Real-World Anti-TNF Dose Escalation in Patients With Crohn’s Disease

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Crohn’s disease is a chronic, progressive, and disabling disease that requires long-term management. It affects approximately 244 per 100,000 people in the United States and may be characterized by progressive structural damage and/or by episodes of acute inflammation of the gut alternating with periods of remission.

Patients with Crohn’s disease consume substantial healthcare resources. From 2003 to 2004, the mean number of annual excess healthcare utilization (control visits minus Crohn’s disease case visits) per 100 patients was estimated to be 21.7, 20.1, and 493 for hospitalizations, emergency department visits, and office visits, respectively. In the United States, the mean total costs for patients with Crohn’s disease are estimated at $10,952 per year, compared with $2898 for matched controls (i.e., individuals with no inflammatory bowel disease, matched for age, sex, health plan, and geographic region). The mean annual Crohn’s disease associated treatment costs were $8265 per patient-year, with pharmaceutical claims accounting for the largest proportion of direct costs (35%).

Due to the high cost of Crohn’s disease, treatment goals with therapy are to modify the course of the disease and prevent long-term complications. Tumor necrosis factor-α (TNFα), a pro-inflammatory cytokine, is expressed in high levels in the blood, intestinal mucosa, colonic tissue, and feces of patients with Crohn’s disease, and may play an integral role in the pathogenesis of Crohn’s disease. As such, anti-TNFα therapies are widely used in the management of moderate to severe Crohn’s disease that is refractory to such conventional treatments as corticosteroids and oral immunosuppressants.

There are 3 anti-TNFα agents—adalimumab, certolizumab pegol, and infliximab—currently approved by the FDA in the United States for use in patients with moderate to severe Crohn’s disease, for whom conventional therapy has not achieved a satisfactory clinical response. However, disease relapse with all anti-TNFα agents is common: up to 40% of patients who initially respond to anti-TNFα therapy may lose response in the first year of treatment. In patients who lose...
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- Rates of anti-TNFα dose escalation differ in patients with Crohn’s disease who were newly prescribed adalimumab, certolizumab pegol, or infliximab.
- We note the proportion of patients who received the labeled loading dose, and the occurrence of inadequate loading doses.
- Comparisons show that certolizumab pegol therapy in patients with Crohn’s disease is associated with lower rates of dose escalation relative to infliximab or adalimumab.

PRACTICAL IMPLICATIONS

Disease relapse occurs in up to 40% of patients with Crohn’s disease who initially respond to anti-tumor necrosis factor-α (TNFα) agents, which has important clinical, cost, and resource utilization implications. This study describes data from 2 health claims databases.

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response to firstline therapy with the anti-TNFα agents, the dose and/or dosing frequency are often increased to recapture response12,15-17; alternatively, clinicians may choose to switch treatments or add concomitant medications rather than increase doses or frequency. Previous analyses of health claims databases have shown that anti-TNFα dose escalation occurs in approximately 24%, 2%, and 28% of patients with Crohn’s disease receiving adalimumab, certolizumab pegol, and infliximab, respectively.18,19 (Note that the statistics for loss of response to treatment and for dose escalation were 2 different measurements; physicians may or may not decide that dose escalation is the proper course of action when a patient loses response.)

The FDA-approved loading dose for adalimumab is 160 mg administered by subcutaneous injection (given as 40 mg injections 4 times in 1 day, or 40 mg injections twice a day for 2 consecutive days), with a second 80 mg dose 2 weeks later. Following clinical response, 2 weeks after the 80 mg dose, adalimumab is administered at a maintenance dose of 40 mg every other week.20 Certolizumab pegol is also administered by subcutaneous injection, an initial dose of 400 mg every 2 weeks for 3 doses (at weeks 0, 2, and 4). If a clinical response occurs, certolizumab pegol is then given at a maintenance dose of 400 mg subcutaneously every 4 weeks.21 (Dose increase is not FDA-approved for either certolizumab pegol or adalimumab.) Infliximab is administered by intravenous infusion at a dose of 5 mg/kg at 0, 2, and 6 weeks, followed by a maintenance regimen of 5 mg/kg every 8 weeks.22 Some adult patients who initially respond to infliximab treatment may benefit from increasing the dose to 10 mg/kg if they later lose their response.

