The management of rheumatoid arthritis is primarily based on the use of disease-modifying antirheumatic drugs (DMARDs). The current guidelines for rheumatoid arthritis recommend conventional synthetic DMARDs as first-line treatment, with the aim of achieving disease remission or reducing disease activity. Although conventional synthetic DMARDs form the basis of care for rheumatoid arthritis, a proportion of patients with moderate-to-severe disease do not respond to conventional synthetic DMARDs. In such cases, the guidelines recommend initiating a biologic DMARD in combination with a conventional synthetic DMARD. Multiple biologic DMARDs, such as adalimumab, etanercept, and infliximab, are available for the treatment of rheumatoid arthritis. Tocilizumab is a humanized anti–interleukin (IL)-6 receptor monoclonal anti-
KEY POINTS

- Rheumatoid arthritis can be managed with subcutaneous (SC) or intravenous tocilizumab, but the SC form is more widely used.
- The goal of this retrospective cohort study was to analyze real-world dose modification patterns with SC tocilizumab in patients with commercial or Medicare coverage.
- Overall, 60% of the Truven MarketScan patients and 68% of the Optum Clinformatics patients initiated or escalated to the higher weekly dose of SC tocilizumab.
- In the Truven cohort, corticosteroid use, age, and anemia were the main predictors for dose escalation; in the Optum cohort, female patients were more likely than males to have dose escalation.
- The SC tocilizumab dose was escalated to every week in >33% of patients who started with every 2 weeks dosing, and the time to dose escalation was approximately 4 months.
- By contrast, <5% of patients who started SC tocilizumab at the every-week dosing had a dose reduction to every 2 weeks.
- Increasing the SC tocilizumab dose not in accordance with current recommendations may increase the cost burden associated with this medication on health plans and patients.

Body that binds to the membrane-bound and soluble IL-6 receptors, inhibiting IL-6 signaling. Tocilizumab is indicated as monotherapy or in combination with conventional synthetic DMARDs for the treatment of patients with moderate-to-severe active rheumatoid arthritis who have had an inadequate response to ≥1 DMARDs.

Tocilizumab can be administered as subcutaneous (SC) injection or as an intravenous (IV) infusion. According to the US prescribing information for tocilizumab, different dosing regimens are recommended, depending on whether a patient receives the IV or SC form. The recommended dose for IV administration is 4 mg/kg every 4 weeks, followed by 8 mg/kg every 4 weeks based on clinical response. The recommended dose for SC administration differs, depending on the patient’s weight. In patients weighing <100 kg, tocilizumab is administered at 162 mg every 2 weeks; in patients weighing ≥100 kg, tocilizumab is administered at 162 mg every week. Based on the patient’s clinical response and at the physician’s discretion, patients starting with the lower SC dose (162 mg every 2 weeks) may be up titrated to 162 mg every week; however, US treatment guidelines for rheumatoid arthritis recommend that therapeutic agents be given for at least 3 months before therapy escalation is considered.

In general, SC tocilizumab is more widely used than IV tocilizumab. There is a paucity of information about real-world treatment patterns associated with SC tocilizumab, although data on other SC therapies and IV tocilizumab are largely well-known. Because IV tocilizumab is generally covered under the medical benefit and SC tocilizumab is covered under the pharmacy benefit, the aim of our study was to understand the real-world dose modification patterns of SC tocilizumab among US patients with rheumatoid arthritis to provide insight about potential pharmacy cost implications.

In this study, we examined retrospectively the starting dose of SC tocilizumab among patients with rheumatoid arthritis who initiated therapy with SC tocilizumab, the frequency of the SC dose modifications during 1-year follow-up, the time to dose modification, and the predictors of dose escalation.

Methods

This retrospective, observational, and descriptive cohort study was based on administrative medical and pharmacy claims data obtained from the Truven MarketScan (currently branded as IBM MarketScan) database and the Optum Clinformatics database of patients with commercial or Medicare Advantage or supplemental insurance between October 1, 2012, and June 30, 2017 (ie, the study period). Data from Optum Clinformatics have been certified as deidentified. Adults meeting the inclusion criteria between October 1, 2013, and June 30, 2016 (ie, patient identification period) were included in the study sample.

