Crohn’s disease is a chronic relapsing form of inflammatory bowel disease and is characterized by inflammation of the gastrointestinal tract. It is estimated that 1.4 million persons in the United States and 2.2 million persons in Europe have inflammatory bowel disease. The most recent and advanced approach to the treatment of Crohn’s disease is biologic therapy designed to neutralize the proinflammatory effects of the cytokine tumor necrosis factor (TNF)-alpha.

In addition to infliximab, the other anti-TNFs approved by the US Food and Drug Administration (FDA) for the treatment of Crohn’s disease include adalimumab and certolizumab pegol. The focus of the current study, however, is on infliximab, which has been shown to be an effective treatment for Crohn’s disease.

The rate of infliximab dose escalation in this study was within the lower range of published estimates for this medication. Studies using larger sample sizes are needed to validate the findings of the current study. In addition, studies that are focused on quantifying and describing the nature of infliximab dose escalation may be useful in the development of successful patient–treatment matching algorithms.
Infliximab is a TNF blocker that is indicated for the treatment of patients with Crohn’s disease; 2 other TNF blockers are approved by the FDA for this condition.

Understanding dose escalation rates for therapies such as infliximab is important for controlling costs, managing patient expectations, spurring provider intervention, and optimizing treatment efficacy.

This study used claims data from a large mid-Atlantic managed care organization and medical charts to quantify the rate of dose escalation in patients diagnosed with Crohn’s disease between 2006 and 2010.

Of the 166 patients identified with infliximab claims, 106 were eligible for the analysis; of these, only 17% had evidence of dose escalation, a rate that is lower than previously published estimates.

Patient eligibility for infliximab therapy should be determined early in the treatment to enhance treatment efficacy and avoid unnecessary costs of ineffective therapies.

Studies using a larger sample size are needed to validate the findings in this exploratory analysis.

interval, because either approach results in an increase in the amount of infliximab that is infused during a period of multiple infusions. Studies have demonstrated the safety and the efficacy of increased infliximab doses (ie, >5 mg/kg every 8 weeks), and each method is likely to be equally effective; however, for convenience, patients may prefer increased dosages versus decreased dosing intervals.

Various studies indicate that increasing the dose of infliximab is a safe and cost-effective treatment pathway for patients with Crohn’s disease. Infliximab has been shown, in a recent cost analysis, to be the most cost-effective biologic for patients with Crohn’s disease who do not respond to standard therapy, and increasing its dose may actually result in more quality-adjusted life-years than switching to another biologic. Furthermore, switching from infliximab to adalimumab could result in the loss of tolerance and efficacy, which suggests that increasing the dose of infliximab to an effective level may be the more successful approach to treatment, especially in chronic diseases such as Crohn’s disease.

Conflicting results have been reported on the rate of infliximab dose escalation. Chao and Mulani have raised some doubt about. Several investigations have demonstrated the rate of loss of response requiring dose escalation to be between 30% and 40%, whereas Waters and colleagues reported that 79% of patients who are new users of infliximab maintained a stable 5-mg/kg dose during the first year.

Understanding the expected rate of dose escalation for medications such as infliximab is critical for controlling costs, managing patient expectations, spurring provider intervention, and optimizing treatment efficacy. Dose escalation will increase ingredient medication costs and may affect the treatment experience of patients. An enhanced overall understanding of the rates of infliximab dose escalation and the characteristics of patients requiring escalation may allow health plans and physicians to begin modeling algorithms that better match patients to therapy and reduce the incidence of treatment failure. Therefore, the goal of the present study was to characterize and to quantify the rate of infliximab dose escalation in a sample of patients with Crohn’s disease.

Methods

Patient data were collected retrospectively from administrative claims and from medical charts. The claims data were secured first and were used to identify the gastroenterology providers who may be willing to supply medical charts for review. The Essex Institutional Review Board approved this study.

Medical and Pharmacy Claims Data

A large mid-Atlantic managed care organization participated in this study as the health plan partner and agreed to provide claims data for its population of patients with Crohn’s disease during the calendar years 2006 through 2010. To be included in the data extraction, a member had to have a primary or a secondary diagnosis code for Crohn’s disease (International Classification of Diseases, Ninth Revision, Clinical Modification code 555.X). Three tables comprised the final database—professional, facility, and pharmacy claims. The data from a total of 27,931 unique members with Crohn’s disease were extracted.

