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Utilization Trends of Anti-TNF Agents and Health Outcomes in Adults and Children with Inflammatory Bowel Diseases: A Single-center Experience

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Abstract

Background—Utilization trends and health effects of infliximab and adalimumab in inflammatory bowel disease (IBD) are incompletely understood. We aimed to describe utilization trends of these 2 anti-tumor necrosis factor (TNF) agents, determine the correlation between utilization with rates of hospitalization and surgery and describe differences in use between adults and children.

Methods—Longitudinal data were analyzed for drug utilization, hospitalization, and abdominal surgery. Descriptive statistics were used to show trends, and utilization quotients were compared for standardization. Multivariate logistic regression analysis assessed the association between drug use and rates of hospitalization and surgery.

Results—Four hundred thirty-eight pediatric and 2514 adult patients with IBD generated a total of 51,882 inpatient and outpatient encounters, representing 1185 Crohn's disease, 1531 ulcerative colitis, and 236 indeterminate colitis patients. From 2007 through 2012, utilization quotients declined for hospitalization but remained unchanged for surgery; adalimumab saw a 3-fold increase, despite continued dominance of infliximab. Median band and mean fitted plots showed downward hospitalization trends from 2006 to 2012. Utilization of infliximab peaked in 2008, Q4

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with gradual decline to 2012, Q2; and adalimumab showed moderate increased utilization since 2007, Q1. Use of infliximab (odds ratio [OR], 0.76; 95% confidence interval [CI], 0.70–0.83) and adalimumab (OR, 0.79; 95% CI, 0.72–0.87) was associated with decreased hospitalization risk but not associated with reduced abdominal surgery risk. Children had increased hospitalization (OR, 2.68; 95% CI, 2.49–2.88) but decreased risk for abdominal surgery (OR, 0.57; 95% CI, 0.46–0.70).

Conclusions—Current infliximab use remains substantially greater than adalimumab use, despite recent increased use of adalimumab. Although trends for hospitalization for IBD are decreasing, it is not reflected in abdominal surgery rates in a tertiary IBD referral center.

Keywords

biologics; infliximab; adalimumab; Crohn's disease; ulcerative colitis; inflammatory bowel disease

Since 1998, biologic agents (monoclonal antibodies that bind tumor necrosis factor alpha [TNF- α]) represent the newest and potentially the most effective medical therapy among all the immune-suppressive medications for Crohn's disease (CD), ulcerative colitis (UC), and indeterminate colitis (IC). Infliximab has been shown in large clinical trials to be efficacious in induction and maintenance of remission for both CD^{1,2} and UC.³ Adalimumab, launched in the early 2007, has established effectiveness in CD⁴⁻⁶ and more recently in UC.^{7,8} Certolizumab has also been shown to be superior to placebo in clinical trials.^{9,10}

Preliminary data suggest that the increasing use of biologics or anti-TNF agents in inflammatory bowel disease (IBD) correlates with improved health outcomes in hospitalization and surgical rates.^{11,12} However, there is some evidence and renewed discussion that increased use of anti-TNF agents does not always yield reduced morbidity from IBD-related hospitalizations and abdominal surgeries, especially considering the waning long-term durability of biologics' efficacy.¹³⁻¹⁹ Precise utilization trends and long-term health outcomes remain incompletely characterized, especially in pediatric IBD. Furthermore, because there are no head-to-head comparative effectiveness trials between infliximab and adalimumab, it is difficult to assess potential differences between the efficacy profiles of the 2 drugs in maintaining IBD clinical remission.

Based on our center's clinical experience in treating IBD, we hypothesize that overall use of anti-TNF agents is increasing and may correlate with impact on hospitalization and IBD-related abdominal surgery rates for IBD exacerbations. The aims of this study were to: (1) describe recent utilization trends of infliximab and adalimumab, (2) determine the correlation of infliximab and adalimumab use with hospitalization and surgery rates, and (3) describe any differences in drug use between adults and children with IBD.

