Comparative Multidatabase Analysis of Dosing Patterns and Infusion Intervals for the First 12 Infliximab Infusions in Patients With Rheumatoid Arthritis

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ABSTRACT

Background: According to prescribing information for rheumatoid arthritis (RA) treatments in the United States, infliximab should be administered at weeks 1, 2, 6, and then every 8 weeks starting at a 3-mg/kg dose, with flexible dosing up to 10 mg/kg and/or every 4 weeks based on clinical response.

Objective: This study evaluated dosing and intervals of the first 12 infliximab infusions in patients with RA across multiple large administrative databases.

Methods: Data were obtained from 4 databases: HealthCore Integrated Research Database (HIRD), IMS LifeLink Health Plan Claims Database (IMS Life-link), Premier Perspective Database (PPD), and Wolters Kluwer Pharma Solutions (WKPS). Patients were aged ≥18 years, diagnosed with RA, and naive to biologic therapy. Patients with other select inflammatory conditions were excluded. The induction period included infusions 1 through 3; the maintenance period included infusions 4 through 12.

Results: Observed dosing patterns from the HIRD, IMS LifeLink, PPD, and WKPS databases demonstrated minimal dose increases from the first infusion (93.5, 103.3, 58.8, and 73.2 mg, respectively) and from the first maintenance infusion (69.1, 64.3, 45.7, and 45.7 mg, respectively) to the highest dose during the first 12 infusions. The mean number of days between infusions in the maintenance period ranged from 53.3 to 63.5 in HIRD, 53.7 to 60.3 in IMS LifeLink, 53.4 to 59.4 in PPD, and 52.3 to 55.0 in the WKPS database.

Conclusion: Data from multiple databases of patients with RA suggest that, in clinical practice, infliximab dosing and intervals are consistent with FDA prescribing information and remain relatively stable during the first 12 infusions. (Clin Ther. 2012;34:2286–2292) © 2012 Elsevier HS Journals, Inc.

Key words: dosing, infliximab, infusion intervals, rheumatoid arthritis.

INTRODUCTION

Guidelines for the use of nonbiologic and biologic disease-modifying antirheumatic drugs (DMARDs) for the treatment of rheumatoid arthritis (RA) were most recently updated by the American College of Rheumatology in 2012. Treatment with nonbiologic and biologic DMARDs should target low disease activity or remission. The use of tumor necrosis factor (TNF)-α inhibitors, the largest therapeutic class of biologic DMARDs, is recommended in patients with new RA, high disease activity, and poor prognostic features and in patients with established RA and moderate or high disease activity, after 3 months of nonbiologic DMARD treatment. Infliximab is a commonly used TNF-α inhibitor administered as an intravenous injection.

Infliximab has been shown to reduce signs and symptoms of RA, inhibit the progression of structural damage, and improve physical function in patients with moderately to severely active RA. For this indication, the US Food and Drug Administration (FDA) recommends that infliximab, in combination with methotrexate, be administered at 3 mg/kg at weeks 0, 2, and 6 (induction period) and every 8 weeks thereafter.

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ter (maintenance period). Based on a patient’s response, the dose may be increased to as much as 10 mg/kg, and maintenance intervals may be decreased to as frequently as every 4 weeks. Approximately 10% of patients treated with infliximab through 1 to 2 years may develop antibodies to infliximab. These antibodies may reduce clinical effect and lead to a need for increased dosing.

To date, several published studies have evaluated dosing patterns of TNF-α inhibitors in clinical studies, patient registries, physician chart reviews, and medical claims databases. The current evidence on infliximab generally demonstrates relatively small dose increases and limited increases in infusion frequency, all of which have been within FDA-recommended dosing. Agarwal et al reported a mean dose increase from 3.15 to 4.39 mg/kg in patients with RA receiving infliximab from 2 US hospital infusion centers. In that same study, patients with a decreased infusion interval had a mean interval of 7.0 weeks compared with 8.7 weeks in those without a decreased infusion interval. Stern and Wolfe, after reviewing infusion records from 2 large rheumatology practices, reported an initial mean dose of 3.6 mg/kg, increasing to 4.9 mg/kg at 1 year and to 5.1 mg/kg at 2 years. In addition, they reported that 95% of infusions were given at 8-week intervals. Retrospective analyses of medical claims data have reported similar results. Harley et al reported that the mean infliximab dose increased from 276 mg at initiation to 329 mg at final infusion, and Etemad et al reported that the mean dose increased from 2.8 vials (1 vial = 100 mg) at initiation to 3.6 vials at final infusion.