The first prescription fill date of SC tocilizumab during the identification period was the index date. The primary grouping variables used were Medicare and commercial insurance; patients with Medicare supplemental coverage during the entire study period were included in the Medicare group, and the remaining patients were included in the commercial group.

Inclusion and Exclusion Criteria

Patients were included if they had ≥1 pharmacy claims for SC tocilizumab during the patient identification period; had ≥1 inpatient or ≥2 outpatient medical claims with rheumatoid arthritis diagnosis that included International Classification of Diseases, Ninth Revision (ICD-9) code 714.XX, and ICD, Tenth Revision (ICD-10) code M05.XX or M06.XX, before the index date; were aged ≥18 years on the index date; and had ≥12 months continuous enrollment in a commercial health plan before and after the index date (ie, the baseline and follow-up periods, respectively).

Patients with ≥1 medical claims during the study for
the following diagnoses were excluded: ankylosing spondylitis (ICD-9 code 720.0x; ICD-10 codes M08.1 and M45.xx), Crohn’s disease (ICD-9 code 555.xxx; ICD-10 code K50.00), juvenile idiopathic arthritis (ICD-9 code 714.3x; ICD-10 code M08.xx), psoriasis (ICD-9 code 696.1x; ICD-10 code L40.x), psoriatic arthritis (ICD-9 code 696.xx; ICD-10 code L40.xx), ulcerative colitis (ICD-9 code 556.xx; ICD-10 code K51.xx), chronic lymphocytic leukemia (ICD-9 code 204.1x; ICD-10 code C91.10), non-Hodgkin lymphoma (ICD-9 code 202.8x; ICD-10 code C85.90), or giant-cell arteritis (ICD-9 code 446.5x; ICD-10 code M13.6x).

**Study End Points**

The average monthly dose of SC tocilizumab was calculated as the quantity dispensed multiplied by the strength per the days of supply and then multiplied by 28.

The following dose categories of SC tocilizumab were used in the study: <324 mg every 28 days (initiated at a lower dose than recommended); 324 mg every 28 days (ie, 162 mg every 2 weeks; recommended starting dose for patients weighing <100 kg); between 324 mg and 648 mg every 28 days; 648 mg every 28 days (ie, 162 mg every week; recommended starting dose for patients weighing >100 kg or escalated dose for patients weighing <100 kg); and >648 mg every 28 days (higher than the recommended dose).

The baseline patient demographic and clinical characteristics included age on the index date, sex, region of patients’ residence, comorbid conditions, Elixhauser comorbidity index score, and previous rheumatoid arthritis treatment (ie, conventional synthetic DMARDs and biologics). The index therapy, including the type (ie, monotherapy or combination therapy) and the index dose, were assessed on the index date or 90 days after the index date.

The number of SC tocilizumab prescription fills for 28 days was calculated using distinct fill dates. Dose escalation was defined as an index dose of 324 mg every 28 days, followed by an average monthly dose of 648 mg every 28 days after the index date. Dose reduction was defined as an index dose of 648 mg every 28 days, then average monthly dose of 324 mg every 28 days after the index date.

The time to first dose escalation was the number of days between the index date and the first prescription fill of SC tocilizumab at an escalated dose. The time to first dose reduction was the number of days between the index date and the first prescription fill at a reduced dose.

During the follow-up period, the number of days the patient had coverage for SC tocilizumab was counted, based on the prescription fill date and the number of days of supply. If the number of supply days for SC tocilizumab prescriptions overlapped, then the prescription start date of the second fill was adjusted to the day after the

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**Figure 1** Attrition Flowchart for Truven MarketScan and Optum Clinformatics Patients

Number of patients with ≥1 subcutaneous tocilizumab-related pharmacy claims in Truven MarketScan and Optum Clinformatics

October 1, 2013–June 30, 2016 (patient identification period)

*Truven MarketScan: N = 2770; Optum: N = 1155*

Number of patients with ≥1 inpatient claims or ≥2 outpatient medical claims with rheumatoid arthritis diagnosis codes before the index date

*Truven MarketScan: N = 2567; Optum: N = 1005*

Number of patients aged ≥18 years on the index date

*Truven MarketScan: N = 2556; Optum: N = 1000*

Number of patients with ≥12 months of continuous enrollment in a health plan before the index date

*Truven MarketScan: N = 2028; Optum: N = 791*

Number of patients with ≥12 months of continuous enrollment in a health plan after the index date

*Truven MarketScan: N = 1480; Optum: N = 513*

Number of patients without any claims for exclusionary medical conditions

October 1, 2012–June 30, 2017 (study period)

*Truven MarketScan: N = 1266; Optum: N = 512*

Number of patients with commercial health insurance coverage during study period

*Truven MarketScan: N = 1127; Optum: N = 351*

Number of patients with Medicare supplemental health insurance coverage during study period

*Truven MarketScan: N = 139; Optum: N = 161*

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*aAnkylosing spondylitis National Drug Code is 50242013801.

