ORIGINAL RESEARCH

Comparing Healthcare Costs Associated with Oral and Subcutaneous Methotrexate or Biologic Therapy for Rheumatoid Arthritis in the United States

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BACKGROUND: Methotrexate (MTX) is the primary disease-modifying antirheumatic drug used for the treatment of rheumatoid arthritis (RA). Optimizing the use of oral and subcutaneous MTX may delay the use of expensive biologic therapies; the effect of such a delay on overall medical costs is currently unknown.

OBJECTIVE: To compare the 5-year healthcare costs of treatment pathways for patients with RA who initiate oral MTX in the United States.

METHODS: We identified patients with RA in the Symphony Health Solutions database (Integrated Dataverse) who initiated treatment with oral MTX in 2009 and had RA-related claims for each year through 2014. We then grouped the patients into 4 treatment cohorts, including those who (1) continued to use oral MTX, (2) switched to subcutaneous MTX, (3) switched to subcutaneous MTX and then added or switched to a biologic therapy, and (4) added or switched to a biologic therapy. The costs (in 2015 US dollars) for pharmaceuticals, office visits, hospitalizations, and emergency department visits were estimated for each cohort.

RESULTS: Of the total 35,640 patients in this study, 15,599 patients continued to use oral MTX, with an average cost of $47,464 per patient in the full study period; 1802 patients switched to subcutaneous MTX, with an average per-patient cost of $59,058; 711 patients switched to subcutaneous MTX and then added or switched to a biologic agent, with an average per-patient cost of $175,391 and a mean time to a biologic use of 1184 days; and 17,528 patients added or switched to a biologic from oral MTX, with an average per-patient cost of $212,595 and a mean time to a biologic use of 478 days. Biologic treatments were responsible for the cost differences between the cohorts; the nondrug costs were similar across the groups.

CONCLUSION: Our findings that patients who switched to subcutaneous MTX incurred lower costs than patients who only used oral MTX before using biologics may provide useful information for patients and providers who are choosing between continued MTX use and adding or switching to a biologic based on treatment guidelines.

KEY WORDS: biologic therapy, healthcare cost, MTX, oral methotrexate, rheumatoid arthritis, subcutaneous methotrexate, treatment pathways

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Rheumatoid arthritis (RA) is the most common autoimmune inflammatory arthritis in adults, with a prevalence of approximately 0.6% in the United States.[1] RA has a significant negative impact on health-related quality of life[2] and imposes a substantial economic burden on the US healthcare system.[3]

Methotrexate (MTX) is the primary disease-modifying antirheumatic drug (DMARD) for the treatment of RA. The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) guidelines recommend MTX as the initial therapy for patients with active RA.[4,5] The ACR and EULAR also recommend switching to a biologic thera-

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py, in combination with MTX if possible, when initial treatment targets are not met.

Biologics are more expensive than MTX and other traditional DMARDs. Before biologics became available, medications constituted the second largest component of RA-related costs after inpatient hospital costs, accounting for approximately 8% to 24% of the total medical expenditures associated with this disease.[6,7] After biologics were introduced, pharmacy expenditures displaced hospital expenditures as the primary driver of RA-related costs.[3]

Given this shift in the magnitude and distribution of RA-related costs, one of EULAR's overarching principles states that it is the responsibility of the rheumatologist to consider economic implications when selecting between treatment strategies and modalities with similar efficacy and safety in the short to intermediate term.[5]

Consequently, recent studies have examined how physicians can optimize RA treatment practices to maximize clinical outcomes and minimize economic costs.[8-12] It is generally accepted that MTX is most frequently administered orally in the United States. However, subcutaneous MTX offers better bioavailability, tolerability, and efficacy, with fewer gastrointestinal side effects than oral MTX.[8-10] Real-world evidence shows that higher-dose titration of oral MTX and the use of subcutaneous MTX are infrequent and underutilized.[11,12]