Chart Review Data

Professional and facility claims were aggregated by physician tax identification number to identify the providers with the largest panels of patients with Crohn’s disease. Targeted providers were then solicited by telephone for recruitment into the study. Interested sites had to confirm their participation with the health plan partner and their general panel size of patients with Crohn’s disease who were also members of the health plan. All providers were offered an initial incentive of $500 for
agreeing to participate in the study, as well as an additional $50 for every chart that was identified as eligible for review. The following inclusion and exclusion criteria were imposed on patient charts:

- A diagnosis of Crohn's disease between 2006 and 2010
- Treatment with infliximab
- Age ≥ 18 years
- Absence of any organic brain disorders and syndromes (eg, schizophrenia, schizotypal)
- Absence of an organic brain disorder and syndromes (eg, head trauma, moderate-to-severe developmental disability with cognitive impairment)
- For female patients, the absence of pregnancy.

To aid in the chart data extraction, an electronic case report form was developed that included fields for demographics, diagnoses, medications, diagnostic tests, surgical procedures, and corresponding dates. Infliximab-specific variables included the dose (mg/kg), weight (kg), administered quantity (mg), and the date of infusion. A total of 5 research staff members comprised the chart review team, with each being trained on the Health Insurance Portability and Accountability Act privacy laws and general research ethics.

As a result of variability in the medical charts composition across practices, inter-rater reliability among chart reviewers was calculated on the initial visit to each provider's office. Any item disagreements were addressed and were corrected before additional charts were reviewed by the team. Overall, 8 gastroenterology practices and infusion centers in the mid-Atlantic area agreed to participate in the study. Charts were reviewed for a total of 161 patients with Crohn's disease who were being treated with infliximab.

**Infliximab Dosing**

Given the variances in the number of captured infusions and in the length of their current treatment with infliximab, only patients with at least 4 infusions were retained for the main analysis in the study. Patients were grouped and were compared according to their dosing pattern into the dose-stable or dose-escalation group.

Each patient's first episode of infliximab care, as it appeared in his or her chart, was examined for dose-escalation episode. Any lapse in therapy of 180 days or longer constituted a second episode of care, and such infusions were dropped from the analyses. For individual infusions for which the dose was missing, illegible, or unavailable (ie, total <5%), the dose was computed based on the administered quantity of infliximab and the patient's weight values. If both the administered quantity and the weight were unavailable in such cases, the dose was coded as missing.

Infliximab dose escalation is typically defined as either an increase in dosing from 5 mg/kg to 10 mg/kg or a decrease in the maintenance interval from every 8 weeks to every 6 weeks. For the present study, evidence of any infliximab dose ≥7.5 mg/kg or a mean maintenance interval of 42 days or less resulted in the placement of a patient in the dose-escalation group. Maintenance infusions were determined based on physician notes, and, when unavailable, were determined by the pattern of infusion intervals during each patient's episode of care. The patients who did not meet the dose-escalation criteria were placed in the stable-dose group.

**Data Analysis**

For the complete infliximab sample, descriptive statistics (including means, standard deviations, frequencies, and percentages) were presented for the infliximab treatment-specific outcomes derived from the charts. Next, bivariate analyses were performed comparing stable-dose patients with dose-escalated patients. Chi-square tests of equality of proportions were used for categorical variables, and independent t-tests were used for scale variables.

**Results**

A total of 925 infliximab infusions were captured from 161 patients. A total of 73 (7.9%) infusions were captured during a second episode of care and were dropped from the analyses. Descriptive statistics on the entire sample (N = 161) are listed in Table 1. The mean patient age (in rounded numbers) was 38 ± 13 years, and 75 (47%) patients were male. Within the study period, the patients' first episode of infliximab care included a mean of 5.3 ± 2.5 infusions (range, 1-8), for a mean length of care of 255 ± 149 days. The mean medication

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Overall Patient Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
<td>Patients in analysis, N</td>
</tr>
<tr>
<td>Age, yrs</td>
<td>161</td>
</tr>
<tr>
<td>Total infusions, N</td>
<td>161</td>
</tr>
<tr>
<td>Starting dose, mg/kg</td>
<td>155</td>
</tr>
<tr>
<td>Ending dose, mg/kg</td>
<td>146</td>
</tr>
<tr>
<td>Maintenance interval, days</td>
<td>134</td>
</tr>
<tr>
<td>Length of therapy, days</td>
<td>148</td>
</tr>
<tr>
<td>Male</td>
<td>160</td>
</tr>
<tr>
<td>Captured patients at induction</td>
<td>161</td>
</tr>
<tr>
<td>Patients with evidence of a lapse in therapy</td>
<td>161</td>
</tr>
</tbody>
</table>
Evidence of dose escalation

