# Clinical Outcomes Associated with Switching or Discontinuation from Anti-TNF Inhibitors for Nonmedical Reasons

Douglas Wolf, MD[1]; Martha Skup, PhD[2]; Hongbo Yang, PhD[3]; Anna P. Fang[3]; Andrew Kageleiry[3]; Jingdong Chao, PhD[2]; Manish Mittal, PhD[2]; and Mark Lebwohl, MD[4]

*[1]Atlanta Gastroenterology Associates, Atlanta, Georgia; [2]AbbVie Inc, North Chicago, Illinois; [3]Analysis Group Inc, Boston, Massachusetts; and [4]Icahn School of Medicine at Mount Sinai, New York, New York*

## ABSTRACT

**Purpose:** This study evaluated clinical outcomes and health care resource utilization associated with nonmedical switching from or discontinuation of anti–tumor necrosis factor (TNF) therapies in US clinical practice.

**Methods:** Responding physicians extracted data from the medical charts of patients with Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriasis, or psoriatic arthritis who achieved response on an anti-TNF therapy. Physicians selected 2 cohorts of patients that were matched on diagnosis: patients who were switched/discontinued, for nonmedical reasons, from the anti-TNF therapy on which they achieved response (*switchers/discontinuers*), and patients who continued on their anti-TNF (*continuers*). Switchers/discontinuers were followed up for 12 months from the date of discontinuation (*index date*); continuers were followed up for 12 months from the date of an office visit within 2 months of the matched switcher/discontinuer's index date. Multivariate regression was used to compare disease flares, disease control, and health care resource utilization between cohorts, with adjustment for baseline characteristics. Subgroup analyses compared data from the continuer cohort to those from (1) patients who were switched to another biologic therapy and (2) patients who were switched to conventional therapy or discontinued from all therapy.

**Findings:** A total of 377 matched pairs of continuers and switchers/discontinuers were analyzed (N = 754), with the latter cohort comprising 284 patients (73.3%) who were and 93 (24.7%) who did not switch to another treatment (biologic or conventional treatment) immediately after discontinuation. Switchers/discontinuers had more frequent flares than did continuers, across severity levels (adjusted incidence rate ratios = 1.67, 2.36, and 3.48 for mild, moderate, and severe flares, respectively; all, $P < 0.05$). Switchers/discontinuers had a lower rate of well-controlled disease symptoms (46.9% vs 88.1%; adjusted odds ratio = 0.11; $P < 0.001$). Switchers/discontinuers also had more frequent inpatient hospitalizations, emergency department visits, and outpatient visits (adjusted incidence rate ratios = 3.58, 5.73, and 1.12, respectively; all, $P < 0.001$). Findings from the subgroup analyses of data from the 183 patients who switched to a biologic therapy and 194 who switched to conventional therapy or discontinued from all therapy were largely consistent with the overall analysis.

**Implications:** In this study, switching/discontinuation from an anti-TNF therapy for nonmedical reasons was associated with significantly worse clinical outcomes and increased health care resource utilization—factors that should be considered when developing treatment algorithms. (*Clin Ther*. 2017;39:849–862) © 2017 The Authors. Published by Elsevier HS Journals, Inc.

**Key words:** anti-TNF, autoimmune, biologic, nonmedical switching, tumor necrosis factor.

## INTRODUCTION

Anti–tumor necrosis factor (TNF) agents are important therapeutic options for a number of autoimmune

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disorders.[1] Common autoimmune diseases include Crohn disease (CD), ulcerative colitis (UC), rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriasis (Ps), and psoriatic arthritis (PsA), among others. The estimated prevalences of these diseases in the United States are: PsA, 0.1%[2]; AS, 0.2% to 0.5%[2]; CD and UC, ~0.25% each[3]; RA, 0.6%[4]; and Ps, up to 3.2%.[5] The clinical and economic burdens associated with these diseases are high, and increase with disease severity.[6–8] For example, the estimated economic costs of RA and CD are $19.3 billion (2005) and $10.9 to 15.5 billion (2008), respectively, in the United States alone.[9] These immunologic diseases manifest in distinct tissues, but their related pathogenesis allows all 6 disorders to be treated with TNF inhibitors.[10,11]

TNF is a pro-inflammatory cytokine involved in systemic inflammation whose dysregulation is associated with certain autoimmune diseases.[10,12] Anti-TNF agents are biologic therapies that target TNF for inhibition, down-regulating abnormal inflammatory response and resulting in clinical remission and improved quality of life in patients with autoimmune disorders.[10,12,13] Multiple anti-TNF therapies, including adalimumab, infliximab, etanercept, certolizumab pegol, and golimumab, have been approved by the US Food and Drug Administration as treatment options for the aforementioned diseases. Adalimumab and infliximab have been approved for all 6 indications[14,15]; etanercept is indicated for RA, Ps, PsA, and AS[16]; certolizumab pegol is indicated for RA, PsA, AS, and CD[17]; and golimumab is indicated for RA, PsA, AS, and UC.[18] Anti-TNF agents are effective in treating these autoimmune diseases. For example, a meta-analysis of data from 67 clinical trials (2–96 weeks in duration) in RA reported that the mean percentage of anti-TNF responders, as defined according to American College of Rheumatology criteria, was 60.8%.[19] A network meta-analysis of data from 15 short-term efficacy trials in Ps found that the response rates among patients receiving various anti-TNF therapies ranged from ~38% to 80%.[20] In a study in patients with UC, the rates of response to anti-TNF therapies at week 8 were ~50% to 60%.[21] Discontinuation of anti-TNF therapy among patients who achieve initial response, however, has been associated with loss of response and risk for relapse.[22,23]

In clinical practice, some patients who achieve stable response on an anti-TNF therapy may switch or discontinue from that therapy for a *nonmedical reason,* defined as a reason unrelated to clinical efficacy or tolerability.[24] Nonmedical reasons may include economic reasons, such as increased copay, change of insurance, job loss, or other economic factors that limit the affordability of a medication. Due to the availability of multiple agents for treatment, a formulary-management strategy may include substitution with a different anti-TNF therapy within a given health plan.[24] In the near future, the introduction of biosimilars to these anti-TNF therapies may provide patients with additional treatment options that might increase the switching and discontinuation from existing anti-TNF agents for nonmedical reasons.[25] However, it is not clear how the switching or discontinuation from an anti-TNF for a nonmedical reason would affect patients with autoimmune disorders.

Prior literature has documented the negative effects of nonmedical switching across numerous disease states. Studies have found that patients with conditions such as hypertension or mental illness who were switched between therapies for nonmedical reasons experienced increases in health care resource utilization and costs.[26,27] A recent claims-based study in patients with CD, RA, AS, Ps, or PsA who were switched from adalimumab for nonmedical reasons demonstrated that being switched to another injectable biologic was associated with significantly higher health care costs.[28] Nonmedical switching has also been associated with decreased treatment efficacy and increased side effects in patients.[29–31] Studies of clinicians' experience with nonmedical switching of therapies have found that physicians tended to observe an increase in adverse experiences as well as decreased efficacy among patients after a nonmedical therapy switch.[30,31]

As the range of treatment options for patients with autoimmune diseases in clinical practice increases, rates of nonmedical switching or discontinuation may also increase. This study evaluated clinical and health care resource utilization outcomes associated with switching or discontinuation of anti-TNF therapy for nonmedical reasons among patients with CD, UC, RA, AS, Ps, or PsA in clinical practice the United States.