Historically, subcutaneous MTX might have been used less frequently because of functional limitations (eg, joint pain or reduced grip strength) in patients with RA that prevented the measurement and injection of a full dose of MTX, because of concerns about needle-stick safety, and because of logistics and regulatory requirements of dispensing a cytotoxic medication.[13,14] However, the ease of use associated with recently introduced prefilled subcutaneous MTX auto-injectors overcomes many of these concerns.[15,16] Therefore, increased use of subcutaneous MTX after nonresponse to oral MTX may provide considerable savings by delaying the use of expensive biologic treatments.[17]

The real-world impact of subcutaneous MTX use on direct medical costs remains unknown. Thus, the objectives of this study were to characterize the different pharmaceutical treatment pathways for patients with RA who initiate oral MTX therapy in the United States, and to estimate the 5-year healthcare costs for patients who initiate and continue to use oral MTX exclusively; switch to subcutaneous MTX; or add or switch to a biologic therapy.

KEY POINTS

- MTX is the primary DMARD for RA treatment, but titration to higher-dose oral MTX and the use of subcutaneous MTX are underutilized.
- This claims-based analysis included 35,640 patients with RA who started oral MTX.
- Patients were divided into 4 cohorts: continuing oral MTX, switching to subcutaneous MTX, switching to subcutaneous MTX then adding/switching to a biologic, or adding/switching to a biologic.
- Switching to subcutaneous MTX delayed initiation of biologic therapy by an average of 706 days.
- The 5-year per-patient drug costs were 4- to 8-fold higher in those who switched to biologics versus those who continued oral or subcutaneous MTX.
- The total costs per patient were 3 to 4 times higher when adding/switching to a biologic than when continuing oral or subcutaneous MTX.
- Nondrug costs were similar across the 4 groups, suggesting that biologic treatment was responsible for the total cost differences between the cohorts.
- Delaying or avoiding the use of biologics may alter the cost burden associated with RA treatment in the United States.

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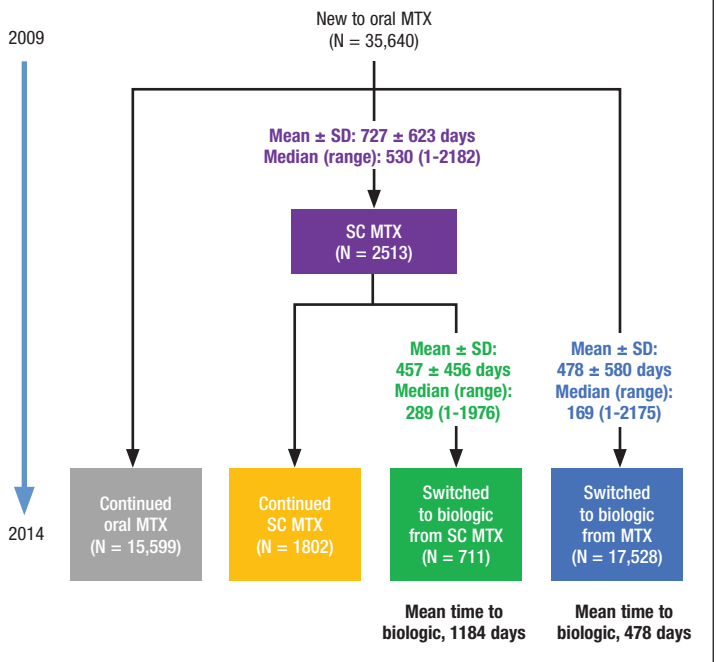
Methods

This analysis is based on the Symphony Health Solutions anonymized patient-level claims data, which capture approximately 274 million US patients and 92% of all drug prescribers in the United States. We included adjudicated and nonadjudicated claims in these analyses.

Patient Population

We selected patients who were diagnosed with RA (*International Classification of Diseases, Ninth Revision* [*ICD-9*] codes 714.0 and 714.30) in 2009 who were eligible for medical and pharmacy benefits and had at least 1 RA-related claim in each year of the study period from January 2009 through December 2014. Patients were

Figure 1 Patient Identification and Treatment Pathway Cohorts



MTX indicates methotrexate; SC, subcutaneous; SD, standard deviation.

required to have started using oral MTX at some point during 2009 without use of MTX in the previous 12 months. The patients' comorbidities were defined based on the presence of an *ICD-9* code submitted during any time of the study (the relevant codes are listed in the **Appendix** at www.AHDBonline.com).

