ORIGINAL RESEARCH

Tumor Necrosis Factor Inhibitor Therapy and the Risk for Depression Among Working-Age Adults with Rheumatoid Arthritis

Arijita Deb, PhD; Nilanjana Dwibedi, PhD; Traci LeMasters, PhD; Jo Ann Hornsby, MD; Wenhui Wei, PhD; Usha Sambamoorthi, PhD

BACKGROUND: Individuals with rheumatoid arthritis (RA) are at high risk for depression because of the overall burden of systemic inflammation. Although some evidence suggests that treatment with powerful anti-inflammatory drugs, such as tumor necrosis factor (TNF) inhibitors, may be effective in reducing the risk for depression in patients with RA, it is unclear whether such reduction in risk is dependent on the response to TNF inhibitor therapy.

OBJECTIVE: To evaluate the association between the response to TNF inhibitor therapy and the risk for depression among working-age adults with RA.

METHOD: This retrospective, observational cohort study design was based on data derived from commercial claims data in the QuintilesIMS Real World Data Adjudicated Claims database between October 1, 2009, and September 30, 2015. A total of 4222 working-age adults (18-62 years) with RA who started treatment with TNF inhibitor therapy and were continuously enrolled during the 3 observation periods (ie, 1-year baseline, 1-year treatment, and 1-year follow-up periods) were included in the study. Treatment response to a TNF inhibitor was measured using prescription drug claims based on a published validated algorithm. Multivariable logistic regression was used to examine the association between treatment response to TNF inhibitor therapy and the risk for depression, after controlling for baseline demographic characteristics, clinical characteristics, and RA-related medication use. An inverse probability of treatment weighting technique was used to control for observable differences in TNF inhibitor responders’ characteristics versus TNF inhibitor nonresponders.

RESULTS: Overall, 359 (8.5%) patients with RA had depression during the follow-up period and 1679 (39.8%) patients responded to TNF inhibitor treatment during the 1-year treatment period. A significantly lower percentage of TNF inhibitor responders (7.1%, N = 119) had depression than TNF inhibitor nonresponders (9.4%, N = 239). After controlling for other risk factors, responders to TNF inhibitors were 20% less likely to have depression during the follow-up period (adjusted odds ratio, 0.80; 95% confidence interval, 0.64-0.98) than nonresponders to TNF inhibitor therapy.

CONCLUSION: The risk for depression was significantly reduced among patients with RA who responded to TNF inhibitor therapy compared with those who did not respond to such therapy. To determine whether the lower rate of depression observed with TNF inhibition is a direct effect of treatment with a TNF inhibitor, or whether it could be attributed to improvement in RA disease secondary to treatment, future studies need to also incorporate a control population of patients with RA who receive other antirheumatic regimens, such as disease-modifying antirheumatic drugs.

KEY WORDS: depression, inflammation, rheumatoid arthritis, treatment response, tumor necrosis factor inhibitors
Patients with rheumatoid arthritis (RA) are at high risk for depression. TNF inhibitors may be effective in reducing that risk.

This retrospective, observational study assessed the link between the response to TNF inhibitors and depression in working-age adults with RA.

Of 4222 patients, 39.8% responded to TNF inhibitor therapy in the 1-year treatment period, and 8.5% of patients had depression in the follow-up period.

Responders to TNF inhibitors were approximately 20% less likely to have depression in the follow-up period than nonresponders (7.1% vs 9.4%).

Clinical and population-based registry studies are needed to determine the link between inflammation and depression in patients with RA.

Future studies need to include a control group of patients with RA who are receiving other antirheumatic regimens.

Rheumatoid arthritis (RA) is a chronic systemic inflammatory condition that negatively affects the physical and mental health of individuals. Adults with RA are at increased risk for depression because of the overall burden of systemic inflammation. Studies have reported an increased risk for depression after a diagnosis of RA. The incident rate of depression in patients with RA is 1.7 times higher than in patients without RA.

The biologic plausibility of the link between RA, depression, and inflammation stems from the robust association between inflammation and depression. It has been reported that patients with RA and depression have significantly elevated levels of inflammatory biomarkers, such as tumor necrosis factor (TNF)-alpha and C-reactive protein, compared with patients with RA without depression.

Studies have demonstrated that the administration of proinflammatory cytokines in healthy individuals triggers depressive symptoms, such as mood disturbances, anhedonia, anorexia, and sleep disturbance.

