Utilization of Biologic Agents in Rheumatoid Arthritis in the United States
Analysis of Prescribing Patterns in 16,752 Newly Diagnosed Patients and Patients New to Biologic Therapy

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Abstract
Background: Treatment of rheumatoid arthritis (RA) has shifted toward earlier and more aggressive therapy with traditional disease-modifying antirheumatic drugs (DMARDs) and biologics. However, the extent to which these agents are used in current clinical practice in the United States (U.S.) has not been systematically evaluated.

Materials and Methods: This analysis of a large claims database assessed patterns of use of biologics within clinical practice in a broad U.S. population with RA. We identified two cohorts of adults with RA using Thomson Healthcare MarketScan® Research databases. Patients newly diagnosed with RA between 1999 and 2004 with 12 months or more of continuous enrollment prior to diagnosis and with 24 months or more post-diagnosis were included in one cohort. The second cohort included RA patients who appeared to be newly treated with biologic therapy and had continuous enrollment for 12 months or more prior to first use of a biologic agent and 18 months or more following initial treatment. A total of 16,752 patients, newly diagnosed with RA, and 8,218, new to biologics therapy, were included.

Results: Utilization of biologics increased from 3% of patients in 1999 to 26% in 2006. Patients initiated biologics both as monotherapy (30%) and in combination with methotrexate (36%). Regimen modifications were frequent, with a large percentage of patients requiring addition or subtraction of methotrexate.

Conclusions: The use of biologics to treat RA is increasing, either as monotherapy or in combination with another DMARD. Modifications to drug regimens are frequent and episodes are often of comparatively short duration.

In recent decades, there has been a shift in treatment patterns for rheumatoid arthritis (RA) toward earlier and more aggressive therapy, with the aim of controlling inflammation to prevent joint damage and other associated sequelae. Early, aggressive treatment strategies using disease modifying antirheumatic drugs (DMARDs) have been associated with substantial improvements in long-term outcomes, including lower mortality rates and lower work disability rates; however, many patients continue to experience a high level of RA disease activity.

Biologic therapy for RA with tumor necrosis factor-α (TNF-α) blockers was first introduced in 1998. More recently other biologics targeting different pathways in the inflammatory process have become available. These include abatacept, which targets cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), and rituximab, which acts by depleting CD20+ B lymphocytes. With the introduction of biologics, came the hope of further slowing disease progression and achieving sustained remission or minimal disease activity over time. A number of studies have shown that, compared with methotrexate or TNF-α blocker monotherapy, the combination of a biologic agent with methotrexate offers higher levels of disease control, symptomatic improvement, and possibly prevention of radiographic progression. Moreover, there is increasing evidence that using biologics early in the course of RA can provide even greater clinical benefit in selected patients than reserving these agents for later.

Guidelines from both the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) note the importance of early...
aggressive treatment with DMARDs to slow disease progression. This is supported by the findings of the BeSt Study,\textsuperscript{18} the Tight Control of Rheumatoid Arthritis (TICORA) study,\textsuperscript{19} and the Finnish Rheumatoid Arthritis Combination Therapy (FIN-RACo) study.\textsuperscript{20} In TICORA, patients randomized to intensive care were monitored regularly and DMARDs were added or titrated up for patients who continued to have a high disease activity score.\textsuperscript{19} In BeSt, the two combination arms proved to be more effective than sequential DMARD monotherapy or step-up therapy (adding a DMARD if initial monotherapy was not effective) during the first year.\textsuperscript{18} However, after 2 years, all groups achieved similar clinical improvement.\textsuperscript{21} The FIN-RACo (Finnish Rheumatoid Arthritis Combination Therapy) study showed 1-year and 2-year disease remission rates that were twice as high in patients receiving combination DMARD therapy, compared with single DMARD use.\textsuperscript{20} Taken together, these results suggest that early and aggressive treatment strategies may be more important than individual DMARD use per se.