## PATIENTS AND METHODS

### Study Design and Data Collection

The study employed an online, physician-administered chart review to collect information on

patients with CD, UC, RA, AS, Ps, or PsA who achieved a physician-assessed stable treatment response on an anti-TNF therapy, some of whom were switched/discontinued from therapy for economic reasons. Gastroenterologists, rheumatologists, and dermatologists (randomly sampled from a panel of 5198 physicians) were recruited from the Physician Consulting Network physicians' panel to participate in the present study. Participating physicians received financial compensation. The panel included physicians from the American Medical Association Physician Masterfile, which was created to be representative of physicians across the United States. Physician sampling was stratified to have an even ratio of gastroenterologists, rheumatologists, and dermatologists participating in the chart review, in order to maintain a representative balance of gastrointestinal, rheumatologic, and dermatologic indications in the resulting patient sample. No patient-identifying information was collected, and thus this study received an exemption from review by the New England Institutional Review Board (January 24, 2014).

This retrospective, matched-cohort study included 2 cohorts of patients who received an anti-TNF therapy for a diagnosis of CD, UC, RA, AS, Ps, or PsA, and who achieved and maintained physician-defined treatment response for at least 6 months on that therapy. Physicians were required to have access to a patient's complete disease-related medical records from 6 months prior to (*baseline period*) to 12 months following (*follow-up period*) the index date (Figure 1). Each physician was instructed to identify all charts meeting the sample-selection criteria and to randomly select up to 5 matched pairs for chart extraction; selection was based on patients' surnames beginning with a computer-generated random letter.[32,33] Data from eligible patients were extracted from patients' charts by participating physicians and were entered into an electronic case-report form, which collected information on baseline characteristics, clinical measures, and physician visits.

The anti-TNF therapies included in this study were adalimumab, infliximab, etanercept, certolizumab pegol, and golimumab. The *switcher/discontinuer cohort* was defined as the group of patients who were discontinued from the anti-TNF for a nonmedical reason between July 2011 and April 2013. No restriction was made as to whether a patient needed to have been switched to a subsequent therapy following the discontinuation. Some of the patients were initiated on a subsequent therapy after discontinuation (*switchers*), and the remaining were discontinued without immediately being switched to a different therapy (*discontinuers*). The subsequent therapy(ies) in the study included any therapy(ies) switched-to immediately after discontinuation, such as other biologic or conventional treatments. *Nonmedical reasons* specifically referred to economic reasons, such as cost of treatment or loss of rebate, change of insurance, job loss, and change in copayment amount, as well as patient preference or other nonmedical, economic reasons that could be listed by

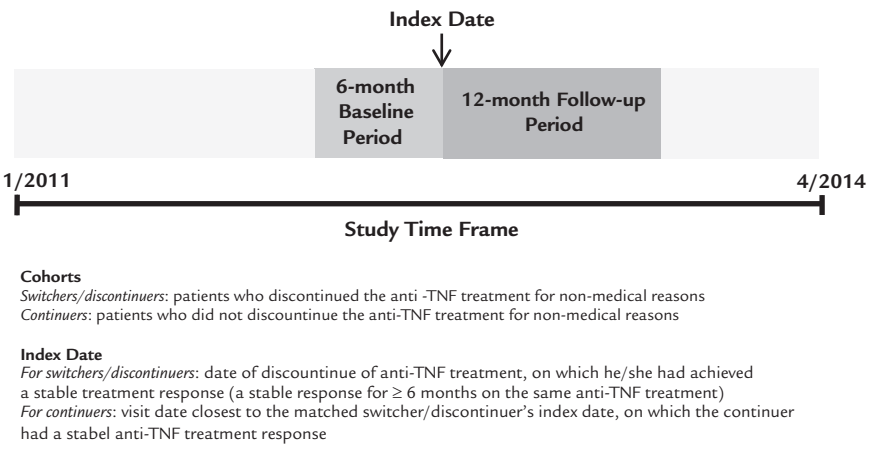


Figure 1. Study design. TNF = tumor necrosis factor.

participating physicians. Within the switcher/discontinuer cohort, a *biologic switcher subgroup* and a *discontinuer/conventional switcher subgroup* were also identified, comprising only patients who were switched to another biologic therapy (biologic switcher subgroup) or who either were switched to a conventional treatment (see **Appendix** in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.03.005) or who were discontinued and not switched to another therapy (discontinuer/conventional switcher subgroup). The *continuer cohort* was defined as the group of patients whose anti-TNF therapy was not changed for a nonmedical reason. Continuers were allowed to have been switched or discontinued for reasons other than nonmedical reasons during the study period following the index date. Each continuer was matched, based on primary diagnosis, to a switcher/discontinuer by the participating physician. The *date of discontinuation* of the anti-TNF agent was defined as the switcher/discontinuer's index date. The date of a visit closest to and within 60 days of the matched switcher/discontinuer's index date was defined as the continuer's index date. All patients were required to have been at least 18 years of age as of the index date.

## Study Measures

Characteristics assessed during the baseline period included demographics such as age, sex, race, employment status, and insurance provider, and disease-related measures such as primary diagnosis, disease severity, and comorbidities. Information on treatment and health care resource utilization during the baseline period was also collected, including the anti-TNF treatment on which patients achieved response for at least 6 months, use of other medi`-cations, inpatient hospitalizations, and emergency department (ED) and outpatient visits.

Clinical outcomes and health care resource utilization during the 12-month follow-up period were assessed. Clinical outcomes included number and severity (mild, moderate, or severe) of disease flares per year, reported by the treating physician based on his or her own assessment over the 12-month follow-up period. Responding physicians also provided an assessment of each patient's mean level of disease control, based on their evaluation, over the 12-month follow-up period. Information on patients' use of health care resources (inpatient hospitalizations, ED visits, and outpatient visits) was also collected.

## Statistical Analysis

Binary and categorical variables were summarized by counts and percentages, and continuous variables, by means (SD). Baseline characteristics were compared between cohorts using the Wilcoxon signed rank test for continuous variables, the McNemar test for categorical variables with 2 categories, and the Bowker test for categorical variables with $>2$ categories.

Clinical outcomes and health care resource utilization during the follow-up period were compared between cohorts and summarized with odds ratios (OR) for binary outcomes and incidence rate ratios (IRR) for continuous outcomes. Logistic regression was employed to estimate ORs for disease flares, well-controlled disease, and a history of at least 1 health care visit during the follow-up period. The number of disease flares and the number of health care visits were compared between groups using a negative binomial generalized linear model. Both univariate and multivariate regression models were used to compare the 2 cohorts (continuers vs switchers/discontinuers), as well as the biologic switcher and discontinuer/conventional switcher subgroups versus the continuer cohort in separate analyses. Multivariate regression adjusted for differences in baseline characteristics between the 2 cohorts, including the anti-TNF agent discontinued/used on the index date (*index anti-TNF agent*); demographic information (sex, age, full-time employment status); number of baseline comorbidities; use of other biologic therapies, immunosuppressants, or corticosteroids during the baseline period; and baseline health care resource utilization.

A sensitivity analysis was conducted on the 2 cohorts' (continuers and switchers/discontinuers) resource utilization and treatment response results, controlling for comorbidities that were statistically different at baseline, with a prevalence of $>5\%$ in lieu of number of comorbidities.