*bRheumatoid arthritis ICD-9 diagnosis codes: ICD-9 code 714.xx; ICD-10 code M05.xx or M06.xx.

*cIndex date is first fill date of subcutaneous tocilizumab during patient identification period.

*dAnkylosing spondylitis, Crohn’s disease, juvenile idiopathic arthritis, psoriasis, psoriatic arthritis, ulcerative colitis, chronic lymphocytic leukemia, non-Hodgkin lymphoma, and giant-cell arteritis.

eICD-9 indicates International Classification of Diseases, Ninth Revision. ICD-10 indicates International Classification of Diseases, Tenth Revision.*
previous fill ended. This helped to consider nonoverlapping days the patient had coverage for SC tocilizumab prescriptions. To calculate the proportion of days the patient had coverage for SC tocilizumab as a percentage for each patient, the number of days covered was divided by the number of days in the follow-up period (ie, 365 days) and was multiplied by 100.

**Statistical Analysis**

Descriptive statistics were used for all study outcomes. The mean, standard deviation, and median values were used to describe the continuous variables and frequency for the categorical variables. The time to first dose modification (ie, escalation and reduction) was analyzed using Kaplan-Meier analysis for patients with a dose modification. A logistic regression model that included primary grouping variables, index therapy (monotherapy SC tocilizumab vs SC tocilizumab plus conventional synthetic DMARD), and baseline patient characteristics was used to identify predictors of the likelihood of dose escalation. A Cox proportional hazards regression model that included primary grouping variables, index therapy, and baseline patient characteristics was used to identify the predictors of time to dose escalation.

**Results**

The study sample included 1266 patients in the Truven cohort and 512 patients in the Optum cohort (Figure 1). The patients' baseline demographics and clinical characteristics are listed in Table 1. Twelve months before the index date, conventional

### Table 1: Study Population Baseline Demographic and Clinical Characteristics, and Treatment Patterns

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Truven MarketScan</th>
<th>Optum Clinformatics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N = 1127)</td>
<td>(N = 139)</td>
</tr>
<tr>
<td>Age, mean, yrs (SD)</td>
<td>50.3 (8.2)</td>
<td>69.1 (6.8)</td>
</tr>
<tr>
<td>Female, N (%)</td>
<td>939 (83)</td>
<td>97 (70)</td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
</tr>
<tr>
<td>North Central, N (%)</td>
<td>184 (16)</td>
<td>35 (25)</td>
</tr>
<tr>
<td>South, N (%)</td>
<td>567 (50)</td>
<td>45 (32)</td>
</tr>
<tr>
<td>West, N (%)</td>
<td>197 (17)</td>
<td>15 (11)</td>
</tr>
<tr>
<td>Unknown, N (%)</td>
<td>12 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Follow-up duration, mean, mo (SD)</td>
<td>26.0 (8.3)</td>
<td>24.4 (8.1)</td>
</tr>
<tr>
<td>Elixhauser comorbidity index score, mean (SD)</td>
<td>1.7 (1.8)</td>
<td>2.8 (2.3)</td>
</tr>
<tr>
<td>Elixhauser comorbidity index group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0, N (%)</td>
<td>341 (30)</td>
<td>22 (16)</td>
</tr>
<tr>
<td>1, N (%)</td>
<td>202 (18)</td>
<td>33 (24)</td>
</tr>
<tr>
<td>≥3, N (%)</td>
<td>280 (25)</td>
<td>63 (45)</td>
</tr>
<tr>
<td>Baseline rheumatoid arthritis treatment patterns</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conventional synthetic DMARDs, N (%)</td>
<td>814 (72)</td>
<td>103 (74)</td>
</tr>
<tr>
<td>Biologics, N (%)</td>
<td>857 (76)</td>
<td>98 (71)</td>
</tr>
<tr>
<td>Corticosteroids, N (%)</td>
<td>828 (73)</td>
<td>104 (75)</td>
</tr>
</tbody>
</table>

