Disability outcomes and dose escalation with etanercept, adalimumab, and infliximab in rheumatoid arthritis patients: a US-based retrospective comparative effectiveness study

Abstract

Introduction:
Rheumatoid arthritis (RA) is a chronic disease that if left untreated may substantially impair physical functioning. Etanercept, infliximab, and adalimumab are tumor necrosis factor (TNF) blockers whose FDA-approved indications in the US include moderate to severe RA. TNF-blocker dose escalation has been well documented in the literature; however, the comparative effectiveness of these agents remains uncertain.

Objective:
To compare the effectiveness and dose escalation rates of etanercept, adalimumab, and infliximab in US community settings. We hypothesized that etanercept would be equivalent to infliximab and adalimumab in patient-reported disability 9–15 months after therapy initiation, and that fewer etanercept patients would experience dose escalation.

Methods:
This is a retrospective analysis of the Arthritis, Rheumatism, and Aging Medical Information System (ARAMIS). Adult patients with no biologic use 6 months before TNF-blocker initiation (index) and with Health Assessment Questionnaire Disability Index (HAQ-DI) scores at index and 9–15 months after index were analyzed (218 etanercept, 93 infliximab, and 40 adalimumab).

Results:
HAQ-DI change scores at 9–15 months did not differ by treatment (−0.12, −0.10, and −0.08 points for etanercept, infliximab, and adalimumab, respectively; p = 0.52). Dose increases were observed in 1.4% of etanercept, 10.8% of infliximab (p < 0.001), and 12.5% of adalimumab patients (p = 0.004). HAQ-DI change was associated with pre-index HAQ-DI score (p < 0.0001) and disease duration (p = 0.001).

Conclusions:
Fewer etanercept patients escalated dose than infliximab or adalimumab patients, but improvements in functional disability were similar. These differences may have been influenced by package labeling, mode of administration, or other factors. RA treatment with infliximab and adalimumab in community settings, characterized by dose escalation, did not yield greater disability improvements compared to etanercept, which remained at a relatively stable dose. Uncontrolled treatment selection in this observational design may have influenced outcomes, and prior methotrexate treatment may partly explain disability improvements smaller than typically observed in clinical trials.
Introduction

Rheumatoid arthritis (RA) is an autoimmune disorder characterized by pain, stiffness, joint swelling and tenderness, and in severe cases, progressive destruction of joint tissue. It is a chronic and disabling disease that can shorten life as well as substantially impair physical functioning and overall quality of life. RA currently affects approximately 1.3 million adults in the US, with women representing more than 70% of affected individuals. In the US, the annual excess health care costs associated with RA (compared to matched controls without RA) were recently estimated to be $8.4 billion (US$ 2005). Including the costs of other RA consequences (e.g., productivity loss), as well as intangible costs of quality-of-life reductions and premature mortality, increases the total estimated annual societal costs to $39.2 billion.

Medications routinely used to treat RA include non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, and corticosteroids. Disease-modifying anti-therapeutic drugs (DMARDs), particularly methotrexate (MTX), are indicated for RA patients who have failed one of these first line therapies. Biologic therapies (including tumor necrosis factor [TNF] blockers) are also commonly used in the US to treat moderately to severely active RA.

Etanercept (Enbrel®), infliximab (Remicade®), and adalimumab (Humira®) are three of the most common TNF-blockers that are Food and Drug Administration (FDA)-approved in the US for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active RA. Etanercept and adalimumab can be taken with MTX or used alone. In the US, infliximab is approved in combination with MTX for the treatment of moderately to severely active RA patients.

There are several potentially important differences between the three TNF-blockers with respect to method of administration, dosage, and dosing schedule. While infliximab is administered as an intravenous infusion, etanercept and adalimumab are administered through subcutaneous injection.

The approved dose of etanercept for RA is 25 mg administered twice weekly, or 50 mg administered once weekly without mention of possible dose escalation. The recommended initial dose of infliximab for RA is 3 mg/kg every 8 weeks (after the first infusion and those following at 2 and 6 weeks). Infliximab dose increases in RA may be achieved by administering more medication per infusion (adjusted up to 10 mg/kg) or by shortening the interval between infusions (as frequently as every 4 weeks) as per FDA-approved label. The recommended initial dose of adalimumab for RA is 40 mg every other week which, per FDA approval, may be increased in frequency to 40 mg per week if needed for improved clinical response.