The risk for depression in patients with RA is worrisome, because of the negative effects depression has on the patient. For example, depression increases the risk for mortality by more than 2-fold, worsens health-related quality of life, reduces adherence and treatment response to antirheumatic drugs, and increases healthcare resource utilization and costs.

Therefore, examining the factors that reduce the risk for depression among patients with RA is important. The inflammatory process that affects depression and RA may represent a unique opportunity to reduce the risk for depression in patients with RA. For example, clinical trials have provided some evidence on the efficacy of anti-inflammatory agents in reducing depressive symptoms.

In this context, specific drugs used for the prevention of RA progression may be of particular significance. Drugs inhibiting TNF-alpha (ie, TNF inhibitors) have been proved to be highly efficacious in reducing inflammation and preventing RA disease progression.

As a result of the positive association between depression and inflammation, it is plausible that drugs that inhibit TNF-alpha may reduce the risk for depression in patients with RA. Some randomized controlled and open-label trials have demonstrated that TNF inhibitor therapy improves depressive symptoms and quality of life in patients with RA. However, in real-world clinical practice, only approximately 33% of patients with RA respond to TNF inhibitor therapy. Therefore, the beneficial effect of TNF inhibitor on depression may be limited to patients with RA who respond to TNF inhibitor therapy.

Furthermore, depression in RA has significant implications for working-age adults (18-64 years) because of the illness burden. Because the onset of RA and depression occur in individuals during the most productive years of midlife, the cumulative impact of RA and depression on productivity loss as a result of missed workdays, work disability, and loss of employment among working-age adults is concerning. Therefore, it is important to understand the pathways that can reduce the risk for depression in working-age adults with RA.

No studies have specifically evaluated treatment response to TNF inhibitor therapy on the risk for depression in this population.

Therefore, the objective of this study was to evaluate the association between treatment response to TNF inhibitor therapy and the risk for depression in working-age patients with RA who are cared for in a real-world practice setting, using administrative claims data. We hypothesize that patients with RA who respond to TNF inhibitor therapy will be less likely to have depression than patients with RA who did not respond to TNF inhibitor therapy.

Methods

We used data from QuintilesIMS Real World Data Adjudicated Claims database for the period October 1, 2009, to September 30, 2015. This is an integrated claims database that includes information on medical and pharmacy claims for more than 95 million enrollees of commercial plans across the United States. The data
include the records of 90% of hospitals, 80% of doctors, and 85% of large companies in the United States. This database also records the demographics of enrollees (eg, year of birth, sex, geographic region), plan type (ie, health maintenance organization [HMO], preferred provider organization [PPO]), payer type (commercial, self-insured), and prescription drug information, and is considered nationally representative of commercially insured individuals aged <65 years in the United States.

This study used a retrospective, observational cohort study design. The index date was defined as the first observed prescription date for a TNF inhibitor biologic between October 2010 and September 2013. The study period was divided into 12 months preindex or the baseline period, the 12-month treatment period during which the treatment response to TNF inhibitor was measured, and the 12-month follow-up period when the risk for depression was assessed (Figure).

The study cohort consisted of adults between ages 18 and 62 years as of the index date, who had a diagnosis of RA in the baseline period and were initiated with TNF inhibitor therapy between October 2010 and September 2013 (Appendix, available online at www.AHDBonline.com). Continuous enrollment for the 12-month baseline period, 12-month treatment period, and 12-month follow-up period was required.

Adults with prevalent depression during the baseline and treatment periods were excluded. In addition, adults who were diagnosed with other autoimmune conditions for which biologics are used (ie, Crohn’s disease, ulcerative colitis, ankylosing spondylitis, psoriasis, psoriatic arthritis, juvenile idiopathic arthritis) during the baseline, treatment, or follow-up period were excluded. Furthermore, adults who were diagnosed with non-Hodgkin lymphoma, chronic lymphocytic leukemia, or HIV/AIDS were also excluded.

**Measures**

**Dependent variable: newly diagnosed depression**

Depression in the follow-up period was identified using a standard algorithm. Adults with International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes of 296.2 (major depressive disorder, single episode), 296.3 (major depressive disorder, recurrent episode), 298.0 (depressive type psychosis), 300.4 (neurotic depression), 309.1 (prolonged depressive reaction), and 311 (depressive disorder, not classified) during the follow-up period were considered to have depression.

