarkable considering that the VHA has an older patient population with more comorbidities. Although ADA persistence is higher in the VHA system, patients in the VHA had slightly lower adherence rates. Because this is a review of administrative data, it is difficult to ascertain why persistence but not adherence is better in the VHA compared with outside health systems. Other comparisons of VHA versus non-VHA care have identified higher quality of care delivery in the VHA system,[23] which may be one reason. We hypothesize that the VHA population has superior ADA persistence due to the combination of an integrated pharmacy system and improved provider communication. There may be other reasons for increased persistence in the VHA population, including disease severity, which we were unable to quantify in this study.

A number of studies have identified that narcotic use is high in the IBD population.[24-26] Narcotic use has also been linked with increased costs and worse postoperative outcomes.[27,28] Despite increasing use of anti-TNFs, narcotic use appears to be stable in the IBD population.[25] Our findings here show that narcotic use was also independently associated with reduced chances of remaining on the anti-TNF at 1 year in the MarketScan cohort. Narcotic use was particularly prevalent in our study, at 20% to 27% (MarketScan and VHA, respectively) around the time of anti-TNF start. This prevalence was similar to the overall prevalence noted in a single-center study.[24] Systematic changes are under way to reduce narcotic prescriptions in the United States. Further studies will need to be conducted to determine if this improves anti-TNF persistence.

## Limitations

The limitations of our study include the reliance on administrative claims data, which are susceptible to errors. To correct for possible errors, we removed patients who had fills of ADA that appeared erroneous based on the ratio of intended days' supply and quantity of injections. Prescriptions with fewer than 2.3 days between injections or more than 15 days per injection were labeled as erroneous. The results of the multivariate analysis in the VHA cohort are limited by sample size, and some significant predictors seen in the MarketScan cohort appear as trends in the same direction in the VHA cohort. We used 2 definitions to classify patients into IBD phenotypes, but we also performed a sensitivity analysis that demonstrated that using consistent diagnosis codes did not change our main findings. The methodology used to classify the VHA patients has been validated in that cohort.[16] There is no validated methodology to classify patients in the private insurance database we used, so we elected to use a methodology previously published for this insurance database and other large insurance databases.[29] The results of the VHA cohort analysis are not likely generalizable to other US cohorts. This is corroborated by the demographic differences, as well as the medication use differences, between the 2 cohorts. It is possible that VHA patients could obtain medications outside of the VHA, but it is more likely that this occurred with the concomitant medications rather than ADA because the cost of this medication is considerably cheaper in the VHA. Other predictors of adherence were not accounted for in our analysis, including specialty pharmacy dispensation versus commercial pharmacy

dispensation.[30] We elected not to perform statistical comparisons between the 2 cohorts because there were small differences in the definitions used to characterize the 2 cohorts and 1 extra year of analyzed data in the VHA cohort, which may have invalidated these comparisons.

## CONCLUSIONS

Persistence with ADA in 2 large IBD cohorts in the United States is approximately 60%. Patients receiving healthcare through a publicly funded integrated healthcare system appeared to have a higher rate of persistence compared with privately insured patients. Patients in a privately insured cohort who were more adherent or underwent dose escalation were more likely to remain on the drug, whereas concomitant immunomodulator use was not noted to have an effect on persistence. Concomitant narcotic use at anti-TNF start was independently associated with a reduced chance of continued use at 1 year. Further studies to identify systemwide differences are necessary to understand the differences in ADA persistence between the 2 cohorts, and it is crucial to focus more efforts on reducing the use of corticosteroids and narcotics in these populations. ■

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**eAppendix Table 1.** Drug Definitions

| **Drug Class** | **Prescription Drugs Included** |
|---|---|
| Narcotics | Dihydrocodeine<br>Fentanyl<br>Hydrocodone<br>Hydromorphone<br>Meperidine<br>Morphine<br>Oxycodone<br>Oxymorphone<br>Pentazocine<br>Propoxyphene<br>Tapentadol<br>Tramadol |
| Steroids | Prednisone<br>Methylprednisolone<br>Prednisolone |
| Immunomodulators | Mercaptopurine<br>Azathioprine<br>Azasan<br>Methotrexate |
| Anti-TNF | Adalimumab |

**eAppendix Table 2.** Characteristics of Adalimumab Users With Consistent Definition for Crohn Disease and Ulcerative Colitis

| | **MarketScan (n = 3264)** | **VHA (n = 1030)** | ***P* (test for difference between cohorts)** |
|---|---|---|---|
| Crohn disease (%) | 2646 (56.7) | 561 (54.5) | <0.01 |
| Ulcerative colitis (%) | 292 (9.0) | 232 (22.5) | |
| Indeterminate colitis (%) | 1118 (34.3) | 237 (23.0) | |

**eAppendix Table 3.** Multivariable Odds Ratios of Adalimumab Persistence at 1 Year in the MarketScan Population and Veteran Population (consistent definition of Crohn disease and UC between cohorts)

| **MarketScan Population (n = 3264)** | | |
|---|---|---|
| | **OR (95% CI)** | ***P*** |
| Age (per decade) | 1.02 (0.96-1.08) | 0.55 |
| Males (vs females) | 1.38 (1.16-1.63) | <0.01 |
| Diagnosis | | |
| Crohn (vs UC) | 1.24 (0.92-1.68) | 0.12 |
| IC (vs UC) | 1.14 (0.84-1.55) | 0.85 |
| MPR >0.86 (vs ≤0.86) | 1.83 (1.45-2.29) | <0.01 |
| On immunomodulator around ADA start | 1.11 (0.91-1.36) | 0.31 |
| On narcotics around ADA start | 0.71 (0.58-0.88) | <0.01 |
| On steroids around ADA start | 0.87 (0.73-1.03) | 0.11 |
| Underwent dose escalation during initial year | 1.82 (1.42-2.33) | <0.01 |
| Hospitalization or new steroid use during year following ADA initiation | 0.04 (0.03-0.05) | <0.01 |
| Charlson comorbidity index (per 1 unit change) | 0.98 (0.82-1.17) | 0.81 |
| **VHA Population (n = 1030)** | | |
| | **OR (95% CI)** | ***P*** |
| Age (per decade) | 1.04 (0.94-1.15) | 0.43 |
| Males (vs Females) | 1.16 (0.74-1.81) | 0.52 |
| Diagnosis | | |
| Crohn (vs UC) | 1.34 (0.95-1.90) | 0.22 |
| IC (vs UC) | 1.31 (0.87-1.97) | 0.19 |
| MPR >0.86 (vs ≤0.86) | 1.17 (0.86-1.60) | 0.31 |
| On immunomodulator around ADA start | 1.09 (0.80-1.49) | 0.58 |
| On narcotics around ADA start | 1.02 (0.74-1.40) | 0.91 |
| On steroids around ADA start | 0.76 (0.55-1.06) | 0.11 |
| Underwent dose escalation during initial year | 1.04 (0.69-1.58) | 0.85 |
| Hospitalization or new steroid use during year following ADA initiation | 0.50 (0.36-0.70) | <0.01 |
| Charlson comorbidity index | 0.98 (0.87-1.11) | 0.76 |