For the present study, we evaluated rates of anti-TNFα dose escalation in patients with Crohn’s disease who were newly prescribed adalimumab, certolizumab pegol, or infliximab, as well as the proportion of patients who received the labeled loading dose, using data from 2 health claims databases.

METHODS

Data Sources

Anonymous patient data from the United States were obtained from 2 sources:

OptumInsight’s Clinformatics Data Mart. This is a single-payer health claims database from a large national health insurer that covers approximately 32 million lives. Patients who were 18 years or older with a diagnosis of Crohn’s disease (International Classification of Diseases, Ninth Revision, Clinical Modification code 555.xx), were naïve to therapy with an anti-TNFα in the 6-month pre-index period, received a prescription for an anti-TNFα (ie, adalimumab, certolizumab pegol, or infliximab) after April 2008, and had continuous enrollment in the database and pharmacy data available for 12 months after the index date, were eligible. The qualifying time period for initiating the drug of interest was January 2009 to May 2011. Eligible patients also had no diagnosis of ulcerative colitis, psoriasis, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, celiac disease, irritable bowel syndrome, or Clostridium difficile infection during the 6 months prior to the index date, and had both medical and prescription coverage. OptumInsight data were used in the analysis of dose escalation and to determine the proportion of patients who received an appropriate loading dose of each anti-TNFα.

Truven Health Analytics MarketScan Research Databases. A retrospective claims analysis was conducted in 2011 by Truven Health Analytics Inc using the Truven Health MarketScan Research Databases, an administrative claims database that is fully compliant with the Health Insurance Portability and Accountability Act, and includes more than 150 contributing employers and 21 health plans throughout the United States. The database includes approximately 37 million covered lives per year, and health insurance claims across the continuum of care (eg, inpatient and outpatient, and mail order and outpatient pharmacy). Adult patients (aged ≥18 years) were eligible if they had a diagnosis of Crohn’s disease and were naïve to therapy with both an anti-TNFα in the 6-month pre-index period and received a new prescription for an anti-TNFα agent (ie, adalimumab, certolizumab pegol, or infliximab) after January 2008. The qualifying time period for initiating the drug of interest was January 2008 to October 2011. For inclusion, patients must have had at least 1 prescription on or after day 29 for adalimumab or day 56 for certolizumab pegol, while infliximab patients must have had at least 2 infusions. Infliximab-treated patients with doses that did not fall between 180 mg and 1360 mg, or who did not have a valid payment field (ie, it was missing or negative) at infusion 1, infusion 2, and all subsequent infusions, were excluded.
Both databases were used in the analysis of dose escalation and to determine the proportion of patients who received an appropriate loading dose of each anti-TNFα.

**Outcome Variable and Analyses**

**Loading dose.** OptumInsight defined the proper loading dose for adalimumab and certolizumab pegol as ≥240 mg and ≥1200 mg, respectively, within the first 35 days. Infliximab was administered by 3 or more intravenous infusions within the first 60 days (and no previous infliximab during the previous 12 months). For the Truven Health databases, the loading dose for adalimumab and certolizumab pegol (assessed on prescription drug claims) was based on the presence of the appropriate amount of product during the induction phase; for infliximab, the loading dose was based on the initial dose, and was deemed as a “proper” loading dose if it was within the dosing parameters.

**Dose escalation.** OptumInsight analyzed US patient claims and reported the number of patients with a dose increase above the approved and initially prescribed maintenance dose of adalimumab, certolizumab pegol, or infliximab as a first treatment change at any point during the 12-month analysis period. Dose escalation was defined as the following: adalimumab, an increase above an average of 40 mg every 2 weeks; certolizumab pegol, an increase above an average of 400 mg every 4 weeks; and infliximab, any increase in the number of vials per week above that initially dispensed during the maintenance phase of dosing. The time to dose escalation was the average number of days until dose increase for all eligible patients.

