

## Treatment Compliance and Dosage Administration Among Rheumatoid Arthritis Patients Receiving Infliximab, Etanercept, or Methotrexate

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### Abstract

**Objective:** To examine treatment compliance and dosage administration associated with infliximab, etanercept, and methotrexate therapy for rheumatoid arthritis (RA).

**Study Design:** Retrospective analysis using administrative and claims data from a large US health plan.

**Patients and Methods:** Patients were Medicare or commercial enrollees in a health plan with a pharmacy benefit and had a diagnosis of RA. The first (index) claim for infliximab, etanercept, or methotrexate occurred between July 1, 1998, and December 31, 2000. Continuous enrollment in the plan was required from 182 days before to 365 days after the index claim. Treatment groups were compared according to compliance (defined as the actual number of therapy administrations or filled prescriptions divided by the expected number) and changes in dosage administration over time. The costs of infliximab therapy also were explored.

**Results:** A total of 2662 patients (infliximab = 141; etanercept = 853; and methotrexate = 1668) were included in the analyses. Infliximab patients were older and more likely to have a Medicare benefit. In addition, infliximab patients had more comorbidities and had greater medical costs preceding the index claim. Compliance with at least 80% of the expected dosages was significantly lower for etanercept (odds ratio [OR] 0.462; 95% confidence interval [CI] 0.290-0.736) and methotrexate (OR 0.385; 95% CI 0.245-0.604) patients than infliximab patients. Methotrexate patients had the largest dosage increases (61.6%), followed by infliximab (37.4%) and etanercept (7.4%) patients. Assuming 6.5 dosages per year, the annual cost of infliximab was \$10 446 to \$12 363, or \$1887 to \$1902 per administration, depending on site of service.

**Conclusions:** Compliance is higher with infliximab compared with etanercept or methotrexate; whereas, fewer etanercept patients change dosages. The cost of infliximab was lower than expected based on previous predictions, even with a 37% increase in dosage.

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The development of the anti-tumor necrosis factor (TNF) agents infliximab and etanercept constitutes a significant development in the management of rheumatoid arthritis (RA), by increasing the available options for effective treatment of this disease.<sup>1</sup> These biologic agents primarily interfere with TNF, a proinflammatory cytokine responsible for major joint damage among patients suffering from RA.<sup>2-4</sup> Presently, infliximab is indicated for the treatment of adult RA and Crohn's disease,<sup>5</sup> whereas etanercept is indicated for the treatment of adult and juvenile RA as well as ankylosing spondylitis and psoriatic arthritis.<sup>6</sup> Alternative, and sometimes complementary, treatment options for RA include other biologic agents such as leflunomide, the disease-modifying antirheumatic drugs (DMARDs) such as methotrexate, oral corticosteroids, and gold compounds (rarely used).

Both infliximab and etanercept have been evaluated extensively in randomized clinical trials of RA,<sup>7-13</sup> and large studies demonstrated that RA patients who took these biologic agents had fewer symptoms compared with those receiving standard therapy, including methotrexate. Nevertheless, enthusiasm for these drugs has been tempered somewhat by concerns over safety and cost.<sup>14</sup> The annual medication costs for the TNF-alpha inhibitors can vary considerably. The recommended initial dosage of infliximab is 3 mg/kg, followed by additional induction dosages 2 and 6 weeks after initial infusion, and then maintenance dosages every 8 weeks thereafter. However, if patients have an incomplete response, infliximab can be

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administered at dosages up to 10 mg/kg and/or as often as every 4 weeks.<sup>5</sup> Consequently, based on the average wholesale price of therapy,<sup>15</sup> the annual cost of infliximab could range from \$11 000 to \$63 000 for a 70-kg patient. The recommended dosage of etanercept is 25 mg twice weekly, and at that dosing regimen the annual cost is approximately \$17 000.