It is reasonable to assume that the evidence cited above may influence physician practice patterns. However, in real-world clinical practice, physicians’ prescribing patterns are often subject to a per-patient trial-and-error approach until the “newness” of the introduced regimen abates. Choice of therapy depends, in part, on physician and patient preferences, which may be influenced by perceptions of efficacy, tolerability, and long-term safety, as well as reimbursement factors.\textsuperscript{22-27}

In the United States (U.S.) currently published literature describing patterns for RA treatment in clinical practice rely largely on questionnaire-based assessments of hypothetical patient scenarios.\textsuperscript{24,26} The aim of the present study was twofold: to assess objectively the degree to which biologics are currently being prescribed (type, number, and duration) in clinical practice in a large, national sample and to evaluate how these agents are being used in clinical practice (as monotherapy, in combination, or sequentially).

**Materials and Methods**

**Data Source**

This retrospective analysis identified patients with RA in the Thomson Healthcare MarketScan\textsuperscript{®} Commercial Claims and Encounters (CCE), and Medicare Supplemental and Coordination of Benefits databases. These databases are derived from employer- and government-funded (Medicare) healthcare insurance plans and include approximately 25 million individuals of all ages. Inpatient and outpatient claims are linked with outpatient prescription drug data via unique encrypted patient identifiers. Physicians and hospitals record diagnostic information to support their reimbursement claims for given services. MarketScan\textsuperscript{®} data have been widely used for health services research.\textsuperscript{28-31} Patient data included in this analysis were de-identified, in compliance with the Health Insurance Portability and Accountability Act and were accordingly not subject to Institutional Review Board approval.

**Study Samples**

Two samples were drawn in support of this analysis. The first (incident cohort) identified patients newly diagnosed with RA between 1999 and 2004. The study index date in this cohort was the first date of diagnosis with RA. The second sample (biologics naïve cohort) identified patients with RA who appeared to be new users of biologic therapy between 1999 and 2005. The study index date in this cohort was the first observed date of the biologics prescription or administration. The 12-month period prior to the start of the study was used to characterize patients’ baseline experiences.

To be eligible for inclusion in either sample, patients were required to be at least 18 years of age and to have a diagnosis of RA (International Classification of Diseases code, ICD-9-CM 714.0x) on three nondiagnostic claims (i.e., excludes lab testing, radiology, and venipuncture management codes) on different days between January 1, 1999, and March 31, 2004. Patients qualifying for the incident cohort were required to have at least 12 months of continuous enrollment before their first RA diagnosis and at least 24 months of continuous enrollment post except in those cases where inpatient death was recorded. Patients qualifying for the biologics naïve cohort were required to have 12 months of continuous enrollment prior to their first biologics prescription or administration and at least 18-months post except in those cases where inpatient death was recorded. These patients must have had a period free of any biologic agent use between 1996 and the first biologic agent prescription during 1999 to 2005. The 18-month post-period was selected to maximize the number of patients included in the study who were prescribed adalimumab, which was not launched until 2003. Patients in both cohorts were followed until inpatient death, disenrollment, or study end (9/30/06). Patients in either sample were excluded if they were admitted to a skilled nursing facility for 3 or more months or did not have both complete medical and pharmacy data availability.

**Data Capture and Statistical Analyses**

Two files were created in support of each cohort, a patient level summary file and a drug treatment episode file. The patient level file included variables on study entry parameters and patient characteristic such as age, gender, insurance plan type, geographic region, urban/rural indicator, payer type, and baseline utilization of a DMARD, nonsteroidal anti-inflammatory drug (NSAID), or corticosteroids. Additionally, this file included aggregate measures of comorbidity such as the Charlson Comorbidity Index (CCI), Chronic Disease Score (CDS), as well as a history of select comorbid conditions. The drug treatment episode file was constructed to capture utilization of any of 16 treatment regimens on or after the study index date (Table 1).
By definition, the initial drug treatment episode in the biologics naïve cohort was limited to regimens 2 to 5, 7 to 10, 13, and 15 (see Table 1). Drug regimens were further stratified by the presence or absence of concurrent corticosteroid administration, which effectively doubled the number of regimens under evaluation (N = 32). These categories were subsequently collapsed into seven groups (Table 2).