**Key independent variable: response to TNF inhibitor**

Treatment response to a TNF inhibitor was measured using the claims-based effectiveness algorithm developed by Curtis and colleagues. Curtis and colleagues used the Veterans Health Administration claims database to operationalize treatment response to biologics and validated it using the gold standard for treatment response (ie, the Disease Activity Score Using 28 Joint Counts [DAS28]) from the Veterans Health Administration Rheumatoid Arthritis registry. The investigators tested the performance of this algorithm in the claims database of commercially insured individuals. There was a high positive predictive value of 87% between the claims-based algorithm and the gold standard measure of treatment response (ie, change in DAS28).

Using this algorithm, treatment response to a TNF inhibitor was measured as a dichotomous variable (yes/no) during a 1-year treatment period (ie, 1 year after the index date), which was dependent on meeting all the following 6 criteria:

1. Adherence to index TNF inhibitor. Adherence to a TNF inhibitor was calculated using a proportion of days covered (PDC). The PDC was calculated by using the date of service and the day supply for each fill of the index TNF inhibitor. Patients with a PDC of at least 80% were considered adherent. Patients receiving infliximab were considered adherent if they had at least 7 infusions in the 1-year treatment period.

2. No increase in TNF inhibitor dose versus first dose. Dose increases were measured based on the type of TNF inhibitor medication. For subcutaneous adalimumab users, the dose-escalation criterion required no more than 40 mg
per week. For subcutaneous certolizumab pegol users, the dose-escalation criterion was ≥200 mg (after 56 days) of the index dose. For subcutaneous etanercept users, the dose-escalation criterion was ≥100 mg per week of the index dose. For intravenous golimumab users, the dose-escalation criterion was 50 mg or more from the first dose to the last dose. For subcutaneous golimumab users, the dose-escalation criterion was ≥25 mg per week postindex (ie, >50 mg monthly postindex). For infliximab users, the dose-escalation criteria were ≥100 mg from the first dose to the last dose, or <11 infusions during the 1-year postindex period or ≥7 weeks between doses (after the third dose).

3. No new conventional synthetic disease-modifying antirheumatic drugs (DMARDs). No addition of methotrexate, sulfasalazine, leflunomide, or hydroxychloroquine in the treatment period in patients with RA who did not have any claims for those drugs in the baseline period.

4. No switch to another biologic drug approved for use in patients with RA.

5. No new or increased oral glucocorticoid dose. Patients with no claims for oral glucocorticoids in the baseline period could not receive more than 30 days of oral glucocorticoids between the index date plus 91 days and the index date plus 365 days; for patients with a claim including oral glucocorticoids, no increase should have been reported in the oral glucocorticoid dose from the sixth to the twelfth month after the index date compared with the 6 months before the index date. The escalation in oral glucocorticoid dose was determined based on the prednisone equivalent dose for all glucocorticoids.

6. At most, 1 parenteral or intra-articular glucocorticoid joint injection on unique days in months 4 to 12 of the postindex period.

Other independent variables

Other independent variables that were measured during the baseline period included demographic characteristics, such as age, sex, and geographical region (East, Midwest, South, and West), insurance and insurance plan type (HMO, PPO); clinical characteristics, such as the total number of chronic physical conditions, and anxiety and substance abuse; healthcare utilization (any outpatient or emergency department visit); and RA-related medication use, including glucocorticoids, DMARDs, nonsteroidal anti-inflammatory drugs (NSAIDs), and opioids. The total number of chronic physical conditions was measured using the Clinical Classifications Software for ICD-9-CM, which is managed by the Agency for Healthcare Research and Quality.

Statistical Analysis

Chi-square test and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) from multivariable logistic regression analyses were used to examine the association between treatment response to TNF inhibitors and newly diagnosed depression after controlling for baseline demographic characteristics, clinical characteristics, and RA-related medication use. Because the rate of newly diagnosed depression was less than 10%, adjusted ORs can be used to approximate relative risk. Therefore, we used the terms risk and ORs interchangeably.

To control for the observable differences in the baseline characteristics of the responders and nonresponders to TNF inhibitors, we used an inverse probability weighting technique. This technique gives weight to each individual based on the inverse of their probability of being in the responders group. Thus, individuals who have a lower probability of being in the responders group were up-weighted, and those with a higher probability of being in the responders group were down-weighted. This helped to balance the probability of being in the responders group versus the nonresponders group.