aConventional synthetic DMARDs include hydroxychloroquine sulfate, leflunomide, methotrexate, and sulfasalazine.
bBiologics include tumor necrosis factor inhibitors (certolizumab, etanercept, golimumab, adalimumab, and infliximab) and non–tumor necrosis factor inhibitors (abatacept, rituximab, tofacitinib, and intravenous tocilizumab).
cCorticosteroids include prednisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, triamcinolone, cortisone acetate, and betamethasone.

DMARD indicates disease-modifying antirheumatic drug; SD, standard deviation.
## Table 2: Subcutaneous Tocilizumab Index Therapy, Dose, Prescription Fills, and Dose Modifications

<table>
<thead>
<tr>
<th>Index therapy, dose</th>
<th>Commercial (N = 1127)</th>
<th>Medicare (N = 139)</th>
<th>Overall (N = 1266)</th>
<th>Commercial (N = 351)</th>
<th>Medicare (N = 161)</th>
<th>Overall (N = 512)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapy, N (%)</td>
<td>499 (44)</td>
<td>54 (39)</td>
<td>553 (44)</td>
<td>174 (50)</td>
<td>67 (42)</td>
<td>241 (47)</td>
</tr>
<tr>
<td>Combination therapy (index date [inclusive] + 90 days) with biologics or conventional synthetic DMARDs, N (%)</td>
<td>628 (56)</td>
<td>85 (61)</td>
<td>713 (56)</td>
<td>177 (50)</td>
<td>94 (58)</td>
<td>271 (53)</td>
</tr>
<tr>
<td>SC tocilizumab + conventional synthetic DMARDs, N (%)</td>
<td>546 (48)</td>
<td>75 (54)</td>
<td>621 (49)</td>
<td>163 (46)</td>
<td>81 (50)</td>
<td>244 (48)</td>
</tr>
<tr>
<td>Hydroxychloroquine sulfate, N (%)</td>
<td>150 (13)</td>
<td>20 (14)</td>
<td>170 (13)</td>
<td>32 (9)</td>
<td>18 (11)</td>
<td>50 (10)</td>
</tr>
<tr>
<td>Methotrexate, N (%)</td>
<td>363 (32)</td>
<td>48 (35)</td>
<td>411 (32)</td>
<td>104 (30)</td>
<td>50 (31)</td>
<td>154 (30)</td>
</tr>
<tr>
<td>Sulfasalazine, N (%)</td>
<td>41 (4)</td>
<td>4 (3)</td>
<td>45 (4)</td>
<td>15 (4)</td>
<td>10 (6)</td>
<td>25 (5)</td>
</tr>
<tr>
<td>SC tocilizumab + biologics, N (%)</td>
<td>39 (3)</td>
<td>4 (3)</td>
<td>43 (3)</td>
<td>0 (0)</td>
<td>5 (3)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>TNF inhibitor, N (%)</td>
<td>28 (2)</td>
<td>3 (2)</td>
<td>31 (2)</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Certolizumab, N (%)</td>
<td>6 (1)</td>
<td>0 (0)</td>
<td>6 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Etanercept, N (%)</td>
<td>9 (1)</td>
<td>2 (1)</td>
<td>11 (1)</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Golimumab, N (%)</td>
<td>4 (0)</td>
<td>0 (0)</td>
<td>4 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Adalimumab, N (%)</td>
<td>8 (1)</td>
<td>1 (1)</td>
<td>9 (1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Infliximab, N (%)</td>
<td>1 (0)</td>
<td>0 (0)</td>
<td>1 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Abatacept, N (%)</td>
<td>3 (0)</td>
<td>1 (0)</td>
<td>4 (0)</td>
<td>1 (0)</td>
<td>0 (0)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>IV tocilizumab, N (%)</td>
<td>8 (1)</td>
<td>0 (0)</td>
<td>8 (1)</td>
<td>0 (0)</td>
<td>3 (2)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>SC tocilizumab + conventional synthetic DMARDs + biologics, N (%)</td>