Consistent with the dosing flexibility allowed in their respective labels, studies have found varying dose trajectories for the TNF-blockers over time. Several observational studies have documented high rates of dose escalation for infliximab, with roughly 30% to 60% of patients having an increase in dose within the first year of therapy. Studies that have directly compared dose escalation among RA patients taking TNF-blockers have reported that infliximab dose escalation rates (reported range 30% to 60%) exceed those of adalimumab (reported range 4% to 34%) or etanercept (reported range 0% to 22%). The high cost of TNF-blocker doses, relative to DMARDs, was cited as a rationale for conducting many of the reviews and observational studies published on dose escalation within this medication class.

Despite the dose escalation observed with infliximab and adalimumab in these studies, the clinical effectiveness of increased doses remains uncertain. Published studies are inconsistent about the benefits of dose escalation. At least one study suggested that dose escalation of infliximab could improve response, while another suggested that such findings may be an artifact of escalating dose during temporary declines in response. Neutralizing antibodies, an immunogenicity response associated with monoclonal antibody therapies, were detected in 33% of infliximab patients and 28% of adalimumab patients in separate studies. Etanercept is a fusion protein rather than a monoclonal antibody; we are not aware of published studies associating etanercept with the formation of neutralizing antibodies. The formation of neutralizing antibodies against anti-TNF monoclonal antibodies (adalimumab and infliximab) has been shown to be associated with reduced treatment response and may lead to dose escalation.

Recently, a randomized, double-blind study of Czech RA patients showed that increasing the infliximab dose from 3 mg/kg to 5 mg/kg in RA patients with residual disease activity did not improve efficacy but increased toxicity. One-year patient outcomes (defined by the clinician-rated 28-joint Disease Activity Score [DAS-28]) showed only mild improvement, with no statistically significant difference between patients randomized to higher or lower doses. In addition, individual components of the DAS-28 and secondary endpoints (swollen joints, tender joints, erythrocyte sedimentation rate, C-reactive protein) were not different between the two arms.

In an observational cohort study of >700 patients from 44 European treatment centers, significantly lower dose escalation rate was found for etanercept (3%) than for either adalimumab (10%, p < 0.001) or infliximab (35%,...
p < 0.001) over an 18-month treatment period. Despite this difference in dose escalation, patient outcomes at 18 months (defined by DAS-28) were similar across the three TNF-blocker therapies and dose escalation showed no measurable benefits on this disease activity outcome.

Another observational study conducted in Europe with registry data showed similar results with higher dose escalation rates in adalimumab and infliximab compared to etanercept but with no statistical difference in clinical benefits between the anti-TNF agents as measured by DAS-28. These studies indicate that the increased dosing of adalimumab and infliximab does not necessarily translate to better health outcomes or additional clinical benefit. Because treatment algorithms and patterns may differ between European and US practice settings, we conducted a similar study to evaluate whether these associations are observed in a US RA patient population.

Objectives

The objectives of this study were to compare the effectiveness (primary) and dose escalation rates (secondary) of etanercept, adalimumab, and infliximab in a US community-based setting. Our a priori hypotheses were that:

(1) The three TNF-blockers, etanercept, adalimumab, and infliximab, would be equivalent relative to patient self-reported functional status approximately 9–15 months after initiating TNF-blocker therapy.

(2) Consistent with prior observational studies, we specifically expected that, compared to adalimumab and infliximab, a smaller percentage of patients treated with etanercept would experience dose escalation and/or would receive doses in excess of the minimum amount indicated in US labeling 9–15 months after treatment initiation.

Patients and methods

Primary data source

This was a retrospective, observational cohort study of RA patients who had initiated TNF-blockers after at least six months without TNF-blocker therapy. Data were from the Arthritis, Rheumatism, and Aging Medical Information System (ARAMIS), a national chronic disease data-bank system consisting of parallel, longitudinal, clinical data sets from US and Canadian locations.

ARAMIS data describe the courses of thousands of patients with rheumatic diseases. Approximately 6500 RA patients (meeting diagnostic criteria of the American College of Rheumatology) have been enrolled, with an average 7.6 years of follow-up. The patients' medical care or specific treatment is not affected as a result of ARAMIS enrollment, and patients continue to receive standard care from their personal physicians.

Patients are surveyed at 6-month intervals, using standardized assessment tools. At time of enrollment, patients provided informed consent, which included permission to routinely contact patients by mail and/or telephone for clarification of questionnaire data. No additional consent was obtained for the current retrospective study. This study was approved by the Stanford University Human Subjects Research Protection Program.

