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Comparative Effectiveness of Infliximab and Adalimumab for Crohn's Disease

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	Study concept and design	Acquisition of data	Analysis and interpretation of data	Drafting of the manuscript	Critical revision of the manuscript for important intellectual content	Statistical analysis	Obtained funding
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Haynes K	X		X		X		
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Zhang J	X		X		X		
Bewtra M	X		X		X		
Brensinger C	X		X		X	X	
Chen L	X		X		X	X	
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Abstract

Background & Aims—Antibodies against tumor necrosis factor- α (anti-TNF) are widely used in the treatment of Crohn's disease (CD). This study compared the effectiveness of infliximab and adalimumab, the two most commonly used anti-TNF medications for CD.

Methods—We conducted a retrospective cohort study utilizing United States Medicare data (2006–2010). Patients with CD who were new users of infliximab or adalimumab after January 31, 2007 were included. Patients over age 85 and those with rheumatoid arthritis, psoriasis, psoriatic arthritis, or ankylosing spondylitis were excluded. The primary outcome measures were persistence on therapy at week 26, surgery (including bowel resection, creation of an ostomy, or surgical treatment of a perforation or abscess), and hospitalization for CD. Propensity score adjusted logistic and Cox regression were used to compute adjusted odds ratios (OR) or hazard ratios (HR) and 95% confidence intervals (CI).

Results—The cohort included 1,459 and 871 new users of infliximab and adalimumab, respectively. After 26 weeks, 49% of infliximab-treated patients remained on drug as compared to 47% of those treated with adalimumab (OR 0.98, 95% CI 0.81–1.19). Patients treated with infliximab had a numerically lower incidence of surgery than those treated with adalimumab, but this was not statistically significant (5.5 vs. 6.9 surgeries per 100 person-years, HR 0.79, 95% CI 0.60–1.05). Rates of hospitalization did not differ between the drugs (HR 0.88, 95% CI 0.72–1.07).

Conclusions—We observed similar effectiveness of infliximab and adalimumab for CD across three clinically important outcome measures.

Keywords

tumor necrosis factor-alpha; persistence; surgery; hospitalization

Introduction

Two classes of biological therapies have been approved by the United States (US) Food and Drug Administration for treatment of Crohn's disease (CD). Natalizumab, an antibody against $\alpha 4$ integrins, has had limited use due to safety concerns. In contrast, medications

directed against TNF- α (anti-TNF) are widely used and are considered by many to be the most efficacious therapies for CD.

There are currently three anti-TNF therapies approved for the treatment of CD in the US. In clinical trials, these medications induce clinical remission in 20–40% of patients.^{2–5} However, in the premarketing clinical trials, remission rates at 4 weeks with certolizumab pegol and adalimumab at the currently marketed dose were somewhat lower than that observed in the trials of infliximab at the marketed doses.^{2–5} Furthermore, in a randomized trial of patients who were in remission while taking infliximab, patients who switched to adalimumab were more likely to relapse than those who continued on infliximab.⁶ These data suggest that at currently approved doses, certolizumab pegol and adalimumab may be somewhat less effective than infliximab for induction of remission. However, qualitative and quantitative comparisons between placebo-controlled trials can be biased if the designs are not comparable,⁷ and there are currently no clinical trials that have directly compared new users of these medications. It is also unlikely that such a clinical trial will ever be conducted. Therefore, we conducted this study to directly compare the effectiveness of the available anti-TNF medications that are approved for the treatment of CD.

Methods

Study design

We conducted a retrospective cohort study of new users of anti-TNF therapy for the treatment of CD among patients with Medicare drug benefits. Medicare is a national health care program in the US that provides hospital and medical benefits for adults at least 65 years old and also for individuals with certain disabilities and chronic diseases.⁹ Medicare Parts A and B cover medically necessary services and supplies, while Part D covers pharmacy benefits, including injectables; Medicare Part C (also called Medicare Advantage) is a type of health plan offered by a private company, such as a health maintenance organization, that contracts with Medicare to provide health benefits. In this study, eligible patients were required to have a minimum of 6 consecutive months of Medicare Part A, B, and D and not be enrolled in Medicare Advantage in every person-month immediately prior to initiating anti-TNF therapy. We excluded patients enrolled in Medicare Advantage due to concern for incomplete data. We used medical and pharmacy claims data from January 1, 2006 through December 31, 2010. Because adalimumab was not approved by the FDA for the treatment of CD until February 2007, data from prior to February 1, 2007 were used only for the collection of covariate data.

