Economic Burden of Patients with Inadequate Response to Targeted Immunomodulators for Rheumatoid Arthritis

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ABSTRACT

BACKGROUND: Targeted immunomodulators (TIMs), including biologic disease-modifying antirheumatic drugs (DMARDs) and JAK/STAT inhibitors, are effective therapies for rheumatoid arthritis (RA), but some patients fail to respond or lose response over time. This study estimated the real-world prevalence of RA patients with inadequate responses to an initial TIM (nonresponders) in the United States and assessed their direct and indirect economic burden compared with treatment responders.

METHODS: Administrative claims data (January 1999–March 2014) from a large private-insurer database were used, which included work-loss data from a subset of reporting companies. Eligible patients (classified as responders and nonresponders) had ≥ 1 claim for a TIM approved for the treatment of RA and ≥ 2 RA diagnoses in the claims history, with continuous pharmaceutical and medical benefit eligibility for 6 months before (baseline) and 12 months after (study period) the date of the first TIM claim (index date). All-cause and RA-related health care resource use (HCRU) and costs, work loss, and indirect costs during the study period were compared for responders versus nonresponders. Multivariable regression was used to adjust for baseline covariates. Sensitivity analyses of HCRU and direct costs were conducted for patients with index dates before and after 2008 to account for different approval dates of TIMs.

RESULTS: Of 7,540 eligible patients with RA, 2,527 (34%) were classified as responders, and 5,013 (66%) were classified as nonresponders; 407 and 723 had work-loss data, respectively. After adjusting for baseline covariates, nonresponders had significantly higher HCRU, including inpatient admissions (incidence rate ratio [IRR]=1.94), outpatient visits (IRR=1.19), emergency department visits (IRR=1.53), and number of prescription fills (IRR=1.09; all, $P<0.001$). Nonresponders also had significantly higher adjusted all-cause (\$12,868 vs. \$9,621, respectively) and RA-related (\$5,740 vs. \$4,495; both, $P<0.001$) medical costs compared with responders. In addition, nonresponders reported significantly more days of work lost compared with responders (22.1 vs. 16.7 days, respectively; IRR=1.21; $P=0.007$) and higher indirect costs (\$3,548 vs. \$2,890; $P=0.002$). Sensitivity analyses of HCRU and direct costs by index date (before and after 2008) were consistent with the full sample.

CONCLUSIONS: A large portion of patients with RA had inadequate responses to their initial TIM therapy with significantly higher economic burden, including higher HCRU, medical costs, and indirect costs due to work loss, compared with TIM therapy responders.

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What is already known about this subject

- Targeted immunomodulators (TIMs), including inhibitors of tumor necrosis factor- α , interleukin-6, B-T cell interactions, B cell depletion, and JAK/STAT interactions, are specifically targeted, highly effective therapies for rheumatoid arthritis (RA); however, some patients still fail to respond or lose response over time.
- When RA is left untreated or remains unresponsive to therapy, inflammation and progressive joint destruction lead to physical impairment, difficulties in maintaining employment, and significant economic burden.

What this study adds

- This study estimated the real-world prevalence of RA patients with inadequate responses to initial TIM therapy in the United States and compared their direct and indirect costs, health care resource utilization, and lost days of work between responders and nonresponders using a large administrative claims database.
- Approximately 66% of RA patients treated with a TIM had inadequate responses to initial treatment and, compared with responders, experienced significantly more inpatient admissions, outpatient visits, emergency department visits, and prescription fills.
- Nonresponders also had significantly higher all-cause and RA-related medical costs, significantly more days of work lost, and higher indirect costs compared with responders.