Measure of functional status (disability)

The Health Assessment Questionnaire (HAQ) is a generic patient-reported outcome assessment instrument. It has been used widely in studies of rheumatic conditions, such as RA. HAQ data include the HAQ Disability Index (HAQ-DI), the HAQ Pain Scale, and the Patient Global Visual Analog Scale (VAS). The HAQ-DI assesses patient functional ability. It has been shown to be reliable and valid in numerous languages and in a variety of clinical and research contexts. The HAQ-DI is the criterion measure used to support all three TNF-blockers’ FDA labeling claims of ‘improved physical function’ in RA patients. It comprises 20 items with 2–3 items in each of eight categories: dressing and grooming, hygiene, arising, reach, eating, grip, walking, and common daily activities. There are four response options, scored 0–3: (0) without any difficulty; (1) with some difficulty; (2) with much difficulty; (3) unable to do. To obtain a HAQ-DI score, the highest score from each category is summed and then divided by 8 to yield a score of 0–3. Zero represents no impairment and 3 represents complete disability.

For this study, we used HAQ-DI scores to assess changes in functional status. We defined change as the difference between the HAQ-DI score from the last assessment available for a patient prior to TNF-blocker initiation and the score closest to 12 months post initiation. Negative change scores represent an improvement in physical function.

Patient selection

Patients were included in this study if they had begun TNF-blocker therapy on or after the respective FDA approval date for RA indications (11/2/1998 for etanercept, 11/10/1999 for infliximab, and 12/31/2002 for adalimumab) and met inclusion but not exclusion criteria. Table 1 shows the study’s inclusion and exclusion criteria in greater detail.

Measures

Use of specific medications is reported for each month of the 6-month period for each survey. Therefore, the timing...
Disability and dose escalation with TNF blockers in RA

HAQ-DI change among the three treatment cohorts. A general linear model tested differences in the primary outcome variable, change in HAQ-DI score. Additional information on validation procedures is available from the corresponding author.

Statistical analyses

Outcomes
The primary outcome variable was change in HAQ-DI score. A general linear model tested differences in HAQ-DI change among the three treatment cohorts.

Dosing data validation procedures for this study included patient interviews during the study period and, to the extent possible, cross referencing to billing data, chart reviews and/or to prescription claims data from IMS LifeLink Longitudinal Prescription Database (LRx). Additional information on validation procedures is available from the corresponding author.

Selection bias and treatment cohort comparisons
In addition to providing information on their use of TNF-blockers, subjects reported their use of prednisone, plaquenil, and methotrexate, as well as physician office utilization for several specialties and a variety of medical co-morbidities.

Data on medication use (corticosteroids in the 6 months before index), resource use (outpatient visits per year per patient), treatment-related costs (total costs), and use of doses above the US label minimum recommendation were also included in the analysis.

Table 1. Inclusion and exclusion criteria.

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>A diagnosis of rheumatoid arthritis recorded in the ARAMIS data bank.</td>
<td>Any diagnosis of psoriasis, psoriatic arthritis, Crohn’s disease, or ankylosing spondylitis at any time before or within 12 months post index date.</td>
</tr>
<tr>
<td>An observed start month (index) between the FDA-approval date and December 2007 for etanercept, infliximab, or adalimumab therapy.</td>
<td>Treatment with any other biologic agent for RA other than a patient’s index therapy within 12 months of continuous treatment with the index TNF-blocker initiation was required. Thus, the current study is limited to therapy ‘completers’. It does not include data for patients with shorter lengths of treatment or with changes in therapy.</td>
</tr>
<tr>
<td>18 years or older on index date.</td>
<td></td>
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<tr>
<td>No use of any biologic treatment within 6 months prior to index date.</td>
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<tr>
<td>12 months after the index date.</td>
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<tr>
<td>Two HAQ-DI scores in the 12-month period after TNF therapy initiation.</td>
<td></td>
</tr>
<tr>
<td>At least one HAQ-DI score during the 6-month assessment period prior to the index date for which no biologic treatment was reported.</td>
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</table>

If the most recent assessment prior to the index date did not qualify, an earlier qualifying assessment was used if it was within 18 months of the index date. At least 9 months of continuous treatment with the index TNF-blocker initiation was required. Therefore, disability scores in this analysis were based on assessments of up to 3 months prior to or following the dates such as the index date or end date of the designated study observational period.

The minimal dose for etanercept is 50 or 25 mg per injection (50 mg per week); the minimal dose for infliximab is 3 mg/kg every 8 weeks; and the minimal dose for adalimumab is 40 mg per injection, every other week. We defined dose escalation as the first occurrence of any upward adjustment in dose or an increase in dosing frequency for each TNF-blocker from the lowest indicated starting dose and unit of time during the post-index period (25 mg biweekly or 50 mg once-weekly for etanercept, 3 mg/kg every 8 weeks after the third infusion for infliximab, 40 mg biweekly for adalimumab).