In addition to dosage, another difference between infliximab and etanercept is that infliximab is administered intravenously, typically at an outpatient facility. Etanercept is administered subcutaneously, most often by the patient or informal caregiver at home. In RA as well as other diseases, the route of administration has been implicated as a factor in compliance with therapy.<sup>16-21</sup>

Despite the fact that these 2 biologic agents have been evaluated extensively in clinical trials, little has been reported on their use in routine clinical practice. The objectives of the present study were to describe the characteristics of patients receiving infliximab, etanercept or methotrexate—a mainstay of DMARD therapy<sup>22</sup> for the first time to identify rates and patterns of compliance with therapy, to examine dosage patterns, and to estimate the cost per administration of infliximab.

## METHODS

### Design and Data Sources

This was a retrospective analysis using eligibility, medical, and pharmacy administrative claims data from a large US health plan. The individuals covered by this health plan were geographically diverse across the United States. The plan provided fully insured coverage for physician, hospital, and prescription drug services. The providers of these services submitted their claims for payment directly to the health plan, which used data derived from these claims for a wide range of safety, utilization, and economic analyses. Patient identifiers were encrypted.

### Study Population

Patients in this study were commercial or Medicare enrollees with a pharmacy bene-

fit, and were selected based on the following criteria:

- Patients filled at least 1 prescription or had a documented administration of infliximab, etanercept, or methotrexate between July 1, 1998, and December 31, 2000 (identification period).
- Patients received no infliximab, etanercept, or methotrexate (methotrexate treatment group only) during the 182 days before the first documented administration during the identification period (index date).
- Patients were enrolled continuously in the health plan for 182 days before the index date and for 365 days after the index date. Gaps of 32 days or fewer in enrollment were bridged and enrollment was treated as continuous.
- Patients had at least 1 claim with a diagnosis of RA (ICD-9 code 714.xx) during the 182 days before the index date or during the 365-day follow-up period. Diagnosis codes could appear in the primary or secondary position on physician or facility claim forms. Claims submitted by laboratories were excluded, as a diagnosis on these claims may be listed as rule-out criteria.

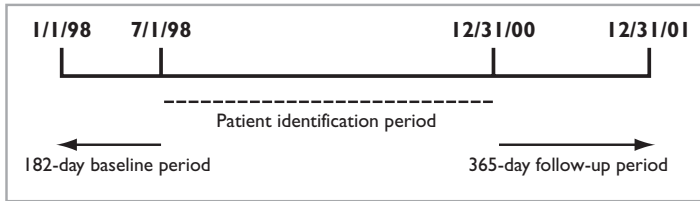
The study design is summarized in **Figure 1**.

Treatment with infliximab was identified in medical claims based on the Healthcare Common Procedure Coding System code J1745. Infliximab was approved for use in the United States in November 1999. Therefore, infliximab patients were identified only between November 1999 and December 31, 2000, and before other patients, to maximize the number in the study with 365 days of follow-up before December 31, 2001—the end of the identification period. Etanercept and methotrexate use was identified using both pharmacy and medical claims, although the majority of claims for both were pharmacy claims. There were no pharmacy claims identified for infliximab users.

### Variables

Patient variables included index treatment (infliximab, etanercept, or methotrexate), age, gender, health plan region

**Figure 1.** Timeline for Study Design



(East/Southeast, South Central, Midwest, or West), benefit type (Medicare or commercial), most common specialty of the prescribing physician administering anti-rheumatic therapy (rheumatologist, generalist, other), comorbidities defined according to ICD-9-CM code groupings, concomitant and prior medications including nonsteroidal anti-inflammatory drugs (NSAIDs) and DMARDs, and total medical and pharmacy costs during the 182 days preceding the index date of therapy.

A compliance (or possession) ratio was computed as the actual number of therapy administrations or filled prescriptions divided by the expected number. Therapy compliance was defined as a ratio of 0.80 or

greater.<sup>23</sup> For infliximab, the expected number of administrations was computed based on the standard schedule: first dosage, 2 weeks, 4 weeks, and every 8 weeks subsequently. Actual administrations were identified from the index therapy through treatment termination. For etanercept and methotrexate, the expected number of administrations was computed based on the standard dosage schedule as well. For etanercept, the expected dosage was 2 times per week. For methotrexate, the expected dosage schedule was weekly administration. Actual dosage schedule was computed based on the days supplied or the review of the number of units field on filled prescriptions or administrations from the index date through treatment termination.