Rheumatoid arthritis (RA) is a chronic disease that can lead to impairment in physical function due to inflammation causing stretching of tendons and ligaments, erosion of cartilage and bone, and ultimately destruction of joints.¹ When active, RA symptoms can include tender and swollen joints, pain, fatigue, loss of energy, lack of appetite, low-grade fever, muscle and joint aches, and stiffness.² RA is estimated to affect 0.5%-1% of adults in the United States, or about 1.5 million.^{3,4} It is more common among women and people aged 40 to 70 years, representing a large proportion of the working population in the United States.^{5,6} If left untreated or unresponsive to therapy, inflammation and progressive joint destruction can lead to impairment in physical function and inability to perform daily tasks, creating difficulties in maintaining employment.¹

RA incurs a significant economic burden to individual patients and society.³ The estimated annual direct health care costs for a patient with RA were \$2,000 more than those for an individual without RA, resulting in total incremental costs of \$22.3 billion (in 2008 U.S. dollars [USD]) among all RA patients in the United States.⁷ In 1997, per capita employer expenditures (including direct health care costs and indirect costs due to disability and absenteeism) for employees with RA who had any disability claims were reported to be approximately 3 times higher (\$17,822 vs. \$6,131) than those without RA.⁸ RA also results in high health care resource use (HCRU) in the United States, estimated at more than 250,000 hospitalizations and 9 million physician visits annually.⁹

Conventional treatment of RA has centered on judicious use of corticosteroids and disease-modifying antirheumatic drugs (DMARDs) such as methotrexate and leflunomide.¹⁰ Since 1998, targeted immunomodulators (TIMs) that inhibit tumor necrosis factor- α (TNFi), interleukin-6, B-T cell interactions, B cell depletion, and JAK/STAT interactions (Jakinibs) have been approved by the U.S. Food and Drug Administration (FDA) for treatment of RA based on efficacy in randomized controlled trials (RCTs) after failure of conventional DMARDs.¹¹⁻¹⁶ TNFis (e.g., adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab) were the first biologic therapies to be approved for RA, and RCT data demonstrate that these therapies are effective at improving clinical, functional, and patient-reported outcomes and halting radiographic structural progression.¹⁷⁻¹⁹ Jakinibs (e.g., tofacitinib) have similar efficacy to biologics.²⁰ However, RCT data also indicate that a substantial proportion of patients do not adequately respond to TIM therapies. Approximately 40% of RA patients treated with the above therapies fail to achieve American College of Rheumatology (ACR) 20% response, and an even higher proportion of patients lose response over time or experience adverse events.^{21,22} Therapeutic failures are not limited to TNFis; similar failure rates associated with other RA treatments (e.g., abatacept, tocilizumab, rituximab, and tofacitinib) have also been reported.²³⁻²⁶

Although previous research has examined the economic burden in the overall RA patient population, limited data exist describing the economic burden of RA patients who fail to respond to TIM treatments.^{7,8} To address this gap in the literature, the objectives of this study were to estimate the real-world prevalence of RA patients who fail or have inadequate responses to initial TIM therapy in the United States and to compare their direct and indirect costs, HCRU, and work loss versus TIM responders.

Methods

Data Source

Data were procured from the database of OptumHealth Care Solutions (January 1999-March 2014), an administrative

claims database of approximately 18.5 million privately insured individuals covered by 84 self-insured Fortune 500 companies with locations in all census areas of the United States (the top 500 public companies in the United States in terms of gross revenue). Data include all claims for all beneficiaries (i.e., employees, spouses, dependents, and retirees) nationwide, as well as short- and long-term disability claims for employees from a subset of 44 companies. This is a retrospective analysis of deidentified claims data compliant with the Health Insurance Portability and Accountability Act; thus, no review by an institutional review board was required.

Study Population

Patients were eligible for inclusion if they met the following criteria: (a) had at least 1 claim for a TIM therapy approved for the treatment of RA (abatacept, tocilizumab, tofacitinib, rituximab, anakinra, and TNFis), with or without the concomitant use of methotrexate, and the date of the first claim for a TIM (index agent) was defined as the index date; (b) had at least 1 diagnosis code for RA (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] code 714.0) in the 6 months before the index date and at least 2 diagnoses of RA at any time in the patient's claims history; and (c) had continuous pharmaceutical and medical benefit eligibility for the 6 months before (baseline period) and 12 months after the index date (study period). Patients were excluded if they had (a) more than 1 TIM prescribed on the index date; (b) inconsistent reimbursement methods for the index agent (e.g., if there is a medical claim for a subcutaneous or oral index agent or a pharmacy claim for an intravenous index agent); or (c) any diagnosis during the baseline period for another condition for which any TIMs considered in this study are indicated (including ankylosing spondylitis, Crohn's disease, juvenile idiopathic arthritis, plaque psoriasis, psoriatic arthritis, and ulcerative colitis).

