An Economic Evaluation of Tofacitinib Treatment in Rheumatoid Arthritis After Methotrexate or After 1 or 2 TNF Inhibitors from a U.S. Payer Perspective

Lindsay Claxton, MMath; Matthew Taylor, MSc; Arif Soonasra, PharmD; Jeffrey A. Bourret, PharmD; and Robert A. Gerber, PharmD

ABSTRACT

BACKGROUND: Treatment cycling with biologic disease-modifying anti-rheumatic drugs, such as tumor necrosis factor inhibitors (TNFi), is common among patients with rheumatoid arthritis (RA) and can result in reduced clinical efficacy and increased economic burden. Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA.

OBJECTIVE: To evaluate and compare the economic effect of tofacitinib 5 mg twice daily (BID) treatment directly after methotrexate (MTX) in the MTX-inadequate responder population, or after MTX and 1 TNFi (adalimumab [ADA] or etanercept [ETN]) or 2 TNFi (ADA and ETN) in TNF-inadequate responder patients with RA, from a U.S. payer perspective.

METHODS: A decision-tree economic model was used to evaluate costs over 2 years. Treatment response was modeled as American College of Rheumatology (ACR) 20/50/70 response. ACR response rates at 6-month intervals were derived from U.S. prescribing information for monotherapy and combination therapy. Safety event rates were sourced from a meta-analysis. It was assumed that 75% of patients switched therapy after an adverse event or lack of response. Cost inputs included drugs, monitoring and administration (including physician visits), health care utilization, and treatment for adverse events. The population comprised all organization members (i.e., RA and non-RA members); RA patients receiving TNFi were estimated using epidemiologic data. Results were based on an organization size of 1 million. Economic endpoints were total 2-year costs, costs per member per month (PMPM), and costs per ACR20/50 responder.

RESULTS: 1,321 patients were included for analysis. Based on ACR20 switch criteria and either 100% or 50% monotherapy rates for all treatments, total 2-year costs and costs PMPM were lower for patients receiving tofacitinib as second-line therapy after MTX and as third-line therapy after MTX and 1 TNFi; costs were highest for patients who cycled through 2 TNFi. Similar trends were observed for switch criteria based on ACR50 response and addition of 20% rebates for ADA and ETN and 0% for tofacitinib, although differences were mitigated slightly.

CONCLUSIONS: A treatment strategy with tofacitinib as either second- or third-line therapy after MTX may be a lower cost treatment option, compared with fourth-line introduction of tofacitinib after cycling through 2 TNFi following MTX.

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What is already known about this subject

- Rheumatoid arthritis (RA) imposes a considerable economic burden that includes direct and indirect costs.
- Patients who do not respond to conventional synthetic disease-modifying antirheumatic drugs, such as methotrexate (MTX), are often treated with tumor necrosis factor inhibitors (TNFi); however, patients with inadequate response to TNFi can experience cycling of TNFi therapies, which can incur further economic costs, depending on treatment sequences.
- A previous economic analysis has shown that tofacitinib 5 mg twice daily, following an MTX inadequate response, may be a cost-effective treatment option, showing lower cost per member per month (PMPM) and lower cost per American College of Rheumatology 20 response (ACR20) versus TNFi.

What this study adds

- This study assessed the economic effect of tofacitinib treatment directly following MTX, or after MTX and 1 or 2 previous TNFi, and results showed that tofacitinib treatment directly following MTX was associated with the lowest total 2-year costs, PMPM costs, and costs per ACR20/50 responder versus adalimumab (ADA) and etanercept (ETN).
- In the TNF-inadequate responder population, tofacitinib treatment after MTX and 1 previous TNFi was associated with lower total 2-year costs, PMPM costs, and costs per ACR20/50 responder versus tofacitinib treatment following MTX and 2 previous TNFi.
- The lower costs associated with tofacitinib following MTX and 1 previous TNFi versus 2 previous TNFi were maintained even with the addition of 20% rebates for ADA and ETN and with adjustments for 100% or 50% monotherapy.

Rheumatoid arthritis (RA) is a chronic, debilitating autoimmune disease that can lead to destruction of the joints and surrounding tissues. RA has an estimated prevalence in the United States of 0.6%-0.7%, affecting an estimated 1.3-1.5 million patients.^{1,2} RA also imposes a considerable economic burden in the United States, with estimated societal costs of \$19.3 billion (2005 U.S. dollars [USD]) and

estimated direct costs of \$374 million in total hospital inpatient fees (mean \$41,000 per patient, 2012 Nationwide Inpatient Survey).^{3,4}

Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), such as methotrexate (MTX), are usually recommended as first-line treatment. Biologic DMARDs (bDMARDs), including tumor necrosis factor inhibitors (TNFi), are among the therapies recommended for patients who have failed first-line treatment with csDMARDs.^{5,6} For established RA, the 2015 American College of Rheumatology (ACR) Guidelines also include tofacitinib, with or without MTX, as an option after the failure of csDMARDs.⁵