METHODS

Data Source and Study Population

All data were extracted using the STRIDE Database (Stanford Translational Research Integrated Database). STRIDE consists of 3 integrated components: a clinical data

warehouse, based on the HL7 Reference Information Model,²⁰ containing clinical information on over 1.6 million pediatric and adult patients cared for at Stanford University Medical Center and Lucile Packard Children's Hospital at Stanford, since 1995; an application development framework for building research data with high-fidelity; and a biospecimen data management system,²¹ with oversight by Stanford's Department of Biomedical Informatics. Stanford University Institutional Review Board approved the protocol for this study. Integrity and accuracy of the data capture through STRIDE have been validated and reported.^{22,23}

Using STRIDE, a data query of all de-identified patients with IBD since 1995 was requested to the Stanford Medical Bioinformatics Department. To ensure completeness and optimal transferring of 2 electronic medical records into 1 longitudinal database for both pediatric and adult patients, data were noted to have the highest clarity after 2006, quarter 1 (Q1). (Original hospital financial and drug use data are organized, de-identified, and made available to clinical investigators in fiscal quarters.) Resulting time capture of all patient records of interest from the STRIDE database was from 2006, Q1 to 2012, Q2. A 100% of the data were captured during this inclusion time frame. All patients with any form of IBD (CD, UC, or IC) were included in the final database based on *ICD-9* codes between the range of 555.0 and 556.9.

Because data are captured by patients' electronic medical records and confirmed by Stanford Medical Bioinformatics Department, a "new" patient in this study was defined as any patient who had not previously received IBD subspecialty care by a gastroenterologist at Stanford University Medical Center/Lucile Packard Children's Hospital. Adult patients with a previous history of CD or UC but managed by non-Stanford clinicians within the community were considered new patients at the time when an inpatient or outpatient financial number was assigned to a unique clinical encounter (of note, 1 exception could occur whereby an established patient with IBD at Stanford was lost to follow-up for >12 consecutive months but re-established care with a different Stanford gastroenterologist.).

Assumptions and Outcome Measures

Diagnostic Codes—Based on previously published literature and clinical expertise, inpatient hospitalization from IBD exacerbations and abdominal surgeries were used as primary outcome measures in this study. IBD exacerbations requiring hospitalization had primary or secondary diagnostic IBD codes tracked through professional billing, hospital billing, and patient encounter and problem-list intake sheets at the time of hospitalization. Current Procedural Terminology codes of intra-abdominal surgeries with high correlation to IBD-related complications requiring a surgical intervention were used (43,200–43,273, 45,300–45,392, 44,360–44,397, 46,600–46,615, and 47,550–47,556). Of note, a patient "encounter" is a single patient interaction captured by electronic medical records and correlates with a unique financial index number generated for billing purposes. As such, for example, 1 hospitalization period and 1 clinic visit are each considered a patient encounter.

Utilization Quotients—For the primary outcome measures of hospitalization and IBD-related abdominal surgery, utilization quotients were calculated for standardization based on

quarterly patient volume. A utilization quotient is defined as the sum of all patient encounters associated with the primary outcome variable of interest divided by the sum of all patients with IBD per fiscal quarter. To standardize each drug utilization for comparison, utilization quotients of infliximab and adalimumab were calculated by taking the sum of all patient encounters associated with each drug administration divided by the sum of all patients with IBD per fiscal quarter. For example, all encounters with confirmed outpatient and inpatient infliximab administration in 2007, Q2 among patients with IBD were divided by the sum of all total number of patients with IBD seen in 2007, Q2. Adalimumab utilization was captured by STRIDE, each time a new prescription was written as an outpatient or administered to patients after being ordered during standard inpatient care.

Statistical Analysis

Longitudinal Analysis—All statistical analyses were performed using Stata 12 (StataCorp, College Station, TX). Primary outcome measures in our analysis were: (1) hospitalization, (2) abdominal surgery, (3) infliximab use, and (4) adalimumab use. Descriptive statistics were performed on all 4 primary outcome measures between 2006, Q1 and 2012, Q2. Individual median bands and mean fitted lines were plotted along time to graphically show utilization trends. Mean fitted lines were plotted separately for children younger than 19 years and patients older than 18 years at the time of the clinical encounter to determine differences between pediatric and adult utilization trends. The Student's *t* test was used to determine statistical difference between the slopes of the fitted lines. A *P* value of $< .05$ was considered statistically significant in all cases.