Standard dosing elements reported on the HAQ include a monthly report over the 6 months during which patients had taken each medication and the average number of injections (for infliximab, number of infusions) over the entire assessment period. Infliximab patients also reported the number of milligrams per kilogram per infusion.

Dosing data validation procedures for this study included patient interviews during the study period and, to the extent possible, cross referencing to billing data, chart reviews and/or to prescription claims data from IMS LifeLink Longitudinal Prescription Database (LRx). Additional information on validation procedures is available from the corresponding author.
month in the 6 months before index), co-morbidity (cardiovascular, pulmonary, neurologic, gastrointestinal conditions), patient demographics (age, sex, race, education, body mass index [BMI]), and RA history (time since RA diagnosis, index HAQ-DI, index date, gap between pre-index HAQ and index date) were analyzed to examine a priori differences among the three treatment cohorts. These characteristics were entered into logistic regression analyses to quantify the influence of patient characteristics on the selection of index therapy (etanercept vs. adalimumab; etanercept vs. infliximab).

Results

Patient characteristics

Between December 1998 and October 2008, 1870 RA patients completed at least one HAQ. Of these, 626 patients reported ever having received treatment with at least one TNF-blocker. Of patients with TNF-blocker use, 478 (76.4%) reported being on their therapy in two consecutive time periods. Table 2 shows reasons for study exclusion by TNF-blocker therapy.

<table>
<thead>
<tr>
<th>Number of RA Patients Initiating on TNF-Blocker</th>
<th>Etanercept</th>
<th>Infliximab</th>
<th>Adalimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exclusion Criteria – not on TNF Drug at least 2 phases</td>
<td>320 100</td>
<td>202 100</td>
<td>104 100</td>
</tr>
<tr>
<td>Excluded</td>
<td>54 16.9</td>
<td>60 29.7</td>
<td>34 32.7</td>
</tr>
<tr>
<td>Remaining</td>
<td>266 83.1</td>
<td>142 70.3</td>
<td>70 67.3</td>
</tr>
</tbody>
</table>

Other Reasons for Exclusion*

- Any patient with use of any biologics within 6 months prior to the patient’s index date
- Patients with <9 months cumulative therapy during first 3 HAQ cycles
- Use of another TNF while on the first TNF during the first two HAQ cycles
- No baseline HAQ within 18 months of index therapy
- Patients excluded for any of the above criteria

Total N of Study Patients 218 68.1 93 46.0 40 38.5

*These counts are not mutually exclusive. Patients could have been excluded based on more than one criterion.

Follow-up (mean 5.3 [SD 2.5] vs. 2.5 [SD 2.5] years, p < 0.001) and more HAQ-DI assessments (mean 9.8 [SD 4.5] vs. 5.6 [SD 4.7], p < 0.001). They also reported more co-morbidities (mean 0.8 [SD 0.9] vs. 0.4 [SD 0.8], p < 0.01). HAQ-DI scores (mean 1.1, SD 0.8) also showed marginally less disability than that observed in excluded patients (mean 1.2, SD 0.7, p = 0.07).

Differences between included and excluded patients were also similar for the infliximab and adalimumab treatment cohorts.

For patients treated with infliximab or adalimumab, included vs. excluded patients did not differ with respect to education level (mean 13.8 [SD 2.9] vs 14.0 [SD 2.5] years, p = 0.75 for infliximab; 13.5 [SD 3.1] vs. 14.0 [SD 2.3], p = 0.36 for adalimumab). Finally, adalimumab patients excluded from the current study had significantly more disability as measured by their index HAQ-DI (mean 0.8 [SD 0.8] vs. 1.2 [SD 0.7], p = 0.01).

Treatment cohort differences at index assessment

Table 3 shows demographics in the overall study sample and among the three treatment cohorts at index and follow-up. Of the 351 study patients, 82.6% (n = 290) were female; the mean age was 57 years (SD 12 years). Mean BMI was 26.9 kg/m² (SD 6.1 kg/m²). The average disease duration across treatment cohorts was 18.9 years (SD 10.9 years). White, non-Hispanic patients accounted for 87.7% of the study sample.

Etanercept patients did not differ significantly from infliximab or adalimumab patients relative to race, or disease duration. Etanercept patients also did not differ from infliximab patients on HAQ-DI index scores, but reported higher HAQ-DI disability compared with adalimumab patients (1.20 vs. 0.92, p < 0.05). Infliximab patients did not differ significantly from adalimumab patients relative to race or disease duration, but differed with HAQ-DI

Table 2. Sample selection.

