An Assessment of Emerging Patterns of Etanercept Use in the Treatment of Rheumatoid Arthritis

by Joseph J. Rebholz and Lee A. Mork

Rheumatoid arthritis (RA) is a systemic autoimmune disease that affects approximately 0.8% of the population. This chronic condition is characterized by progressive joint damage; it produces significant morbidity and contributes to early mortality. Drug treatment for RA has consisted of nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and a set of drugs that are thought to alter the course of RA and are often collectively referred to as disease-modifying antirheumatic drugs (DMARDs) (e.g., methotrexate, hydroxychloroquine).

In the past, the traditional approach to drug treatment for RA was early use of NSAIDs, with DMARDs reserved for second-line use when the response to NSAID therapy became unsatisfactory. This approach has been challenged by evidence that joint damage and disability can occur early in the course of the disease. Aggressive early treatment with DMARDs is being used in the belief that it will slow early disease progression and delay joint deformity, although only a few evaluations of this approach have been published. While short-term, randomized, placebo-controlled trials of DMARDs have demonstrated their ability to provide clinical improvement, far fewer studies have attempted to measure long-term outcomes.

Clinical management of DMARD therapy is based primarily on individual patient response over time. The efficacy and toxicity of each agent varies widely from patient to patient and over the course of treatment. The consensus is that weekly low-dose methotrexate should be the first DMARD tried because of its comparative efficacy, rapid onset of action, and lower toxicity. These properties explain why methotrexate has the highest rate of continued long-term therapy. Beyond this consensus, empirically-driven patient management and the absence of established clinical guidelines have fostered an environment in which many different drug regimens are being used in the absence of firm clinical data describing their comparative efficacy or tolerability. These include combination dual- and triple-DMARD therapy. Use of these combination therapies is widespread. A 1995 survey of 207 rheumatologists indicated that 93% used combination DMARDs in their clinical practice, even though trials on the benefits of combination therapy have produced mixed results.

Recently, another drug has become available for the treatment of RA. Etanercept is a new DMARD that was first approved for use by the Food and Drug Administration (FDA) in November 1998, with an indication for moderate to severe RA.
in patients unresponsive to one or more DMARDs. This indication was expanded to cover juvenile RA in May 1999. In June 2000, etanercept was approved for first-line use to delay structural damage in patients with moderately to severely active RA. Etanercept is a genetically engineered version of the p75 tumor necrosis factor (TNF) receptor that binds and inactivates TNF, preempting its role in the inflammatory response associated with RA.\(^9\) Randomized, double-blind, placebo-controlled trials have demonstrated etanercept’s efficacy as monotherapy and in combination with methotrexate.\(^11-23\) For RA therapy, etanercept is given as twice-weekly subcutaneous injections.

Given the variety of drug regimens already employed for the treatment of RA, an obvious question surrounds the types of drug regimens incorporating etanercept that are being used in clinical practice. Is etanercept being used with DMARDs other than methotrexate, or in combination with more than one DMARD? The purpose of this study is to describe the early, emerging patterns of etanercept use in one health plan. For patients who have started therapy with etanercept, this study describes pre-etanercept treatment regimen types, initial etanercept treatment regimen types, and changes to initial etanercept treatment regimens over the first three months of treatment.

### Methods

**Data Source**

Data for this retrospective drug-utilization analysis came from the outpatient pharmacy claims data for a 500,000-member Midwestern health plan. Claims for prescriptions filled from November 1, 1998, through June 30, 1999, were reviewed to identify patients with at least one claim for etanercept. Claims histories covering etanercept and other DMARDs for the period March 1, 1998, through June 30, 1999, were collected and assembled into patient-level utilization patterns over time. The other DMARDs included were auranofin, aurothioglucone, azathioprine, chlorambucil, cyclophosphamide, cyclosporin, hydroxychloroquine, leflunomide, methotrexate, penicillamine, and sulfasalazine.

**Patient Selection and Regimen Classification**

All patients who submitted a pharmacy claim for etanercept from its FDA approval date of November 1998 through June 1999 were eligible for inclusion in the study. Each patient in the study had his or her eligibility dates with the health plan reviewed to determine the patient-specific date window within which pharmacy claims could be expected. Patients whose initial eligibility dates were within 60 days of their first etanercept claim were excluded from the study population because of uncertainty about when they initiated etanercept therapy.