Table 2 Infliximab Dosing Analysis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dosing pattern</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stable dosing (N = 88)</td>
<td>Dose escalation (N = 18)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td>P value</td>
</tr>
<tr>
<td>Age, yrs</td>
<td>38.11</td>
<td>12.1</td>
<td>39</td>
<td>14.41</td>
<td>.785</td>
</tr>
<tr>
<td>Total infusions, N</td>
<td>6.78</td>
<td>1.5</td>
<td>6.72</td>
<td>1.53</td>
<td>.876</td>
</tr>
<tr>
<td>Starting dose, mg/kg</td>
<td>5.03</td>
<td>0.28</td>
<td>6.39</td>
<td>1.96</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Ending dose, mg/kg</td>
<td>5.08</td>
<td>0.35</td>
<td>7.78</td>
<td>2.25</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Maintenance interval, days</td>
<td>60.21</td>
<td>12.8</td>
<td>46.3</td>
<td>12.35</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Length of therapy, days</td>
<td>333.2</td>
<td>106.7</td>
<td>257.22</td>
<td>97.46</td>
<td>.006</td>
</tr>
<tr>
<td>Male</td>
<td>47 (53.4)</td>
<td>4 (22.2)</td>
<td>.016</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Captured patient at induction</td>
<td>12 (13.6)</td>
<td>4 (22.2)</td>
<td>.354</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evidence of lapse in therapy</td>
<td>5 (5.7)</td>
<td>2 (11.1)</td>
<td>.398</td>
<td></td>
<td></td>
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<tr>
<td>Evidence of dose escalation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased dosage</td>
<td></td>
<td></td>
<td>12 (66.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>To 7.5 mg/kg</td>
<td></td>
<td></td>
<td>4 (22.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>To 10 mg/kg</td>
<td></td>
<td></td>
<td>8 (44.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased interval</td>
<td></td>
<td></td>
<td>9 (50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Either type of dose escalation</td>
<td></td>
<td></td>
<td>18 (100)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SD indicates standard deviation.

interval during the maintenance phase of treatment was 59 ± 18 days. A total of 25 (15.5%) patients showed a lapse in their infliximab treatment, defined as a gap between any 2 infusions of 180 days. Induction infusions were identified in 27 (16.8%) samples, indicating that the majority of the captured infusion data were during the patients’ maintenance phase of treatment.

Table 2 shows the results from the infliximab-dosing analysis. Overall, 110 patients received at least 4 infusions, but 4 patients had missing dose and interval data, resulting in a total of 106 patients of the 166 patients (ie, 66%) who were qualified for the dosing analysis. Patients in both groups received a mean of 6.7 infusions.

A total of 18 (17%) patients showed evidence of dose escalation. Of the 18 patients, 9 (50%) showed a decrease in maintenance interval, whereas 12 (66.7%) showed an increase in their dosage to either 7.5 mg/kg (N = 4; 22.2%) or to 10 mg/kg (N = 8 [44.4%]). Three patients (16.7%) showed both an increase in dose and a reduction in maintenance interval.

Patients in the infliximab dose-escalation group had a significantly shorter length of therapy (257 vs 333 days, respectively; χ²[1, N = 106] = 5.82; P = .016) compared with the stable-dose patients. The majority of patients in both dose groups were in the maintenance phase of treatment (86.4% vs 77.8%, respectively; χ²[1, N = 106] = 0.86; P = .354).

Discussion

The aim of the present study was to examine dosing patterns in a sample of patients with Crohn’s disease who were treated with infliximab. Existing reports of infliximab dose-escalation rates vary and complicate the estimates of costs and efficacy. Overall, the rate of infliximab dose escalation observed in the present study was within the lower range of published estimates.10 Studies focused on quantifying and describing the nature of infliximab dose escalation may be useful in the development of successful patient treatment-matching algorithms, which may ultimately help to minimize the amount of time and the expenditure lost from ineffective treatments.