Subgroup analyses were conducted among matched continuers and the biologic switcher and discontinuer/conventional switcher subgroups, and subgroups of patients with a primary indication of inflammatory bowel disease (CD or UC), RA, Ps, or PsA, using a similar methodology as in the overall analysis.

All analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC).

## RESULTS

### Patient Characteristics

A total of 111 physicians contributed 754 patients' charts, for 377 matched pairs of switchers/discontinuers and continuers (Table I). The switcher/discontinuer cohort included 284 (75.3%) switchers (to any therapy) and 93 (24.7%) discontinuers (discontinued all therapy). The 2 cohorts had similar ages at the index date (overall mean, 43.6 years), although the switcher/discontinuer cohort had a higher percentage of male patients compared with that in the continuer cohort (59.2% vs 48.0%; $P < 0.001$). The switcher/discontinuer cohort also had a higher percentage of patients without insurance than did the continuer cohort (4.8% vs 0.5%; $P < 0.001$). The 2 cohorts also differed significantly on employment status, with 49.1% of switchers/discontinuers employed full-time compared to 66.6% of continuers ($P < 0.001$).

The cohorts were matched on primary diagnosis, with Ps (34.7%), CD (22.3%), and RA (22.0%) being the most common primary indications in the study population. The 2 cohorts had similar disease severities at baseline. Comorbidities were largely similar between the 2 groups, with the exception of 4 conditions: Anemia (12.2% vs 8.5%; $P = 0.035$), psychiatric disorders (5.6% vs 2.7%; $P = 0.048$), and sleep apnea (2.9% vs 0.8%; $P = 0.033$) were significantly more prevalent in the switcher/discontinuer cohort, while cardiovascular disease was significantly more prevalent among continuers (0.3% vs 2.1%; $P = 0.008$).

Of the reasons listed for switching or discontinuing anti-TNF treatment, 48.3% (n = 182) of the patients in the switcher/discontinuer cohort lost or changed insurance, 23.3% (n = 88) switched to a lower-cost drug, 14.3% (n = 54) experienced job loss in the household, 14.1% (n = 53) experienced a change in copayment amount, 4.5% (n = 17) lost a rebate or coupon, and 0.3% (n = 1) preferred another drug. An additional 1.3% (n = 5) were listed as having an "other nonmedical reason."

The distribution of index anti-TNF agents, that is, the agent on which patients achieved response for at least 6 months, was similar between the 2 cohorts. The most commonly used agents among switchers/discontinuers and continuers were adalimumab (37.7% vs 41.1%), etanercept (27.9% vs 27.6%), and infliximab (25.2% vs 22.8%). Use of other medications during the 6-month baseline period differed slightly between the 2 groups. Patients in the switcher/discontinuer cohort had more use of corticosteroids (30.0% vs 23.6%; $P = 0.008$), while the continuer cohort had a higher percentage of patients who received an immunosuppressant (6.1% vs 10.1%; $P = 0.004$) or a biologic treatment other than the index anti-TNF (7.2% vs 11.1%; $P = 0.011$). Switchers/discontinuers had a higher rate of use of outpatient services at baseline, while more continuers had used inpatient medical services at baseline. There were no significant differences in ED use at baseline.

### Clinical Response During the Follow-Up Period

Patients in the switcher/discontinuer cohort had a significantly greater risk for any disease flare, with 79.6% of switchers/discontinuers experiencing flares compared with 53.6% of matched continuers (Table II). The adjusted OR was 3.34 ($P < 0.001$). This result was consistent across flare severity levels, with an adjusted OR of 1.65 for mild, 5.49 for moderate, and 5.55 for severe flares (all, $P < 0.001$). Switchers/discontinuers also had a greater number of flares compared with that in the continuer group (adjusted IRR = 1.91; $P < 0.001$). This trend was consistent across all severity levels, with an adjusted IRR of 1.67 for mild flares ($P < 0.001$), 2.36 for moderate flares ($P = 0.003$), and 3.48 for severe flares ($P = 0.011$).

The majority of patients who were switched/discontinued had uncontrolled (11.1%) or partially controlled (41.9%) disease symptoms, while the majority (88.1%) of the continuer cohort had well-controlled disease symptoms (Figure 2). Significantly fewer switchers/discontinuers were assessed by the physician as having well-controlled disease symptoms (adjusted OR = 0.11; $P < 0.001$) (Table II). The results of the sensitivity analyses conducted on treatment response data in the 2 cohorts (continuers and switchers/discontinuers), controlling for comorbidities with a prevalence of >5% (anemia and psychiatric disorders) that were statistically different at baseline, were consistent with those from the main analyses. For significantly different comorbidities with a prevalence of <5% (sleep apnea and cardiovascular disease), the model did not converge.

Table I. Baseline characteristics.

| Characteristic | Switchers/Discontinuers (n = 377) | Continuers (n = 377) | *P* |
|---|---|---|---|
| Age at index date, mean (SD) | 43.30 (12.83) | 43.92 (12.69) | 0.880 |
| Male, no. (%) | 223 (59.2) | 181 (48.0) | <0.001* |
| No insurance provider, no. (%) | 18 (4.8) | 2 (0.5) | <0.001* |
| Employed full-time,† no. (%) | 185 (49.1) | 251 (66.6) | <0.001* |
| Primary diagnosis,‡ no. (%) | | | |
| Psoriasis | 131 (34.7) | 131 (34.7) | – |
| Crohn's disease | 84 (22.3) | 84 (22.3) | – |
| Rheumatoid arthritis | 83 (22.0) | 83 (22.0) | – |
| Ulcerative colitis | 47 (12.5) | 47 (12.5) | – |
| Psoriatic arthritis | 26 (6.9) | 26 (6.9) | – |
| Ankylosing spondylitis | 6 (1.6) | 6 (1.6) | – |
| Disease severity,§ no. (%) | | | 0.582 |
| Asymptomatic | 97 (25.7) | 107 (28.4) | |
| Mild | 164 (43.5) | 167 (44.3) | |
| Moderate | 93 (24.7) | 75 (19.9) | |
| Severe | 15 (4.0) | 20 (5.3) | |
| Unknown | 8 (2.1) | 8 (2.1) | |
| Any comorbidity,‖ no. (%) | 225 (59.7) | 225 (59.7) | 1.000 |
| Hypertension | 93 (24.7) | 81 (21.5) | 0.265 |
| Anemia | 46 (12.2) | 32 (8.5) | 0.035* |
| Hyperlipidemia | 44 (11.7) | 51 (13.5) | 0.406 |
| Obesity/overweight | 41 (10.9) | 36 (9.5) | 0.466 |
| Thyroid disease | 27 (7.2) | 28 (7.4) | 0.886 |
| Dyslipidemia | 25 (6.6) | 21 (5.6) | 0.527 |
| Diabetes mellitus (type I or II) | 24 (6.4) | 28 (7.4) | 0.546 |
| Psychiatric disorder | 21 (5.6) | 10 (2.7) | 0.048* |
| Sleep apnea | 11 (2.9) | 3 (0.8) | 0.033* |
| Cardiovascular disease | 1 (0.3) | 8 (2.1) | 0.008* |
| No. of comorbidities, mean (SD) | 1.11 (1.26) | 1.03 (1.16) | 0.247 |
| Anti-TNF on which patients achieved response for ≥6 mo, no. (%) | | | 0.994 |
| Adalimumab | 142 (37.7) | 155 (41.1) | |
| Etanercept | 105 (27.9) | 104 (27.6) | |
| Infliximab | 95 (25.2) | 86 (22.8) | |
| Certolizumab pegol | 23 (6.1) | 23 (6.1) | |
| Golimumab | 12 (3.2) | 9 (2.4) | |
| Other medication use,¶ no. (%) | | | |
| Corticosteroid | 113 (30.0) | 89 (23.6) | 0.008* |
| Other disease-modifying antirheumatic drug | 71 (18.8) | 73 (19.4) | 0.724 |
| 5-Aminosalicylic acid | 64 (17.0) | 62 (16.4) | 0.695 |
| NSAID | 53 (14.1) | 58 (15.4) | 0.446 |
| Use of a biologic agent other than index anti-TNF | 27 (7.2) | 42 (11.1) | 0.011* |
| Immunosuppressant | 23 (6.1) | 38 (10.1) | 0.004* |