The initial drug episode was assigned by reviewing the medical and pharmacy claims in the first 90 days of follow-up. Patients who did not have a medical or pharmacy claim for a DMARD or corticosteroid during the first 90 days were classified as untreated at index. Since receipt of a biologic agent as therapy was a requirement for entry into the biologics naïve cohort, 100% of these patients were treated at index. A drug treatment episode began on the first day of the prescription or injectable administration and continued until an eligible episode-ending event was recorded. Valid reasons for ending a drug treatment episode included an interruption in therapy of at least 60 days, the addition of a new medication (including corticosteroids), or the switching of one medication for another. Episode duration was calculated as the difference between episode start and end dates. Total treatment duration was calculated as the difference between the beginning of the earliest treatment episode and end of the last treatment episode.

Aggregate comorbidity constructs, such as the Deyo-adapted Charlson Comorbidity Index (CCI)\(^\text{32}\) and Chronic Disease Scores (CDS),\(^\text{33}\) were measured. Annual baseline expenditure was also captured with expenditures to the 2006 price levels, using the medical care component of the Consumer Price Index. Medical and pharmacy claims were evaluated during the baseline period for evidence of any of the following specific conditions: hypertension, diabetes, cardiac conditions, respiratory or opportunistic infection, chronic obstructive pulmonary disease (COPD), malignancy, osteoporosis, cerebrovascular disease, gastrointestinal (GI) disorders, pulmonary embolism, or tuberculosis.

A patient was flagged as having the condition of interest if they had a primary diagnosis indicative of that condition on an inpatient claim or if the definition of the condition included specific pharmacologic treatment (e.g., antidiabetic agents) or if the diagnosis was recorded on nondiagnostic (not laboratory, radiology, or venipuncture) claims on 2 or more days during the baseline period.

Categorical variables were summarized in frequency tables. Continuous and other numeric variables were summarized by presenting the number of observations, the mean, and standard deviation (SD). Chi square tests were used to assess the statistical significance of differences between categorical variables; t-tests and ANOVA were used for continuous variables. Differences with \(p\) values less than 0.05 were considered statistically significant, and \(p\) values

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Regimens Reflecting Drug Treatment Episode File</th>
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<tbody>
<tr>
<td>1. Methotrexate monotherapy</td>
<td></td>
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<tr>
<td>2. Etanercept monotherapy</td>
<td></td>
</tr>
<tr>
<td>3. Infliximab monotherapy</td>
<td></td>
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<tr>
<td>4. Adalimumab monotherapy</td>
<td></td>
</tr>
<tr>
<td>5. Non-TNF-α blocker biologic agent monotherapy</td>
<td></td>
</tr>
<tr>
<td>6. Other DMARD monotherapy (except regimens 1-5)</td>
<td></td>
</tr>
<tr>
<td>7. Methotrexate + etanercept</td>
<td></td>
</tr>
<tr>
<td>8. Methotrexate + infliximab</td>
<td></td>
</tr>
<tr>
<td>9. Methotrexate + adalimumab</td>
<td></td>
</tr>
<tr>
<td>10. Methotrexate + non-TNF-α blocker biologics</td>
<td></td>
</tr>
<tr>
<td>11. Methotrexate + leflunomide</td>
<td></td>
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<tr>
<td>12. Methotrexate + other DMARD (except regimens 7-11)</td>
<td></td>
</tr>
<tr>
<td>13. Multiple biologic combinations include the use of ≥2 biologic agents</td>
<td></td>
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<tr>
<td>14. All other DMARD combination (except regimens 7-13)</td>
<td></td>
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<tr>
<td>15. Tricropic therapy (1 biologic agent + ≥2 DMARD agents)</td>
<td></td>
</tr>
<tr>
<td>16. Corticosteroid ± NSAIDs in the absence of any DMARD</td>
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</table>

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Collapse of Treatment Categories into Seven Groups</th>
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</thead>
<tbody>
<tr>
<td>Group</td>
<td>Regimen</td>
</tr>
<tr>
<td>1. Methotrexate monotherapy</td>
<td>1</td>
</tr>
<tr>
<td>2. Other DMARD monotherapy</td>
<td>6</td>
</tr>
<tr>
<td>3. Biologics monotherapy</td>
<td>2-5</td>
</tr>
<tr>
<td>4. Methotrexate plus a biologic agent</td>
<td>7-10</td>
</tr>
<tr>
<td>5. Methotrexate plus other DMARD</td>
<td>11,12</td>
</tr>
<tr>
<td>6. Other DMARD combination</td>
<td>13-15</td>
</tr>
<tr>
<td>7. Corticosteroid ± NSAIDs in the absence of any DMARD</td>
<td>16</td>
</tr>
</tbody>
</table>
Results