We identified all patients who newly initiated treatment with infliximab, adalimumab, or certolizumab pegol after January 31, 2007 and who had at least one physician diagnosis for CD in the 12 months prior to starting anti-TNF therapy. To be categorized as a new user, the patient could not have received a dispensing of any of these medications during the 12 months preceding the date of their first anti-TNF prescription in the Medicare data (the index date). If there were less than 12 months of available data prior to the index date (15.8% of overall cohort), we required a minimum of 6 months of available data and that there were no prescriptions for anti-TNF medications prior to the index prescription. We excluded patients who were hospitalized with a diagnosis of inflammatory bowel disease

during the 8 weeks prior to the index date to assure that we did not misclassify the start date of therapy. Patients were also excluded if they were over age 85 on the index date, were diagnosed with other indications for anti-TNF therapy (rheumatoid arthritis, psoriasis, psoriatic arthritis, or ankylosing spondylitis) within the 12 months prior to the index date, received more than one type of anti-TNF therapy on the index date, had more ulcerative colitis diagnoses than CD diagnoses in the available data prior to the index date, or had a diagnosis of ulcerative colitis on or immediately preceding the index date.

Outcome measures

We employed three primary outcome measures: persistence on therapy, hospitalization for CD, and surgery. Persistence on therapy at 26 weeks was used to estimate response to therapy since patients are unlikely to continue these very expensive and potentially harmful therapies if they are not receiving clinical benefit. Persistence was defined as continued use of the medication at week 26, without surgery for CD and without prescriptions for steroids (budesonide, prednisone, or equivalents) during weeks 18–30 following initiation of therapy. We selected this definition as it is the closest definition using administrative data to steroid-free remission that is commonly used in more recent randomized trials for CD.¹⁰ Our primary definition of hospitalization required that CD be the primary discharge diagnosis. Our third outcome was need for surgery, including bowel resection, creation of an ostomy, or surgical treatment of a perforation or abscess. One author (JDL) manually reviewed the administrative claims data for all patients identified as undergoing surgery for CD to identify surgeries that appeared unrelated (such as for diverticulitis). These surgeries were not included in our primary definition of the outcome but were included in a sensitivity analysis. This categorization was made by the reviewer without knowledge of which anti-TNF treatment the patient had received.

Covariates

Covariates were measured using data available either in the 12 months prior to the index date (for baseline demographic information) or 90 days prior to index date (for disease severity- or medication-related variables). See Supplemental Methods for additional details of how covariates were measured and categorized.

Statistical analysis

The statistical analysis compared the effectiveness of infliximab and adalimumab. Because there were only 153 patients treated with certolizumab pegol, this group was not included in the analysis.

Because of the large number of potential covariates relative to the number of patients who required surgery, we combined these covariates into a single propensity score. The propensity score was estimated from a logistic regression model with infliximab relative to adalimumab as the dependent variable. We subsequently excluded patients with propensity scores at the extreme of the distribution such that there was no overlap with the other group. The remaining patients were then stratified by propensity score quintile. Covariate balance between the infliximab and adalimumab groups was assessed by examining the distribution stratified by quintile and by measuring the mean of the standardized difference of the mean

for each propensity score quintile. Values of 0.1 are consistent with minimal differences between the groups.¹²

To compare the effectiveness of infliximab and adalimumab, we used logistic regression for the persistence outcome and Cox regression for hospitalization and surgery, which we analyzed as time-to-event outcomes. Follow-up started on the index date. For the persistence outcome, we restricted the analysis to patients with at least 26 weeks of follow-up after the index date. For Cox regression analyses, follow-up continued until the earliest of the following events: the outcome of interest, initiation of another anti-TNF drug, death, loss of Medicare prescription benefits, or the end of the available data.

Analyses adjusted for the propensity score quintile. We examined additional models including the propensity score plus variables with the greatest degree of imbalance between the two medication groups after stratifying on propensity score. One model included the propensity score, age, sex, and disability status at time of first qualifying for Medicare. Another included the propensity score and an alternative definition of use of immunomodulators (categorized as monotherapy without prior immunomodulator therapy, monotherapy with prior immunomodulator therapy, combination therapy with prior immunomodulator therapy, and new combination therapy). The results of these models were not materially different from the primary models and are therefore not shown.