Patients who started oral MTX therapy were classified into 4 treatment cohorts that included those who (1) continued to use oral MTX, (2) switched to subcutaneous MTX, (3) switched to subcutaneous MTX and then added or switched to a biologic therapy, or (4) added or switched to a biologic therapy from oral MTX. The claims for patients in each cohort were then aggregated by code to form the dataset for the analysis.

Direct Medical Costs

The claims from the Symphony Health Solutions database had detailed utilization data, but they did not contain cost information or paid amounts. We therefore linked the appropriate code in each claim to external sources to obtain cost information (in 2015 US dollars). Claims covered all healthcare services, not only those related to RA.

The cost of each office-based encounter was obtained by linking each claim's Healthcare Common Procedure Coding System (HCPCS) code to the Centers for Medicare & Medicaid Services (CMS)'s fee schedules for clinical laboratories[18]; durable medical equipment, prosthetic, orthotics, and supplies[19]; ambulance[20]; and physicians.[21]

Hospitalization costs were calculated by applying each hospitalization's diagnosis-related group (DRG)-specific relative weight to the sum of the national base labor ($3753.31), nonlabor ($1639.38), and capital ($434.26) cost components obtained from CMS.[22,23] DRG codes were not provided in the Symphony Health Solutions data; we derived them from diagnosis codes and procedure codes using general equivalent mappings, which were also obtained from CMS.[24] Nonadjudicated claims were included in these analyses.

The costs of each emergency department encounter were calculated as the sum of the costs of each encounter's procedures. Procedure costs were obtained from the CMS ambulatory payment classification (APC) Hospital Outpatient PPS October 2015 Addendum B file.[25] APC codes were not included in the Symphony Health Solutions data; we derived the APC codes by matching the descriptions of the HCPCS codes in the Addendum A file to the APC code descriptions.

Pharmaceutical costs were calculated by multiplying the dispensed metric quantities by the Medispan unit price (ie, the Average Wholesale Price) for each National Drug Code (both included in the Symphony Health Solutions database). A small percentage (0.2%) of pharmaceutical costs were derived from medical claims by matching HCPCS codes with the Medicare Average Sales Price list.[26] These include the biologic injections that are covered under the medical benefit. (The HCPCS-based pharmaceutical cost estimates were conservative, because the claims listed only a single code and did not reflect instances in which multiple units were dispensed.)

Because the prescription dataset lacked diagnosis codes, we considered a pharmaceutical drug to be related to RA if its National Drug Code matched the list of DMARDs found in the Healthcare Effectiveness Data and Information Set Disease-Modifying Antirheumatic Drug Therapy for Rheumatoid Arthritis (ART)-C file.[27] MTX was categorized by oral or injectable (subcutaneous) route of administration.

The relevant biologic therapies included etanercept, adalimumab, golimumab, certolizumab pegol, abatacept, infliximab, rituximab, and anakinra. The non-MTX nonbiologic therapies included nonsteroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors, glucocorticoids, hydroxychloroquine, sulfasalazine, leflunomide, and other conventional DMARDs. Non–RA-related drugs were grouped together and were categorized as "other drugs."

Analyses

The background demographic characteristics for each

cohort were summarized by their means, medians, standard deviations, ranges, and proportions. The total costs were calculated based on aggregated claim counts in each category (office-based, hospitalizations, emergency department, and pharmaceutical). Per-patient costs were calculated by dividing the total costs by the number of patients in each cohort.

Results

We identified 35,640 patients who started using oral MTX in 2009 (**Figure 1**). The majority of these patients used either oral MTX alone (44%) through 2014 or added or switched to a biologic agent from oral MTX (49%). The 7% remaining patients used subcutaneous MTX in some manner: 75% switched to and continued to receive subcutaneous MTX (5%), and 25% switched to subcutaneous MTX before adding or switching to a biologic agent (2%).

The total 5-year pharmaceutical costs for patients who switched to biologics were 4 to 8 times higher than the costs of patients who continued to use oral or subcutaneous MTX.