Truven Health analyzed dose escalation for adalimumab, certolizumab pegol, or infliximab during 12 months of follow-up. Dose escalation was defined as the following: adalimumab, ≥160 mg every 4 weeks; certolizumab pegol, ≥800 mg every 4 weeks; infliximab, any infusion greater than the first infusion or 6 weeks or less between 2 infusions beginning with infusion number 4.

**Statistical Analysis**

For OptumInsight data, the mean time on therapy of dose-escalated patients was based on their actual claim-level activity. For the Truven analysis, univariate analyses were performed (χ² for categorical outcome variables and t test for continuous outcome variables).

**RESULTS**

**Patients**

The patient demographics from both databases are shown in the Table. In the OptumInsight database, 1463 patients met the criteria for inclusion and had 12 months of available data. Of these eligible patients, 44% (n = 650) were newly initiated to adalimumab, 18% (n = 257) to certolizumab pegol, and 38% (n = 556) to infliximab.

In the Truven Health databases, 1023 patients were eligible for inclusion: 379 (37%) were newly initiated to adalimumab, 361 (35%) to certolizumab pegol, and 283 (28%) to infliximab.

**Loading Dose**

The proportion of patients who received a loading dose of each anti-TNFα agent (range = 47%-85%) is shown in Figure 1. Similar results were seen in both databases. The proportion of adalimumab patients receiving a loading dose was 80% (OptumInsight) and 86% (Truven Health) (P < .0001 vs certolizumab pegol). This number decreased in the certolizumab groups to 62% and 74%, respectively. For infliximab, only approximately 50% of patients received a loading dose (P < .001 vs certolizumab pegol).

**Dose Escalation**

From the OptumInsight database analyses, 9% (n = 59), 5% (n = 13), and 28% (n = 156) of patients who initiated...
treatment on adalimumab, certolizumab pegol, or infliximab, respectively, had an increase from their initial maintenance dose as a first treatment change over 12 months (Figure 2[A]). Similar results were obtained from dose escalation analyses on the Truven Health databases (Figure 2[A]): 16% (n = 58; \( P = .0055 \) vs certolizumab pegol), 9% (n = 29), and 28% (n = 70; \( P < .0001 \) vs certolizumab pegol) of patients receiving adalimumab, certolizumab pegol, or infliximab, respectively, dose-escalated over 12 months. Significantly more patients receiving infliximab had a dose increase compared with certolizumab pegol (\( P < .0001 \) in both databases). It is worth noting that some patients who lose response will undergo treatment switching or other adjustments rather than dose escalation.

The mean length of time to dose escalation, as a first treatment change over 12 months in the OptumInsight and Truven Health databases, was 163 and 132 days (\( P = .02 \) vs certolizumab pegol), respectively, for adalimumab, 197 and 190 days for certolizumab pegol, and 178 and 179 days (\( P = .58 \) vs certolizumab pegol) for infliximab (Figure 2[B]).

**DISCUSSION**

When comparing rates of dose escalation between anti-TNFα agents from 2 data sources, fewer patients prescribed certolizumab pegol for the treatment of Crohn’s disease had a detectable dose increase as a first treatment change within the 12-month period, compared with adalimumab or with infliximab (\( P < .0001 \)). Most patients in the adalimumab and certolizumab pegol groups received the labeled loading dose, while only half of patients in the infliximab group received the appropriate loading dose of therapy.

Dose escalation, in terms of actual administered dose or an increase in dosing frequency, can be in response to a disease flare or attenuation and loss of response to therapy. In the present study, dose escalation ranged from 5% to 28%, depending on the data and analysis type and medication administered. These claims data consistently showed a lower rate of dose escalation for certolizumab pegol patients at 5% and 8%, inclusive of varying escalation definitions. Additionally, rates of dose escalation may be impacted by a lack of flexibility in dosing recommendations or denial of insurance coverage; however, physician-determined need for maximizing therapeutic response prior to treatment changes is an accepted treatment paradigm among most gastroenterologists, and previous studies of patients with Crohn’s disease receiving biologic therapy have found that dose escalation is common. As this issue has significant clinical and cost implications,23,24 prospective studies are needed to further investigate the extent of the impact of this issue.