<td>43 (4)</td>
<td>6 (4)</td>
<td>49 (4)</td>
<td>14 (4)</td>
<td>8 (5)</td>
<td>22 (4)</td>
</tr>
<tr>
<td>Corticosteroid use (index date [inclusive] + 90 days), N (%)</td>
<td>539 (48)</td>
<td>72 (52)</td>
<td>611 (48)</td>
<td>171 (49)</td>
<td>96 (60)</td>
<td>267 (52)</td>
</tr>
<tr>
<td>Prednisone, N (%)</td>
<td>444 (39)</td>
<td>63 (45)</td>
<td>507 (40)</td>
<td>139 (40)</td>
<td>84 (52)</td>
<td>233 (44)</td>
</tr>
<tr>
<td>Dexamethasone, N (%)</td>
<td>2 (0)</td>
<td>0 (0)</td>
<td>2 (0)</td>
<td>1 (0)</td>
<td>4 (2)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Hydrocortisone, N (%)</td>
<td>7 (1)</td>
<td>0 (0)</td>
<td>7 (1)</td>
<td>1 (0)</td>
<td>0 (0)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Methylprednisolone, N (%)</td>
<td>110 (10)</td>
<td>14 (10)</td>
<td>124 (10)</td>
<td>27 (9)</td>
<td>13 (8)</td>
<td>40 (8)</td>
</tr>
<tr>
<td>Prednisolone, N (%)</td>
<td>1 (0)</td>
<td>0 (0)</td>
<td>1 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Triamcinolone, N (%)</td>
<td>28 (2)</td>
<td>4 (3)</td>
<td>32 (3)</td>
<td>11 (3)</td>
<td>4 (2)</td>
<td>15 (3)</td>
</tr>
<tr>
<td>Cortisone acetate, N (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Betamethasone, N (%)</td>
<td>3 (0)</td>
<td>1 (1)</td>
<td>4 (0)</td>
<td>1 (0)</td>
<td>1 (1)</td>
<td>2 (0)</td>
</tr>
<tr>
<td>SC tocilizumab index dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;324 mg/28 days, N (%)</td>
<td>68 (6)</td>
<td>3 (2)</td>
<td>71 (6)</td>
<td>4 (1)</td>
<td>7 (4)</td>
<td>11 (2)</td>
</tr>
<tr>
<td>324-648 mg/28 days, N (%)</td>
<td>533 (47)</td>
<td>75 (54)</td>
<td>608 (48)</td>
<td>168 (48)</td>
<td>77 (48)</td>
<td>245 (48)</td>
</tr>
<tr>
<td>648 mg/28 days (ie, 162 mg every wk), N (%)</td>
<td>477 (42)</td>
<td>54 (39)</td>
<td>531 (42)</td>
<td>174 (50)</td>
<td>76 (47)</td>
<td>250 (49)</td>
</tr>
<tr>
<td>&gt;648 mg/28 days, N (%)</td>
<td>5 (0)</td>
<td>0 (0)</td>
<td>5 (0)</td>
<td>1 (0)</td>
<td>0 (0)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Missing dose, N (%)</td>
<td>1 (0)</td>
<td>3 (2)</td>
<td>4 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>SC tocilizumab fills/28 days during follow-up period, mean, N (SD)</td>
<td>6.8 (4.3)</td>
<td>6.0 (3.9)</td>
<td>6.7 (4.3)</td>
<td>7.0 (4.4)</td>
<td>7.3 (4.8)</td>
<td>7.1 (4.5)</td>
</tr>
</tbody>
</table>

### Dose modifications

| Index therapy with 324 mg/28 days (ie, 162 mg every 2 wks), N (%) | 533 (47) | 75 (55) | 608 (48) | 168 (48) | 77 (48) | 245 (48) |
| Dose escalation, N (%) | 204 (38) | 19 (25) | 223 (37) | 73 (43) | 24 (31) | 97 (40) |
| Index therapy with 648 mg/28 days (ie, 162 mg every wk), N (%) | 477 (42) | 54 (40) | 531 (42) | 174 (50) | 76 (47) | 250 (49) |
| Dose reduction, N (%) | 110 (10) | 14 (10) | 124 (10) | 27 (9) | 13 (8) | 40 (8) |
| Proportion of days covered, mean (SD) | 0.5 (0.3) | 0.5 (0.3) | 0.5 (0.3) | 0.4 (0.3) | 0.5 (0.3) | 0.4 (0.3) |

*Rituximab and tofacitinib had no prescriptions filled in either database during the study period.