To derive the inverse probability weighting technique weights, logistic regression was at first conducted for treatment response to a TNF inhibitor and probabilities of being in the responders versus nonresponders group were calculated, the weights were created using the inverse of probabilities. To account for the differences in group sizes, the weights were further stabilized by dividing them by the sample size of each group. All analyses were conducted using SAS version 9.4 (SAS Institute Inc; Cary, NC).

Results

Of the 4222 working-age adults with RA who initiated treatment with a TNF inhibitor and did not have depression during the baseline and treatment periods, 3167...
### Table 2  Selected Baseline Characteristics of Responders and Nonresponders to TNF Inhibitors

<table>
<thead>
<tr>
<th>Baseline characteristic</th>
<th>Before applying inverse probability weighting method</th>
<th>After applying inverse probability weighting method</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Responders, %</td>
<td>Nonresponders, %</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>74.6</td>
<td>76.8</td>
</tr>
<tr>
<td>Male</td>
<td>25.4</td>
<td>23.2</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-34 yrs</td>
<td>7.4</td>
<td>8.6</td>
</tr>
<tr>
<td>35-44 yrs</td>
<td>15.1</td>
<td>17.5</td>
</tr>
<tr>
<td>45-54 yrs</td>
<td>36.0</td>
<td>35.8</td>
</tr>
<tr>
<td>55-62 yrs</td>
<td>41.4</td>
<td>37.1</td>
</tr>
<tr>
<td>Region</td>
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<td></td>
</tr>
<tr>
<td>East</td>
<td>18.0</td>
<td>17.0</td>
</tr>
<tr>
<td>Midwest</td>
<td>31.9</td>
<td>28.6</td>
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<tr>
<td>South</td>
<td>41.2</td>
<td>46.0</td>
</tr>
<tr>
<td>West</td>
<td>8.9</td>
<td>4.1</td>
</tr>
<tr>
<td>Insurance plan type</td>
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<td></td>
</tr>
<tr>
<td>HMO</td>
<td>9.7</td>
<td>10</td>
</tr>
<tr>
<td>PPO</td>
<td>76.0</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>14.3</td>
<td>11.2</td>
</tr>
<tr>
<td>Number of chronic conditions</td>
<td>.160</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>63.5</td>
<td>63.5</td>
</tr>
<tr>
<td>1-3</td>
<td>34.2</td>
<td>33</td>
</tr>
<tr>
<td>&gt;3</td>
<td>2.3</td>
<td>4.1</td>
</tr>
<tr>
<td>NSAIDs use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>56.3</td>
<td>55.3</td>
</tr>
<tr>
<td>No</td>
<td>43.7</td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>76.4</td>
<td>70.7</td>
</tr>
<tr>
<td>No</td>
<td>23.6</td>
<td>29.3</td>
</tr>
<tr>
<td>Other DMARDs&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>51.0</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>48.0</td>
<td>50.5</td>
</tr>
<tr>
<td>Glucocorticoids</td>
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</tr>
<tr>
<td>Yes</td>
<td>67.4</td>
<td>75.0</td>
</tr>
<tr>
<td>No</td>
<td>32.6</td>
<td>25.0</td>
</tr>
<tr>
<td>Narcotics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>51.9</td>
<td>58.6</td>
</tr>
<tr>
<td>No</td>
<td>48.1</td>
<td>41.2</td>
</tr>
</tbody>
</table>

<sup>a</sup>Other DMARDs include sulfasalazine, leflunomide, hydroxychloroquine, azathioprine, chloroquine, cyclophosphamide, cyclosporine, minocycline, and sodium aurothiomalate. DMARDs indicates disease-modifying antirheumatic drugs; HMO, health maintenance organization; NSAIDs, nonsteroidal anti-inflammatory drugs; PPO, preferred provider organization.
(75%) were female (mean age, 50 years). A total of 1917 (45.4%) patients were living in the Southern region of the United States, 2491 (59%) had 1 to 3 additional chronic conditions, 3103 (73.5%) were receiving methotrexate, and 2326 (55.1%) were receiving NSAIDs during the baseline period (data not presented in tabular form).