Selected patients were categorized as nonresponders or responders using a validated claims-based algorithm for determining treatment effectiveness developed by Curtis et al. (2011).²⁷ Specifically, patients in the sample were classified as responders if they met all 6 of the following criteria in the study period:

1. *High adherence*: (a) For self-administered subcutaneous or oral agents (abatacept, adalimumab, anakinra, certolizumab, etanercept, golimumab, tocilizumab, and tofacitinib), this was determined as a medication possession ratio of $\geq 80\%$, and (b) for agents administered via infusions (abatacept, golimumab, infliximab, and tocilizumab), this was determined as a number of infusions $\geq 80\%$ of that recommended in their FDA labels.²⁸
2. *No increase in biologic dose or frequency during the maintenance period*: (a) Within patients' claims, the number of infusions was within 120% of the number of scheduled infusions recommended in their FDA label, and (b) within patients'

FIGURE 1 Classification of TIM Responders Versus Nonresponders

DMARD = disease-modifying antirheumatic drug; TIM = targeted immunomodulator.

claims, the weekly dose remained less than twice the standard weekly dose based on the FDA label.

3. No claim for another TIM approved for treatment of RA.
4. No claim for a new DMARD that the patient had not received at baseline.
5. No new or increased glucocorticoid treatment (in months 4-12 of the study period, no new oral glucocorticoid [≥ 30 -day supply] that the patient had not received at baseline; in months 7-12, no increase $\geq 20\%$ in dose of an existing oral glucocorticoid that the patient had received at baseline).
6. No parenteral or intra-articular glucocorticoid injection more than once over months 4-12 of the study period.

Criteria 1 and 2 did not apply to patients using rituximab because the FDA label does not provide a single recommended dosing schedule or glucocorticoid regimen for infusion. Patients who failed to meet any of the listed criteria were classified as nonresponders.

Study Outcomes

Baseline demographics (i.e., age, sex) were measured at the index date, and comorbidities and RA treatment history were measured during the baseline period. HCRU quantified during the study period included inpatient admissions and total length of stay, emergency department (ED) visits, outpatient visits, number of prescription fills, and other resource use (e.g., lab tests and services at home). All-cause direct health care costs (in 2014 USD) measured during the study period included pharmacy and medical service costs. Medical service costs excluding RA-related TIMs were separately estimated because responders likely received longer treatment by definition, and some agents were reimbursed in the medical claims. Thus, medical services costs excluding RA-related therapies may better reflect the actual burden in costs of medical services. RA-related costs were also estimated, including (a) costs in medical claims associated with a primary or secondary diagnosis of RA and (b) costs of RA-related therapies (TIMs, corticosteroids,

nonbiologic DMARDs, and nonsteroidal anti-inflammatory drugs [NSAIDs]).

Days of disability and medically related work loss measured during the study period were based on data provided in disability claims. Medically related absenteeism was imputed based on use of medical services during business days (Monday through Friday) and gap days after the injury date and before the start of disability. It was assumed that each inpatient and ED visit accounted for a full day of work loss, while outpatient and other visits accounted for a half day of work loss. Indirect costs associated with disability and medically related absenteeism measured during the study period were based on actual short- and long-term disability payments paid by employers. Medically related absenteeism costs were calculated as the product of days of medically related absenteeism and the individual daily wage of each employee.

Data Analysis

For baseline characteristics, categorical characteristics were compared between responders and nonresponders using chi-square tests (Fisher's exact tests were used for outcomes with expected frequency < 5). Continuous characteristics were compared between responders and nonresponders using Wilcoxon rank-sum tests.