The study also examined changes in dosage administration over time. Increases in dosage were calculated by subtracting the dosage of the final prescription or administration from the dosage of the index prescription or administration. Percent change in dosage per person was calculated and compared among the treatment groups.

The average cost of infliximab administration was calculated by site of service, defined as provider's office, patient's home, outpatient facility, and other sites using codes associated with each administration of therapy. Data for only paid claims were included in the analysis. Administration-related codes are presented in **Table 1**. The additional procedure codes were required to have the same service date and site of service as the infliximab injection claim (J1745) to be included in the calculation of infliximab administration costs. For each patient, the costs of infliximab administration were added up by site and then divided by the total number of administrations by site.

**Statistical Analysis**

Patient characteristics were compared among the treatment groups using chi square tests for nominal variables and analysis of variance for continuous variables. Compliance, defined as a ratio of actual-to-expected number of therapy administrations of 0.80 or greater, was compared among the treatment groups using a multivariate logistic regression model,

**Table 1.** Procedures Attributed to Infliximab Administration

Procedure Codes	Procedure Description
J1745 (CPT)	Injection, infliximab, 10 mg
J7050 (CPT)	Infusion, normal saline solution, 250 cc
90780 (CPT)	IV infusion for therapy administered by physician or under direct supervision. Up to 1 hour.
90781 (CPT)	Each additional hour up to 8 hours
Q0081 (CPT)	Temporary code for infusion therapy other than chemotherapy
99211-99215, 99201-99205 (CPT)	Office or other outpatient visit
99341- 99350 (CPT)	Home visit
90784, 90799 (CPT)	Unlisted therapeutic, prophylactic, or diagnostic injection
99.29 (ICD-9-CM)	Injection of other therapeutic substance
250, 258, 260-269, 270-272, 760, 761 (revenue codes)	Pharmacy (250), IV solutions (258), IV therapy (260-269), Med-Sur supplies (270-272), treatment room (760-761)

which adjusted for age, gender, baseline cost, benefit type, health plan region, history of therapy for RA, and most common type of prescribing physician.

RESULTS

There were 141 patients in the infliximab group, 853 patients in the etanercept group, and 1668 patients in the methotrexate group. Patient characteristics are presented in Table 2. As shown, infliximab patients were significantly older than either etanercept or methotrexate patients, and methotrexate patients were significantly older than those receiving etanercept. The percentage of males was similar across the treatment groups. A smaller proportion of infliximab than etanercept or methotrexate patients received concurrent NSAID therapy. More than half of all patients receiving anti-TNF therapy received concurrent methotrexate therapy.

Almost all etanercept patients had a commercial benefit type compared with two thirds of infliximab patients and 79% of methotrexate patients. Overall, infliximab patients had higher rates of comorbidities than etanercept, and the sum of all medical and pharmacy costs in the 182-day period preceding the index date of therapy was significantly higher, by approximately \$1000, for infliximab than etanercept, and by approximately \$1500 than methotrexate.

Figure 2 shows the distribution of compliance ratios (total number of treatments/expected number of treatments) by treatment cohort. More than 80% of infliximab patients were at least 80% compliant with therapy as compared with slightly more than two thirds of etanercept, and less than two thirds of methotrexate patients (Table 3).

Multivariate analysis, adjusting for potential confounding characteristics, showed infliximab patients were more than twice as likely to be compliant with therapy compared with etanercept or methotrexate patients (Table 3), and etanercept patients were more compliant than methotrexate patients.

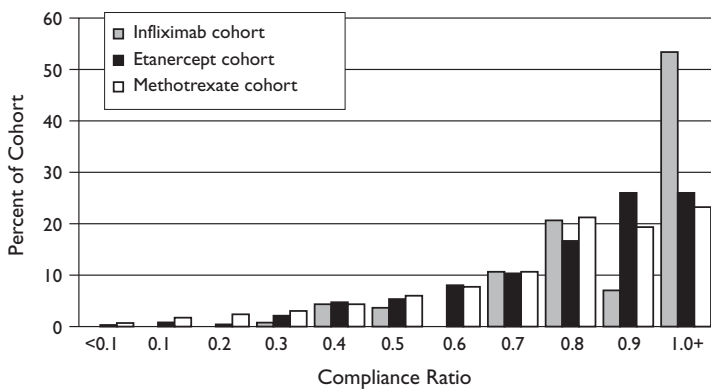
Data on patterns of dosage administration during the observation period are reported