Patient utilization patterns were reviewed for classification in three periods: a pre-etanercept period based on DMARD therapy in the two months before the first etanercept prescription; an initial etanercept period based on therapy in the first 30 days after the first etanercept prescription; and a 90-day etanercept period based on therapy three months after the first etanercept prescription.

For the pre-etanercept period, patients were classified into categories of DMARD therapy: monotherapy for single DMARD use, dual therapy for concurrent use of two DMARDs, triple therapy for concurrent use of three DMARDs (see Table 1, above). Patients with no DMARD prescriptions in the two months before their first etanercept prescription were classified as follows: None, if they had nine months of history with no DMARD use prior to their first etanercept claim; None with HX, if they had DMARD use prior to two months before their first etanercept prescription; Inadequate HX, if they showed no DMARD use but were eligible with the health plan for less than nine months before their first etanercept prescription. Because of the prevalence of methotrexate use in DMARD therapy and its reported results in combination therapy with etanercept, two regimen types of the DMARD therapy classifications were created to distinguish between instances when methotrexate was and was not part of the regimen.

For the initial and 90-day etanercept periods patients were

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### Table 1

<table>
<thead>
<tr>
<th>Pre-etanercept Regimen Type</th>
<th>None</th>
<th>None Hx</th>
<th>Monotherapy</th>
<th>Dual Therapy</th>
<th>Triple Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (n=60)</td>
<td>5 (8.3%)</td>
<td>2 (3.3%)</td>
<td>29 (48.3%)</td>
<td>18 (30.0%)</td>
<td>6 (10.0%)</td>
</tr>
<tr>
<td>Without methotrexate (n=23)</td>
<td>—</td>
<td>—</td>
<td>17 (27.4%)</td>
<td>5 (8.0%)</td>
<td>1 (1.6%)</td>
</tr>
<tr>
<td>With methotrexate (n=30)</td>
<td>—</td>
<td>—</td>
<td>12 (19.4%)</td>
<td>13 (21.0%)</td>
<td>5 (8.1%)</td>
</tr>
</tbody>
</table>

Note: Patients were classified into categories of disease-modifying antirheumatoid drug (DMARD) therapy as follows: “Monotherapy” for single DMARD use; “Dual Therapy” for concurrent use of two DMARDs; “Triple Therapy” for concurrent use of three DMARDs; “None” if they had nine months of history with no DMARD use prior to their first etanercept claim; “None HX” if they had DMARD use prior to two months before their first etanercept claim.
An Assessment of Emerging Patterns of Etanercept Use in the Treatment of Rheumatoid Arthritis

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Initial Etanercept Drug Treatment Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre- etanercept Regimen Type</td>
<td>Etan</td>
</tr>
<tr>
<td>All (n=60)</td>
<td>23 (38.3%)</td>
</tr>
<tr>
<td>Without methotrexate (n=22)</td>
<td>9 (15.0%)</td>
</tr>
<tr>
<td>With methotrexate (n=30)</td>
<td>7 (11.7%)</td>
</tr>
</tbody>
</table>

classified into categories of etanercept/DMARD therapy as follows: Etan for etanercept alone; Etan+1 for etanercept with concurrent use of one DMARD; and Etan+2 for etanercept with concurrent use of two DMARDs (see Table 2, above). To look more specifically at therapies using methotrexate, two regimen types of the Etan+1 and Etan+2 categories were again created to distinguish when methotrexate was part of the regimen. Patients who had less than two months of eligibility with the health plan after their initial etanercept prescription were classified as lost to follow-up, and patients who had no etanercept prescriptions in their period of interest were classified as discontinued.

Statistical Analysis

Fisher's exact test was applied to patient counts to test for differences in how patients in pre- etanercept therapy categories with and without methotrexate transitioned into etanercept therapy categories. The small sample size limits the power of this test, and a difference in proportions below 25% will not produce a p value less than .05. The chi-square test was used to compare the highest prescriber’s regimen against those of all other prescribers combined, to test if the high prescriber’s regimen demonstrated a statistically significant difference compared to all other prescribers.