The use of subcutaneous MTX was associated with the delayed use of a biologic therapy. Patients who switched to subcutaneous MTX initiated biologic therapy, on average, 706 days later than patients who did not use subcutaneous MTX (mean of 1184 days vs 478 days from the start of oral MTX to the start of a biologic therapy among those who eventually initiated a biologic therapy).

Patient demographic and baseline characteristics were broadly similar across the cohorts (**Table 1**). The patients who continued to use oral MTX tended to be older than those in the other cohorts, and the patients who switched to subcutaneous MTX were more likely to be women.

Pharmaceutical Costs

Table 2 shows the total 5-year per-patient pharmaceutical costs by treatment cohort. In ascending order, the per-patient pharmaceutical costs were $25,221 for patients who continued to use oral MTX, $34,581 for patients who switched to and continued using subcutaneous MTX, $154,032 for patients who switched to subcutaneous MTX and then added or switched to a biologic, and $190,812 for patients who added or switched to a biologic directly after oral MTX. The total 5-year pharmaceutical costs for patients who switched to bio-

Table 1 Baseline Patient Characteristics

Characteristics	Patients who continued to use oral MTX (N = 15,599)	Patients who switched from oral to SC MTX and remained (N = 1802)	Patients who switched from oral to SC MTX and then to a biologic (N = 711)	Patients who switched from oral MTX to a biologic (N = 17,528)
Age, yrs, mean ± SD	66.2 ± 11.8	59.6 ± 14.9	53.9 ± 15.2	59.0 ± 13.0
Median (range)	68 (8-80)	62 (8-80)	56 (9-80)	60 (7-80)
Sex, %				
Male	23.8	18.4	18.4	21.6
Female	76.2	81.6	81.6	78.4
Race/ethnicity, %				
African American	10.3	8.2	7.5	9.7
Asian	0.7	0.4	0.7	0.8
Caucasian	58.8	59.0	57.5	56.7
Hispanic	6.0	5.8	7.2	7.8
Missing/unknown	24.2	26.5	27.1	25.1
Educational level, %				
Less than high school	1.0	0.7	0.4	1.0
Bachelor's degree	9.9	9.4	9.6	10.9
High school graduate	31.3	27.7	28.8	28.5
Master's degree	0.2	0.3	0.7	0.3
Some college/ associate's degree	37.2	39.0	37.6	38.3
Unknown	20.5	22.9	22.9	21.1
Comorbidities, %				
Ischemic cardiovascular disease	18.8	15.4	12.4	14.0
Hypertension	61.2	54.1	48.2	53.1
Heart failure	8.7	7.2	5.8	5.6
Atrial fibrillation	16.5	14.0	11.5	12.6
Diabetes	29.6	28.2	25.0	27.4
COPD	14.1	12.8	9.1	10.9
Asthma	13.9	17.6	17.7	15.4
Gastrointestinal disease	47.4	51.9	52.6	49.1
Depression	15.2	21.6	23.1	19.4
Additional treatments for RA, %				
NSAIDs/coxibs	87.7	93.3	93.4	91.0
Glucocorticoids	89.0	94.2	96.3	92.3
Hydroxychloroquine	33.1	47.2	45.7	29.8
Sulfasalazine	9.8	18.2	21.2	12.5
Leflunomide	9.1	18.0	27.4	15.5
Other conventional DMARD	9.1	18.4	28.7	15.8

COPD indicates chronic obstructive pulmonary disease; DMARD, disease-modifying antirheumatic drug; MTX, methotrexate; NSAIDs, nonsteroidal anti-inflammatory drugs; RA, rheumatoid arthritis; SC, subcutaneous; SD, standard deviation.