Based on the algorithm,31 1679 (39.8%) patients were classified as responders to TNF inhibitor treatment during the 1-year treatment period after the index date (Table 1). The most common reason for nonresponse to TNF inhibitor therapy was low adherence to an index TNF inhibitor (42.9%).

Significant differences were found in the baseline characteristics of the TNF inhibitor responders and TNF inhibitor nonresponders in sex, age, insurance, region, insurance plan type, and use of RA-related medications in the baseline period (Table 2). For example, a significantly greater proportion of adults in the TNF inhibitor nonresponders group used glucocorticoids (75% vs 67.4%) and opioids (58.8% vs 51.9%). Conversely, the use of methotrexate in the baseline period was lower in the TNF inhibitor nonresponders group than in the TNF inhibitor responders group (70.7% vs 76.4%, respectively).

To derive the inverse probability weighting technique, we conducted a multivariable logistic regression on TNF inhibitor treatment response in which we controlled for sex, age, insurance plan type, region, and other RA-related medications use during baseline (data not presented in tabular form). In this regression, women were less likely than men to respond to a TNF inhibitor (adjusted OR, 0.87; 95% CI, 0.75-0.91). Also, patients with RA with a baseline use of NSAIDs (adjusted OR, 1.32; 95% CI, 1.21-1.47), methotrexate (adjusted OR, 1.33; 95% CI, 1.14-1.53), or other DMARDs (adjusted OR, 1.21; 95% CI, 1.06-1.36) were more likely to respond to TNF inhibitor therapy, whereas patients with RA with a baseline use of glucocorticoids (adjusted OR, 0.62; 95% CI, 0.54-0.72) or opioids (adjusted OR, 0.82; 95% CI, 0.72-0.93) were less likely to respond to TNF inhibitor therapy.

Table 2 shows differences in the patients’ characteristics by TNF inhibitor treatment response before and after the application of the inverse probability weighting technique. As seen in Table 2, the differences in characteristics between the TNF inhibitor responders and nonresponders were no longer statistically significant.

Overall, 8.5% of patients had depression during the follow-up period. A lower percentage of TNF inhibitor responders had depression during the 1-year follow-up period after treatment than TNF inhibitor nonresponders (7.1% vs 9.4%; P < .005). After controlling for potential confounders, TNF inhibitor responders were 20% less likely to have depression than TNF inhibitor nonresponders (adjusted OR, 0.80; 95% CI, 0.64-0.98; Table 3).

Other baseline risk factors for depression included female sex (adjusted OR, 2.12; 95% CI, 1.64-2.74), the number of chronic conditions (>3 vs 0, adjusted OR, 1.97; 95% CI, 1.34-2.88), opioid use (adjusted OR, 2.07; 95% CI, 1.69-2.52), and having an emergency department visit (adjusted OR, 1.32; 95% CI, 1.04-1.68).

Discussion

In the depression-free cohort at baseline of working-age patients with RA who received a TNF inhibitor, the overall rate of newly diagnosed depression was 8.5%. In a previous study of 83 Turkish patients with RA who received treatment in an outpatient rheumatology clinic, the researchers reported a markedly lower prevalence of depressive disorders among patients who received a TNF inhibitor (6.3%) compared with patients who received other drugs (41.8%).35

Most epidemiologic studies in patients with RA have examined the prevalence of depression in patients with RA; only a few studies examined the incidence of depression in this patient population.36 A systematic review of 72 studies in patients with RA reported a 16.8% prevalence of major depressive disorder.4 In one UK study, approximately 30% of patients had depression within 5 years of being diagnosed with RA.5 Therefore, in light of these previous findings, the rate of newly diagnosed de-

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### Table 3 Newly Diagnosed Depression in Adults with RA After Initiation of TNF Inhibitor Therapy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted odds ratio (95% CI)</th>
<th>P value range</th>
<th>P value range</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF inhibitor response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.80 (0.64-0.98)</td>
<td>.01 ≤ .05</td>
<td></td>
</tr>
<tr>
<td>No (reference)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (reference)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>2.12 (1.84-2.74)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Emergency department visit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.32 (1.04-1.68)</td>
<td>.01 ≤ .05</td>
<td></td>
</tr>
<tr>
<td>No (reference)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opioid use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2.07 (1.89-2.50)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>No (reference)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of clinical conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 (reference)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-3</td>
<td>1.15 (0.80-1.64)</td>
<td>.01 ≤ .05</td>
<td></td>
</tr>
<tr>
<td>&gt;3</td>
<td>1.97 (1.34-2.88)</td>
<td>&lt;.001</td>
<td></td>
</tr>
</tbody>
</table>