<table>
<thead>
<tr>
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Other Reasons for Exclusion*

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Total N of Study Patients 218 68.1 93 46.0 40 38.5

*These counts are not mutually exclusive. Patients could have been excluded based on more than one criterion.
Table 3. Demographics at index date and length of follow-up available after index date.

<table>
<thead>
<tr>
<th></th>
<th>Etanercept</th>
<th>Mean</th>
<th>SD/Mdn</th>
<th>Infliximab</th>
<th>Mean</th>
<th>SD/Mdn</th>
<th>Adalimumab</th>
<th>Mean</th>
<th>SD/Mdn</th>
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<tbody>
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<td>55.1</td>
<td>11.6/54.9</td>
<td>93</td>
<td>60.2***</td>
<td>12.8/59.9</td>
<td>40</td>
<td>56.6</td>
<td>13.0/56.0</td>
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<td>31–45</td>
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<td>84.4</td>
<td>78</td>
<td>83.9</td>
<td>28</td>
<td>70.0*</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

| At treatment initiation | | | | | | | | | |
| Education (years) | 14.50 | 2.20 | | 13.75* | 2.93 | | 13.45* | 3.13 | |
| Disease duration (years) | 18.52 | 10.88 | | 19.66 | 11.36 | | 19.16 | 10.19 | |
| Number of HAQsa | 9.80 | 4.53 | | 7.74* | 3.13 | | 5.08* | 1.95 | |
| Follow-up (years)b | 5.25 | 2.54 | | 4.09* | 1.79 | | 2.80* | 1.29 | |
| # comorbid conditionsc | 0.79 | 0.94 | | 1.02* | 1.02 | | 1.28* | 0.96 | |
| HAQ-DI (0–3, 3 = worst) | 1.20 | 0.73 | | 1.24 | 0.72 | | 0.92 | 0.76 | |

| Other Treatments | | | | | | | | | |
| Using methotrexate | 137 | 62.8 | 62 | 66.7 | 25 | 62.5 | |
| Using prednisone | 133 | 61.0 | 47 | 50.5 | 21 | 52.5 | |

| Methotrexate, mg/wk | 13.8 | 4.7 | 14.2 | 4.4 | 13.5 | 7.1 | |
| Prednisone, mg/day | 6.9 | 5.6 | 7.4 | 5.3 | 5.9 | 3.3 | |

*aNumber of HAQs: number of questionnaires available for patients after the initiation of the drug (most endpoints calculated only from the index and two following questionnaires).

bFollow-up time in years: time period in years from (date of the last questionnaire – date of the index questionnaire; most endpoints calculated only in the 9–15 months after index).

cComorbid conditions: hypertension, heart attack, other heart conditions (angina or heart valve), stroke, diabetes, cancer, kidney problems, lung problems, ulcers/stomach problems, liver problems, neurological problems.

Comparisons (vs. etanercept) significant at the 0.05 level are indicated by * and at p<0.001 by ***.

index scores (1.24 vs 0.92, p<0.05). Also, there were significant differences between etanercept and infliximab patients for gender, and between etanercept and adalimumab patients for age at treatment initiation and age at disease onset.

As Table 3 also shows, several characteristics differed significantly between etanercept patients and the other two treatment cohorts. Etanercept patients were younger than infliximab patients at the time of TNF-blocker treatment initiation (mean 55 years, SD 11.6 vs. 60 years, SD 12.8; p<0.001), and at the age of RA diagnosis (mean 37 years, SD 13.4 vs. 41 years, SD 15.8; p<0.05). Compared to adalimumab patients, a higher percentage of those treated with etanercept were female (84.4% vs.
70.0%, p < 0.05). Etanercept patients tended to have on average significantly more education (14.5 years) than infliximab (13.8 years, p < 0.05) or adalimumab patients (13.5 years, p < 0.05). Those treated with etanercept also differed significantly from those treated with either infliximab or adalimumab relative to number of follow-up assessments available after index date (mean 5.3 for etanercept vs. 4.1 for infliximab; 2.8 years for adalimumab; p < 0.05 for both comparisons to etanercept) and number of co-morbidities (0.79 for etanercept vs. 1.02 for infliximab vs. 1.28 for adalimumab; p < 0.05 for both comparisons to etanercept).