Using multiple US-specific data sources with similar study designs, the present study sought to corroborate infliximab dosing patterns and infusion intervals in patients with RA in clinical practice. The study evaluated both the quantity of dose per infusion (in milligrams) and the number of days between the first 12 infliximab infusions in patients with RA across 4 large databases.

PATIENTS AND METHODS
Study Design and Patients

Data were obtained separately from 4 administrative databases: HealthCore Integrated Research Database (HIRD), IMS LifeLink Health Plan Claims Database (IMS LifeLink), Premier Perspective Database (PPD), and Wolters Kluwer Pharma Solutions (WKPS). These 4 databases were selected because they are large and capture administrative claims data at a national level. Infusion data are captured from the most common sites of care—in-office infusion suites in physicians’ offices and hospital outpatient departments. These databases allowed the evaluation of patients receiving infliximab from the following perspectives: (1) the nationally representative, commercially insured population and (2) the hospital outpatient.

The HIRD has longitudinal medical and pharmacy claims for >33 million members of 14 commercial health insurance plans in the southeastern, mid-Atlantic, central, and western United States. These 14 health plans include health maintenance organizations, point-of-service plans, preferred-provider organizations, and indemnity plans. IMS LifeLink comprises commercial health plan information for >70 million members obtained from 100 managed care plans in the United States. The WKPS database integrates US health care claims data from physician practices, pharmacies, and hospitals for a longitudinal view of health care delivery and usage patterns for >115 million members.

The PPD is a large US hospital-based, service-level, all-payer, comparative database containing information on ~5.5 million annual hospital discharges (approximately one sixth of all hospitalizations in the United States) from primarily nonprofit, nongovernmental, community, and teaching hospitals as well as health systems. The Premier data include hospitalizations from >600 hospitals for the period from 2000 to present.

Patient inclusion and exclusion criteria varied only slightly across the databases and are detailed in the Table. The following general criteria were applied to each of the 4 databases: patients were aged ≥18 years at index infliximab claim, were diagnosed with RA (International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] diagnostic code 714.xx), had a 6- to 12-month period without biologic use prior to initiating infliximab, and were persistent with infliximab for a select period of time. Patients with other selected inflammatory diseases, as identified by ICD-9-CM diagnosis codes, were excluded. The excluded inflammatory diseases were ankylosing spondylitis (720.0), Crohn’s disease (555.xx), psoriasis (696.1), psoriatic arthritis (696.0), and ulcerative colitis (556.xx).
Study Measures

In each database, treatment with infliximab was identified from claims containing the Healthcare Common Procedure Coding System code for infliximab (J1745). Dosing was defined as the total number of milligrams infused at a single infusion event for the induction (infusions 1–3) and maintenance (infusions 4–12) periods. In HIRD and IMS LifeLink, the dose was derived by dividing the allowed cost by the wholesale acquisition cost (WAC) of infliximab at the time of the claim. In PPD, the dose was calculated from the number of 100-mg infliximab vials billed per infusion. In WKPD, the dose was calculated from the number of service units charged, where 1 unit = 100 mg. Infusion intervals were calculated as the number of days between a given infliximab infusion and the subsequent infusion.

Infliximab dosing and infusion intervals were analyzed in each database for the first 12 infusions, including both the induction and maintenance periods. The first 12 infusions were chosen because they represent the first ~18 months of treatment. After the first 12 infusions, sample sizes became small due to loss to follow-up within each database over time.

Statistical Analyses

All analyses were conducted separately within each of the 4 databases. Descriptive analyses were conducted for patient demographic characteristics as well as for dosing and infusion intervals. The mean (SD) dose at each infusion and mean (SD) days between each infusion were calculated within each database. Also, changes in dose from the first infusion of the induction period to the highest maintenance dose and from the first infusion of the maintenance period to the highest maintenance dose were calculated.

RESULTS

Across the 4 databases, a total of 17,301 patients with RA using infliximab were identified. Of these, 938 (5%) were from HIRD, 1089 (6%) were from IMS LifeLink, 2185 (13%) were from PPD, and 13,089 (76%) were from WKPS. Due to study differences in

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HIRD = HealthCore Integrated Research Database; IMS LifeLink = IMS LifeLink Health Plan Claims Database; PPD = Premier Perspective Database; RA = rheumatoid arthritis; WKPS = Wolters Kluwer Pharma Solutions.
postindex and persistency criteria across databases, the HIRD and WKPS sample sizes did not decline until infusion 5. At infusion 12, 60% to 75% of the sample remained in the HIRD, IMS LifeLink, and WKPS databases. In the PPD, which did not have a postindex time requirement, only 29% of the sample remained at infusion 12. The majority of patients in all databases were female (73% in HIRD, 75% in IMS LifeLink, 79% in PPD, and 78% in WKPS). Mean patient age was ~60 years in all databases (59, 58, 60, and 61 years, respectively).