Limitations

This study looked at one health plan’s pattern of etanercept regimens in the first eight months after FDA approval of the drug. It is possible that the first patients using etanercept are more likely to have conditions refractory to conventional DMARD therapy and their etanercept treatment regimens reflect a more aggressive approach than would otherwise be the case. Drug treatment regimens for RA have been shown to be heavily influenced by individual prescriber preference.24, 25

One prescriber had written prescriptions for 17 of the 62 patients in this study, far more than the next-highest prescriber, who wrote prescriptions for 7 patients. Chi-square tests of the pre- etanercept and initial etanercept regimens of the patients of the high prescriber against those of the remaining patients did not show a statistically significant difference (p=.42 and .54 respectively), but this prescriber may be exerting a bias on the results. Finally, etanercept is in the early phase of clinical adoption and the consequent small study population of 62 patients offers limited statistical power to detect differences. The null findings in particular should be interpreted with caution.

Results

Patient Characteristics

Sixty-two patients were identified as having initiated etanercept therapy from November 1, 1998, through June 30, 1999, and were included in the study population. The study population was overwhelmingly female (54 of 62) with an age distribution consistent with that expected for RA (median age 45 years, interquartile range 38–53 years). Only one patient was younger than 17 years old. The 8 male patients were somewhat older than the 54 female patients (median age 51 years). Analysis of the study population’s etanercept and DMARD claims by DEA number indicated that 45 unique DEA numbers were associated with these claims.

Pre- etanercept Treatment Regimens

The pre- etanercept treatment regimens are summarized in Table 1. Of the 60 patients whose claims history and prior health plan eligibility were adequate to determine a pre- etanercept treatment regimen, single DMARD therapy was the most common category, with 29 patients (48%). Combination DMARD therapy (dual and triple therapy) was used by 24 patients (40%). Five patients had no history of DMARD use in the preceding nine months, and two others had less than nine months of prior health plan eligibility to reach a determination. Of the 58 patients whose pre- etanercept regimen could be identified, 30 (52%) included methotrexate.

Initial Etanercept Treatment Regimens

The initial etanercept treatment regimens are summarized in Table 2. Of the 60 patients, 23 (38%) were started on etanercept monotherapy, while 27 (45%) were started on etanercept in combination with a single DMARD. Methotrexate was the most common single DMARD and was used by 18 patients, followed by azathioprine and hydroxychloroquine with 3 each, and sulfasalazine, leflunomide, and auranofin with 1 each. Ten patients (17%) were started on etanercept in combination with two DMARDs. All 10 of these combinations used methotrexate as one of the DMARDs. Six of the combinations used hydroxychloroquine as the other DMARD, followed by sulfasalazine with three, and azathioprine with one.

Although the number of patients in this study is relatively low, it is possible to look for differences in how pre- etanercept treatment categories with and without methotrexate transition into initial etanercept treatment categories. Transition differences were tested using Fisher’s exact test and are summarized in Table 3, page 59. Pre- etanercept dual DMARD regimens that
include methotrexate show a statistically significant difference from those that do not include methotrexate (p=0.047 and p=0.036). Regimens that include methotrexate are more likely to add etanercept to the existing dual DMARD regimen, while regimens that do not include methotrexate are more likely to substitute etanercept for one of the DMARDs.

Changes to Etanercept Treatment Regimens
Of the 60 patients whose initial etanercept regimen could be identified, 54 had the necessary three months of additional health plan eligibility after their initial etanercept prescription to evaluate changes from one therapy category to another. Two of these patients apparently discontinued etanercept therapy, leaving 52 patients to be evaluated for changes in therapy category at the 90-day point. Table 4, above, summarizes the therapy category changes at the three-month mark. Two patients had a DMARD added to their initial regimen, while nine patients had a DMARD removed from their initial regimen. DMARD removal was particularly evident for patients who began with etanercept in combination with two DMARDs, with four of ten patients changing to etanercept/single-DMARD therapy.