Patient Characteristics

In total, 16,752 patients met all inclusion/exclusion criteria for the incident (newly diagnosed) cohort. Females represented 72% of the sample. The mean (± SD) age of the cohort was 59.8 (± 13.5) years. Thirty-eight percent of patients had Medicare as their primary payer. Patients were followed for an average of 3.9 (± 1.4) years, with nearly 19% of patients having more than 5 years of follow-up. The most frequent comorbid conditions were hypertension (12.8%), diabetes (10.0%), and cardiac conditions (7.4%). The mean (± SD) baseline comorbidity indices were CCI of 0.81 (± 1.21) and CDS of 5.81 (± 3.87). Table 3 summarizes common comorbidities observed during the 12 months prior to diagnosis with RA.

The biologics naïve cohort included 8218 patients. Overall demographics were similar to the incident cohort. Seventy-four percent of the biologics naïve cohort were female, with a mean (± SD) age of 57.2 (± 12.7) years. Patients were followed for a mean of 3.3 (± 1.4) years from start of study, with 11% having more than 5 years of follow-up. The majority of patients were insured by commercial payers (70.8%). The biologics naïve cohort had a higher rate of comorbidity than did the incident cohort (average [± SD] CCI: 1.47 [± 1.14]; CDS: 7.15 [± 3.66]), and incurred higher baseline medical expenditure. The most frequent comorbid conditions were hypertension (12.2%), diabetes (10.7%), and cardiac conditions (6.7%). Table 3 summarizes common comorbidities observed during the 12 months prior to initiating biologic therapy.

Nearly 86% of patients in the biologics naïve cohort received DMARD therapy during the 12 months prior to receipt of their first biologic agent. This finding is consistent with ACR guidelines, which recommend that biologic agents be used after an inadequate response to other DMARDs.17 Speciﬁcally, 66% of patients in the biologics naïve sample were previously treated with methotrexate, while 52% were treated with another DMARD. Three-quarters of all patients received corticosteroids, with or without an NSAID, during this time frame. Almost 6% of patients appeared to be untreated in the year prior to initiating biologics.

Post-Index Treatment Patterns

The use of biologic agents among patients newly diagnosed with RA increased markedly over time, rising from 3% of all patients identiﬁed with RA in 1999 to 26% in 2006. This increase was driven both by increased use of biologics as monotherapy (2.4% in 1999, 17.8% in 2006) and by the use of biologic agents in conjunction with methotrexate (0.9% in 1999, 14.5% in 2006). By the end of 2006, one in four patients with RA was prescribed a biologic agent. The vast majority (98.3%) of biologic agents used during this time frame were TNF-α blockers. Accompanying the increase in biologics therapy there was a decrease in patients treated solely with a DMARD other than methotrexate, or those treated with corticosteroids, with or without an NSAID, in the absence of a DMARD. Figure 1 shows the percentage of patients prescribed each drug regimen under evaluation by year of receipt.

The study also examined the percentage of patients whose ﬁrst observed exposure to biologics was as monotherapy, biologic therapy in conjunction with methotrexate, or biologic therapy in conjunction with another DMARD. As shown in Figure 2, the percentage of patients initiating on a biologic agent in combination with methotrexate increased (29% in 1999, 43% in 2005), while the percentage of patients initiating on a biologic agent in combination with a nonmethotrexate DMARD decreased during the same time frame (41% in 1999, 30% in 2005). During the same period, nearly 30% of patients were initiated on biologic monotherapy regimen, with modest change from 30% (1999) to 28% (2005). Of note, 43% of patients (N = 1223) who initiated a biologic agent in combination with a DMARD other than methotrexate did so in combination with at least two DMARDs.