Figure 1 summarizes infliximab dosing for the first 12 infusions within each of the 4 databases. Observed dosing patterns from the HIRD, IMS LifeLink, PPD, and WKPS databases were fairly consistent. The mean (SD) doses administered at the first induction infusion (infusion 1) were 308.0 (149.0), 345.9 (185.8), 338.2 (156.8), and 336.0 (128.8) mg, respectively. The mean (SD) doses administered at the first maintenance infusion (infusion 4) were 332.4 (135.9), 384.9 (200.6), 351.3 (149.6), and 363.5 (138.5) mg. In all 4 databases, the highest mean (SD) dose was observed at infusion 12. The highest mean (SD) doses were 401.5 (162.2), 449.2 (240.3), 397.0 (169.8), and 409.2 (155.0) mg. There were minimal dose increases from the first induction infusion (infusion 1) to the highest maintenance dose (infusion 4) to the highest maintenance dose (69.1, 64.3, 45.7, and 45.7 mg).

Figure 2 summarizes infliximab infusion intervals, measured as the number of days between infusions, for the first 12 infusions within each of the 4 databases. Intervals between infliximab infusions were consistent across observations in the HIRD, IMS LifeLink, PPD, and WKPS databases. Within individual databases, the mean (SD) number of days between infusions in the maintenance period (intervals 3–4 through intervals 11–12) ranged from 53.3 (23.0) to 63.3 (65.5) days, 53.7 (23.8) to 60.3 (43.4) days, 53.4 (20.3) to 59.4 (26.3) days, and 52.3 (14.6) to 55.0 (16.4) days, respectively.

DISCUSSION
Because of the extent of flexibility in infliximab dosing and infusion intervals, there has been increasing interest in understanding the magnitude of infliximab dosing patterns in patients with RA in clinical practice. The findings from the present study suggest that the dosing patterns observed across 4 different large US databases were consistent with FDA-approved prescribing information. Infliximab dosing and infusion intervals were observed to have been relatively consistent for the first 12 infusions.

![Figure 1](image1.png)

**Figure 1.** Infliximab dosing at each infusion within selected databases. HIRD = HealthCore Integrated Research Database; IMS LifeLink = IMS LifeLink Health Plan Claims Database; PPD = Premier Perspective Database; WKPS = Wolters Kluwer Pharma Solutions.

![Figure 2](image2.png)

**Figure 2.** Infliximab infusion intervals within selected databases. HIRD = HealthCore Integrated Research Database; IMS LifeLink = IMS LifeLink Health Plan Claims Database; PPD = Premier Perspective Database; WKPS = Wolters Kluwer Pharma Solutions.
In the literature, some studies of infliximab dosing patterns have reported only the percentage of patients with a dose increase in a given time period.9–13 These limited data, however, do not have enough detail to assess the magnitude of dose increase. Results of the current study demonstrated infliximab dose increases over time, but the increase within each of the 4 databases was minimal. During the first 12 infusions, the doses were increased, on average, by 93.5, 103.3, 58.8, and 73.2 mg in the HIRD, IMS LifeLink, PPD, and WKPS databases, respectively. There was a ~≤100-mg (1-vial) dose increase observed from the first induction infusion to the highest observed maintenance dose administered to patients over 12 infusions, regardless of the selected database.

The mean infliximab dosing at each infusion across these databases was consistent with those reported in other analyses of claims data.7–8 Due to the nature of claims data, however, studies that use administrative databases, including the present study, may overestimate the actual use of infliximab in clinical practice. Infliximab is dispensed in single-use, 100-mg vials. Although only a partial vial may be needed to achieve appropriate dosing in clinical practice, payments are made for the entire vial, including any wastage. Claims contained within the database reflected payments and therefore assumed full vial usage without any wastage.

Assuming that a 100-mg dose increase occurred, on average, at infusion 6 and that the current infliximab WAC is US $690.11 per 100-mg vial (Analysource/First DataBank, March 8, 2011), there is an additional cost of $4140.66 (6 infusions × $690.11 WAC) per patient over 12 infusions or the first 18 months of therapy. Assuming 3 vials (300 mg) for infusions 1 through 5 and 4 vials (400 mg) for infusions 6 through 12, dose increases account for only 16.3% of the estimated total treatment costs of infliximab over this period of ~18 months. Furthermore, the infusion interval during the maintenance period was ~8 weeks.