Prescriber-Patient Count Differences
One prescriber had written prescriptions for 17 of the 62 patients in this study. The next-highest prescriber had written for seven patients. Chi-square tests were performed to test if the high prescriber’s regimens demonstrated a statistically significant difference compared with all other prescribers. The patient counts for pre-etanercept regimens of monotherapy/dual therapy/triple therapy for this high prescriber were 5/5/2 compared with 24/13/4 for all other prescribers, yielding a nonsignificant test result for differences in proportions (p=0.42). Similarly, patient counts for initial etanercept regimens of Etan/ Etan+1/Etan+2 for this high prescriber were 9/8/3 compared with 18/19/7 for all other prescribers, yielding a nonsignificant test result as well (p=0.54).

Discussion
As a new addition to the portfolio of DMARDs, how is etanercept being used in clinical practice? For this study population, it is being used in a wide variety of combination regimens. Of the 60 initial etanercept regimens, 41 (68%) were the etanercept-only or etanercept-plus-methotrexate regimens that have been reported in the literature. The remaining 19 regimens (32%) featured eight distinct combinations, indicating considerable diversity in how etanercept is being combined with other DMARDs. As is the case with standard DMARD combination therapy, it would appear that clinicians are taking a more liberal approach to using this new drug. They are not hesitant to combine etanercept with DMARDs other than methotrexate or with more than one other DMARD, even in the absence of reported trials data on comparative efficacy and safety.

For patients on DMARD monotherapy who are being transitioned to etanercept, the clinician faces the choice of substituting etanercept for the previous DMARD or combining the previous DMARD with etanercept. While this decision depends heavily on the specifics of the individual patient situation, in this study a slight majority of patients had etanercept added to an existing DMARD. This was true whether or not the DMARD was methotrexate, even though only the etanercept-methotrexate combination has been reported in the literature with favorable results. However, 90 days after initiating etanercept regi-
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moms, 5 of 24 patients had switched from etanercept plus a DMARD to etanercept monotherapy, while 1 of 24 patients started on etanercept monotherapy had added a DMARD to their regimen. This suggests some reluctance to initially discontinue the previous DMARD agent, perhaps until the addition of etanercept has demonstrated its benefit.

Etanercept does appear to be used with methotrexate somewhat differently than with the other DMARDS in certain circumstances. Patients whose pre-etanercept regimen consisted of methotrexate in combination with another DMARD were considerably more likely to have etanercept simply added to the regimen, compared with patients on dual DMARD therapies that did not include methotrexate. These patients therefore started on etanercept therapy in combination with methotrexate and another DMARD. Interestingly, 4 of the 10 patients initiated on this regimen eliminated one of the DMARDS within 90 days of starting etanercept therapy. The retained DMARD was methotrexate in three of the four cases. This may be indicative of a step-down approach to transitioning patients on combination DMARD therapy where etanercept is added to the regimen and its impact is evaluated before the regimen is simplified.

The many different etanercept combination therapies identified in this study raise an obvious question of comparative efficacy and safety. It would appear that etanercept is assuming a place in therapy as a DMARD that can be mixed and matched in combination with other DMARDS. Very little if anything is currently known about which combinations are the most efficacious, what side effects or toxicities they may produce, and how these compare to those of non-etanercept DMARD combinations. A need for comparative clinical trials is clear.

The tumor-necrosis factor that is inactivated by etanercept is so named because of its presumed role in cancer suppression, and it also plays a role in defense against infection. It is possible that combining etanercept's action on the immune system with those of other DMARDS may have undesirable long-term consequences for certain combinations. As an FDA-approved first-line drug, etanercept will be subject to postmarketing surveillance. In the meantime, as etanercept use increases, the appropriate level of discretion in combining it with DMARDS other than methotrexate, and when it should replace the other DMARD combinations whose shortcomings are better understood, are issues that merit consideration.

**Conclusions**

Etanercept is used in a wide variety of combinations with other DMARDS over and above those that have been reported in the literature. These include etanercept and methotrexate with a third DMARD. The current trend appears to involve transitioning the patient to an etanercept regimen by adding it to the current regimen, and then attempting to reduce the number of agents after the impact of etanercept has been demonstrated. This is particularly true for patients transitioning from a regimen of methotrexate in combination with another DMARD. Comparative trials of the etanercept combination therapies are needed to establish the optimum place in therapy for etanercept.

**References**

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