For HCRU, days of disability, and medically related work loss, incidence rates (IRs) and overall proportions of events were estimated, and negative binomial and logistic regressions were used to obtain unadjusted and adjusted incidence rate ratios (IRRs) and odds ratios (ORs) comparing responders versus nonresponders. Adjusted covariates included age, sex, index year, Charlson Comorbidity Index (CCI),²⁹ and individual baseline covariates with significant differences between the 2 cohorts. For direct and indirect health care cost outcomes, unadjusted costs were compared between cohorts using Wilcoxon rank-sum tests. Adjusted costs were estimated using a generalized linear model with a gamma distribution. For outcomes with $\geq 5\%$ zeroes, a Tweedie distribution with an

TABLE 1 Baseline Characteristics of Responders and Nonresponders to TIMs for RA

Characteristics	Responders n = 2,527	Nonresponders n = 5,013	P Value
Age, mean (SD)	56.9 (12.7)	56.1 (13.2)	0.005 ^a
Male, n (%)	730 (28.9)	1,151 (23.0)	<0.001 ^a
Year of index date, n (%)			
1998-2001	219 (8.7)	390 (7.8)	0.182
2002-2005	824 (32.6)	1,511 (30.1)	0.029 ^a
2006-2009	806 (31.9)	1,494 (29.8)	0.062
2010-2013	678 (26.8)	1,618 (32.3)	<0.001 ^a
Comorbidities			
CCI, mean (SD)	1.4 (0.9)	1.5 (1.0)	0.002 ^a
Selected comorbidities, n (%)			
Osteoarthritis	500 (19.8)	1,197 (23.9)	<0.001 ^a
Gastrointestinal disease	367 (14.5)	1,010 (20.1)	<0.001 ^a
Osteoporosis	177 (7.0)	471 (9.4)	0.001 ^a
Enteropathic arthritis	7 (0.3)	6 (0.1)	0.143
Reactive arthritis	3 (0.1)	14 (0.3)	0.165
Extra-articular manifestation of RA			
Sjögren's syndrome	38 (1.5)	101 (2.0)	0.120
Rheumatoid nodules	20 (0.8)	31 (0.6)	0.387
Rheumatoid lung	11 (0.4)	23 (0.5)	0.886
Felty's syndrome	5 (0.2)	12 (0.2)	0.720
Treatment received during baseline period, n (%)			
Glucocorticoid	1,568 (62.0)	3,373 (67.3)	<0.001 ^a
Pain medication	1,776 (70.3)	3,537 (70.6)	0.804
Prescription NSAIDs	1,369 (54.2)	2,486 (49.6)	<0.001 ^a
Narcotic analgesics	932 (36.9)	2,408 (48.0)	<0.001 ^a
Non-narcotic analgesics	51 (2.0)	136 (2.7)	0.067
Nonbiologic DMARDs	2,125 (84.1)	3,942 (78.6)	<0.001 ^a
Methotrexate	1,733 (68.6)	3,076 (61.4)	<0.001 ^a
Hydroxychloroquine	605 (23.9)	1,079 (21.5)	0.017 ^a
Leflunomide	348 (13.8)	761 (15.2)	0.103
Sulfasalazine	233 (9.2)	403 (8.0)	0.082
Minocycline	31 (1.2)	71 (1.4)	0.501
Gold compound	8 (0.3)	11 (0.2)	0.427
Mycophenolate	4 (0.2)	17 (0.3)	0.160
Other	8 (0.3)	14 (0.3)	0.777

^a $P < 0.05$.

CCI = Charlson Comorbidity Index; DMARD = disease-modifying antirheumatic drug; NSAID = nonsteroidal anti-inflammatory drug; RA = rheumatoid arthritis; SD = standard deviation; TIM = targeted immunomodulator.

Results

Of 7,540 eligible RA patients identified, 2,527 were categorized as responders and 5,013 as nonresponders (Figure 1). The most common index agent was etanercept (43% of all patients), followed by adalimumab (26%) and infliximab (22%). Others included abatacept, rituximab, golimumab, anakinra, certolizumab pegol, tocilizumab, and tofacitinib (all <3%). Of the 6 criteria used to classify TIM responders and nonresponders, the criteria with the highest failure rates were “high adherence” (47% of patients), “no new or increased glucocorticoid treatment” (16%), and “no claim for another biologic” (14%). Among all patients, 1,130 (407 responders and 723 nonresponders) were identified as the primary policy holder and continuously employed at a company that provided work-loss data during the entire study period, making them available for use in the work-loss and indirect-cost analyses.