A more precise, product-level examination of the ﬁrst observed biologic agent during this time frame reﬂects the entry of new biologic agents into the treatment paradigm (Fig. 3). Overall, there was a notable decrease in etanercept-based regimens, while the use of both infliximab and adalimumab increased. Etanercept monotherapy decreased from 29.5% of biologics users in 1999 to approximately 12.2% in 2005. Use of etanercept plus methotrexate decreased from 29.3% of biologics users in 1999 to 15.9% in 2005, with an attendant increase in the use of infliximab (to 15.3% in 2005) and adalimumab (to 11.2%). The non-TNF-α blocking biologic agent, anakinra, was ﬁrst marketed in November 2001, but its use quickly peaked, in 2002 (9.4%), and then remained under 1% in 2005 and 2006.

On average, each patient had 5.8 drug treatment episodes

### Table 3 Baseline Comorbid Conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incident cohort N (%)</th>
<th>Biologic-Naïve Cohort N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients</td>
<td>16,752</td>
<td>8218</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2144 (12.8)</td>
<td>1003 (12.2)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1681 (10.0)</td>
<td>883 (10.7)</td>
</tr>
<tr>
<td>Cardiac conditions</td>
<td>1235 (7.4)</td>
<td>550 (6.7)</td>
</tr>
<tr>
<td>Respiratory infection</td>
<td>789 (4.7)</td>
<td>405 (4.6)</td>
</tr>
<tr>
<td>Opportunistic infection</td>
<td>528 (3.2)</td>
<td>273 (3.3)</td>
</tr>
<tr>
<td>COPD</td>
<td>495 (3.0)</td>
<td>270 (3.3)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>487 (2.9)</td>
<td>207 (2.5)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>289 (1.7)</td>
<td>102 (1.2)</td>
</tr>
<tr>
<td>GI disorders</td>
<td>232 (1.4)</td>
<td>86 (1.0)</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>211 (1.3)</td>
<td>178 (2.2)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>28 (0.2)</td>
<td>17 (0.2)</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>9 (0.1)</td>
<td>7 (0.1)</td>
</tr>
</tbody>
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COPD, chronic obstructive pulmonary disease; GI, gastrointestinal
during 3.3 years of follow-up. Seventy-five percent of the cohort had three or more drug treatment episodes. Not surprisingly, treatment episodes were generally of short duration, with mean treatment length of 4.3 (± 5.5) months. While used less frequently, treatment with the combination regimen of a TNF-α blocker and methotrexate had the longest duration, 5.1 (± 5.7) months, compared with 4.4 (± 6.2) months for biologic monotherapy (p < 0.0001, Fig. 4). For those who had three or more treatment episodes, less than 5% were treated exclusively with biologic agents after the introduction of biologics. The majority of patients received a mix of biologic and nonbiologic regimens, at some point, after receipt of the index regimen.

An evaluation of post-index drug therapies in patients who initiated on biologic monotherapy shows that 7% of these patients (mean ± SD follow-up: 3.5 [± 1.4] years) subsequently received a biologic agent in conjunction with methotrexate (Fig. 5). Conversely, 13% of patients who initiated on a biologic agent in conjunction with methotrexate subsequently received monotherapy with a biologic agent (mean ± SD follow-up: 3.4 [± 1.4] years). Moreover, regardless of which of the two regimens patients received, between 21% and 38% of patients subsequently repeated their index regimen during the follow-up period.

Only 7.2% of patients experienced a treatment interruption. Treatment interruption was less likely to occur during episodes of TNF-α blocking therapy in conjunction with methotrexate (0.3%) than during episodes of TNF-α blocker monotherapy (5.3%). Altogether, 58% of patients switched their treatment regimen, with switching more likely to oc-
The introduction of additional TNF-α-initiated directly on these agents. It is important to note that 15% of patients appeared to be therapy did so after exposure to DMARD therapy. However, the extent to which these findings have impacted actual clinical practice is not known.

Although frequently modified during the course of the study, 59% of patients who initiated on biologic monotherapy were, at the end of study, either still receiving biologic monotherapy or a biologic agent in conjunction with methotrexate (mean ± SD duration follow-up: 3.2 ± 1.4 years). This proportion was higher (67%) for patients who initiated on a biologic agent in conjunction with methotrexate.