DMARD indicates disease-modifying antirheumatic drug; IV, intravenous; SC, subcutaneous; SD, standard deviation; TNF, tumor necrosis factor.
synthetic DMARDs, biologics, and corticosteroids were frequently used among patients in both cohorts (Table 1). The baseline rheumatoid arthritis treatment patterns in the 2 cohorts distinguishing between commercial and Medicare coverage are also shown in Table 1.

**Treatment Patterns**

In this sample, 90 days before the index date, 22% of Truven patients and 25% of Optum patients did not receive therapy, and 47% patients in either cohort were receiving monotherapy. A total of 31% of Truven patients and 29% of Optum patients received a combination of conventional synthetic DMARDs and biologics, and 51% of Truven and 57% of Optum patients had received corticosteroids. Among patients with commercial and Medicare coverage, respectively, 47% and 44% of Truven patients and 46% and 48% of Optum patients received monotherapy, and 30% and 35% of Truven patients and 29% and 27% of Optum patients received combination treatment with conventional synthetic DMARDs and biologics (see Appendix Table 1, available at www.AHDBonline.com).

Approximately half of the patients initiated SC tocilizumab as monotherapy (Truven, 44%; Optum, 47%); the other half initiated the drug in combination with other therapy (Truven, 56%; Optum, 53%; Table 2). Among the patients with commercial or Medicare coverage, respectively, more than one-third initiated SC tocilizumab as monotherapy, whereas more than half initiated SC tocilizumab as combination therapy (Table 2). Among the patients who initiated SC tocilizumab with conventional synthetic DMARDs, methotrexate was the most often used conventional synthetic DMARD; a few patients initiated SC tocilizumab with another biologic DMARD (Table 2). Most patients started treatment with a recommended SC tocilizumab dose of 162 mg every 2 weeks or 162 mg every week. The remaining patients initiated a lower dose of the drug than currently recommended or were receiving between 162 mg every 2 weeks and 162 mg every week (Table 2).

**Dose Modification**

During the 1-year follow-up period, of those who started with the 162 mg every 2 weeks dose, 37% of Truven patients and 40% of Optum patients escalated to 162 mg every week. Among those who started with the 162 mg every-week dose, only 3% of Truven patients and 4% of Optum patients, respectively, had a dose reduction to 162 mg every 2 weeks (Table 2).

Overall, 60% and 68% of patients in the Truven and Optum cohorts, respectively, initiated or escalated to the higher weekly dose. Among patients with commercial or Medicare coverage, respectively, 60% and 53% of Truven and 70% and 62% of Optum patients initiated or escalated to the higher weekly dose, whereas 0% and 6% of the Truven and 3% and 5% of the Optum patients had a dose reduction to 162 mg every 2 weeks. The mean number of SC tocilizumab prescription fills per 28 days during the follow-up period was 6.7 for Truven patients and 7.1 for Optum patients. The mean proportion of days covered in the study sample was approximately 50% (Table 2).

Among patients who had dose escalation, the mean time to dose escalation was 126 days for the Truven cohort and 112 days for the Optum cohort (Figure 2).

**Likelihood of Dose Escalation**

Using logistic regression, among Truven patients, corticosteroid use, age, and anemia (defined by ICD-9 and ICD-10 diagnosis codes) were the 3 main predictors for dose escalation. Corticosteroid use within 90 days from the index date (odds ratio [OR], 0.70; P = .02), patients aged 35 to 44 years versus patients aged 18 to 34 years (OR, 0.54; P = .05), or patients with anemia versus...
no anemia (OR, 0.50; P = .04) had reduced odds of dose escalation (Table 3).

In the Optum cohort, female patients had increased odds of dose escalation compared with male patients (OR, 2.54; P = .02), whereas patients from North Central (OR, 0.50; P = .05) and Northeastern (OR, 0.27; P = .04) regions had lower odds of dose escalation than patients from the South (Table 3).9 Other factors were not significant.