Nonresponders were slightly younger (56.9 vs. 56.1 years, respectively; $P = 0.005$) and more likely to be female (71.1% vs. 77.0%; $P < 0.001$; Table 1). They had a significantly higher CCI than responders (mean score of 1.5 vs. 1.4, respectively; $P = 0.002$) and were more likely to have osteoarthritis (23.9% vs. 19.8%), gastrointestinal disease (20.1% vs. 14.5%), and osteoporosis (9.4% vs. 7.0%; all $P < 0.001$). Additionally, nonresponders were significantly more likely to have taken glucocorticoids (67.3% vs. 62.0%, respectively) and narcotic analgesics (48.0% vs. 36.9%; both, $P < 0.001$) than responders but less likely to have received prescription NSAIDs (49.6% vs. 54.2%; $P < 0.001$), methotrexate (61.4% vs. 68.6%; $P < 0.001$), or hydroxychloroquine (21.5% vs. 23.9%; $P = 0.017$). There were slight differences between patients with index dates before versus after 2008: those with index dates after 2008 had a higher prevalence of osteoarthritis but a lower prevalence of osteoporosis or stroke. There was also lower use of pain medications (primarily prescription NSAIDs) among patients with index dates after 2008.

Nonresponders had significantly higher HCRU across all resource categories examined (Table 2): more inpatient admissions (0.4 vs. 0.2 events, respectively; IRR = 1.94; 95% confidence interval [CI] = 1.70-2.21), days of hospitalization (2.3 vs. 0.8 days; IRR = 2.46; 95% CI = 2.0-2.93), outpatient visits (IRR = 1.19; 95% CI = 1.16-1.23), ED visits (IRR = 1.53; 95% CI = 1.38-1.69), and number of total prescription fills (IRR = 1.09; 95% CI = 1.06-1.13) after adjustment for baseline covariates. Furthermore, the odds of any inpatient admission (OR = 1.89; 95% CI = 1.65-2.17), ED visit (OR = 1.60; 95% CI = 1.43-1.79), or other visit (OR = 1.17; 95% CI = 1.06-1.30) were all higher for nonresponders than responders after adjustment for baseline characteristics. Consistent with the full sample, for patients with an index year either before or after 2008, nonresponders had significantly higher HCRU across all categories: inpatient admissions, outpatient visits, ED visits, other visits, and number of prescription fills (all $P < 0.05$).

exponent of 1.67 was used. Adjusted covariates included age, sex, index year, CCI, and individual baseline covariates with significant differences between the 2 cohorts.

Because different TIMs were approved over the period for the treatment of RA (etanercept, infliximab, adalimumab, abatacept, rituximab, and anakinra were approved before 2008; tocilizumab, golimumab, tofacitinib, and certolizumab pegol were approved after 2008), the patterns of HCRU and direct health care costs might vary across different periods. Thus, as a sensitivity analysis, the analyses of HCRU and direct costs were further stratified by index year (before and after 2008).

TABLE 2 Comparison of Health Care Resource Utilization and Work Loss Between Responders and Nonresponders to TIMs for RA

	Responders	Nonresponders	Adjusted IRR (95% CI)	P Value
Health care resource utilization	n = 2,527	n = 5,013		
Number of events per patient per year, IRR				
Inpatient admissions	0.2	0.4	1.94 (1.70-2.21)	<0.001 ^a
Days of hospitalization	0.8	2.3	2.46 (2.06-2.93)	<0.001 ^a
Outpatient visits	18.8	23.6	1.19 (1.16-1.23)	<0.001 ^a
ED visits	0.4	0.7	1.53 (1.38-1.69)	<0.001 ^a
Other visits	3.2	3.9	1.14 (1.05-1.23)	0.001 ^a
Prescription fills	42.5	49.0	1.09 (1.06-1.13)	<0.001 ^a
Any events (% of patients), OR				
Any inpatient admission	13.6	23.7	1.89 (1.65-2.17)	<0.001 ^a
Any ED visit	23.6	34.8	1.60 (1.43-1.79)	<0.001 ^a
Any other visit	56.5	61.7	1.17 (1.06-1.30)	0.002 ^a
Work loss	n = 407	n = 723		
Days of work loss, IRR				
Total days of work loss	16.7	22.1	1.21 (1.05-1.39)	0.007 ^a
Days of disability	7.2	10.6	0.95 (0.18-5.08)	0.953
Days of medically related absenteeism	9.5	11.5	1.14 (1.04-1.24)	0.006 ^a
Any work loss (% of patients), OR				
Any disability	6.1	8.4	1.17 (0.71-1.95)	0.536

^aP<0.05.