In this study, the mean length of time to dose escalation among patients prescribed adalimumab, certolizumab pegol, or infliximab over 12 months was also different between anti-TNFαs. Overall, there were differences in duration of therapy before dose escalation. The mean length of time to dose escalation as a first treatment change over 12 months for patients receiving adalimumab, certolizumab pegol, and infliximab, ranged from 129 to 163, 190 to 197, and 178 to 180 days, respectively. These results may suggest that patients receiving infliximab and certolizumab pegol had a longer duration of efficacy before dose escalation was required, although it is also possible that the aforementioned unavailability of flexible dosing or denial of coverage from the insurance carrier may have influenced this outcome.

An additional aspect to consider as a potential factor in both rate and time to dose escalation in patients with Crohn’s disease is the proper medication utilization. All 3 agents approved for treating patients with Crohn’s disease include use of a loading dose prior to maintenance therapy. In a retrospective claims study of certolizumab pegol, patients receiving initiation of therapy with a loading dose showed increased persistence versus those who did not.25 Loading dose is also associated with improved rates of clinical remission in controlled clinical trials.26 Thus, presence or absence
of a loading dose in patients with Crohn’s disease potentially impacts overall maintenance of disease. In this study, the use of the labeled loading dose was variable. It is postulated that inappropriate dosing strategies and issues with patient compliance to medication can contribute to the development of suboptimal drug levels and to a subsequent loss of response to anti-TNFα therapy.27-29

Our results provide further evidence of these findings in the literature, most prominently in the infliximab group. Only 50% of patients received a loading dose in the infliximab group and this group also demonstrated the highest rates of dose escalation. These observations support the hypothesis that adherence to the prescribed dosing regimen may improve clinical outcomes for patients over the long term. Additional research is needed to confirm the benefit of induction and prescriber usage patterns of loading doses in the real-world clinical setting.

Limitations

There are a number of limitations to this analysis. As this was a retrospective study, it was not possible to consider patient diaries or assess returned drugs. We were also unable to assess the proportion of patients who received 200 mg certolizumab pegol every 2 weeks, which is a type of pharmacokinetic dose increase. A further limitation was the difficulty in directly comparing the incidence of dose escalation between the different anti-TNFα agents, as well as the absence of drug level data to further understand pharmacokinetic changes and differences. The metric and threshold for detecting a dose increase differed between treatments (ie, milligrams vs vials), and different definitions for dose escalation were necessary for each treatment. Moreover, dose increase is not approved for adalimumab or certolizumab pegol, and this may impact the number of patients having an increase from their maintenance dose over 12 months. There is also the possibility of an overlap between the OptumInsight and Truven Health MarketScan Research databases, since Truven includes some claims that fall within the OptumInsight database. However, this potential overlap of a small number of patient claims is not anticipated to affect the overall results. Another limitation to this study is that, as a claims data analysis, the incorrect use of treatment doses may be an artifact of the data source; additional studies with alternative data sources (eg, chart audit data) need to be conducted to validate the current findings.
CONCLUSIONS

In summary, certolizumab pegol has lower rates of dose escalation among anti-TNFαs for up to 12 months. Further studies are needed to explore prescribing and utilization patterns with anti-TNFαs, such as choice for first anti-TNFα and rates of dose escalation, and their impact from both a clinical and economic perspective for patients with Crohn’s disease.

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REFERENCES

20. HUMIRA (adalimumab) [prescribing information]. North Chicago, IL: AbbVie Inc; 2013.
22. REMICADE (infliximab) [prescribing information]. Horsham, PA: Janssen Biotech, Inc; 2013.