Multivariate Regressions—Multivariate logistic regression models were constructed for the primary outcome measures of hospitalization and abdominal surgery. For both models, clinically relevant parameters were dummy-coded as categorical or ordinal variables and used as explanatory variables to control the model: (1) IBD type (CD, UC, or indeterminate), (2) age, (3) gender, (4) race, (5) insurance status, (6) any treatment with infliximab, and (7) any treatment with adalimumab.

RESULTS

Patient Demographics

Table 1 shows the baseline characteristics of the patients represented in the study between 2006, Q1 and 2012, Q2. Our study included 2952 unique patients with IBD (438 pediatric; 2514 adult patients), representing 1185 patients with CD, 1531 patients with UC, and 236 patients with IC with a mean age of 39.7, 44.3, 37.5 years, respectively, at the time of patient encounter. Total patient encounters were 20,318 for CD, 19,851 for UC, and 11,713 for IC. Approximately equal distribution of men and women were observed for CD and UC. Consistent with racial demographics reported in the existing IBD literature, the majority of our patients were categorized as white (60.8%–70.2%), although there was a substantial proportion of Asian patients (6.2%–8.4%), most likely representing the higher concentration of Asians in northern California compared with the national average in the United States. More than two-thirds of our patients were privately insured at the time of patient encounter. Table 1 shows the proportion of patient encounters associated with procedures (endoscopy

or surgery), hospitalization, and use of therapeutic agents, including anti-TNF agents. Figure, Supplemental Digital Content 1, <http://links.lww.com/IBD/A472> shows the distribution of new versus established patients, as approximated using an upper-bound estimate of the proportion of patients seen once an year or less: 509 (17.2%) patients of the total 2952 were seen once an year or even less frequently.

Utilization Trends

Utilization trends are graphically captured using median band curves and mean fitted lines. Utilization trends are standardized by dividing the number of each health care encounter of interest (i.e., actual inpatient or outpatient drug delivery of infliximab or adalimumab, hospitalization for IBD exacerbations, or IBD-related abdominal surgery) by the number of all-case IBD encounters in a fiscal quarter. Figures 1-3 summarize trends from 2006, Q1 to 2012, Q2 for utilization of infliximab and adalimumab, hospitalization for IBD exacerbations, and abdominal surgery. In each of the 3 figures, time is plotted on the x-axis against the y-axis, showing relative utilization based on total patient encounters.

Infliximab and Adalimumab Utilization—Figure 1 shows that infliximab use peaked in 2008, Q3. After showing increasing use between 2006, Q1 to 2008, Q4, both pediatric and adult infliximab utilization trends showed modest declines by 2012, although pediatric utilization trends show slightly more rapid decline in use ($P < 0.01$, comparing slopes of mean fitted lines). Among pediatric patients, a more gradual rate of increase in infliximab use was evident between 2006, Q1 and 2008, Q4 than in adult patients ($P < 0.01$). Figure 1 shows modest rise in adalimumab use between 2007, Q2 and 2012, Q2 for both pediatric and adult patients with IBD. Pediatric adalimumab use was more rapid than adult use ($P < 0.01$) throughout this time period. Compared with infliximab use, adalimumab use remains as a small contributor to the cumulative use of anti-TNFs in IBD.

Hospitalization Utilization—Figure 2 shows an overall downward trend in hospitalization rates for IBD exacerbations requiring standard inpatient care between 2006, Q1 and 2012, Q2. Both adult and pediatric patients exhibit this clear trend of decreased utilization of hospitalization, although there seems to be a plateauing of the trend after 2009, Q4. Pediatric patients with IBD show a greater rate of decline, as indicated by the steeper slope of the mean fitted line ($P < 0.01$).

Surgery Utilization—Figure 3 shows utilization of IBD-related abdominal surgery, which seems relatively stable between 2006, Q1 and 2012, Q2. Fluctuations were minor over the 7-year period. Mean fitted lines show that there may be a slight increased trend in surgery utilization throughout this period, with pediatric patients showing a greater rate of increasing utilization than adult patients with IBD ($P < 0.01$).