A total of 8 gastroenterology sites were recruited to participate in a chart review study. These sites were targeted by an analysis of Crohn’s disease patient service and pharmacy utilization data; member patient data were provided by a large mid-Atlantic managed care organization. In all, the charts of 161 patients with Crohn’s disease who received infliximab were reviewed. As a whole, the sample appeared to be receiving infliximab treatment in accordance with the FDA-approved prescribing information, with a mean starting dose of 5.29 mg/kg and a mean maintenance interval just more than 8 weeks (59 days).

Of these 161 patients receiving infliximab, 106 patients met the inclusion criteria for the dosing analysis, the majority of whom (85%; N = 90) were in the maintenance phase of treatment. A total of 17% of the patients receiving infliximab showed evidence of dose escalation.

Patients who had dose escalation were more likely to be female and had significantly shorter lengths of therapy compared with the patients in the stable-dose group. These results are consistent with differences in sex that have been reported in patients with Crohn’s disease and the skewing of the complications of Crohn’s disease toward female patients.24,25 There was no difference between the dose-escalation and dose-stable groups with regard to the number of patients showing a lapse in therapy or regarding the proportion of patients who were captured during induction.

Although the rate of dose escalation of infliximab observed in the present study was within the lower range of published estimates, comparison across studies is diffi-
cult. Gisbert and Panes found that the risk of infliximab dose escalation was 13% per patient-year, although the authors acknowledge that patient follow-up periods varied markedly across studies. Other investigators have reported rates of 1-year infliximab postinduction loss of response requiring dose escalation to be between 30% and 40%.6,13,21,22

The design of the current study was distinct from previous investigations in several ways, including the focus on a single health plan, the 5-year measurement window, and the capture of infusion episodes at various time points over the maintenance phase of treatment. This study did validate previous research showing a greater proportion of increased dosages as opposed to decreased intervals (66.7% vs 50%, respectively) among the dose-escalation population16; however, the level to which physician preferences affect these results remains unknown.

Although medication ingredient costs will certainly increase with dose escalation, compliance with infliximab has already been shown to be associated with reduced emergency department and inpatient hospital utilizations, which are primary concerns to payers and to patients.26

As the SWITCH trial has previously demonstrated, some proportion of patients receiving infliximab will benefit more from persisting with and optimizing their current treatment dose than from switching to another biologic.19 This type of evidence can facilitate the development of management algorithms that maximize the cost-benefit of therapies for the treatment of Crohn’s disease.

A pilot study conducted in southern Ohio focused on the site of care of infliximab demonstrated that the collaborative efforts of the health plan, provider, and specialty pharmacy were able to formulate an intervention that reduced out-of-pocket patient costs and maintained continuity of care.27 Obviously, the first step in the current effort is to better quantify the rate of dose escalation.

It may also be worth reexamining the concept of dose escalation, because many patients who require higher doses of infliximab during the course of treatment may be better described as “dose optimized” if treatment effectiveness is achieved and maintained at the higher dose. This may also serve to remove the negative connotations associated with dose escalation.

A study by Schnitzler and colleagues that examined infliximab interventions that are aimed at keeping the disease under control demonstrated that more than 70% of patients receiving an increased dose or reinduction of infliximab were eventually able to return to the standard 5-mg/kg dose.22 In addition, approximately 60% of patients with both an increased dose and shortened interval were able to return to the standard 5-mg/kg dose and 8-week maintenance interval.28 This evidence suggests that the dose escalation of infliximab may be useful practice in the treatment of disease flares, and that reinitiating the standard dose is possible.

Several studies have previously examined factors to facilitate the maintenance of infliximab dose response; however, further testing is needed. Being a nonsmoker29 and having higher C-reactive protein levels30 may each increase the likelihood of maintained response and remission.

In the present study, being female was associated with dose escalation. Although the implication of this result is presently unclear, it is consistent with other reports of worse disease in female patients.34,35 A previous study found that young age and concomitant immunosuppressive treatment were both predictors of short-term response to infliximab.31 Ultimately, as previously stated, the goal is to successfully identify patients, early in treatment, who may be suitable for infliximab therapy to avoid the high costs associated with and to prevent the prolonged use of ineffective treatment. The formation of antibodies against infliximab is associated with a reduced duration of response to treatment.32 As of the writing of this manuscript, a study that is aimed at predicting nonresponse and loss of response to infliximab at the initial diagnosis is in the recruitment phase.33 In addition, the emerging field of pharmacogenomics has already produced early models for the prediction of infliximab response using genotypic markers.34,35

Limitations

There are several limitations to the current study. As previously noted, the majority of the patient data extracted from charts did not include induction infusions, making it unfeasible to know how long patients were receiving therapy before the dose escalation. The identification of patients at their initial infusion would have assuaged this confound, but this approach was impractical, because of the need to temporally match patient charts to the claims file, and because of the use of multiple infusion centers by some patients.