When the Cox model was used among patients with dose escalation, Truven patients from the Northeast had an increased hazard ratio (HR) of dose escalation versus patients from the South (HR, 1.80; P = .01; Appendix Table 2, available at www.AHDBonline.com). Optum patients with depression had an increased HR of dose escalation compared with patients with no depression (HR, 3.51; P = .04), and patients with a 2014 or 2015 index year had a lower HR of dose escalation compared
Dose Modification Patterns of Subcutaneous Tocilizumab

Discussion

Tocilizumab is approved in the United States for the treatment of adults with moderate-to-severe rheumatoid arthritis (among other indications) who have had an inadequate response to ≥1 DMARDs.6 Over the past decade, multiple studies have demonstrated the safety and effectiveness of tocilizumab treatment in patients with rheumatoid arthritis.11-16 Dose modification patterns among patients with rheumatoid arthritis who receive IV tocilizumab have been examined17,18; however, similar data among patients with rheumatoid arthritis receiving SC tocilizumab are limited.17 We believe our study is the first to investigate SC tocilizumab dose modification in a real-world setting.

According to our findings, many patients used an every-week dose of SC tocilizumab at initiation or during dose escalation, whereas few patients who started treatment with the every-week dose of SC tocilizumab had dose reduction.

The dose-escalation patterns observed in this study are aligned with a study from Pappas and colleagues that prospectively looked at dosing patterns of IV tocilizumab in US patients with rheumatoid arthritis, and showed that 51.6% of patients had dose escalation from 4 mg/kg to 8 mg/kg.6 Although the mode of tocilizumab administration in our study was different from that of Pappas and colleagues, both studies demonstrated that approximately 50% of patients who receive tocilizumab (IV or SC) require escalation to the higher dose.

Other studies have examined the clinical outcomes of patients receiving the lower dose versus the higher dose of IV tocilizumab.13,15,18 A double-blind, randomized, controlled clinical trial showed that patients receiving a higher dose of IV tocilizumab (8 mg/kg) achieved a greater reduction in Disease Activity Score (DAS)-28 than patients receiving IV tocilizumab 2 mg/kg or 4 mg/kg.18 In addition, 2 randomized, double-blind, placebo-controlled trials demonstrated that more patients achieved American College of Rheumatology responses at 6 months with an 8-mg/kg dose of IV tocilizumab than patients who received a 4-mg/kg dose of IV tocilizumab.13,15

An open-label extension study of Japanese patients with rheumatoid arthritis has examined the efficacy of SC tocilizumab once every week versus SC tocilizumab every 2 weeks, showing that patients who received SC tocilizumab every week had a greater improvement in DAS-28 scores than those who received SC tocilizumab every 2 weeks.19 Although in our study we did not examine physicians’ reasoning for dose escalation, the studies discussed here may provide some insights into why physicians escalated the dose of SC tocilizumab in almost 50% of the patients.

The other half of the patients in this study were started with the higher dose of SC tocilizumab 162 mg every week. However, only a small proportion of these patients (Truven, 3%; Optum, 4%) had a reduction in SC tocilizumab dose. Because this study was based on claims data, the reasoning for dose reduction was not examined. However, previous studies that have looked at the reasoning for dose reduction could provide some insight into why particular trends were observed in our study.

First, it is possible that the small number of patients could have achieved a sufficient clinical response with tocilizumab 162 mg every week and therefore warranted a dose reduction, because studies have shown that dose reduction is feasible in a proportion of patients with low disease activity.10 Alternatively, dose reduction could have been used to manage certain dose-related laboratory test changes associated with the higher dose of tocilizumab, including elevated liver enzymes, neutropenia, and thrombocytopenia.4 Finally, it is possible that these patients had weight reduction during the follow-up period, which would warrant dose reduction based on the prescribing information for tocilizumab.4

Of the patients whose dose of tocilizumab was escalated, the time to dose escalation was observed at approximately 4 months in both cohorts in our study. The study by Pappas and colleagues showed that patients had their IV tocilizumab dose escalated after their 3-month visit; although our study was conducted among patients receiving SC tocilizumab, the observed trends are similar between these 2 studies.6 The results from both studies correlate with US treatment guidelines, which recommend that a therapeutic treatment be given for at least 3 months before dose escalation is considered.1

Although the impact of SC tocilizumab dose escalation on costs was not formally examined in our study, it is important to consider the potential economic burden of dose escalation. Previous studies have examined the cost implication of dose escalation of multiple IV biologic DMARDs for the treatment of rheumatoid arthritis, including IV tocilizumab.21,22 These studies showed that the mean cost for patients whose dose of an IV biologic DMARD was escalated was significantly higher than for patients whose dose was not escalated (P < .01).