We conducted multivariate logistic regressions to predict the likelihood of being prescribed infliximab or adalimumab relative to etanercept and infliximab relative to adalimumab. After removing non-significant predictors, only age at index date (p = 0.0008) was predictive of infliximab vs. etanercept use. A similar model for the selection of adalimumab (vs. etanercept) showed that only education (p = 0.0019) and HAQ-DI prior to index (p = 0.0009) remained significant predictors of treatment selection. Because the number of independent variables associated with treatment selection was small, significant predictors were included directly as covariates in subsequent multivariate models to assess any differences in functioning or dose escalation outcomes.

**HAQ-DI scores**

Table 4 shows HAQ-DI scores for each study group at index, first post-index assessment, and second post-index assessment. Figure 1 shows the mean HAQ-DI change scores by TNF-blocker treatment, 9–15 months post-index. HAQ-DI score decreased by 0.12 points for etanercept patients, 0.10 for infliximab and 0.08 for adalimumab patients. Within the general linear model constructed to test predictors of HAQ-DI change scores over 9–15 months, the omnibus test for choice of index treatment was not significant (F [2,306] = 0.66, p = 0.52). However, the magnitude of HAQ-DI improvement was greater with higher HAQ-DI scores at index (F [1,306] = 31.44, p < 0.0001) and with shorter disease duration prior to index (F [1,306] = 10.85, p = 0.001).

To test our pre-planned contrasts, we constructed 90% CI for the difference in HAQ-DI change scores between etanercept and each of the other TNF-blockers. Etanercept patients showed a mean HAQ-DI improvement that was 0.02 points greater than the mean change for infliximab (t[309] = 0.36, p = 0.72). While the 90% CI (−0.11, 0.07) included zero, the interval was not contained within the pre-defined range of −0.022 to 0.022 to support a claim of equivalence. The interval on each side of the difference in change scores (0.09) was wider...
than the pre-specified range, indicating that the cohort did not have adequate power to evaluate equivalence. Etanercept patients also showed a mean HAQ-DI improvement that was 0.04 points greater than the mean change for adalimumab ($t[256]=0.53, p=0.60$). Again, the 90% CI ($-0.16, 0.08$) included zero, but the interval was not contained within the pre-defined range for equivalence, and the mean difference itself was outside that range. Thus, while the HAQ-DI differences between treatments were neither significantly different nor as large as the minimally important differences in community settings, the study was not adequately powered to determine equivalence.

**Dose escalation**

Table 4 shows the dose escalation pattern for patients in each of the three treatment cohorts. Within 12 months post-index, three etanercept patients increased their dose (1.4%), as well as ten infliximab (10.8%) and five adalimumab (12.5%) patients. Dose escalation rates were not consistent across treatment cohorts ($X^2 [2 df]= 16.82, p<0.001$). Dose escalation was observed in significantly fewer etanercept patients than infliximab patients ($p<0.001$) or adalimumab patients ($p=0.004$). All but one of the dose escalations observed in this study occurred 7–12 months post-index, after patients previously had reported one HAQ-DI following initiation of their TNF-blocker.

Figure 2 displays the time to dose escalation reported as Kaplan–Meier curves showing each of the three TNF-blocker cohorts. The figure suggests that an increased hazard of dose escalation persists for infliximab and adalimumab after the 9–15-month period planned for these analyses. Separate Cox proportional hazards regressions, including covariates for age, education, and pre-index HAQ-DI score, showed significantly higher hazards of dose escalation for infliximab (HR = 15.76, $p<0.001$) and adalimumab (HR = 8.26, $p<0.001$) relative to etanercept. None of the covariates significantly predicted dose escalation.

For the entire study cohort, TNF-blocker dosing in excess of US labeling was rare, occurring with only 12 (3.4%) patients within 12 months after index. This suggests that most dose escalation occurred within the dosing limits recommended by US label. Infliximab patients did not report excess dosing at a greater frequency ($n=3$, 3.2%) than did etanercept patients ($n=2$, 0.9%, $p=0.171$). However, adalimumab patients were more likely than were etanercept patients to report dosing in excess of label recommendations ($n=7$, 17.5%, $p<0.001$).

**Discussion**

Among RA patients prescribed TNF-blockers, disability improvements were comparable for those taking etanercept, infliximab, or adalimumab. Despite this similarity in effectiveness, the dosing patterns for the three TNF-blockers varied during the 1-year study period. Increases in the index dose were observed significantly more often among infliximab and adalimumab patients than among etanercept patients. Although adalimumab patients were more likely than etanercept patients to report dosing in excess of the minimum US label recommendations, dosage in excess of US label was rare.
Because the US FDA-approved labels for adalimumab and infliximab permit flexible dosing, we expect to see higher dose escalation rates for these agents compared to etanercept, whose label does not include variable dosing for RA. Why did the treatment cohorts show comparable improvements in disability despite varying rates of dose escalation? First, RA patients taking infliximab or adalimumab may have experienced smaller initial disability improvements than did etanercept patients, with dose escalation used to achieve a level of improvement more consistent with expectations (and with the level experienced by etanercept patients). Conversely, patients may lose response to TNF-blockers over time, necessitating an increased dose over the course of therapy.