Five-year Comparison Using Utilization Quotients

Since the Food and Drug Administration approval of adalimumab in 2007, Q1 for moderate-to-severe CD in adults, adalimumab utilization trends, and its impact on anti-TNF utilization trends are unknown. In addition to showing trends, we calculated utilization quotients between 2007, Q1 and 2011, Q4 because these 2 fiscal quarters represent different clinical

practices in anti-TNF use. Table 2 shows a comparison of utilization quotients between 2007, Q1 and 2011, Q4—a span of 5 years. Utilization quotients take into consideration changes in the number of available patients for a specific health care intervention (e.g., anti-TNFs). As described, our center has substantially increased the number of patients with IBD since 2007. Utilization quotients are calculated by dividing the sum of all encounters linked to the primary outcome measures of interest (e.g., hospitalization) by the sum of patients with IBD seen in a given fiscal quarter.

Compared with 2007, Q1, adalimumab use in 2011, Q4 increased from 0.01 to 0.03, a 3-fold increase ($P < 0.05$). Despite adalimumab's rise in utilization, overall anti-TNF use in IBD remains to be predominantly driven by infliximab, which recorded an increase from 0.15 in 2007, Q1 to 0.18 in 2011, Q4. Hospitalization rates for IBD exacerbation showed a significant decline from 0.67 in 2007, Q1 to 0.24 in 2011, Q4 ($P < 0.01$). Abdominal surgery rates for IBD complications remained stable at 0.05 and 0.04 for 2007, Q1 and 2011, Q4, respectively.

Multivariate Regression Models

To understand the significance of association between the use of anti-TNFs and rates of hospitalization and abdominal surgery, multivariate logistic regressions were run as previously described.

Risk of Hospitalization—Table 3 summarizes the effect of the predictor variables on hospitalization risk. Prior use of infliximab or adalimumab were both statistically significant in reducing risk of hospitalization, with infliximab reducing odds of hospitalization by 24% (odds ratio [OR], 0.76; 95% confidence interval [CI], 0.70–0.83) and adalimumab by 21% (OR, 0.79; 95% CI, 0.72–0.87) compared with no previous exposure to anti-TNFs. A diagnosis of childhood IBD (age < 19 yr) correlated to nearly 3-fold increased odds of being hospitalized (OR, 2.68; 95% CI, 2.48–2.88). Government-subsidized insurance status (OR, 1.37; 95% CI, 1.28–1.47) was also a significant predictor for increased hospitalization risk. It should be noted that the decrease in hospitalization rates for IBD exacerbations is accompanied by a simultaneous increase in outpatient care visits. Figure, Supplemental Digital Content 2, <http://links.lww.com/IBD/A473> graphically depicts inpatient and outpatient use among adult patients with IBD after the initial presentation at our center. As shown, there is increasing use of outpatient IBD care visits over time relative to initially higher proportion of inpatient events for IBD exacerbation.

Risk of Abdominal Surgery—Table 3 summarizes the effect of the predictor variables on abdominal surgery risk. Neither infliximab (OR, 0.86; 95% CI, 0.69–1.07) nor adalimumab (OR, 1.51; 95% CI, 1.20–1.90) were associated with lower abdominal surgery risk. Children (age < 19 yr) were less likely to undergo surgery (OR, 0.57; 95% CI, 0.46–0.70). Government-subsidized insurance status (OR, 1.60; 95% CI, 1.35–1.89) and UC (OR, 1.79; 95% CI, 1.48–2.18) were associated with higher risk for abdominal surgery.

DISCUSSION

Based on a detailed analysis of nearly 3000 patients with IBD over a 7-year span from a large urban university IBD center, our investigation outlines utilization trends for both infliximab and adalimumab, the 2 most commonly used biologic agents for induction and maintenance of remission in IBD. We also attempt to link hospitalization and abdominal surgery risk with the use of these drugs and characterize the potential differences in pediatric and adult IBD utilization trends.^{16,24}

To summarize the major findings, frequency of infliximab use remains substantially higher than adalimumab use, although adalimumab use is on the rise while infliximab use has tapered since late 2008. Overall hospitalization rates have consistently declined since 2006, although there seems to be a plateauing of this trend since late 2009. The change in hospitalization rates is more pronounced in children than in adults and is also consistent with the increase in outpatient visits seen in our study. Meanwhile, cumulative abdominal surgery rates are static or minimally increasing since 2006 to 2012, with greater changes in pediatric surgery rates. Infliximab and adalimumab are associated with similar protective effects for hospitalization risk, and both anti-TNFs seem to be ineffective in lowering abdominal surgery risk, consistent with other reports raising the question of anti-TNF agents' true effectiveness in reducing IBD-related abdominal surgery risk.^{15-17,25,26} Our results also support the established literature that pediatric IBD has worse disease severity and higher acuity,^{27,28} as highlighted by our result showing nearly a 3-fold increase in odds of hospitalization among children. In terms of the reduced abdominal surgery odds in children, we conjecture that this may be an effect of standard clinical practice in pediatrics because patients' parents may be more risk-averse for choosing surgery as an early viable treatment modality. In explaining higher risk for hospitalization and abdominal surgery if patients did not have private insurance, we theorize that government-subsided insurance status is a tightly correlated surrogate marker for lower socioeconomic status, which is linked to worse overall health in complex chronic disease states.