CI=confidence interval; ED=emergency department; IRR=incidence rate ratio; OR=odds ratio; RA=rheumatoid arthritis; TIM=targeted immunomodulator.

In addition to higher HCRU, nonresponders also had significantly higher all-cause (\$12,868 vs. \$9,621, respectively) and RA-related (\$5,740 vs. \$4,495; both $P<0.001$; Figure 2) medical costs after adjustment for baseline characteristics. Excluding costs of RA-related TIMs that were noted to be reimbursed in medical claims, adjusted all-cause inpatient (\$2,789 vs. \$1,305, respectively), outpatient (\$4,861 vs. \$3,798), ED (\$393 vs. \$285), and other (\$402 vs. \$312; all, $P<0.05$) costs were all higher for nonresponders. A similar finding was evident for RA-related medical costs, although differences between the cohorts' inpatient and ED costs were not statistically significant (Figure 2). In the sensitivity analysis, considering patients with index years either before or after 2008, all-cause and RA-related total medical costs were higher for nonresponders (all, $P<0.001$). All 4 components of all-cause medical costs (inpatient, outpatient, ED, and other) were higher for nonresponders in the sensitivity analysis, although differences in ED and other costs were not statistically significant in patients with index years before 2008.

Comparing the cohorts' work loss, nonresponders had significantly more days of work loss than responders (22.1 vs. 16.7, respectively; IRR=1.21; 95% CI=1.05-1.39), primarily driven by days of medically related absenteeism (11.5 vs. 9.5 days; IRR=1.14; 95% CI=1.04-1.24; Table 2). The number of days of disability was numerically higher for nonresponders (10.6 vs. 7.2 days); however, adjusted IRR comparing the 2 groups was not statistically significant. In addition, the

percentage of patients in each cohort with any work loss was similar (responders=6.1%, nonresponders=8.4%; IRR=1.17; 95% CI=0.71-1.95). After adjustment for baseline covariates, nonresponders had significantly higher indirect costs (\$3,548 vs. \$2,890, respectively; $P=0.002$), driven primarily by higher medically related absenteeism costs (\$2,323 vs. \$2,071; $P=0.047$; Figure 3). Disability costs were numerically higher among nonresponders but did not differ significantly between the 2 cohorts (\$816 vs. \$575; $P=0.458$).

Discussion

This retrospective claims study found that among RA patients treated with TIM therapy, approximately two thirds had inadequate responses to the first TIM they initiated. Treatment non-responses were associated with increased HCRU and higher all-cause (difference of \$3,247 per patient) and RA-related (difference of \$1,247 per patient) medical costs during the study period. In addition, nonresponders experienced significantly higher indirect costs by \$658 due to higher costs of medically related absenteeism and more days of work lost. These results were consistent across 2 different time periods encompassing different FDA approval dates: patients who initiated therapies during 1998-2007 or 2008-2013 had similar outcomes to the full sample.

While TIMs significantly improved outcomes in RA patients compared with conventional synthetic DMARDs, a substantial proportion of patients fail to respond to these therapies.

FIGURE 2 Comparison of Direct Health Care Costs Between Responders and Nonresponders to TIMs for RA

^a $P < 0.05$: all-cause ED costs, $P = 0.001$; all-cause other costs, $P = 0.041$; RA-related other costs, $P = 0.002$; all others, $P < 0.001$.

ED = emergency department; RA = rheumatoid arthritis; TIM = targeted immunomodulator; USD = United States dollars.