*The cut-offs for level of significance were P < .001, .001 ≤ P < .01, and .01 ≤ P < .05. CI indicates confidence interval; RA, rheumatoid arthritis; TNF, tumor necrosis factor. Copyright © 2019 by Engage Healthcare Communications, LLC; protected by U.S. copyright law. Photocopying, storage, or transmission by magnetic or electronic means is strictly prohibited by law.
pression observed in the current study of patients with RA who received a TNF inhibitor is somewhat lower.

A noteworthy finding of our study is that response to TNF inhibitor therapy in patients with RA was associated with a 20% lower risk for depression. Some plausible explanations for this finding is that patients who respond to TNF inhibitor therapy may have improved RA-related outcomes that may lower the risk for psychological conditions, including depression. TNF inhibitor therapy may also suppress inflammation and lower the risk for subsequent depression. To determine whether the lower rate of depression is a direct effect of treatment with a TNF inhibitor or whether it could be attributed to improvement in RA disease secondary to treatment, future studies need to also incorporate a control population of patients with RA who receive other antirheumatic regimens, such as DMARDs.

The reduction in the risk for depression in patients who respond to therapy with a TNF inhibitor has clinical implications for the treatment of RA, as well as depression. Our findings suggest that intervention with TNF inhibitor therapy may improve RA-related outcomes, as well as reduce the risk for depression. Our study findings offer the possibility of including anti-inflammatory agents in the treatment of existing depression, and testing whether including anti-inflammatory agents in depression treatment regimens alleviates depressive symptoms. Future studies also need to evaluate the direct effect of TNF inhibitor treatment on the levels of inflammatory cytokines among patients with RA and comorbid depression.

In our study population of depression-free adults with RA, 39.8% responded to TNF inhibitor therapy. The response rate to a TNF inhibitor in this subgroup is slightly higher compared with the response (DAS28-based response criteria) rate to TNF inhibitor therapy observed in the population with RA in previous studies using registry and administrative claims data. These differences in the analysis could be attributed to differences in databases, as well as in the subpopulation used. Our study excluded patients with depression at baseline.

It has been documented that adults with depression have lower rates of response to TNF inhibitor therapy than patients without depression. One study using Danish registry data reported a response rate of 25% to TNF inhibitor therapy. Using the Veterans Health Administration database, Curtis and colleagues reported a response rate of 27% to TNF inhibitor therapy based on the algorithm-defined treatment response. Other studies using the same algorithm, with data from different databases, such as the Medco Health Solutions pharmacy benefit manager database and the Texas Medicaid database, reported 32% and 15.7% response rates, respectively, with TNF inhibitor therapy in patients with RA.

Our study findings showed that the major reason for nonresponse to TNF inhibitors therapy was low adherence, with approximately 42% of the patients with RA having low adherence to TNF inhibitors. This finding is consistent with previous studies of patients with RA that also highlighted nonadherence to TNF inhibitors as one of the major contributing factors for poor response to TNF inhibitor therapy. For example, in a prospective, multicenter, large-cohort study conducted in the United Kingdom, researchers demonstrated that self-reported nonadherence to TNF inhibitors was a strong predictor of poor response to TNF inhibitor therapy, independent of sociodemographic and clinical characteristics of the patients. Therefore, physicians should encourage patients to adhere to RA treatment regimens and make them aware that low adherence to TNF inhibitor medications adversely affects treatment response.

This study adds to the nascent literature on how treatment response to antirheumatic therapy may have benefit in reducing psychiatric comorbidities, such as depression, in patients with RA based on the use of nationally representative data of commercially insured working-age adults, the use of longitudinal study design to track individuals across different providers over 3 years. The use of real-world prescription drug claims, the ability to measure treatment response with readily available claims data, and the large study’s sample size and high validity add to the strength of this study’s findings.

Limitations

The findings of this study should be interpreted in light of several limitations, including the lack of severity measures for chronic conditions and a lack of information on individual characteristics, such as race, body mass index, exercise, and smoking status that may predict depression. Furthermore, the study’s findings are not generalizable beyond commercially insured working-age adults.