Table 2 Per-Patient Pharmaceutical Costs, in the Full Study Period, by Drug Category

Drug category	Continued to use oral MTX, $	Switched to SC MTX, and remained, $	Switched to SC MTX then to a biologic, $	Switched to a biologic, $
Oral MTX[a]	2993	2029	1088	2076
Injectable MTX[a]	1	327	434	30
Biologics[a]	22	63	116,555	157,240
NSAIDs/coxibs	975	1290	1043	1204
Glucocorticoids	152	281	259	209
Hydroxychloroquine	1045	1287	1067	612
Sulfasalazine	53	101	58	52
Leflunomide	217	354	399	296
Other conventional DMARD	378	1096	3631	1988
Other drug costs[b]	19,385	27,753	29,498	27,105
Total 5-year costs	25,221	34,581	154,032	190,812

[a]Nonzero drug costs for injectable MTX and biologics in Cohort 1 (ie, continued oral MTX), for biologics in Cohort 2 (ie, switched to subcutaneous MTX and continued its use), and for injectable MTX in Cohort 4 (ie, switched to a biologic) are the result of the use of these drugs for non–RA-related reasons.

[b]Costs for non–RA-related drug expenses.

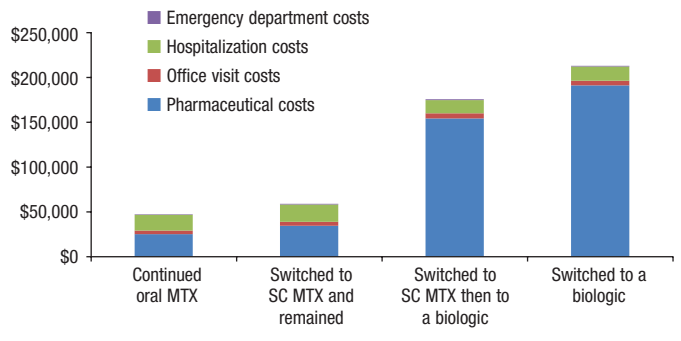
DMARD indicates disease-modifying antirheumatic drug; MTX, methotrexate; NSAIDs, nonsteroidal anti-inflammatory drugs; SC, subcutaneous.

Table 3 Average Total Per-Patient Costs in the Full Study Period

Cost category	Continued to use oral MTX, $	Switched to SC MTX, and remained, $	Switched to SC MTX then to a biologic, $	Switched to a biologic, $
Office visit	3963	4478	5602	5107
Hospitalization	17,597	19,203	14,794	15,938
Emergency department	683	796	963	738
Total nonpharmaceutical 5-year costs	22,243	24,477	21,359	21,783
Total pharmaceutical 5-year costs	25,221	34,581	154,032	190,812
Total 5-year costs	47,464	59,058	175,391	212,595

MTX indicates methotrexate; SC, subcutaneous.

Figure 2 Total Per-Patient Costs in the Full Study Period



MTX indicates methotrexate; SC, subcutaneous.

logics were 4 to 8 times higher than the costs of patients who continued to use oral or subcutaneous MTX.

RA-related drug costs accounted for 20% to 25% of total drug costs for patients who used only oral or subcutaneous MTX. In contrast, the RA-related drug costs accounted for 80% to 85% of the total drug costs for patients who eventually started biologic therapies. Patients who eventually started a biologic therapy had much higher RA-related drug costs than the other patients in this study. However, patients who switched to subcutaneous MTX before adding or switching to a biologic therapy incurred lower costs than those who added or switched to a biologic therapy directly after oral MTX.

Service Setting Costs

Table 3 shows the per-patient medical expenditures by place of service in the full study period. Patients who used biologics tended to have higher office visit costs and lower hospitalization costs than patients who continued to use oral or subcutaneous MTX. Overall, the total nonpharmaceutical costs were similar across the cohorts, ranging from $21,359 (patients who switched to subcutaneous MTX and then to a biologic) to $24,477 (patients who switched to subcutaneous MTX), indicating that patients received similar underlying care despite using different treatments for their RA.

Total Medical Costs

Table 3 and **Figure 2** show the total per-patient costs for each cohort for the full study period. The patients who continued to use oral MTX incurred the lowest per-patient costs, followed by patients who switched to subcutaneous MTX and continued the drug, patients who switched to subcutaneous and then added or switched to a biologic, and patients who switched to a biologic from oral MTX. Total costs were 3 to 4 times higher for patients who added or switched to a biologic than patients who continued to take oral or subcutaneous MTX.