We admit that the single-center experience in this report is a limitation when attempting to derive generalizations for the U.S. IBD population as a whole. Currently, as a growing IBD referral center for a large geographical area, we show in Figure, Supplemental Digital Content 1, <http://links.lww.com/IBD/A472>, that our overall referrals from the community have been increasing with higher disease acuity. Although beyond the scope of this analysis, potential differences in the native disease severity of newly referred patients versus established patients may contribute to the substantial IBD-related abdominal surgery rates we are reporting, because potentially increasing medical complexity of patients with IBD were not tracked longitudinally in this retrospective analysis. Regardless, understanding the true treatment effect of anti-TNF agents on reducing IBD-related abdominal surgery has been previously highlighted as an outcome measure to explore, since nationally representative data in adults and children have also reported increasing surgery rates and IBD-related complications despite wider use of anti-TNF agents.^{29,30} In our cohort, potentially decreasing surgery trends for established patients as a cohort may be attenuated by an influx of higher risk new referrals for surgery, considering that dynamic changes are possible in gastroenterology and colorectal surgery within our patient catchment area since

2006. Our analysis attempts to account for this potential effect by evaluating outcomes as a standardized ratio (i.e., per total encounter within a fiscal quarter) rather than relying on raw number of events.

Our investigation adds to the growing literature evaluating the economics, utilization, and effectiveness of anti-TNFs in IBD, although firm treatment guidelines with anti-TNFs are not established (e.g., “top-down” versus “step-up”) and research conclusions are not always reproducible.^{12-14,31-34} We believe the unique value of this study is that it offers a quantitative “snapshot” of utilization trends, although single-center, under standard of care models for IBD in a large tertiary academic center. To our knowledge, no study has tried to describe and compare longitudinal utilization trends for both infliximab and adalimumab. Although it is clear that anti-TNFs will be an enduring treatment option for IBD in the foreseeable future, the lack of comparative effectiveness data continue to make informing clinical decisions difficult. Our report is an attempt to build on this important sub-field of IBD clinical research.

Although we attempt to show causality of biologics’ effects on hospitalization and abdominal surgery through controlled multivariate models, the heterogeneity of individual patient data, a wide spectrum of disease severity, and clinical practice differences between health care providers (among Stanford’s 33 gastroenterologists and 12 pediatric gastroenterologists, not including fellows, adjunct staff, nurse practitioners, and physician assistants) make it difficult to isolate the true effect of anti-TNFs on health outcomes. For example, although qualitative data and regression models show hospitalization trends declined with infliximab and adalimumab use, we acknowledge that hospitals’ incentives for achieving cost-efficiency were a driving force for many inpatient services to transition to alternative outpatient services providing higher level of care (e.g., short stay units, infusion units, same-day surgery centers, in-home care networks, etc.). In keeping pace with the national political and economic climate, recent health policy aims and improvements in primary care models have also shortened hospital length of stay overall.³⁵⁻³⁷

Future direction for comparative effectiveness research in IBD would benefit greatly from head-to-head prospective trials of anti-TNFs, measuring the clinical effectiveness based on standard health outcome measures. Understanding precise differences in benefits and risks for various anti-TNFs among pediatric patients is another area lacking evidence. Finally, considering the disproportionately large representation of infliximab in overall utilization of anti-TNFs, a precise cost analysis that considers the indirect costs of the intravenous administration requirement of infliximab will help to generate discussion on the rationale of choosing between individual anti-TNFs based on efficacy profiles, patient preferences (i.e., self-delivered subcutaneous injections versus intravenous route), and total drug and nondrug costs.