The present study was not designed to test directly whether clinicians decided to escalate dose after an assessment of inadequate or declining response. Most of the observed dose escalation occurred 7–12 months post-index, consistent with time to TNF dose escalation reported elsewhere33,50, and after the first post-index set of HAQ-DI scores were collected for study subjects. The assessments 6 months post-index may have been available to clinicians, who could then recommend dosage changes before the end of our study period. However, those first post-index HAQ-DI scores represented changes of −0.14 for etanercept patients, −0.13 for infliximab patients and −0.11 for adalimumab patients. Thus, there appears to be little support for an explanation of differing response in the first 6 months of the study. At least one other study has suggested that TNF-blocker response differences emerge only after 6 months16, but the ARAMIS database would not contain sufficient detail to examine disability differences in the months between the 6- and 12-month post-index assessments.

Second, dose increases may have occurred for reasons other than clinical lack of efficacy on HAQ-DI scores. Changes in clinical response that were weakly correlated to HAQ-DI scores may have prompted dosing changes, or dosing may have been escalated to permit reduced dosing of concomitant medications. However, we found no evidence for other treatment patterns that could consistently predict higher dose escalation rates among infliximab and adalimumab patients. The percentage of patients who used corticosteroids at index (61.0% etanercept, 50.5% infliximab, 52.5% adalimumab, both p > .05 vs. etanercept) and at 9–15 months (52.3% etanercept, 45.1% infliximab, 43.6% adalimumab, both p > 0.05 vs. etanercept) were comparable across TNF-blocker therapies. Similarly, changes in the number of outpatient visits were comparable across treatment groups, with the exception of a slight increase in visits for infliximab patients (likely associated with the receipt of drug infusions).

Interestingly, these findings, consistent with a few prior studies, suggest that treatment of RA with infliximab and adalimumab in community settings, while associated with dose escalation, does not yield greater disability improvements compared with etanercept treatment, which is characterized by stable dosing27,28,32,33. This suggests two corollary conclusions. First, the clinician, deciding between dose escalation and change of medication, is not likely to see additional benefit from escalation. Consequently, a better decision might be to select another anti-TNF drug or a biologic agent from a different therapeutic class. Second, cost-effectiveness of TNF-blocker treatments is likely to be greater when escalation is not practiced, because costs increase directly with dose, while benefits do not.

Study limitations

As with prior observational studies of dose escalation in TNF-blocker treatments32, this study is subject to several limitations. First, patients were not randomized to treatments. Therefore, the treatment cohorts selected for this study may have had observed or unobserved differences associated with choice of index TNF-blocker therapy. For example, patients treated with etanercept or infliximab tended to be older and/or to have participated in ARAMIS longer, and also had larger study samples, which is likely a function of these medications’ earlier FDA approval dates for RA compared to adalimumab. We did not directly test year of index date as a covariate in our regression models. Differences between drugs in third party reimbursement may have affected treatment choices. Prior to the Part D drug benefit introduced with the Medicare Modernization Act, coverage of infusions through the Part C benefit resulted in easier access to Medicare reimbursement for infliximab than for other TNF-blockers. The difference in reimbursement may persist for some Medicare Part D patients who reach the ‘donut hole’ threshold for reimbursement. Private payers also have mechanisms for establishing preferred drugs within a class, which may have contributed to unknown effects in this study.

The level of disability reduction observed is a function of the settings in which subjects were recruited. The overall decrease in HAQ-DI scores (0.11) is consistent with the mean response rate observed after methotrexate treatment in RA community populations (0.11 HAQ-DI points)31. It is half of the minimal clinically important difference of 0.22 referenced in randomized clinical trials16–49, but comparable to recent estimates of the minimally important difference in clinical practice settings (0.09 HAQ-DI points for improvement)52. Such differences between clinical trials and observational studies have been observed elsewhere; the higher responses observed in trials have been attributed to selection of more severe and less treatment-experienced patients, plus an increased risk of flare activity at baseline due to washout requirements53.
Additionally in this study, patients were not naïve to methotrexate, and more than half were using methotrexate at index. Widespread use of methotrexate may have reduced the overall range of potential improvement, and possibly our ability to detect improvement differences, among the TNF-blockers.