Table 2. Patient Characteristics

Characteristic	Treatment Groups		
	Infliximab n = 141	Etanercept n = 853	MTX n = 1668
Age (mean [SD])	56.3* [13.1]	47.4* [12.6]	53.3* [14.7]
Gender (% male)	27.0	26.3	26.9
Concurrent Drug Use (%)			
DMARDs	34.0	41.0	37.9
NSAIDs	51.8*	66.1	68.9*
Glucocorticoids	71.6	68.3	70.0
Analgesics	35.5	43.3*	39.0
MTX	58.2	51.8*	100.0*
Physician Specialty (%)			
Rheumatologist	48.9*	70.5*	59.4*
Generalist	3.6*	16.5*	29.1*
Other	47.5*	13.0	11.5*
Benefit Type (%)			
Commercial	68.1*	98.6*	79.2*
Medicare	31.9*	1.4*	20.7*
Health Plan Region (%)			
East/Southeast	45.4	38.7*	30.2*
Midwest	31.9*	46.3*	54.9*
South Central	17.7*	9.1	10.1*
West	5.0	5.9	4.7
Comorbidities (%)			
Infectious and parasitic diseases	35.5*	24.3	27.0*
Neoplasms	34.0	28.6	26.3*
Endocrine, nutritional, and metabolic disorders	61.0*	45.8*	54.9
Blood and blood-forming organs	29.1	21.9	24.1
Mental disorders	22.7	21.9	24.9
Diseases of the nervous system	59.6	55.6*	60.6
Diseases of the circulatory system	57.4*	48.5*	56.9
Diseases of the respiratory system	56.0	56.4	59.1
Diseases of the digestive system	51.1*	36.1*	42.0*
Diseases of the genitourinary system	51.1	52.9	51.3
Complications of pregnancy, childbirth	0.7	1.4	1.4
Diseases of the skin	51.8*	40.2	42.7*
Diseases of the musculoskeletal system	80.9	74.9	77.8
Congenital abnormalities	9.2	7.2	6.4
Perinatal period conditions	1.4	0.6	0.8
Injury and poisoning	44.0	47.0	45.4
Other	78.7	74.4*	79.9
Baseline Cost (mean [SD])	\$5283* [\$7706]	\$3287* [\$4007]	\$2791* [\$4733]

\*Significant difference between infliximab and etanercept cohorts at  $P < .05$ .  
 †Significant difference between etanercept and methotrexate cohorts at  $P < .05$ .  
 ‡Significant difference between infliximab and methotrexate cohorts at  $P < .05$ .  
 NOTE: Chi square tests were performed for differences in proportions. A one-way analysis of variance (ANOVA) with Scheffe test was performed for differences in means. DMARDs indicates disease-modifying antirheumatic drugs; MTX, methotrexate; NSAIDs, nonsteroidal anti-inflammatory drugs; SD, standard deviation.

**Figure 2.** Distribution of Compliance Ratios by Treatment Cohort



**Table 3.** Compliance With Therapy

	Treatment Group		
	Infliximab	Etanercept	MTX
Compliance $\geq$ 80%			
Percent (unadjusted)	80.9*	68.4†	63.7‡
Multivariate§ Odds Ratio	REF	0.462	0.385
[95% CI]		[0.290-0.736]	[0.245-0.604]

\*Significant difference between infliximab and etanercept cohorts at  $P < .05$ .  
 †Significant difference between etanercept and methotrexate cohorts at  $P < .05$ .  
 ‡Significant difference between infliximab and methotrexate cohorts at  $P < .05$ .  
 §Analysis adjusts for age, gender, baseline cost, benefit type, health plan region, history of therapy of rheumatoid arthritis, comorbidities, and type of physician.  
 NOTE: Chi square tests were performed for differences in proportions. For multivariate analysis:  
 Etanercept coefficient  $P$  value = .001.  
 MTX coefficient  $P$  value < .0001.  
 Etanercept (1) vs MTX (0) odds ratio and  $P$  value: OR = 1.200,  $P$  = .059.  
 CI indicates confidence interval; MTX, methotrexate; OR, odds ratio.