Previous research has also demonstrated that adjustments in dosing patterns more often include a dose increase rather than any shortening of infusion intervals.8 Results from this multidatabase study corroborate with those from prior reports in the literature.6–13 Observed infusion intervals in the maintenance period were very close to the 8-week (56-day) FDA-approved prescribing recommendation. Maintenance infusion intervals ranged from 52.3 to 63.5 days, on average, across the 4 databases.

This study evaluated data from a total of 17,301 patients with RA using infliximab across 4 large US administrative databases: HIRD, IMS LifeLink, PPD, and WKPS database. Observed infliximab dosing patterns and infusion intervals were consistent across the 4 databases. Also, infliximab-treated patients within each of the 4 databases were predominantly female and older, which is consistent with the higher prevalence of RA in these populations.14 The large sample size and expected demographic distributions based on accepted prevalence estimates support the generalizability of these results to the US population of patients with RA using infliximab. The consistency of results across multiple databases, even with differing patient populations, demonstrate that these results are not merely the artefact of a single data source and further support the generalizability of the study results.

Study Limitations

Data from the present study were taken from administrative databases. Because the primary purpose of these databases is the submission and payment of claims for health care services, only data directly applicable for these purposes were available. Patients’ weights for calculating dosing by weight were not available in any of the 4 databases, nor were other clinical measures or metrics of disease activity or health status. Infliximab utilization is derived from an estimate of vial usage based on “allowable” charge amounts and WAC cost per unit from 2 of the databases and number of vials or service units charged in the other 2 databases. Without the knowledge of or ability to calculate dosing by weight, the interpretability of dosing was limited to evaluating the mean change in overall utilization. Based on data from the 2010 US National Health and Wellness Survey,15 the median weight of a patient diagnosed with RA was 81.6 kg. Assuming for simplicity that a patient with RA weighs ~80 kg, on average, the dose increase over 12 infusions would range from 0.74 to 1.29 mg/kg. Also, evaluations of clinical response, reasons for changes in dosing or infusion intervals, and dosing-related outcomes could not be assessed.

Only 3 (HIRD, IMS LifeLink, and WKPS) of the 4 databases required patients to persist on infliximab therapy for a set time period, and the required time period varied by database. As a result of these varying persistence requirements, the data may not be fully comparable across the databases. Patients who were
switched to another biologic agent instead of having their infliximab doses increased, or who were discontinued from biologic therapy instead of continued on the infliximab dose, were not included in the present analysis. Additionally, the present study included only the first 12 infusions because sample sizes became small due to loss of follow-up within databases over time. These first 12 infusions may not have fallen within the persistence requirement for all patients, so an additional number of patients may have been lost from the databases, which may have influenced the results. Also, it was not possible to assess whether dosing and infusion intervals remained consistent after infusion 12.

This study describes dosing trends within 4 separate administrative databases. These databases may have different patient populations and different methods for ensuring data capture and quality. Sex and age distributions were similar across the databases, but other patient characteristics may not have been captured, which may have affected the study results in unintended ways. Also, while inclusion and exclusion criteria were similar across the databases, some slight differences were evident, which may have affected the study results. Therefore, these 4 databases are not directly comparable, and indirect comparisons should be interpreted with caution.

CONCLUSIONS
Data across multiple large US databases suggest that, in clinical practice, infliximab dosing and infusion intervals in patients with RA for the first 12 infusions, which represent the first ~18 months of treatment, were consistent with FDA prescribing recommendations. Any infliximab dose change appears to be predominantly due to dose increases versus shortening of the infusion interval. The mean overall infliximab dose escalation over the 12-infusion treatment period studied resulted in <16.3% variation from the expected treatment costs (ie, treatment costs with no dose increases).

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All of the authors contributed equally and actively participated in the study design, decisions about the data sources, development and refinement of the analytical plans, interpretation of the results, and writing of the manuscript.

CONFLICTS OF INTEREST
This study was funded by Janssen Scientific Affairs, LLC, Horsham, Pennsylvania, which provides internal scientific support to Janssen Biotech, Inc, the manufacturers of infliximab. All of the authors are employees of Janssen Scientific Affairs, LLC, and hold stock in the parent company, Johnson & Johnson. The author have indicated that they have no other conflicts of interest with regard to the content of this article.

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