(continued)

Table I. (continued).

| Characteristic | Switchers/Discontinuers (n = 377) | Continuers (n = 377) | *P* |
|---|---|---|---|
| Health care resource utilization | | | |
| ≥1 Outpatient visit, no. (%) | 342 (90.7) | 326 (86.5) | 0.014* |
| No. of outpatient visits, mean (SD) | 2.49 (1.86) | 2.15 (1.54) | <0.001* |
| ≥1 Emergency department visit, no. (%) | 23 (6.1) | 22 (5.8) | 0.869 |
| ≥1 Inpatient hospitalization, no. (%) | 10 (2.7) | 22 (5.8) | 0.014* |

TNF = tumor necrosis factor.
*$P < 0.05$.
†*P* was calculated using Bowker's test; other categories included part-time, student, unemployed, retired, and unknown.
‡Patients in the switcher/discontinuer cohort and the continuer cohort were matched on primary diagnosis.
§Severity of disease was assessed by the responding physician at a single visit during the baseline period.
‖Only comorbidities with a prevalence of >5% in either cohort or comorbidities that were significantly different between the 2 cohorts are presented.
¶Other medication use does not include the index anti-TNF therapy; only medications with a prevalence of >10% in either cohort are presented.

### Health Care Resource Utilization During the Follow-Up Period

After adjustment for baseline characteristics, switchers/discontinuers had significantly increased risks for at least 1 inpatient hospitalization (adjusted OR = 2.94; $P = 0.009$) and ED visit (adjusted OR = 5.21; $P < 0.001$) during the study period compared with those in continuers (Table III). The switcher/discontinuer cohort likewise had significantly higher risks for inpatient hospitalization (adjusted IRR = 3.58; $P < 0.001$), outpatient visits (adjusted IRR = 1.12; $P = 0.001$), and ED visits (adjusted IRR = 5.73; $P < 0.001$). The results of the sensitivity analysis were consistent with the core analysis results.

Table II. Clinical response during the follow-up period (overall).

| Parameter | Switchers/Discontinuers (n = 377) | Continuers (n = 377) | Unadjusted OR/IRRs* | Adjusted OR/IRRs* |
|---|---|---|---|---|
| Patients with ≥1 disease flare, no. (%) | 300 (79.6) | 202 (53.6) | 3.38† | 3.34† |
| Mild | 226 (59.9) | 181 (48.0) | 1.62† | 1.65† |
| Moderate | 190 (50.4) | 64 (17.0) | 4.97† | 5.49† |
| Severe | 62 (16.4) | 11 (2.9) | 6.55† | 5.55† |
| Number of disease flares, mean (SD) | 2.7 (7.8) | 1.5 (7.7) | 1.82† | 1.91† |
| Mild | 1.3 (2.8) | 0.8 (2.2) | 1.60† | 1.67† |
| Moderate | 1.1 (3.8) | 0.6 (4.2) | 2.02† | 2.36† |
| Severe | 0.3 (1.6) | 0.2 (1.5) | 2.22† | 3.48† |
| Patients with well-controlled disease, no. (%) | 177 (46.9) | 332 (88.1) | 0.12† | 0.11† |

IRR = incidence rate ratio; OR = odds ratio.
*Binary variables were assessed with ORs; counts were assessed with IRRs. ORs were calculated as the ratio of $p_1/[1 - p_1]$ to $p_2/[1 - p_2]$, where $p_1$ and $p_2$ represent the probability of the outcome among the 2 cohorts.
†$P < 0.05$.

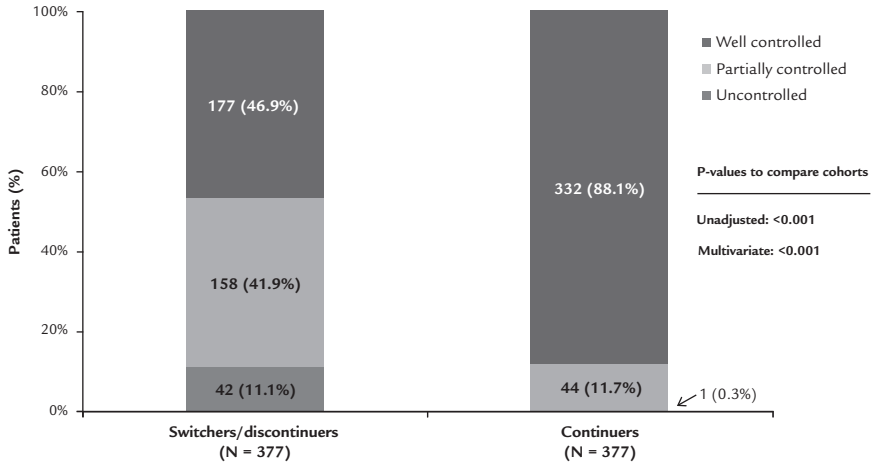


Figure 2. Comparison of disease control in biologic switchers/discontinuers versus matched continuers.

## Subgroup Analyses of Biologic Switchers and Discontinuers/Conventional Switchers

Subgroups of the switcher/discontinuer cohort included 183 patients who were switched to another biologic therapy (biologic switcher subgroup) and 194 patients who either were switched to a conventional therapy (n = 101) or were discontinued from all therapy (n = 93) (discontinuer/conventional switcher subgroup). The results of the adjusted analyses conducted among the biologic switcher subgroup (Table IV and Figure 3A) and the discontinuer/conventional switcher subgroup (Table V and Figure 3B) in comparison with matched continuers were largely consistent with the comparative results from the main cohorts. In the comparison of clinical response in the biologic switcher subgroup and the continuer cohort, the groups were still significantly different in terms of number of patients with at least 1

Table III. Health care resource utilization during the follow-up period (overall).

| Health Care Resource | Switchers/Discontinuers (n = 377) | Continuers (n = 377) | Unadjusted OR/IRRs* | Adjusted OR/IRRs* |
|---|---|---|---|---|
| Hospitalizations | | | | |
| Patients with ≥1, no. (%) | 19 (5.0) | 13 (3.4) | 1.49 | 2.94† |
| No. per patient, mean (SD) | 0.08 (0.42) | 0.06 (0.39) | 1.43 | 3.58† |
| Emergency department visits | | | | |
| Patients with ≥1, no. (%) | 54 (14.3) | 16 (4.2) | 3.77† | 5.21† |
| No. per patient, mean (SD) | 0.23 (0.73) | 0.05 (0.22) | 5.18† | 5.73† |
| Outpatient visits | | | | |
| Patients with ≥1,‡ no. (%) | 377 (100) | 377 (100) | – | – |
| No. per patient, mean (SD) | 4.28 (3.55) | 3.54 (2.44) | 1.21† | 1.12† |

IRR = incidence rate ratio; OR = odds ratio.
*Binary variables were assessed with ORs; counts were assessed with IRRs. ORs were calculated as the ratio of $p_1/[1 - p_1]$ to $p_2/[1 - p_2]$, where $p_1$ and $p_2$ represent the probability of the outcome among the 2 cohorts.
†$P < 0.05$.
‡The OR for patients with ≥1 outpatient visit was not calculated because all patients were required to have had an outpatient visit (index visit) during the study period.