In addition, although it was not the goal of the present study, the collection of greater clinical data could have allowed for an examination of the relationship between disease symptoms and dose escalation. The majority of patient data were retrieved from medical charts, but more than 33% of patient data were restricted to the infusion worksheets within the chart, which was limited specifically to indicators of treatment with infliximab.

Also, the results of the studies that incorporate insurance claims data may only pertain to the insured population and may not apply to uninsured patients.

Finally, the dosing group sample sizes, particularly those of the dose-escalation group (N = 18), were very small, raising concerns of power and the level to which
this small sample is representative of the larger population of patients with Crohn's disease who receive infliximab therapy.

Conclusion

The rate of infliximab dose escalation in the present study was within the lower range of published estimates. Although additional studies utilizing larger sample sizes are needed to validate the current findings, the methodology of using administrative claims to identify sites for medical chart reviews proved to be a useful technique. Overall, the ultimate goal is to develop successful patient treatment-matching algorithms to avoid wasteful spending, to prevent the prolonged use of ineffective treatment, and to identify which cases would be best served by dose optimization versus by switching to an alternate therapeutic medication. The incorporation of patient demographic, treatments, service utilization, and even genetic data is crucial for the advancement of these efforts.

The type of evidence presented in this study is crucial for the development and modification of reimbursement policies for advanced therapeutics, including biologic agents. Specifically, this type of evidence can facilitate the development of management algorithms that maximize the cost-benefit of therapies for the treatment of Crohn's disease. In an attempt to further reduce waste, managed care organizations may seek to reduce the number of failed trials of expensive therapeutics and begin modeling algorithms that better match patients to a therapy and reduce the probability of treatment failure. The involvement of all stakeholders is crucial to this effort.

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Author Disclosure Statement

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References

Payers/Providers: Are you familiar with the phrase “Start low and go slow”? During my pharmacist training and into my professional career, this has been the mantra for initiating drug therapy for the treatment of patients with all forms of disease states. Most medications require some form of titration to achieve the optimal dose for effective treatment. This is the recommended approach to the dosing of infliximab for the treatment of Crohn’s disease.

After the initial initiation phase with infliximab, which utilizes dosing of 5 mg/kg at 0, 2, and 6 weeks, the maintenance dose is 5 mg/kg every 8 weeks. The catch is that some patients may benefit from dosing up to 10 mg/kg every 8 weeks. Pretty straightforward, correct? Well, not exactly. The issue is that the majority of payers are experiencing a higher-than-expected number of patients who are receiving infliximab at doses of more than 5 mg/kg every 8 weeks, and some patients are receiving higher doses at less frequent intervals, such as every 6 weeks.

In their article in this issue, using medical chart reviews, Tkacz and colleagues found that approximately 17% of patients with Crohn’s disease within one health insurance plan had some form of infliximab dose escalation, and that this prevalence of dose escalation was at the lower end of the dose escalation that had been reported in previously published studies.

Payers/Patients: This should be great news to payers, providers, and especially for patients; however, we do have to realize the following issue. According to the Centers for Medicare & Medicaid Services, the payment limit for infliximab—based on the average sales price plus 6%—for the time period of April 1, 2014, through June 30, 2014, is $713.47 per 100 mg.

For a patient weighing 80 kg, the average drug cost for an infliximab infusion that is dosed at 5 mg/kg would be $2853.88 (with an annual drug cost of $17,123.28). For a patient population of 100 patients, the annual drug cost would be $1,712,328. Now, take into account 17% of patients receiving infliximab at a dose of 7.75 mg/kg, and the annual cost of infliximab becomes $1,872,430, an annual increase of $160,102. If this same methodology was applied to a patient population of 1000 patients, the annual drug costs for infliximab would exceed $1.6 million. The point is that, although 17% may appear low by itself, the implications of this seemingly low dose-escalation rate can be very significant to payers, as well as to patients.

We have to find ways to better manage patients with Crohn’s disease in a more cost-effective manner. Taking drug cost into account will help us to better manage the disease effectively, without sacrificing the quality of care for the patient.