in Tables 4 and 5. As shown in Table 4, the median index dosages of infliximab (per administration) and etanercept (per week) were identical to the final dosages, whereas the median weekly dosage of methotrexate increased from the first week to the last week of the observation period. Assuming an average patient weight of 70 kg, the median dosage of infliximab was approxi-

mately 4.28 mg/kg. Assuming 2 administrations per week, the median dosage of etanercept was 25 mg per administration. Patients receiving etanercept were least likely to experience a dosage change during the 365-day follow-up period, followed by infliximab, and then methotrexate (Table 5). Methotrexate patients were most likely, and etanercept patients were least likely, to have their dosages increased.

The average cost per infliximab administration was calculated by site of service (Table 6). The cost of administration took into account drug cost, physician cost, and other fees associated with the administration. The total administrative cost was highest in the outpatient setting and lowest in the home setting, although very few administrations were provided at home. The material cost of infliximab comprised a large percent of total cost in each setting: 94.7% office, 93.2% home, and 88.9% outpatient. Based on the observed cost per administration, the expected cost of infliximab during the maintenance phase of therapy, assuming 6.5 administrations per year, is \$10 446 to \$12 363, depending on site of service.

## DISCUSSION

A study was conducted using claims data to compare therapy compliance and changes in dosage between infliximab, etanercept, and methotrexate. This appears to be the first study to investigate patterns of compliance and changes in the dosage of infliximab and etanercept using actual claims data. Thus, it provides insight into how these agents are being used in routine clinical practice.

Several of the findings are noteworthy. First, infliximab patients were older, had higher costs for medical care during the 6 months before beginning study therapy, and in general, appeared to have more comorbidities than patients receiving etanercept or methotrexate. It is possible, therefore, that infliximab patients may have had a longer history of RA and/or more severe disease. However, this could not be confirmed by the data available.

Multivariable analysis suggests that infliximab patients were more compliant than

**Table 4.** Dosage Administration Data

	Index Dosage (mg)			Final Dosage (mg)		
	Mean	SD	Median	Mean	SD	Median
Infliximab (per administration dosage)	276.31	111.08	300.00	328.51	136.81	300.00
Etanercept (weekly dosage)	59.02	59.37	50.00	53.73	32.41	50.00
Methotrexate (weekly dosage)	16.22	31.05	10.00	20.25	33.36	14.00

SD indicates standard deviation.

either etanercept or methotrexate patients, although the reasons for the observed differences are unclear. One explanation is that the route and frequency of administration differ among the 3 therapies. For instance, infliximab is administered intravenously in an outpatient facility setting approximately once every 8 weeks during the maintenance phase of therapy, whereas etanercept is self-administered subcutaneously twice per week. Previous studies have shown patients with other diseases, such as diabetes, who administer therapy subcutaneously frequently miss injections,<sup>16,17</sup> fail to obtain all of their prescribed medication,<sup>18</sup> and that patients with RA and diabetes miss injections because of anxiety,<sup>16,19</sup> and are reluctant to administer injections to themselves.<sup>16,20</sup> Further, patients with RA who switch from self-administered subcutaneous injection to intravenous infusion prefer the latter.<sup>16,21</sup>

In this study, less than half of infliximab and etanercept patients experienced any dosage change during the study follow-up period, compared with 65% of methotrexate patients. In all 3 groups, the majority of the dosage changes consisted of increases in dosage: 81% of changes in the infliximab and methotrexate groups, and 54% in the etanercept group. On average, methotrexate patients had dosage increases of more than 60%, compared with 37% for infliximab patients, and 7% for etanercept patients. Possible explanations for changes in dosage include adverse events resulting in decreases in dosage, concerns about safety prevent-