Table IV. Clinical response and health care resource utilization during the follow-up period (biologic switcher subgroup).

| Parameter | Biologic Switchers (n = 183) | Continuers (n = 183) | Unadjusted OR/IRRs* | Adjusted OR/IRRs* |
|---|---|---|---|---|
| Clinical response | | | | |
| Disease flare | | | | |
| Patients with ≥1, no. (%) | 131 (71.6) | 110 (60.1) | 1.67† | 1.52† |
| Mild | 100 (54.6) | 102 (55.7) | 0.96 | 0.83 |
| Moderate | 75 (41.0) | 38 (20.8) | 2.65† | 2.68† |
| Severe | 28 (15.3) | 7 (3.8) | 4.54† | 4.22† |
| No. per patient, mean (SD) | 2.9 (10.9) | 2.2 (10.9) | 1.27† | 1.57† |
| Mild | 1.3 (3.7) | 1.1 (3.0) | 1.20† | 1.27 |
| Moderate | 1.2 (5.3) | 0.9 (6.0) | 1.26 | 2.02† |
| Severe | 0.4 (2.1) | 0.3 (2.1) | 1.62 | 3.13† |
| Patients with well-controlled disease, no. (%) | 122 (66.7) | 153 (83.6) | 0.39† | 0.37† |
| Health care resource utilization | | | | |
| Hospitalizations | | | | |
| Patients with ≥1, no. (%) | 8 (4.4) | 5 (2.7) | 1.63 | 3.03† |
| No. per patient, mean (SD) | 0.05 (0.27) | 0.05 (0.47) | 1.00 | 3.16† |
| Emergency department visits | | | | |
| Patients with ≥1, no. (%) | 18 (9.8) | 10 (5.5) | 1.89 | 1.73 |
| No. per patient, mean (SD) | 0.13 (0.44) | 0.05 (0.23) | 2.40† | 2.05 |
| Outpatient visits | | | | |
| Patients with ≥1,‡ no. (%) | 183 (100) | 183 (100) | – | – |
| No. per patient, mean (SD) | 3.91 (2.71) | 3.45 (2.25) | 1.13† | 1.05 |

IRR = incidence rate ratio; OR = odds ratio.
*Binary variables were assessed with ORs; counts were assessed with IRRs. ORs were calculated as the ratio of $p_1/[1 - p_1]$ to $p_2/[1 - p_2]$, where $p_1$ and $p_2$ represent the probability of the outcome among the 2 cohorts.
†$P < 0.05$.
‡The OR for patients with ≥1 outpatient visit was not calculated because all patients were required to have had an outpatient visit during the study period.

moderate or severe flare and the number of moderate or severe flares per patient, but the differences in the percentage of patients with at least 1 mild disease flare (54.6% vs 55.7%; respectively; adjusted OR = 0.83) and the number of mild disease flares (1.3 [3.7] vs 1.1 [3.0]; adjusted OR = 1.27) failed to reach significance. All significant differences noted in the main analysis of clinical response held true in the comparison of the discontinuer/conventional switchers and matched continuers.

In the comparison of health care resource utilization among the biologic switcher subgroup and matched continuers, the groups were still significantly different in terms of percentage of patients with an inpatient hospitalization and the mean number of inpatient hospitalizations, but were no longer significantly different in terms of percentage of patients with at least 1 ED visit (9.8% vs 5.5%; respectively; adjusted IRR = 1.73), number of ED visits per patient (0.13 [0.44] vs 0.05 [0.23]; adjusted IRR = 2.05), and number of outpatient visits (3.91 [2.71] vs 3.45 [2.25]; adjusted IRR = 1.05). In the comparison of health care resource utilization among the discontinuer/conventional switcher subgroup and matched continuers, the groups were still significantly different across all outcomes, with the exception of the percentage of

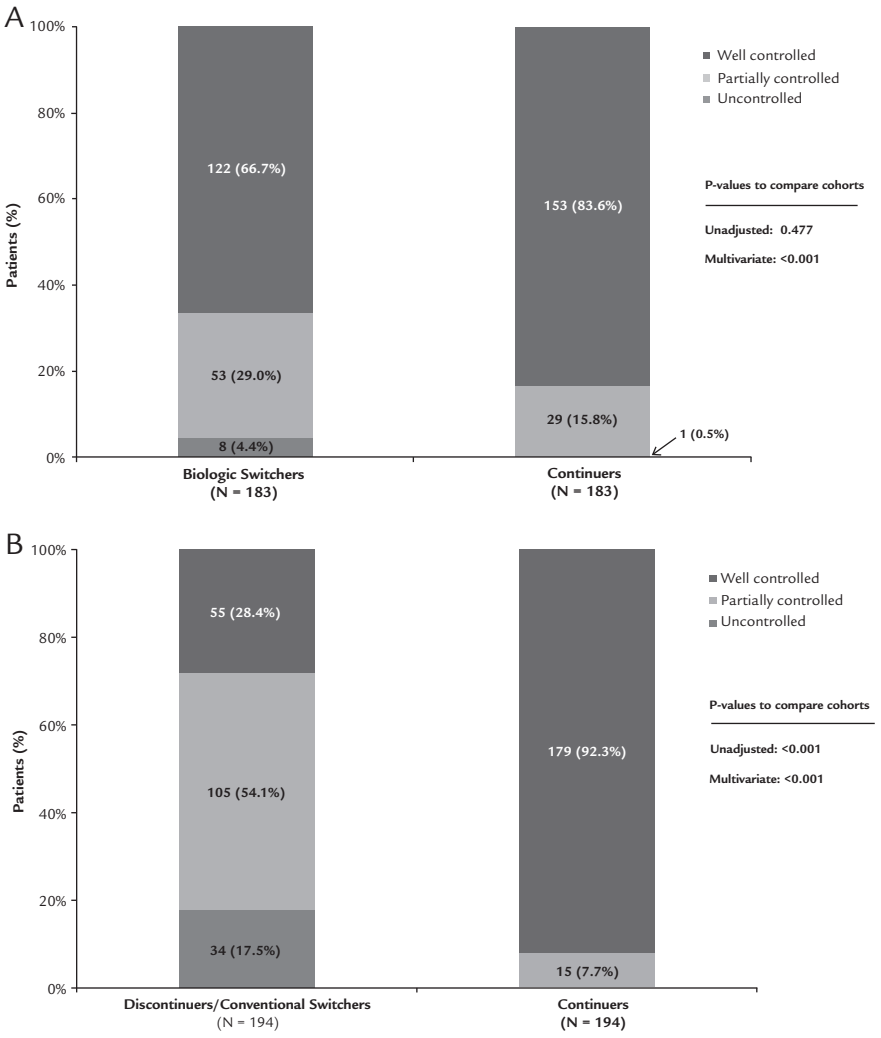


Figure 3. Comparisons of disease control in the subgroups of biologic switchers (A) and discontinuer/conventional switchers (B) versus matched continuers.

patients with at least 1 inpatient hospitalization, which was no longer statistically significantly different (5.7% vs 4.1%; respectively; adjusted IRR = 2.65).

