Comparative Effectiveness of Infliximab and Adalimumab for Crohn's Disease

Mark T. Osterman,[*] Kevin Haynes,[‡,§] Elizabeth Delzell,[‖] Jie Zhang,[‖] Meenakshi Bewtra,[*,‡,¶] Colleen Brensinger,[‡] Lang Chen,[#] Fenlong Xie,[#] Jeffrey R. Curtis,[‖,¶] and James D. Lewis[*,‡,§,¶]

[*]Department of Medicine, [‡]Center for Clinical Epidemiology and Biostatistics, [§]Center for Pharmacoepidemiology Research and Teaching, and [¶]Department of Biostatistics and Epidemiology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania; [‖]Department of Epidemiology, University of Alabama at Birmingham School of Public Health, Birmingham, Alabama; and [#]Division of Clinical Immunology and Rheumatology, University of Alabama at Birmingham, Birmingham, Alabama

BACKGROUND & AIMS: **Antibodies against tumor necrosis factor-α are widely used to treat patients with Crohn's disease (CD). This study compared the effectiveness of infliximab and adalimumab, the 2 most commonly used anti–tumor necrosis factor agents, in patients with CD.**

METHODS: **We conducted a retrospective cohort study by using U.S. Medicare data from 2006 through 2010. Patients with CD who were new users of infliximab (n = 1459) or adalimumab (n = 871) after January 31, 2007, were included. Patients older than age 85 and those with rheumatoid arthritis, psoriasis, psoriatic arthritis, or ankylosing spondylitis were excluded. The primary outcome measures were disease 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 hazard ratios and 95% confidence intervals (CIs).**

RESULTS: **After 26 weeks of treatment, 49% of patients receiving infliximab remained on drug, compared with 47% of those receiving adalimumab (odds ratio, 0.98; 95% CI, 0.81–1.19). Fewer patients treated with infliximab underwent surgery than those treated with adalimumab, but this difference was not statistically significant (5.5 vs 6.9 surgeries per 100 person-years; hazard ratio, 0.79; 95% CI, 0.60–1.05). Rates of hospitalization did not differ between groups (hazard ratio, 0.88; 95% CI, 0.72–1.07).**

CONCLUSIONS: **We observed similar effectiveness of infliximab and adalimumab for CD on the basis of 3 clinically important outcome measures.**

Keywords: Tumor Necrosis Factor-α; Persistence; Surgery; Hospitalization.

Two classes of biological therapies have been approved by the United States Food and Drug Administration for treatment of Crohn's disease (CD). Natalizumab, an antibody against α4 integrins, has had limited use because of safety concerns. In contrast, medications directed against tumor necrosis factor (TNF)-α (anti-TNF) are widely used and are considered by many to be the most efficacious therapies for CD.

There are currently 3 anti-TNF therapies approved for the treatment of CD in the United States. In clinical trials, these medications induce clinical remission in 20%–40% of patients.[1–4] 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 those observed in the trials of infliximab at the marketed doses.[1–4] 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.[5] 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,[6] and currently there are no clinical trials that have directly compared new users of these

Abbreviations used in this paper: CD, Crohn's disease; CI, confidence interval; HR, hazard ratio; OR, odds ratio; TNF, tumor necrosis factor.

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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 United States that provides hospital and medical benefits for adults who are at least 65 years old and also for individuals with certain disabilities and chronic diseases.[7] Medicare Parts A and B cover medically necessary services and supplies, and 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 Parts A, B, and D and not be enrolled in Medicare Advantage in every person-month immediately before initiating anti-TNF therapy. We excluded patients enrolled in Medicare Advantage because of concern about incomplete data. We used medical and pharmacy claims data from January 1, 2006 through December 31, 2010. Because adalimumab was not approved by the Food and Drug Administration for the treatment of CD until February 2007, data from before 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 before 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 before 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 before the index prescription. We excluded patients who were hospitalized with a diagnosis of inflammatory bowel disease during the 8 weeks before the index date to ensure that we did not misclassify the start date of therapy. Patients were also excluded if they were older than 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 before 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 before the index date, or had a diagnosis of ulcerative colitis on or immediately preceding the index date.

Outcome Measures

We used 3 primary outcome measures: persistence on therapy, hospitalization for CD, and surgery. Persistence on therapy at 26 weeks was used to estimate response to therapy because 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 after initiation of therapy. We selected this definition because it is the closest definition that uses administrative data to steroid-free remission that is commonly used in more recent randomized trials for CD.[8] 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 (J.D.L.) 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 by using data available either in the 12 months before the index date (for baseline demographic information) or 90 days before index date (for disease severity–related or medication-related variables). Supplementary Methods section provides 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