A number of sensitivity and subgroup analyses were performed. For the persistence outcome, we repeated the analysis allowing for steroids and also extending follow-up to 52 weeks. For the surgery outcome, we repeated the analysis including the patients who were excluded based on manual review. Because the results were nearly identical to the primary analysis, these data are not reported. For the hospitalization outcome, an alternative definition allowed for CD to be a secondary discharge diagnosis if the primary diagnosis were consistent with CD (e.g., abdominal pain). Two additional sensitivity analyses for the outcomes of hospitalization and surgery censored follow-up at day 365 for all patients and 90 days after patients discontinued anti-TNF therapy, respectively. This allowed time for events to occur but did not allow for indefinite follow-up which would be more likely to be influenced by subsequent therapies. Given that Medicare includes a large proportion of elderly patients, in a post hoc analysis we tested for interaction by age (<65 vs. ≥65 years) for the primary analyses. Finally, in order to increase the likelihood that patients were first time users of anti-TNF therapy, we conducted subgroup analyses limited to patients with at least two years of data prior to the first prescription for anti-TNF therapy.

Although the study included a fixed sample size, based on a priori defined minimal clinically important absolute differences of 10% for short-term clinical response, 5% for hospitalization rates, and 2.5% for surgery rates, we projected that approximately 523, 1595, and 1212 new users of each medication with 1 year of follow-up time would be required to achieve 90% power for each outcome, respectively. With longer follow-up, fewer patients would be needed for the same statistical power.

The study was approved by the institutional review boards at the University of Pennsylvania and the University of Alabama at Birmingham.

Results

There were 1,459 new users of infliximab and 871 new users of adalimumab. An additional 20 patients (6 adalimumab and 14 infliximab) were excluded for non-overlapping propensity scores, resulting in 2,310 patients included in the final analysis. The patients had a median of 16 diagnostic codes for CD prior to or on the index date, with <1% having only one diagnostic code. More women than men were included in the study cohorts and most of the patients were white (Table 1). Approximately 47% of patients were treated with oral steroids and 35% with thiopurines or methotrexate in the 90 days prior to index date. Prior to stratifying on propensity score, older patients were more likely to have received infliximab while younger patients were more likely to have received adalimumab. The two groups demonstrated similar characteristics after stratifying on propensity score quintile (Supplemental Table 1).

After 26 weeks of therapy, 49% of patients treated with infliximab remained on drug as compared to 47% of those treated with adalimumab (adjusted OR 0.98, 95% CI 0.81–1.19). Similar results were observed for the alternative definitions of persistence. Using a definition of persistence that allowed for steroid use at week 26 but no surgery, the proportion of patients who were still receiving their index anti-TNF medication at week 26 was 60% and 59% for infliximab and adalimumab, respectively (adjusted OR 0.99, 95% CI 0.81–1.21). Extending follow-up to 52 weeks also showed that the drugs had comparable rates of persistence: 31% vs. 28% (adjusted OR 1.08, 95% CI 0.86–1.37) without steroid use and 50% vs. 49% (adjusted OR 1.04, 95% CI 0.84–1.28) allowing for steroid use.

In the analysis of time to first surgery, median follow-up (and interquartile range) was 1.5 (0.7–2.6) years both for patients treated with infliximab and adalimumab. Patients treated with infliximab had a numerically lower incidence of surgery than those treated with adalimumab, but this did not meet criteria for statistical significance (5.5 vs. 6.9 surgeries per 100 person-years, adjusted HR 0.79, 95% CI 0.60–1.05) (Table 2). Limiting follow-up to the first year attenuated any difference between the drugs in terms of surgery rates (adjusted HR 0.88, 95% CI 0.61–1.27). Likewise, when we censored follow-up 90 days after discontinuation of the index anti-TNF therapy there was no significant difference between rates of surgery (adjusted HR 0.84, 95% CI 0.58–1.23). Results for hospitalization were generally similar to those for persistence and surgery (Table 2).