### Subgroup Analyses by Indication

In the analyses of data from the subgroups with inflammatory bowel disease (see Supplemental Table S1 and Figure S1 in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.03.005), RA (see Supplemental Table S2 and Figure S2), and Ps/PsA (see Supplemental Table S3 and Figure S3), results were largely consistent with the overall results across indications. In all 3 subgroups, patients who were switched/discontinued had significantly worse clinical outcomes in terms of disease flares and disease control, as well as an increased risk for health care visits, compared with those in the continuer cohort.

## DISCUSSION

This chart review study provides an assessment from clinical practice of how patient outcomes may be affected by switching or discontinuing anti-TNF therapies when not clinically necessary. Patients who were switched or discontinued from their stable anti-TNF treatment for nonmedical, economic reasons had significantly worse clinical outcomes, with increased disease flares and poor disease control, compared with

Table V. Clinical response and health care resource utilization during the follow-up period (discontinuer/conventional switcher subgroup).

| Parameter | Discontinuers/Conventional Switchers (n = 194) | Continuers (n = 194) | Unadjusted OR/IRRs* | Adjusted OR/IRRs* |
|---|---|---|---|---|
| Clinical response | | | | |
| Disease flare | | | | |
| Patients with ≥1, no. (%) | 169 (87.1) | 92 (47.4) | 7.49† | 7.84† |
| Mild | 126 (64.9) | 79 (40.7) | 2.70† | 2.68† |
| Moderate | 115 (59.3) | 26 (13.4) | 9.41† | 11.85† |
| Severe | 34 (17.5) | 4 (2.1) | 10.09† | 11.61† |
| No. per patient, mean (SD) | 2.6 (2.4) | 0.8 (1.3) | 3.25† | 3.26† |
| Mild | 1.2 (1.4) | 0.5 (0.8) | 2.35† | 2.38† |
| Moderate | 1.1 (1.2) | 0.2 (0.6) | 5.05† | 4.97† |
| Severe | 0.3 (0.8) | 0.1 (0.7) | 4.58 | 5.33† |
| Patients with well-controlled disease, no. (%) | 55 (28.4) | 179 (92.3) | 0.03† | 0.02† |
| Health care resource utilization | | | | |
| Hospitalizations | | | | |
| Patients with ≥1, no. (%) | 11 (5.7) | 8 (4.1) | 1.40 | 2.65 |
| No. per patient, mean (SD) | 0.10 (0.52) | 0.06 (0.31) | 1.82 | 2.61† |
| Emergency department visits | | | | |
| Patients with ≥1, no. (%) | 36 (18.6) | 6 (3.1) | 7.14† | 14.18† |
| No. per patient, mean (SD) | 0.33 (0.92) | 0.04 (0.21) | 9.14† | 11.77† |
| Outpatient visits | | | | |
| Patients with ≥1,‡ no. (%) | 194 (100) | 194 (100) | – | – |
| No. per patient, mean (SD) | 4.63 (4.17) | 3.62 (2.60) | 1.28† | 1.17† |

IRR = incidence rate ratio; OR = odds ratio.

*Binary variables were assessed with ORs; counts were assessed with IRRs. ORs were calculated as the ratio of $p_1/[1 - p_1]$ to $p_2/[1 - p_2]$, where $p_1$ and $p_2$ represent the probability of the outcome among the 2 cohorts.

†$P < 0.05$.

‡The OR for patients with ≥1 outpatient visit was not calculated because all patients were required to have had an outpatient visit during the study period.

those in patients who continued on their anti-TNF agent. Switchers/discontinuers also had increased health care resource utilization across all types of medical visits. These results were consistent among patient populations with specific indications, including inflammatory bowel disease, RA, and Ps/PsA.

To date, few studies have evaluated the clinical impact of nonmedical switching of anti-TNF therapies across different autoimmune indications. One such study using data from electronic health records, recently published in abstract format,[29] found that patients with RA, UC, CD, AS, Ps, or PsA who were switched from one anti-TNF treatment to a different anti-TNF treatment for cost-related reasons had an increased likelihood of treatment adjustment within the subsequent year due to lack of efficacy or to side effects. The present study included a broad patient population, that is, patients who either were switched to any other treatment or simply were discontinued from the original anti-TNF therapy for any nonmedical, economic reason after achieving clinical response on the original therapy. In addition, the present study included clinical outcomes such as disease flares and disease control, as well as different types of resource utilization. The present study observed negative clinical

outcomes in patients who were discontinued for nonmedical reasons compared with patients who were not, consistent with the negative effects observed in the literature.[26-31] The same negative outcomes were observed in both (1) the subgroup of patients who were discontinued and not immediately switched to a subsequent therapy or were switched to conventional therapy and (2) the subgroup of patients who were discontinued and immediately were switched to a different biologic treatment. These results suggest that payers should consider such potential adverse outcomes when making formulary decisions in patients who have achieved stable response on an anti-TNF therapy and are being considered for a discontinuation or switch from such treatment for nonmedical reasons. Future research evaluating instances in which a formulary decision might have an impact on the discontinuation of a biologic therapy for nonmedical reasons in clinical practice would shed additional light on this research question.

### Limitations

This study was subject to several limitations. Despite the inclusion of quality checks in the study design, retrospective chart review data are difficult to verify due to a reliance on the accuracy of both data entry and medical records. Disease control and symptom flares were based on responding physicians' assessments rather than on objective evaluation by an instrument, which may have led to variations in the assessed outcomes. However, subjective assessment is less likely to have affected the results given that the same physician assessed both switcher/discontinuer and the corresponding control. Despite adjustment for baseline characteristics, comparison of cohorts could still have been biased by unobserved confounding factors, such as duration of prior treatment and number of prior treatments before the initiation of the anti-TNF therapy on which patients achieved a stable response. Finally, the 1-year study period may not have been representative of longer-term outcomes, and any extrapolation of the results should be considered with caution. Longer-term outcomes of nonmedical switching may be associated with greater adverse effects; the assessment of such outcomes requires further evaluation.

## CONCLUSIONS

Switching or discontinuation from an anti-TNF therapy for nonmedical or economic reasons following stable response was associated with significantly worse clinical outcomes (disease flares and severity) and increased health care resource utilization among patients with CD, UC, RA, AS, Ps, or PsA. Treatment algorithms for these anti-TNF–treated diseases may consider including specific considerations related to nonmedical switching. Third-party payers might also want to consider the risk associated with policies that may result in nonmedical switching when making formulary decisions.

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The authors participated in the interpretation of the data and the preparation, review, and final approval of the manuscript. All authors contributed to the development of the manuscript and maintained control over the final content.