This study was not designed to capture additional factors that may have influenced decisions to increase dose; ARAMIS does not include physician reports or clinical findings needed to calculate outcomes such as ACR improvement criteria or EULAR scores. We also did not have the data to study the role of physician incentives, if any, in escalating any of these agents. Prospective studies could test the time-dependent relationship between disability improvements, other clinical outcomes, and decisions to increase TNF-blocker dosing. Furthermore, our measure of dose escalation counted the first increase in dose, rather than requiring patients to remain at increased dose for a minimum period to count as escalation. The level of detail available in our dosing data did not support sensitivity analyses of other dose escalation definitions. Our measure may therefore overestimate dose escalation rates, although the risk of overestimation should be equal across TNF-blockers.

The study design required that patients persist on therapy for at least 9 months. This approach has been used in other studies measuring dose escalation among TNF-blockers where dose escalation is of greater interest than other potential treatment modifications. The limitation of this design choice is that the cohort may exclude patients who showed no response to treatment, where discontinuation or switching may have been a more appropriate treatment modification. However, comparable discontinuation and switch rates among etanercept, adalimumab, and infliximab patients within the first 12 months of initiating biologic treatment have been reported elsewhere. Indeed, cohort exclusions in our study due to early discontinuation ranged from 1.9%–6.4% among the three treatment cohorts, and exclusions due to the presence of a second TNF within 9 months of index ranged from 6.3%–13.5% of the treatment cohorts (Table 2). This suggests that exclusions due to switching or discontinuation did not disproportionately affect one of the treatment cohorts over others.

The ARAMIS databank is representative of RA patients who seek care at the sites participating in the registry. However, the largest ARAMIS sites by patient counts are academic medical centers. It is possible that this may result in a higher percentage of individuals gaining access to aggressive medical treatment (such as biologic therapies) or a higher percentage receiving treatment according to practice guidelines than would be observed in the nation as a whole. Direct costs for the treatment of RA are driven in large part by medication costs, particularly biologic agents. Moreover, the potential financial burden of biologic treatment is strongly influenced by the substantial heterogeneity in medical practices.

Without a clear determination that TNF-blockers have differential real-world effectiveness on disability and other relevant outcomes, the cost-effectiveness of these treatments will be influenced to a greater degree by the quantity of treatment resources consumed by patients. To the degree that the costs of these drug regimens at usual starting doses are comparable, treatment with stable dosing patterns should be more cost-effective than treatment patterns with dose escalation. Yet because the US labels for infliximab and adalimumab give clinical discretion to escalate doses, while the label for etanercept does not, the clinician’s choice of TNF-blocker influences the potential for dose and cost increases during RA treatment. Among studies published to date, there is scant evidence to support clinical benefit from dose escalation of TNF-blocker treatment. Additional studies are needed to assess the short- and long-term cost-effectiveness of these TNF-blocker therapies and to quantify any specific, non-medication cost offsets that may result from improved function in patients with RA.

Conclusions

In this study, RA patients taking etanercept, infliximab, or adalimumab reported comparable disability improvements within 9–15 months, but increases in the index dose were observed significantly more often among infliximab and adalimumab patients than among etanercept patients. The degree of disability improvement observed across treatment groups in this study is consistent with estimates of minimally important differences in community settings, but less than that reported in clinical trials. With limited evidence of the additional benefits of dose escalation of TNF-blockers, cost-effectiveness of TNF-blocker treatments is likely to be greater when escalation is not practiced.

Transparency

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Declaration of financial/other relationships

D.R.G. and D.J.H. were employed by Amgen and owned Amgen stock during the conduct of the study. D.R.G. contributed to the study design and interpretation of the results. V.F.S., B.B., C.F.F., B.L. and J.F.F. have disclosed that they have no significant relationships with or financial interests in any commercial companies related to this study or article. D.J.H. contributed to the study design, oversaw study execution, and contributed to
interpretation of the results. V.F.S. contributed to the study design, oversaw study execution, contributed to interpretation of the results, and drafted the manuscript. B.B. contributed to the study design, oversaw data validation, contributed to interpretation of the results. C.F.F. contributed to the study design, performed some of the statistical analysis and contributed to the interpretation of the results. B.L. performed the majority of statistical analysis and contributed to the interpretation of the results. J.F.F. contributed to the study design, oversaw study execution, and contributed to interpretation of the results. All authors read and approved the final manuscript.

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