For example, approximately 30%-40% of RA patients treated with a TNFi fail to achieve an ACR 20% response, and more lose responses over time or experience adverse events.²¹ Nonresponses lead to treatment discontinuations or switching, and a recent claims database study of newly initiated TNFi continuers, discontinuers, and switchers noted that approximately one third of patients initiating a TNFi either switched therapies or discontinued within the first year and 50% within 2 years.^{30,31} Long-term TIM discontinuation rates are even higher among RA patients. A study examining self-reported discontinuation during 1998-2011 found that 48% discontinued TNFi or switched therapies; this rate was lower than the discontinuation rate of non-TNFi therapies (for first biologic, hazard ratio = 0.49 [95% CI = 0.34-0.71]).³² Until recently, treatment options were limited for patients who were not satisfactorily responding to TIM therapies. Patients with RA who discontinue a TIM therapy are still likely to exhibit a significant response to a subsequent agent within the same category (e.g., TNFi).³³ However, research in clinical practice settings has suggested that the best option

for managing TIM nonresponders may be switching the patient to a drug with a different mechanism of action instead of to a different TNFi.^{17,34,35} For example, the 2015 ACR guidelines now conditionally recommend switching to a non-TNFi agent after initial TNFi failure.³⁶ Similarly, it is possible that switching to a TIM agent with a mechanism of action unrelated to the initial treatment may also be a more effective option for TIM agents other than TNFis.

A better understanding of the reasons for a patient's inadequate response to an initial TIM may improve clinical decision making by helping to predict the response and tolerance to a subsequent TIM. However, the mechanism of suboptimal therapeutic response to TIMs for some patients with RA is still not well understood. New potential treatment options for this challenging patient population are under clinical investigation. For example, in a phase IIb clinical trial, upadacitinib (ABT-494), a selective JAK1 inhibitor, added to methotrexate showed rapid improvement in RA signs and symptoms among patients with inadequate response or intolerance to a TNFi.³⁷

FIGURE 3 Comparison of Indirect Costs Between Responders and Nonresponders to TIMs for RA

^a $P < 0.05$: total indirect costs, $P = 0.002$; medically related absenteeism costs, $P = 0.047$.

RA = rheumatoid arthritis; TIM = targeted immunomodulator; USD = U.S. dollars.

The findings of this study should be interpreted in light of several limitations. First, the data used in this analysis were limited to patients in commercial insurance plans; therefore, findings may not be generalizable to populations beyond the commercial plans. In particular, patients without insurance coverage or with public plans (e.g., Medicaid or Veterans Administration plans) may be likely to experience even greater burdens. Moreover, for patients over 65 years old, who could be partially covered by Medicare, the data capture the portion covered by private insurers but not the portion covered by Medicare; thus, HCRU and costs may be underestimated for these patients. Second, response to TIM treatment was evaluated using an algorithm based on administrative claims data, which may lead to misclassification. However, previous studies have validated the algorithm against a clinical evaluation of response (sensitivity=0.75, specificity=0.90).²⁷ Third, confounding factors beyond those measured at baseline, such as the severity of RA or type of job, were not available and were not controlled for. Finally, this study is subject to the limitations of retrospective studies based on health care claims data.

These limitations may include (a) possible coding errors or omissions of claims, (b) multiple identities associated with the same individual if the individual changed employer and both employers contribute data to the database, and (c) unavailability for data outside the period of data coverage. One potential impact to this study is that, although patients were identified as having initiated TIM therapy, it is possible that they had used a TIM agent prior to the 6-month baseline period if that use occurred outside the coverage of the database. For example, it could be at a job with a different employer not included in the database or prior to the date that the employer started contributing data to the database. However, the current sample selection criteria ensured that the patient did not have any prescription of TIM for a period of at least 6 months prior to the index date. Therefore, the index drug captured in this study can be the first initiation of the drug or reinitiation after a discontinuation period of at least 6 months. These claims data-related limitations likely affect both the responder and nonresponder cohorts similarly and are therefore unlikely to bias the main findings.

Conclusions

A considerable proportion of RA patients had inadequate responses to the first TIM they initiated, which was associated with increased HCRU, medical costs, and indirect costs due to medically related absenteeism. This high burden underscores the need for future research on mechanisms of nonresponses in RA, the development of effective therapies with lower rates of failure, and expansion of treatment approaches to address nonresponders, such as switching between TIMs in appropriately selected patients.

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DISCLOSURES

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Study concept and design were contributed by Tundia, Song, and Macaulay, along with other authors. Data analyses were designed and conducted by Song and Macaulay. All authors contributed to data interpretation. Writing of the manuscript was led by Tundia, Song, and Macaulay, with revisions by all authors.

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