At baseline, 1,094 patients were taking steroids. We repeated the analysis stratified by baseline steroid exposure. Among patients on steroids at baseline, persistence without surgery or steroids at 26 weeks was 40.0% and 40.1% among users of infliximab and adalimumab, respectively (Table 3). Across all outcomes studied, persistence was better and the likelihood of hospitalization was lower among people not using steroids at baseline. However, there was no evidence of effect modification by steroids, as the adjusted hazard ratios comparing infliximab to adalimumab were nearly identical for all outcomes.

Because our cohort of patients with CD was relatively old, we tested for interaction by age (<65 vs. ≥65 years) for all of the above analyses. We found no evidence of interaction for any of the outcomes except for likelihood of surgery, in which infliximab appeared to be

protective compared to adalimumab in patients under 65 (adjusted OR 0.66, 95% CI 0.47–0.93).

To assess whether our results could have been biased by the definition of new user, we repeated all primary and secondary analyses restricted to 1,047 patients with at least two years of data prior to their first prescription for an anti-TNF agent. None of the adjusted ORs or HRs changed appreciably among this subgroup (Supplemental Table 2).

Discussion

Infliximab and adalimumab are the two most widely used anti-TNF medications for CD. Despite numerous high-quality placebo-controlled trials demonstrating their efficacy, data comparing the effectiveness of the two agents in clinical practice are limited. In this large retrospective cohort study of new users of these medications, there was no significant difference across three different metrics of clinical effectiveness: steroid- and surgery-free persistence on therapy at 26 or 52 weeks, hospitalization for CD, and surgery rates. Together, these data suggest comparable effectiveness of these medications as used in clinical practice.

While this study is one of the first to directly compare the effectiveness of these two therapies for CD, persistence has been compared between biologic agents in several cohorts of patients with rheumatoid arthritis. The results of those studies have been inconsistent, with some demonstrating greater persistence with infliximab, some less persistence with infliximab, and comparable persistence in others.^{18–24} Some of the differences in results could be related to the definition of persistence, such as whether dose escalation is considered as loss of persistence.^{22,25} Since the focus of our study was effectiveness and not cost of anti-TNF therapy, we allowed for dose escalation, as the goal of therapy is to induce and maintain remission regardless of the dose required.

Persistence on therapy can be influenced by effectiveness at improving symptoms, adverse events, and factors that influence adherence. The lower rates of persistence on both drugs at 52 weeks is not surprising, as this reflects what has been observed in clinical trials of these agents in CD.^{10,26,27} In general, the safety profile of infliximab and adalimumab are believed to be similar with a few exceptions. Severe adverse reactions leading to discontinuation of therapy appear to be more common with infliximab than with adalimumab.^{23,24} Recent data also suggest that the risk of serious infection may be slightly higher with infliximab.²⁸ As the focus of this study was effectiveness, we did not compare rates of adverse events between the two therapies. Lastly, many patients choose between infliximab and adalimumab on the basis of convenience of dosing. Prior to this study, it was difficult to know how the combination of these factors may influence the likelihood of discontinuing infliximab relative to adalimumab.

Persistence, even steroid- and surgery-free, as used in our study, is an imperfect measure of effectiveness. Therefore, we also assessed surgery and hospitalization rates. Prevention of the debilitating consequence of surgery is a major goal of therapy for CD.^{30,31} In our study, hospitalization and surgery rates were not significantly different between the two drugs.

Furthermore, these results were robust to a variety of sensitivity analyses. Our results are supported by those of a prior analysis of the short-term (6-month) cost of therapy with these two medications showing similar hospitalization rates despite lower total healthcare costs with adalimumab.³⁵

We selected our study dates to allow for equal availability of adalimumab and infliximab. Additionally, to account for the possibility that users of adalimumab may have previously lost response to infliximab and thus were not new users of anti-TNF therapy, we repeated all primary and secondary analyses restricted to patients with at least two years of data prior to their first prescription for an anti-TNF drug and found similar results.

A limitation of all observational studies is the potential for residual confounding from unmeasured variables. We included a large number of covariates in our propensity score and demonstrated good balance among the treatment groups after stratifying on propensity score. Substantial residual confounding would require a variable that is strongly associated with choice between anti-TNF agents and the outcome of interest, but not highly correlated with any of the other variables in the propensity score. While there could be additional variables associated with the outcomes, such as Montreal classification (which is not reliably captured in Medicare), it is unlikely that the variables would be associated with the choice between infliximab and adalimumab and not be correlated with the many variables included in our propensity score.