Discussion

Current clinical thinking for the management of RA supports early and aggressive treatment, potentially including biologic therapy in selected patients.16,17 This approach has been shown to slow radiographic disease progression, reduce signs and symptoms of RA, and achieve higher rates of disease remission.10,18-20 Additionally, some studies suggest that early and aggressive control of RA-associated inflammation may contribute to reduced morbidity and mortality, especially relating to cardiovascular disease.7,9,34,35 However, the extent to which these findings have impacted actual clinical practice is not known.

The aim of the current study was to quantify the relative use of biologic agents in the management of patients with RA, as well as to characterize their use in a real-world clinical practice setting. Most patients who received biologic therapy did so after exposure to DMARD therapy. However, it is important to note that 15% of patients appeared to be initiated directly on these agents.

The introduction of additional TNF-α blockers during the study window had a notable impact on the pattern of TNF-α blocker prescribing between 1999 and 2005. In the first 2 to 3 years of this analysis, etanercept was the preferred biologic agent, usually as monotherapy. However, etanercept declined as a proportion of biologic prescriptions between 1999 and 2002 while prescriptions for other biologics increased, especially in years when a new agent was launched: 2001 (anakinra) and 2002 (adalimumab). The use of non-TNF-α blocking biologic agents showed a sharp peak in 2002 (year following anakinra launch), but, thereafter, dropped and remained low, presumably because anakinra appears to be not as effective in routine clinical practice.36

Our data showing a low level of non-TNF-α blocking biologic therapy are consistent with international data.37,38 For example, in the British Rheumatology Society Registry (BRSR), only 1.7% of patients receiving biologics between 2001 and 2004 received anakinra.37 However, in the BRSR analysis, the remainder of patients was evenly split between etanercept and infliximab, whereas our data showed a consistent preference for etanercept, at least for monotherapy, in all years except 2002; use of etanercept or infliximab, in combination with methotrexate, in our analysis was more closely matched, especially after 2003. Use of abatacept or rituximab was rare during the study timeframe.

Another finding from the present study was that a significant proportion of patients were treated with biologic monotherapy as their first observed treatment (around 30%) in each year of our analysis. There are considerably more clinical data to support the use of biologics in combination with methotrexate than as monotherapy, and infliximab is approved only for use in combination with methotrexate, although patients in the current study were as likely to receive infliximab as monotherapy as they were to receive it in combination with methotrexate.

Our findings are broadly consistent with data from Germany, showing that 50% of patients receiving etanercept did not receive concomitant DMARD therapy and 33% received etanercept in combination with methotrexate.40 However, in the German analysis, 64% of patients receiving infliximab were taking concomitant methotrexate and only 11% received infliximab monotherapy.40 In this respect, prescribing practices in Germany appear to mirror more closely the labeling for infliximab. Similarly, the pattern of biologic use in the United Kingdom, between 2001 and 2004, in data from the BRSG, showed that 69% of patients receiving biologics do so in combination with a DMARD.37 This likely reflects the National Institute of Clinical Excellence’s (NICE) guidance on use of biologics, which recommends reserving them after the failure of at least two DMARDs, including methotrexate.41 In our study, etanercept was the mostly commonly prescribed TNF-α blocker. It is possible, therefore, that our finding of considerable TNF-α blocker monotherapy prescriptions

![Figure 5](https://example.com/figure5.png)

**Figure 5** Subsequent use of biologic therapy; patients who initiated on biologic monotherapy versus those who initiated on methotrexate in conjunction with a biologic agent. MTX, methotrexate.
Quick turnaround on treatment regimen was noted with short duration of treatment episodes in our analysis (5.1 ± 5.7 months for biologics plus methotrexate, and 4.4 ± 6.2 months for biologics monotherapy). Certainly, other U.S. data indicate a high rate of treatment modification in RA patients. For example, a retrospective review of pharmacy and medical records from 183 RA patients treated with infliximab at Brigham and Women’s Hospital, Boston, showed that 69% required a dose escalation during a mean 58 weeks of follow-up.32 Moreover, 48% discontinued infliximab during the first year, and 67% discontinued at any time during follow-up.32 This discontinuation rate is higher than reported elsewhere; data from The Netherlands showed that 50% of patients discontinued therapy with TNF-α blockers within 37 months.31 In this Dutch study, about 70% of patients were still receiving biologic therapy at the end of the first year of treatment. Although these studies are not directly comparable to our data, and do not report how many patients had biologic therapy reinitiated after discontinuation, it is interesting to note that we found 59% to 67% of patients who initiated on biologics, with or without concomitant methotrexate, were on either biologics monotherapy or a biologic agent in conjunction with methotrexate at the close of the study, despite frequent modifications to treatment.