Table 4 and **Figure 3** show the total costs for each cohort in the full study period. Patients who continued to use oral or subcutaneous MTX were underrepresented in overall costs in relation to their proportion of the study sample. Patients who continued to use oral MTX represented 44% of the sample, but only 15.7% of all of the costs; patients who continued to use subcutaneous MTX represented 5% of the sample, but only 2.3% of all of the costs.

Conversely, patients who added or switched to a biologic therapy were overrepresented in the overall costs; the patients who switched to subcutaneous MTX before adding or switching to a biologic therapy represented 2% of the sample and 2.7% of all costs, whereas patients who

switched to biologics directly from oral MTX represented 49% of the sample and 79.3% of all costs.

Discussion

We used a large, nationally representative sample of patients with RA to analyze their healthcare utilization patterns for 5 years. We found that patients who continued to use oral or subcutaneous MTX incurred much lower total per-person medical costs during the 5-year study period than patients who added or switched to biologic therapies. The use of biologics was responsible for this cost difference (office-based, hospital, and emergency department costs were similar across the cohorts).

We also found that among patients who switched to biologics, those who switched to subcutaneous MTX and then added or switched to a biologic incurred lower total per-person medical costs than those who switched directly from oral MTX to a biologic. The cost difference is largely attributable to intermediate subcutaneous MTX treatment that delayed the use of expensive biologics—mean time to the use of a biologic was 1184 days after switching from subcutaneous MTX versus 478 days when switching directly from oral MTX (Figure 1).

Limitations

This study has several limitations. We only had access to aggregated claim counts and costs for each cohort. Without individual-level claims data, we were unable to adjust for differences in a patient baseline characteristics or to estimate costs stratified by patient characteristics, such as age.

In addition, we did not have access to reimbursed costs. Imputing costs based on CMS fee schedules and average wholesale prices provides a standardized cost reference, but these costs are higher than the actual costs incurred after adjustments have been made for claim denials and for drug rebates.

Finally, because this analysis is based on claims data, we did not have data on patients' RA severity, response to therapy, or clinical outcomes, which prevented an analysis of patient channeling bias between cohorts.

Conclusion

MTX is the preferred initial DMARD recommended by international RA treatment guidelines. The findings of this study suggest that increasing the use of oral or subcutaneous MTX in appropriate patients can shift patients from higher-cost treatment pathways to lower-cost treatment pathways.

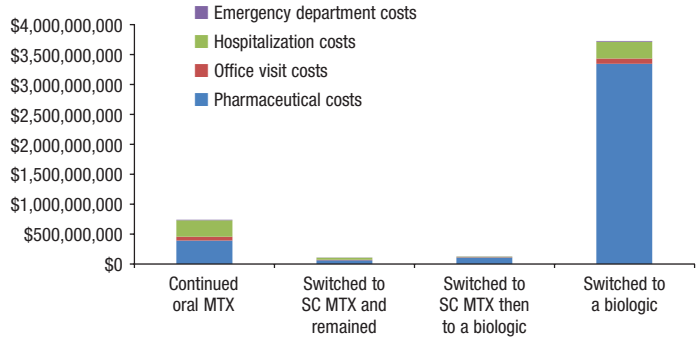
Avoiding or delaying the use of expensive biologic therapies for this patient population will alter the cost distribution and may reduce the economic burden of RA on the US healthcare system. Because RA is a chronic disease, more research is needed to understand the long-term costs and clinical benefits of RA treatment patterns in the United States. ■

Table 4 Total Costs in the Full Study Period

Cost category	Continued to use oral MTX, $	Switched to SC MTX and remained, $	Switched to SC MTX then to a biologic, $	Switched to a biologic, $	Total, $
Pharmaceutical	393,425,758	62,315,061	109,516,465	3,344,545,985	3,909,803,269
Office visit	61,814,079	8,068,737	3,982,885	89,521,811	163,387,512
Hospitalization	274,495,214	34,604,050	10,518,513	279,355,584	598,973,362
Emergency department	10,647,283	1,434,819	684,376	12,938,354	25,704,831
Total	740,382,334	106,422,667	124,702,239	3,726,361,734	4,697,868,974

MTX indicates methotrexate; SC, subcutaneous.