In conclusion, the use of anti-TNF agents in IBD is driven by infliximab, although frequency of its use has declined somewhat in recent years with modest rise in adalimumab use. Overall decrements in hospitalization during the previous 7 years may be attributed to increased use of these 2 drugs, despite seemingly unchanged or minimally increasing

abdominal surgery rates during the same time period. Infliximab and adalimumab are associated with reduced hospitalization risk, but not abdominal surgery risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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FIGURE 1.
Utilization trends of infliximab and adalimumab.

FIGURE 2.
Trends in hospitalization from IBD exacerbations.

FIGURE 3.
Trends in abdominal surgery related to IBD.

TABLE 1

Patient Demographics

	CD (%)	UC (%)	IC (%)
No. of encounters	20,318	19,851	11,713
No. of unique patients	1185	1531	236
Gender			
Female	583 (49.2)	760 (49.6)	122 (51.7)
Male	602 (50.8)	769 (50.2)	114 (48.3)
Unreported	0 (0.0)	2 (0.1)	0 (0.0)
Race			
White	791 (66.4)	932 (60.8)	167 (70.2)
Black	48 (4.0)	42 (2.7)	7 (2.9)
Native American	1 (0.1)	5 (0.3)	0 (0.0)
Asian	74 (6.2)	128 (8.3)	20 (8.4)
Pacific Islander	8 (0.7)	8 (0.5)	2 (0.8)
Unreported	269 (22.6)	418 (27.3)	42 (17.6)
Median age, yr			
Initial encounter	39	45	35
Time of study	42	47	39
Insurance coverage			
Private	819 (69.1)	997 (65.0)	172 (71.7)
Government subsidized	120 (10.1)	151 (9.8)	27 (11.3)
Medicare	213 (18.0)	340 (22.2)	41 (17.1)
Unknown	34 (2.9)	46 (3.0)	0 (0.0)
Medications by encounter			
Steroids	2662 (13.1)	4132 (20.8)	1404 (12.0)
Immunomodulators			
Azathioprine	322 (1.6)	283 (1.4)	157 (1.3)
Mercaptopurine	774 (3.8)	738 (3.7)	394 (3.4)
Methotrexate	123 (0.6)	183 (0.9)	110 (0.9)
Biologics			
Infliximab	875 (4.3)	527 (2.7)	885 (7.6)
Adalimumab	412 (2.0)	65 (0.3)	220 (1.9)
Procedures, by encounter			
Endoscopy	791 (3.9)	944 (4.8)	355 (3.0)
Surgery	170 (0.8)	303 (1.5)	90 (0.8)
Hospitalizations	1422 (7.0)	1491 (7.5)	704 (6.0)

TABLE 2

Five-year Point Comparison of Utilization Quotients

	2007, Q1	2011, Q4
Infliximab	0.15	0.18
Sum of encounters	28	162
Sum of patients	183	899
Adalimumab	0.01 ^a	0.03 ^a
Sum of encounters	2	29
Sum of patients	183	899
Hospitalization	0.67 ^b	0.24 ^b
Sum of encounters	122	218
Sum of patients	183	899
Abdominal surgery	0.05	0.04
Sum of encounters	9	37
Sum of patients	183	899

^a $P < 0.05$.^b $P < 0.01$.

TABLE 3**Risk of Hospitalization and Abdominal Surgery**

	ORs (95% CI)
Predictors for hospitalization	
IBD type	
CD	—
UC	1.01 (0.93–1.09)
IC	0.88 (0.80–0.97)
Male gender	0.72 (0.67–0.77)
White race	0.89 (0.87–0.91)
Age < 19 yr	2.68 (2.49–2.88)
Government-subsidized insurance	1.37 (1.28–1.47)
History of any infliximab use	0.76 (0.70–0.83)
History of any adalimumab use	0.79 (0.72–0.87)
Predictors for abdominal surgery	
IBD type	
CD	—
UC	1.79 (1.48–2.18)
IC	0.93 (0.71–1.21)
Male gender	0.77 (0.65–0.91)
White race	0.95 (0.90–0.99)
Age < 19 yr	0.57 (0.46–0.70)
Government-subsidized insurance	1.60 (1.35–1.89)
History of any infliximab use	0.86 (0.69–1.07)
History of any adalimumab use	1.51 (1.20–1.90)