Nondifferential misclassification of exposure or outcome data can bias results toward the null, thereby making two therapies appear more comparable. Several factors argue against such bias in this study. The primary exposures of interest were very expensive medications that can only be obtained with a prescription. We limited our study to patients with Part D prescription benefits and excluded those with a hospitalization within 8 weeks of starting therapy so as to capture all prescriptions. We also used three different outcomes, each of which is well captured in Medicare data. Given the similar results across each outcome, it is unlikely that misclassification contributed to the lack of an observed difference between the two drugs.

Our study was conducted among Medicare beneficiaries. Medicare provides hospital and medical benefits for adults at least 65 years old and also for individuals with disability due to health conditions, including CD. Medicare includes approximately 94% of the United States population age 65.³⁶ A substantial proportion of our study population was <65 and received Medicare benefits because of disability. While we were unable to distinguish whether CD was the qualifying disability based on the available claims data, our results did not differ between patients <65 and 65 except for surgery, in which infliximab appeared to be protective compared to adalimumab in patients under 65. We suspect that this age effect likely occurred by chance as there is no biological reason to suspect that infliximab and adalimumab would have differential effects by age. Overall, however, our results appear to be generalizable to the elderly, those with severe disability, and likely the broader population with CD.

Head-to-head clinical trials of anti-TNF therapies are unlikely to ever be undertaken due to the extreme cost to conduct such studies and the financial risk that such trials would entail for the manufacturers. In the absence of such trials, observational comparative effectiveness studies provide the best evidence of the relative effectiveness of these agents. In this large cohort of patients with CD throughout the US, we observed similar effectiveness of infliximab and adalimumab across three clinically important outcome measures. This provides justification for allowing patients' preferences to be a major factor when choosing between these two medications. Ultimately, comparative effectiveness studies such as this allow patients, physicians, and insurers to develop rational treatment strategies and guidelines.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. van der Valk ME, Mangen MJ, Leenders M, et al. Healthcare costs of inflammatory bowel disease have shifted from hospitalisation and surgery towards anti-TNFalpha therapy: results from the COIN study. *Gut*. 2012
2. Sandborn WJ, Feagan BG, Stoinov S, et al. Certolizumab pegol for the treatment of Crohn's disease [see comment]. *New England Journal of Medicine*. 2007; 357:228–38. [PubMed: 17634458]
3. Kozuch PL, Hanauer SB, Kozuch PL, et al. Treatment of inflammatory bowel disease: a review of medical therapy. *World Journal of Gastroenterology*. 2008; 14:354–77. [PubMed: 18200659]
4. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis.[see comment][erratum appears in *N Engl J Med*. 2006 May 18;354(20):2200]. *New England Journal of Medicine*. 2005; 353:2462–76. [PubMed: 16339095]
5. Peyrin-Biroulet L, Deltenre P, de Suray N, et al. Efficacy and Safety of Tumor Necrosis Factor Antagonists in Crohn's Disease: Meta-Analysis of Placebo-Controlled Trials. *Clinical Gastroenterology and Hepatology*. 2008; 6:644–653. [PubMed: 18550004]
6. Van Assche G, Vermeire S, Ballet V, et al. Switch to adalimumab in patients with Crohn's disease controlled by maintenance infliximab: prospective randomised SWITCH trial. *Gut*. 2012; 61:229–34. [PubMed: 21948942]
7. Song F, Altman DG, Glenny AM, et al. Validity of indirect comparison for estimating efficacy of competing interventions: empirical evidence from published meta-analyses. *BMJ*. 2003; 326:472. [PubMed: 12609941]
8. Lewis JD. Anti-TNF antibodies for Crohn's disease--in pursuit of the perfect clinical trial [see comment][comment]. *New England Journal of Medicine*. 2007; 357:296–8. [PubMed: 17634466]
9. [Accessed April 2013] www.medicare.gov
10. Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. *New England Journal of Medicine*. 2010; 362:1383–95. [PubMed: 20393175]
11. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol*. 1992; 45:613–9. [PubMed: 1607900]
12. Mamdani M, Sykora K, Li P, et al. Reader's guide to critical appraisal of cohort studies: 2. Assessing potential for confounding *Bmj*. 2005; 330:960–2.