Although these studies examined the costs associated with the escalation of IV biologic DMARDs for the treatment of rheumatoid arthritis,21,22 it is likely that similar trends would be observed with the dose escalation of SC tocilizumab. Currently, the economic implications of SC tocilizumab dose escalation are unknown, which highlights a potential area for future research.

Among Truven patients, corticosteroid use within 90
days of the index date, an age of 35 to 44 years, and the presence of anemia had an OR of <1 for dose escalation. Female patients in the Optum and Truven groups had an increased OR of dose escalation, which was significant in Optum patients. It has been shown that female patients had worse levels of disease activity and function than male patients.23

Of note, when the Cox model was used among patients with dose escalation, Optum patients with depression had an increased risk for dose escalation. In patients with rheumatoid arthritis, depression is a common disorder,24 affecting between 14% and 39% of patients.25 The co-occurrence of rheumatoid arthritis and depression is associated with increased levels of pain,26 fatigue,27 and disease activity,28 which may lead a physician to increase the patient’s dose to control disease symptoms and improve quality of life, and could explain the results observed in our study.

In addition, Optum patients who initiated SC tocilizumab therapy in 2014 or in 2015 had a lower risk for dose escalation than patients who initiated SC tocilizumab therapy in 2016. The greater number of Optum patients initiating SC tocilizumab in 2014 and 2015 after its approval in 201329 would explain the lower risk for dose escalation in these years versus 2016. In addition, the lower uptake of SC tocilizumab in 2016 among Optum patients could result from increased experience of rheumatologists in relation to dose escalation among patients with rheumatoid arthritis who are receiving a lower dose of SC tocilizumab.

Limitations

These study findings must be interpreted in light of the limitations. First, although this was intended to be a claims study from a clinical surrogate response perspective, the populations studied through the claims analyses were in commercially insured or Medicare Advantage or supplemental populations between 2013 and 2016. A confounding issue in both groups could have been significant changes in medical or pharmacy benefit coverage rules during this time that are known to affect drug selection or management, such as the route of administration, along with any dose escalation.

Second, retrospective observational studies are subject to uncertainty because of the generalizability of the findings. The study sample was drawn from patients with commercial or Medicare Advantage or supplemental coverage in the United States and may not be generalizable to all patients with rheumatoid arthritis, nor other countries. The known issues with accurate interpretations from databases such as Truven and Optum and the use of traditional pharmacy benefit management measures further limit the ability to draw conclusions.

In addition, the small sample size means that the study results should be interpreted with caution. Finally, the study only examined the administrative pharmacy claims for patients who initiated SC tocilizumab. Therefore, it was not possible to determine the exact reasoning behind the trends observed with regard to dose escalation and reduction.

Conclusions

Using real-world data, this study demonstrated that, overall, the utilization of a weekly dose of SC tocilizumab at initiation or at dose escalation was 60% and 68% in Truven and Optum patients, respectively. The dose escalation of SC tocilizumab occurred in more than 33% of patients who initiated the every 2-week dose of SC tocilizumab, and the time to dose escalation was approximately 4 months. In contrast, less than 5% of patients starting at the every-week dose had a dose reduction of SC tocilizumab to every 2 weeks.

These results indicate that physicians take advantage of the option to increase the dose of SC tocilizumab, but few providers choose to reduce the dose, which results in many patients ultimately receiving the higher dose of the drug. The trend in dose escalation could result in increased economic burden.

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Author Disclosure Statement

Dr Punekar is an employee of and owns stocks in Sanofi; Dr Choi is a former employee and stockholder of Sanofi; Ms Boklage is an employee of and owns stocks in Regeneron Pharmaceuticals; Dr Iglesias-Rodriguez is an employee of Sanofi Genzyme; Dr Nola is a consultant to Gilead and Sanofi Regeneron, and a consultant to and speaker for Coheris.

References

23. van Vollenhoven RF. Sex differences in rheumatoid arthritis: more than meets the eye.... Br J Rheumatol. 1994;33:211-213.