**Table 5.** Changes in Dosage

Measure of Change	Treatment Group		
	Infliximab (n = 141)	Etanercept (n = 853)	MTX (n = 1668)
Any Dosage Change (% of cohort)	45.4	40.7	65.2
Titration			
Up (% of cohort)	36.9	22.0	52.6
Down (% of cohort)	8.5	18.6	12.5
Mean Percent Change Between First and Last Dosage	+37.4	+7.4	+61.6

MTX indicates methotrexate.

ing increases in dosage, or poor response to therapy with lower dosages resulting in dosage increases. Differences between infliximab and etanercept in the proportion of patients receiving an increase in dosage could be the result of differences in prescribing recommendations. These differences could also be a reflection of differences in prescribing patterns through the pharmacy benefit compared with administration through the medical benefit. This may also be influenced by differences in billing practices across benefit type. Again, this study did not attempt to determine the specific reasons for these dosage changes because of the limitations of the available claims data. Further research on trends in dosage over time is required to gain additional insight on

**Table 6.** Administrative Costs of Infliximab

Measure of Change	Site of Service		
	Office (n = 108)	Home (n = 9)	Outpatient (n = 41)
Total Administrative Cost			
Mean (\$)	1887	1607	1902
[SD] (\$)	[838]	[860]	[1236]
Infliximab Cost			
Mean (\$)	1787	1498	1690
[SD] (\$)	[811]	[839]	[1203]
Associated Cost			
Mean (\$)	107	139	222
[SD] (\$)	[47]	[66]	[229]

SD indicates standard deviation.

this issue. For instance, dosage increases shortly following the index dosage might suggest a preplanned strategy to increase dosage regardless of clinical response. Dosage increases occurring late in therapy might be suggestive of a poor response. Early dosage decreases might suggest a response to an adverse event.

The cost per administration of infliximab is consistent with dosage administration of 3 to 4 mg/kg in a 70-kg patient, and is at the low end of the range of potential costs given the potential range in dosage per administration. The estimated annual cost of infliximab, based on the average cost per administration, assuming 6.5 administrations per year (\$10 446 to \$12 363 depending on site of service), is considerably lower than reported in a previous comparison of infliximab and etanercept costs.<sup>24</sup> This study, which was based on an economic model, reported that whereas annual drug costs were similar (infliximab = \$12 610 and etanercept = \$12 534), costs related to administering the drug were considerably higher for infliximab (\$5048) than etanercept (\$107). The findings from the present study indicate that the facility costs related to infliximab are only \$107 to \$222 per administration, or approximately \$695.50 to \$1443 per year.

Although the results suggest there may be some benefits to the use of infliximab with respect to compliance, they should be considered within the context of several limitations of this study. Actual use of oral or subcutaneous therapies cannot be observed using claims data, and although it is possible to identify filled prescriptions, it is not known if the medications were used as prescribed. In addition, infliximab is indicated for administration every 56 days (8 weeks). However, it appears that some providers in the outpatient facility setting did not use a specific drug J-code in every instance to bill infliximab administration. Rather, a constellation of codes and costs suggest infliximab, but the provider only used a code to indicate drug infusion—drug unspecified. This could result in missing some administrations for infliximab, perhaps artificially decreasing the measure of compliance and increasing treatment failure. This same limitation to the claims data may have resulted in categorizing some infliximab users as new users when in fact these patients were continuing therapy. Preliminary exploratory analysis indicated that it might be possible to identify infliximab administrations based on the constellation of codes associated with the therapy to better refine a count of drug use.

Another limitation stems from the small sample size of infliximab patients. Although there was adequate power to conduct the comparisons of interest, it was not possible to employ statistical analyses that would have allowed for correction of possible selection bias related to treatment choice. Disease severity for RA is not captured in this study and this may impact both selection of drug as well as compliance with therapy. Depending upon the direction of these effects the correlation in the error terms may bias the estimates for the compliance analysis. This is an issue of unobserved variables, which may influence treatment selection and the outcome of interest.

Despite these limitations, the study provides important insight into the use of anti-rheumatic therapy in routine clinical practice, and suggests advantages for infliximab over both etanercept and methotrexate with respect to treatment compliance.

Further, the estimated cost per administration of infliximab is at the low end of the potential range, suggesting low facility costs and dosage administration in the range of 3 to 4 mg/kg.

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