## CONFLICTS OF INTEREST

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## SUPPLEMENTARY MATERIAL

A supplemental appendix accompanying this article can be found in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.03.005.

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**Address correspondence to:** Douglas Wolf, MD, 5671 Peachtree Dunwoody Road, Suite 600, Atlanta, GA 30342. E-mail: m4desk@aol.com

## SUPPLEMENTARY MATERIAL
## Appendix: Switched-to Therapies

| Switched-to Therapy, N (%) | Switchers[*,†] (N = 284) |
|---|---|
| Other anti-TNF | 171 (60.2%) |
| Adalimumab | 86 (30.3%) |
| Etanercept | 28 (9.9%) |
| Infliximab | 32 (11.3%) |
| Certolizumab pegol | 18 (6.3%) |
| Golimumab | 7 (2.5%) |
| Other | 0 (0.0%) |
| Other biologic[‡] | 12 (4.2%) |
| Other DMARD | 36 (12.7%) |
| Toficitinib | 3 (1.1%) |
| Immunosuppressant | 40 (14.1%) |
| Steroid | 44 (15.5%) |
| NSAID | 9 (3.2%) |
| Other[§] | 8 (2.8%) |
| Unknown/Not Sure | 2 (0.7%) |

DMARD = disease-modifying anti-rheumatic drug. NSAID = nonsteroidal anti-inflammatory drug.

[*]For the switcher/discontinuer cohort, patients discontinued their anti-TNF therapy on the index date. A subset of these patients switched to another disease-related treatment option after discontinuation.

[†]Physicians selected the treatment(s) that the patient switched to immediately following discontinuation. Physicians could select multiple treatments in case of combination therapy.

[†]Other switched-to biologics included ustekinumab, brodalumab, ixekizumab, and tocilizumab.

[§]Other switched-to therapies included Taclonex, UVB therapy, Soriatane, PUVA therapy, and Clobex spray.

See Fig. S1–Fig. S3.

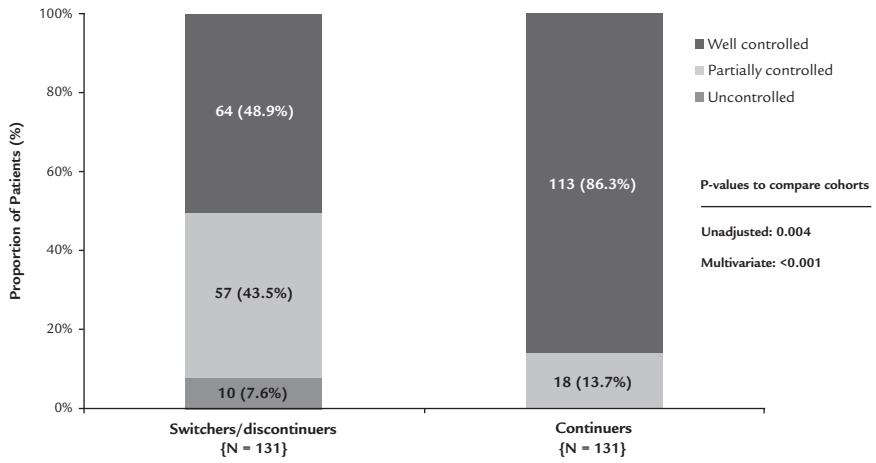


Fig. S1. Comparison of disease control in biologic switchers/discontinuers versus matched continuers among patients with inflammatory bowel disease.

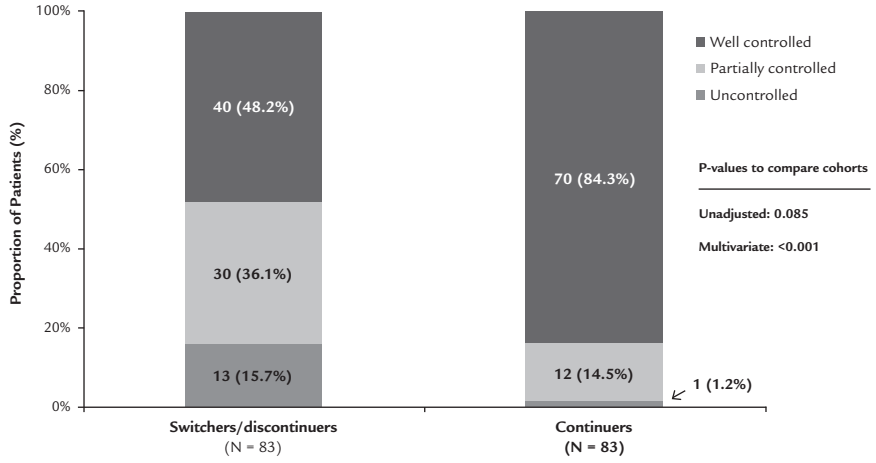


Fig. S2. Comparison of disease control in biologic switchers/discontinuers versus matched continuers among patients with rheumatoid arthritis.

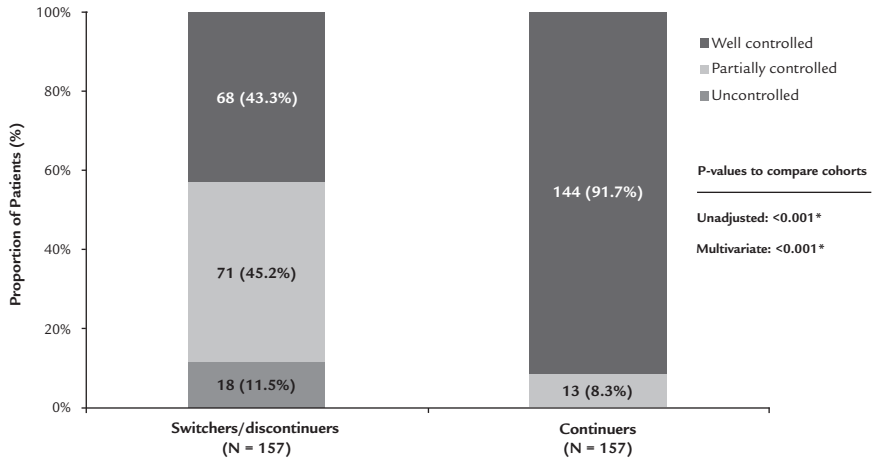


Fig. S3. Comparison of disease control in biologic switchers/discontinuers versus matched continuers among patients with psoriasis or psoriatic arthritis.

See Table SI.