13. St Clair EW, Wagner CL, Fasanmade AA, et al. The relationship of serum infliximab concentrations to clinical improvement in rheumatoid arthritis: results from ATTRACT, a multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis and Rheumatism*. 2002; 46:1451–9. [PubMed: 12115174]
14. Vermeire S, Noman M, Van Assche G, et al. Effectiveness of concomitant immunosuppressive therapy in suppressing the formation of antibodies to infliximab in Crohn's disease [see comment]. *Gut*. 2007; 56:1226–31. [PubMed: 17229796]
15. Baert F, Noman M, Vermeire S, et al. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease [see comment]. *New England Journal of Medicine*. 2003; 348:601–8. [PubMed: 12584368]
16. Maser EA, Vilella R, Silverberg MS, et al. Association of trough serum infliximab to clinical outcome after scheduled maintenance treatment for Crohn's disease. *Clin Gastroenterol Hepatol*. 2006; 4:1248–54. [PubMed: 16931170]
17. Karmiris K, Paintaud G, Noman M, et al. Influence of trough serum levels and immunogenicity on long-term outcome of adalimumab therapy in Crohn's disease. *Gastroenterology*. 2009; 137:1628–40. [PubMed: 19664627]
18. Hyrich KL, Lunt M, Watson KD, et al. Outcomes after switching from one anti-tumor necrosis factor alpha agent to a second anti-tumor necrosis factor alpha agent in patients with rheumatoid arthritis: results from a large UK national cohort study. *Arthritis and Rheumatism*. 2007; 56:13–20. [PubMed: 17195186]
19. Zink A, Listing J, Kary S, et al. Treatment continuation in patients receiving biological agents or conventional DMARD therapy. *Annals of the Rheumatic Diseases*. 2005; 64:1274–9. [PubMed: 15708884]
20. Tang B, Rahman M, Waters HC, et al. Treatment persistence with adalimumab, etanercept, or infliximab in combination with methotrexate and the effects on health care costs in patients with rheumatoid arthritis. *Clinical Therapeutics*. 2008; 30:1375–84. [PubMed: 18691998]
21. Markenson JA, Gibofsky A, Palmer WR, et al. Persistence with anti-tumor necrosis factor therapies in patients with rheumatoid arthritis: observations from the RADIUS registry. *Journal of Rheumatology*. 2011; 38:1273–81. [PubMed: 21572150]
22. Greenberg JD, Reed G, Decktor D, et al. A comparative effectiveness study of adalimumab, etanercept and infliximab in biologically naive and switched rheumatoid arthritis patients: results from the US CORRONA registry. *Annals of the Rheumatic Diseases*. 2012; 71:1134–1142. [PubMed: 22294625]
23. Du Pan SM, Dehler S, Ciurea A, et al. Comparison of drug retention rates and causes of drug discontinuation between anti-tumor necrosis factor agents in rheumatoid arthritis. *Arthritis Rheum*. 2009; 61:560–8. [PubMed: 19405000]
24. Hetland ML, Christensen IJ, Tarp U, et al. Direct comparison of treatment responses, remission rates, and drug adherence in patients with rheumatoid arthritis treated with adalimumab, etanercept, or infliximab: results from eight years of surveillance of clinical practice in the nationwide Danish DANBIO registry. *Arthritis Rheum*. 2010; 62:22–32. [PubMed: 20039405]
25. Blum MA, Koo D, Doshi JA. Measurement and rates of persistence with and adherence to biologics for rheumatoid arthritis: a systematic review. *Clinical Therapeutics*. 2011; 33:901–13. [PubMed: 21715007]
26. Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet*. 2002; 359:1541–9. [PubMed: 12047962]
27. Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease. *Gastroenterology*. 2007; 132:52–65. [PubMed: 17241859]
28. Grijalva CG, Chen L, Delzell E, et al. Initiation of tumor necrosis factor-alpha antagonists and the risk of hospitalization for infection in patients with autoimmune diseases. *JAMA*. 2011; 306:2331–9. [PubMed: 22056398]
29. Peake ST, Landy J, Hussein M, et al. Patient preference in choosing biological therapy in Crohn's disease. *Inflamm Bowel Dis*. 2011; 17:E79. [PubMed: 21538722]