Also, because of the nature of claims data, we were only able to document the prescription of medications and not the actual use of the medications.

Other limitations include selection bias as a result of unobserved variables and the underdiagnosis of depression in claims data.

Conclusion

 Patients with RA who responded to TNF inhibitor therapy were less likely to have depression than patients with RA who did not respond to TNF inhibitor therapy. This finding highlights the need for optimal treatment response to a TNF inhibitor to attenuate the heightened risk for depression associated with RA. To determine whether the lower rate of depression observed with TNF inhibition is a direct effect of treatment with a TNF in-
Tumor necrosis factor alpha (TNF) inhibitor, or whether it could be attributed to improvement in RA disease secondary to treatment, future studies need to also incorporate a control population of patients with RA who receive other antirheumatic regimens, such as DMARDs. Prospective clinical and population-based registry studies are also needed to investigate the role of inflammation in the pathogenesis of depression in patients with RA.

Acknowledgments

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Author Disclosure Statement

Dr Deb is an employee of Merck & Co; Dr Dwibedi, Dr LeMasters, Dr Hornsby, and Dr Sambamoorthi have no conflicts of interest to report; Dr Wei is an employee of Regeneron Pharmaceuticals and owns stocks of Regeneron and of Sanofi US.

References


Rheumatoid arthritis (RA) is a systemic, inflammatory form of arthritis that results in joint inflammation, pain, swelling, and stiffness.1 Approximately 1.5 million people in the United States currently have RA.2 Although new treatment strategies that focus on early diagnosis, aggressive treatment, and consistent disease monitoring have helped many patients achieve their treatment goals, RA continues to present clinical and economic challenges to patients, employers, physicians, and payers.

PATIENTS: It is plausible that based on the findings of Deb and colleagues in their study,1 patients who respond to tumor necrosis factor (TNF) inhibitor therapy may have improved RA-related outcomes that may also lower the risk for psychological problems, such as depression.3,5 Many treatment options are available today for patients with RA, although it is unclear whether the reduction in depression is specifically dependent on the response to a TNF inhibitor.

With working-age adults, physical and mental functionality is a critical component, so any clinically favorable and cost-effective treatments for RA must focus on the prevention of disease progression and on improving patients’ quality of life and productivity.

PROVIDERS/Employers: Coupled with the wide variety of treatment options available today for patients with RA, and with more drugs currently in the pipeline, providers are faced with the challenge of ensuring that selected treatments for the individual patient support disease remission and maintain patients’ productivity.

In accordance with the 2015 American College of Rheumatology guidelines, physicians prescribe ≥1 treatment options for patients with established RA, including disease-modifying antirheumatic drugs, anti-TNF agents, JAK inhibitors, interleukin (IL)-6 and IL-17A inhibitors, or monoclonal antibodies.1 This raises the subjects of multitherapy treatments, the reduction of depression in patients with RA, and the association with remission rates.

An additional study on remission and depression in working-age adults with RA may lead to even more precise conclusions than presented by Deb and colleagues,3 because many patients may stop working as a result of disease-related physical or mental disability, which could have a profound impact on employers. The goal of disease remission has led to the aggressive treatment of RA; however, remission is difficult to achieve in patients with established disease. Thus, physicians focus heavily on their patients achieving remission as early as possible.

Although only 10% to 20% of patients with established RA will achieve remission, the rates of remission among patients with early RA (ie, 6-12 months) range from 30% to 40%.3 Within 2 years of diagnosis, patients with RA may become moderately disabled; after 10 years, 30% of patients are severely disabled. In addition, approximately 33% of patients with RA stop working because of their disability,6 making this disease a valid concern for employers.

PAYERS: RA is a complex disease with demonstrated comorbidities that have an expressed link to depression, as Deb and colleagues demonstrate.3 Understanding that RA can be physically and mentally debilitating, all stakeholders, including payers, must be keenly aware of the need to achieve remission early.

Although new treatment strategies that are focused on early diagnosis, aggressive treatment, and consistent monitoring have helped many patients achieve their therapy goals, RA continues to present clinical and economic challenges to patients, physicians, and payers. With a wide variety of treatment options currently available, and more in the pipeline, payers will continue to be faced with the challenge of cost-effective management strategies that improve productivity for their employer customers.