Table SI. Clinical Response and Healthcare Utilization during the Follow-Up Period among Patients with Inflammatory Bowel Disease.

| | Switchers/ discontinuers (N = 131) | Continuers (N = 131) | Unadjusted OR/IRRs[†] | Adjusted OR/ IRRs[†] |
|---|---|---|---|---|
| **Clinical Response** | | | | |
| Patients with at least one disease flare, N (%) | 99 (75.6%) | 67 (51.1%) | 2.96[*] | 3.23[*] |
| Mild | 75 (57.3%) | 56 (42.7%) | 1.79[*] | 2.00[*] |
| Moderate | 64 (48.9%) | 22 (16.8%) | 4.73[*] | 5.63[*] |
| Severe | 14 (10.7%) | 2 (1.5%) | 7.72[*] | 6.81[*] |
| Number of disease flares, mean ± SD | 1.7 ± 1.6 | 0.9 ± 1.3 | 1.91[*] | 1.76[*] |
| Mild | 0.8 ± 0.9 | 0.6 ± 0.8 | 1.47[*] | 1.46[*] |
| Moderate | 0.7 ± 0.8 | 0.3 ± 0.6 | 2.85[*] | 2.47[*] |
| Severe | 0.2 ± 0.6 | 0.1 ± 0.8 | 2.10 | 6.62[*] |
| Patients with well-controlled disease, N (%) | 64 (48.9%) | 113 (86.3%) | 0.15[*] | 0.15[*] |
| **Healthcare Utilization** | | | | |
| ≥1 inpatient hospitalization, N (%) | 14 (10.7%) | 11 (8.4%) | 1.31 | 1.16 |
| Number of hospitalizations per patient, mean ± SD | 0.18 ± 0.65 | 0.11 ± 0.40 | 1.71 | 1.45 |
| ≥1 emergency department (ED) visit, N (%) | 41 (31.3%) | 14 (10.7%) | 3.81[*] | 4.06[*] |
| Number of visits per patient, mean ± SD | 0.51 ± 0.91 | 0.11 ± 0.34 | 4.47[*] | 4.21[*] |
| ≥1 outpatient visit[‡], N (%) | 131 (100.0%) | 131 (100.0%) | - | - |
| Number of visits per patient, mean ± SD | 3.92 ± 2.85 | 3.35 ± 2.02 | 1.17[*] | 1.11[*] |

OR = odds ratio. IRR = incidence rate ratio. N = number. SD = standard deviation.
[*]P <0.05.
[†]Binary variables were assessed with ORs; counts were assessed with IRRs. ORs were calculated as the ratio of p1/[1-p1] to p2/[1-p2], where p1 and p2 represent the probability of the outcome among the two cohorts, respectively.
[‡]The OR for patients with ≥1 outpatient visit was not calculated because all patients were required to have an outpatient visit during the study period.

See Table SII.

Table SII. Clinical Response and Healthcare Utilization during the Follow-Up Period among Patients with Rheumatoid Arthritis.

| | Switchers/ discontinuers (N = 83) | Continuers (N = 83) | Unadjusted OR/ IRRs[†] | Adjusted OR/ IRRs[†] |
|---|---|---|---|---|
| **Clinical Response** | | | | |
| Patients with at least one disease flare, N (%) | 64 (77.1%) | 42 (50.6%) | 3.29[*] | 3.63[*] |
| Mild | 53 (63.9%) | 40 (48.2%) | 1.90[*] | 2.26[*] |
| Moderate | 41 (49.4%) | 12 (14.5%) | 5.78[*] | 5.76[*] |
| Severe | 15 (18.1%) | 6 (7.2%) | 2.83[*] | 2.88[*] |
| Number of disease flares, mean ± SD | 3.8 ± 12.1 | 2.3 ± 12.0 | 1.63[*] | 3.73[*] |
| Mild | 1.7 ± 4.0 | 1.1 ± 3.9 | 1.53[*] | 2.51[*] |
| Moderate | 1.5 ± 6.1 | 0.9 ± 6.0 | 1.68 | 5.83[*] |
| Severe | 0.6 ± 2.4 | 0.3 ± 2.2 | 1.88 | 10.10[*] |
| Patients with well-controlled disease, N (%) | 40 (48.2%) | 70 (84.3%) | 0.17[*] | 0.15[*] |
| **Healthcare Utilization** | | | | |
| ≥1 inpatient hospitalization, N (%) | 4 (4.8%) | 2 (2.4%) | 2.05 | 3.87 |
| Number of hospitalizations per patient, mean ± SD | 0.06 ± 0.29 | 0.08 ± 0.67 | 0.71 | 3.57 |
| ≥1 emergency department (ED) visit, N (%) | 8 (9.6%) | 2 (2.4%) | 4.32[*] | 6.94[*] |
| Number of visits per patient, mean ± SD | 0.19 ± 0.93 | 0.02 ± 0.15 | 8.00[*] | 9.85[*] |
| ≥1 outpatient visit[‡], N (%) | 83 (100.0%) | 83 (100.0%) | - | - |
| Number of visits per patient, mean ± SD | 4.70 ± 3.33 | 4.14 ± 2.25 | 1.13 | 1.09 |

OR = odds ratio. IRR = incidence rate ratio. N = number. SD = standard deviation.

[*]P <0.05

[†]Binary variables were assessed with ORs; counts were assessed with IRRs. ORs were calculated as the ratio of p1/[1-p1] to p2/[1-p2], where p1 and p2 represent the probability of the outcome among the two cohorts, respectively.

[‡]The OR for patients with ≥1 outpatient visit was not calculated because all patients were required to have an outpatient visit during the study period.

See Table SIII.

Table SIII. Clinical Response and Healthcare Utilization during the Follow-Up Period among Patients with Psoriasis or Psoriatic Arthritis.

| | Switchers/ discontinuers (N = 157) | Continuers (N = 157) | Unadjusted OR/IRRs[†] | Adjusted OR/IRRs[†] |
|---|---|---|---|---|
| **Clinical Response** | | | | |
| Patients with at least one disease flare, N (%) | 135 (86.0%) | 91 (58.0%) | 4.45[*] | 4.20[*] |
| Mild | 97 (61.8%) | 83 (52.9%) | 1.44 | 1.42 |
| Moderate | 83 (52.9%) | 30 (19.1%) | 4.75[*] | 4.63[*] |
| Severe | 32 (20.4%) | 3 (1.9%) | 13.14[*] | 11.81[*] |
| Number of disease flares, mean ± SD | 3.1 ± 8.1 | 1.6 ± 8.0 | 1.90[*] | 1.92[*] |
| Mild | 1.4 ± 3.0 | 0.8 ± 1.7 | 1.71[*] | 1.64[*] |
| Moderate | 1.3 ± 3.7 | 0.6 ± 4.8 | 1.97 | 2.40[*] |
| Severe | 0.4 ± 1.7 | 0.2 ± 1.6 | 2.58 | 3.61 |
| Patients with well-controlled disease, N (%) | 68 (43.3%) | 144 (91.7%) | 0.07[*] | 0.06[*] |
| **Healthcare Utilization** | | | | |
| ≥1 inpatient hospitalization, N (%) | 1 (0.6%) | 0 (0.0%) | - | - |
| Number of hospitalizations per patient, mean ± SD | 0.01 ± 0.08 | 0.00 ± 0.00 | - | - |
| ≥1 emergency department (ED) visit, N (%) | 5 (3.2%) | 0 (0.0%) | - | - |
| Number of visits per patient, mean ± SD | 0.03 ± 0.18 | 0.00 ± 0.00 | - | - |
| ≥1 outpatient visit,[‡] N (%) | 157 (100.0%) | 157 (100.0%) | - | - |
| Number of visits per patient, mean ± SD | 4.47 ± 4.15 | 3.41 ± 2.80 | 1.31[*] | 1.19[*] |

OR = odds ratio. IRR = incidence rate ratio. N = number. SD = standard deviation.

[*] $P < 0.05$

[†] Binary variables were assessed with ORs; counts were assessed with IRRs. ORs were calculated as the ratio of p1/[1-p1] to p2/[1-p2], where p1 and p2 represent the probability of the outcome among the two cohorts, respectively.

[‡] The OR for patients with ≥1 outpatient visit was not calculated because all patients were required to have an outpatient visit during the study period.