30. Hommes D, Colombel JF, Emery P, et al. Changing Crohn's disease management: need for new goals and indices to prevent disability and improve quality of life. *J Crohns Colitis*. 2012; 6 (Suppl 2):S224–34. [PubMed: 22463929]
31. Hanauer SB, Kirsner JB. Treat the patient or treat the disease? *Dig Dis*. 2012; 30:400–3. [PubMed: 22796805]
32. Feagan BG, Vreeland MG, Larson LR, et al. Annual cost of care for Crohn's disease: a payor perspective. *Am J Gastroenterol*. 2000; 95:1955–60. [PubMed: 10950042]
33. Feagan BG, Panaccione R, Sandborn WJ, et al. Effects of adalimumab therapy on incidence of hospitalization and surgery in Crohn's disease: results from the CHARM study. *Gastroenterology*. 2008; 135:1493–9. [PubMed: 18848553]
34. Lichtenstein GR, Yan S, Bala M, et al. Infliximab maintenance treatment reduces hospitalizations, surgeries, and procedures in fistulizing Crohn's disease. *Gastroenterology*. 2005; 128:862–9. [PubMed: 15825070]
35. Sussman DA, Kubiun N, Mulani PM, et al. Comparison of medical costs among patients using adalimumab and infliximab: a retrospective study (COMPAIRS). *Inflamm Bowel Dis*. 2012; 18:2043–55. [PubMed: 22241679]
36. Health Care Financing Administration. Data User Reference Guide (DURG). Baltimore, MD: Health Care Financing Administration; 2000.

Table 1

Characteristics of the study cohort

Characteristic	Infliximab (n=1,445)	Adalimumab (n=865)	Mean of Standardized Mean Difference Across Propensity Score Quintiles
Age			
20–29	71 (4.9%)	64 (7.4%)	0.11
30–39	187 (12.9%)	168 (19.4%)	0.07
40–49	218 (15.1%)	214 (24.7%)	0.03
50–59	229 (15.8%)	140 (16.2%)	0.12
60–69 with disability	144 (10.0%)	78 (9.0%)	0.07
60–69 without disability	247 (17.1%)	81 (9.4%)	0.10
70+ with disability	27 (1.9%)	14 (1.6%)	0.06
70+ without disability	322 (22.3%)	106 (12.3%)	0.09
Female sex	892 (61.7%)	558 (64.5%)	0.11
Race			
White	1,255 (86.9%)	745 (86.1%)	0.11
Black	141 (9.8%)	90 (10.4%)	0.09
Other	49 (3.4%)	30 (3.5%)	0.05
Medicaid eligible	639 (44.2%)	532 (61.5%)	0.06
Skilled nursing facility	56 (3.9%)	32 (3.7%)	0.04
Emergency department visit	170 (11.8%)	96 (11.1%)	0.06
Bowel resection	12 (0.8%)	4 (0.5%)	0.02
Perianal disease	184 (12.7%)	101 (11.7%)	0.08
CT scan	326 (22.6%)	180 (20.8%)	0.08
MRI	21 (1.5%)	15 (1.7%)	0.12
Colonoscopy or sigmoidoscopy	490 (33.9%)	236 (27.3%)	0.04
Upper endoscopy	134 (9.3%)	89 (10.3%)	0.09
Endoscopic dilation	10 (0.7%)	10 (1.2%)	0.07
Small bowel follow-through exam	142 (9.8%)	64 (7.4%)	0.10
Small bowel obstruction	79 (5.5%)	41 (4.7%)	0.06
Narcotics	609 (42.1%)	478 (55.3%)	0.07
Oral steroids			
None	759 (52.5%)	457 (52.8%)	0.06
New steroids within 28 days prior	126 (8.7%)	76 (8.8%)	0.05
Steroids within 90 days prior	560 (38.8%)	332 (38.4%)	0.07
Oral mesalamine	471 (32.6%)	261 (30.2%)	0.10
Rectal mesalamine	51 (3.5%)	23 (2.7%)	0.10
Rectal steroids	39 (2.7%)	17 (2.0%)	0.06
Thiopurine or methotrexate			
None	948 (65.6%)	563 (65.1%)	0.13
New combination therapy	51 (3.5%)	29 (3.4%)	0.07
Prior thiopurines or methotrexate	446 (30.9%)	273 (31.6%)	0.11
Number of medications not related to CD			

Characteristic	Infliximab (n=1,445)	Adalimumab (n=865)	Mean of Standardized Mean Difference Across Propensity Score Quintiles
0	275 (19.0%)	160 (18.5%)	0.04
1	334 (23.1%)	183 (21.2%)	0.06
2	296 (20.5%)	183 (21.2%)	0.06
3	211 (14.6%)	133 (15.4%)	0.10
4 or more	329 (22.8%)	206 (23.8%)	0.07

Data are presented as number of patients (and percent of the total) for each medication before stratification into propensity score quintiles. The mean of the standardized mean difference provides a measure of balance between the groups after stratification into propensity score quintiles.