Figure 3 Total Costs in the Full Study Period



MTX indicates methotrexate; SC, subcutaneous.

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Author Disclosure Statement

Dr Lee, Mr Pelkey, and Dr Ganz are employees of Evidera, which received funding from Medac Pharma; Ms Gubitosa is an employee of Symphony Health Solutions, which received funding from Medac Pharma; and Mr Henrick is an employee of Medac Pharma.

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STAKEHOLDER PERSPECTIVE

Identifying the Most Clinically and Economically Effective Therapies for Rheumatoid Arthritis Remains a Challenge for Providers and Payers

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Approximately 1.3 million people in the United States currently have rheumatoid arthritis (RA). Within 2 years of diagnosis, patients may experience moderate disability, and after 10 years, 30% of patients are severely disabled.[1]

PROVIDERS: The management of patients with RA can be challenging, because RA therapies and the treatment approaches vary widely, depending on physician preferences and the individual patient response to therapy and specific needs. In recent years, the treat-

STAKEHOLDER PERSPECTIVE *Continued*

ment of patients with RA has become more aggressive, as physicians incorporate the use of expensive biologic agents earlier in the disease progression.[1]

In the past, payers might have expected physicians to begin treatment for newly diagnosed patients with RA with oral disease-modifying antirheumatic drugs, then with self-injectable biologics, and finally with infused drugs as the last treatment option for a more advanced stage of the disease. Currently, however, rheumatologists often choose to begin treatment with multiple pharmaceutical options at once, and then phase out drugs as the patient begins to show signs of improvement. Such a combination therapy approach is consistent with the American College of Rheumatology's 2012 treatment recommendations for patients with high disease activity and poor prognosis.[2]

One reason for this aggressive treatment approach is that remission in established RA is difficult to achieve. Physicians, therefore, focus heavily on achieving remission as early as possible.[1] Although methotrexate is often recommended as a preferred first-line therapy as described in this issue by Lee and colleagues,[3] many physicians prefer to have relatively open access to a selection of drugs that will aggressively manage the individual patient to reduce joint damage and other systemic effects that result from untreated or undertreated RA.

PAYERS: Payers often believe that they are aiming for a moving target when designing management strategies for RA. Many patients switch between multiple therapies as a result of intolerance of or nonresponse to therapy, adding complexity to the treatment protocol as well as formulary design related to RA therapies. As rheumatologists continue to embrace more aggressive therapeutic options for RA, payers must be diligent in reviewing emerging treatments and new treatment recommendations. Understanding the use of biologic therapies across the medical and pharmacy benefits may help payers keep up with changes in treatment, particularly concerning RA-related doublet and triplet therapies.[1]

RA continues to present clinical and economic challenges to patients, physicians, and payers. With a wide variety of treatment options currently available, and those in the pipeline, payers are faced with the challenge of identifying the most clinically and economically effective allocation of treatments for RA.[4]

The challenge for payers is compounded by the patient's response to treatment. Although only 10% to 20% of patients with established RA will achieve disease remission, for patients with early-stage RA (between 6 months and 1 year), remission rates range between 30% and 40%.[1] As noted above, because of the high incidence of the disease, the associated disability, and the progressive nature of RA,[1] it is critically important to quickly identify and implement clinically favorable and cost-effective treatments that are focused on preventing disease progression and improving patients' quality of life.

It is critically important to quickly identify and implement clinically favorable and cost-effective treatments that are focused on preventing disease progression and improving patients' quality of life.

The study by Lee and colleagues demonstrates that the use of oral or subcutaneous methotrexate that is optimized according to the guidelines can be a financially appealing medication option,[3] but this drug does not successfully address the patient's systemic condition. Because RA is a progressive and debilitating disorder, addressing the patient's RA-related systemic effects does more than relieve pain and improve the patient's quality of life—it slows joint damage with the goal of helping patients to maintain productivity and avoid severe disability over time. ■

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