It is difficult to ascertain the precise clinical intent of these changes in treatment using an administrative database. Further research is needed to determine the reasons for these patterns, and the relative influence of patient (e.g., comorbidities, disease history, preference), physician (clinical experience), and reimbursement factors, and will also help identify best practices for the use of these agents.

Consistent with other international data, we found that RA patients with moderate to severe disease have a high number of comorbidities. The incidence of COPD (3%), cardiac disease (7%), and a history of malignancy (2.5%) in our study was similar to the incidence among biologic users enrolled in the BRSR (COPD 5%, heart disease 6%, and malignancy 3% in their analysis).41 However, the BRSR contained a higher proportion of patients with hypertension than those in our analysis (22% in the BRSR compared with 11% in our analysis) and a lower proportion of patients with diabetes (5% in the BRSR versus 11% in our analysis).37 Interestingly, in analysis of the BRSR, 2% to 3% of patients had a history of tuberculosis or malignancy and yet received biologic therapy.37 Similarly, the biologics naïve cohort in our study included a low number who were clearly at high risk of complications, including those with malignancy (2.5%), lymphoproliferative disorders (0.6%), opportunistic infections (3.3%), or tuberculosis (0.1%). This may reflect physicians’ and patients’ willingness to accept the risks of biologic therapy in order to achieve disease control.

While the present study was based on a large and diverse sample of RA patients, it is not a random population sample. The MarketScan databases comprise employer-sponsored coverage for active employees, dependents, and retirees. It is possible that the use of biologic agents may be dissimilar among patients who are uninsured or who have coverage from other payers (e.g., Medicaid, military). Studies have suggested that insurance coverage may have significant influence on the prescribing of biologic agents by U.S. physicians.22,23,25 Furthermore, the literature suggests that, even among payers covered in the current study, a preference for infliximab over etanercept may exist because of the Medicare reimbursement of infused agents prior to the introduction of the Medicare Modernization Act in 2006.23,44

Several other limitations of this study should be considered when interpreting the results. Physicians and hospital workers record diagnostic information to support patient’s claims for reimbursement for particular services, but no diagnoses are recorded on pharmacy claims for prescription drugs. Consequently, patients with mild RA who are otherwise healthy and who have infrequent physician visits may have been under sampled. Institutionalized patients may also have been under sampled, as patients who were institutionalized for more than 3 months were excluded from the study due to the limited detail available on their claims. The reader should also note that diagnoses are recorded to the extent they are required for reimbursement, but otherwise the clinical information available to researchers were limited.

These limitations notwithstanding, this is one of the largest evaluations of actual use of biologic agents in RA patients in the U.S. The findings provide important insights into real-world clinical practice that cannot be derived from clinical trials.

Conclusions

The results from this national, retrospective analysis show that the use of biologics as a treatment for RA continues to increase, consistent with trends toward earlier and more aggressive treatment. In total, one in four RA patients was treated with a biologic agent by the end of 2006. Irrespective of the initial treatment decision, changes in biologic treatment regimens were frequent, with some treatment modification required after approximately 4 months. Despite frequent changes in therapy, more than half of patients initiating biologic monotherapy or biologic/methotrexate combination remained on one of these regimens 39 months after initiation. These data also highlight the need for further treatment options in the management of RA.

Acknowledgments

We would like to thank Kathy Schulman, Thomson Healthcare, Cambridge, MA, USA, for her lead role in the study this manuscript is based on, and Amelito Torres, Thomson Healthcare, Washington DC, USA, for his work on SAS programming. Editorial support was provided by PHOCUS Inc.
Disclosure Statements

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