Table 2

Comparison of cumulative incidence of hospitalization and surgery

	IFX (n=1,445)	ADA (n=865)	Unadjusted HR (95% CI)	Adjusted HR [†] (95% CI)
Surgery	122 (5.5)	91 (6.9)	0.81 (0.61–1.06)	0.79 (0.60–1.05)
In first year of follow-up	79 (6.9)	52 (7.6)	0.92 (0.65–1.31)	0.88 (0.61–1.27)
Censoring follow-up 90 days after discontinuation of therapy	77 (5.8)	47 (7.0)	0.87 (0.61–1.25)	0.84 (0.58–1.23)
Hospitalization with CD as primary diagnosis	245 (11.8)	185 (15.4)	0.78 (0.65–0.95)	0.88 (0.72–1.07)
In first year of follow-up	165 (8.0)	117 (9.7)	0.85 (0.67–1.07)	0.95 (0.74–1.22)
Censoring follow-up 90 days after discontinuation of therapy	163 (12.8)	101 (16.0)	0.86 (0.67–1.10)	0.96 (0.74–1.25)
Hospitalization with CD as primary or secondary diagnosis	369 (19.5)	263 (24.0)	0.83 (0.71–0.98)	0.90 (0.77–1.07)
In first year of follow-up	284 (27.7)	178 (29.1)	0.96 (0.80–1.16)	1.05 (0.87–1.28)
Censoring follow-up 90 days after discontinuation of therapy	283 (23.5)	165 (27.8)	0.92 (0.76–1.12)	1.00 (0.81–1.22)

IFX – infliximab; ADA – adalimumab; Data presented as number of patients experiencing the outcome and annual rate per 100 person-years

Hazard ratios compare infliximab users to a reference group of adalimumab users

[†] Adjusted for propensity score quintile

Table 3

Clinical outcomes according to baseline steroid exposure*

	IFX	ADA	Unadjusted OR/HR (95% CI)	Adjusted [†] OR/HR (95% CI)
Persistence				
Steroids (n=911)	227 (40.0%)	138 (40.1%)	1.00 (0.76–1.31)	0.86 (0.64–1.11)
No steroids (n=993)	353 (56.0%)	195 (53.7%)	1.10 (0.85–1.42)	1.10 (0.84–1.44)
Surgery				
Steroids (n=1,094)	59 (5.6)	47 (7.2)	0.78 (0.53–1.15)	0.77 (0.51–1.14)
No steroids (n=1,216)	63 (5.3)	44 (6.5)	0.83 (0.56–1.22)	0.82 (0.55–1.23)
Hospitalization with CD as primary diagnosis				
Steroids (n=1,094)	126 (13.1)	100 (17.3)	0.77 (0.59–1.00)	0.86 (0.65–1.12)
No steroids (n=1,216)	119 (10.7)	85 (13.5)	0.80 (0.61–1.06)	0.90 (0.67–1.20)
Hospitalization with CD as primary or secondary diagnosis				
Steroids (n=1,094)	179 (20.3)	140 (27.4)	0.77 (0.61–0.95)	0.82 (0.65–1.04)
No steroids (n=1,216)	190 (18.7)	123 (21.0)	0.91 (0.73–1.15)	1.00 (0.78–1.26)

IFX – infliximab; ADA – adalimumab; Data presented as number of patients experiencing the outcome and percent of patients for persistence and annual rate per 100 person-years for other outcomes

Odds ratios for persistence and hazard ratios for hospitalization and surgery compare infliximab users to a reference group of adalimumab users

* Steroid use defined as filling at least 1 prescription for an oral steroid (including budesonide) within the 90 days prior to starting anti-TNF therapy

[†] Adjusted for propensity score quintile