A recent retrospective claims analysis showed that approximately 70% of patients with RA were nonresponders to TNFi 12 months after the date of the first claim.⁷ Patients who discontinue TNFi because of inadequate response (IR) or adverse events frequently switch to an alternative TNFi, termed TNF cycling.⁸⁻¹⁰ In addition, economic rebates to payers have led to common benefit designs and formulary restrictions that require patients to fail 2 TNFi before they gain access to other non-TNFi (data on file, Managed Markets Insight & Technology, rheumatoid arthritis formulary data, first quarter 2016). TNF cycling is often associated with reduced efficacy and increased likelihood of switching to a third-line non-TNFi bDMARD and may not be a cost-effective strategy.¹¹⁻¹³ A recent economic evaluation in the United States showed higher overall mean annualized costs for patients who switched from 1 TNFi to another TNFi (\$14,200-\$15,400) versus those who received single (\$13,800) or interrupted therapy (\$12,800-\$13,200 USD, year not provided).¹⁴ Patients who received a single or interrupted therapy with a single TNFi presented with a lower level of disease activity compared with those who switched TNFi therapy; as such, higher costs may be associated with the treatment switching and dose escalation required to treat the higher level of disease. However, TNF cycling can lead to improvements in efficacy outcomes for some TNF-IR patients when administered in combination with MTX,¹⁵ although a diminished response and persistence of efficacy outcomes has been observed in patients who have switched TNFi versus biologic-naïve patients who have not switched.¹⁶

Real-world analysis has shown that TNFi pharmacy costs within the first 12 months post-index (defined as the period from the date of the first claim) vary according to treatment patterns from \$6,563 for discontinuing patients to \$17,446 for switching patients and \$18,743 for continuing patients, with a total mean pharmacy cost of \$16,431 per patient (USD, 2010-2013).¹³ Although treatment with non-TNFi biologics has been shown to be more effective in TNF-IR patients compared with a second TNFi,¹⁷ patients who switched to non-TNFi bDMARDs experienced higher costs versus those who switched to another TNFi, attributed to in-office administrations.¹³ TNF cycling

was associated with an increased likelihood of switching to a third bDMARD compared with patients receiving a non-TNFi bDMARD; 37% of patients who switched to a second-line TNFi then switched to a third-line bDMARD versus 28% of those who had switched to a non-TNFi bDMARD.¹³

Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA. Tofacitinib 5 mg twice daily (BID) is approved in the United States for use in adults with moderately to severely active RA and an IR or intolerance to MTX.¹⁸ A once-daily extended-release formulation of tofacitinib 11 mg has also been approved for this indication.¹⁸ Tofacitinib can be administered as monotherapy or in combination with MTX or other csDMARDs.¹⁸ A previous economic evaluation compared tofacitinib with the most commonly prescribed TNFi and non-TNFi bDMARDs for RA, including etanercept (ETN), adalimumab (ADA), certolizumab, tocilizumab, rituximab, and abatacept.¹⁹ This evaluation showed that in U.S. MTX-IR patients, tofacitinib 5 mg BID was associated with lower costs per patient than ADA or ETN as either monotherapy or combination therapy.¹⁹ In TNF-IR patients (with IR to both MTX and TNFi), tofacitinib 5 mg BID in combination with MTX was associated with lower costs per patient than ADA plus MTX.¹⁹

A greater understanding of the economic costs associated with patients with primary nonresponse to TNFi and TNF cycling, and the clinical consequences of benefit design, may have implications for future decision making. In this analysis, we focus on the 2 most commonly prescribed TNFi in the United States and present a reanalysis of a 2-year decision-tree model with additional scenarios and updated data to evaluate and compare the economic effect of tofacitinib 5 mg BID as second-line treatment after MTX, third-line treatment after MTX and 1 TNFi (ADA or ETN), or fourth-line treatment after MTX and 2 TNFi (ADA and ETN).

Methods

Patients

Tofacitinib 5 mg BID was evaluated in MTX-IR and TNF-IR (after MTX) populations of patients with RA from a U.S. payer perspective. A patient cohort was based on 1 million members of a hypothetical health care organization, including those with and without RA. The number of RA patients entering the model was based on the RA prevalence rate and the proportion of patients estimated to be receiving TNFi. The organization size was assumed to be constant at 1 million members throughout the model, with an equal rate of patients joining and leaving. Full details of this decision-tree model have been previously published.¹⁹ The RA prevalence rate of 0.72% was obtained from The Rochester Epidemiology Project, the most recently published evidence relating to RA prevalence in the United States,² with other epidemiologic data (e.g., diagnosis rate [87%], csDMARD treatment rate [57%], csDMARD and

bDMARD combination treatment rate [37%], and first TNF failure rate [40%]) derived from the IMS LifeLink Health Plan Claims Database 2007-2011, a national database containing 64 million unique Medicaid, Medicare, and commercially insured patients, representing approximately 70% of the commercially insured population. This combination of data resulted in an estimated 6,264 patients diagnosed with RA, of whom 1,321 were treated with TNFi in the MTX-IR and TNF-IR (after MTX) populations.

Model Structure and Comparators

An Excel-based (Microsoft, Redmond, WA) decision-tree economic model from the perspective of a U.S. payer, with a 2-year time horizon to reflect the short-term planning horizon of U.S. payers, was developed, and MTX-IR patients entered the model and started treatment with either tofacitinib, ADA, or ETN. The model presented here includes updated inputs to those previously published,¹⁹ including drug costs; response criteria ACR20 and ACR50 (20% or 50% improvement in tender and swollen joint counts and at least 20% or 50% improvement in 3 of the 5 other core measures)²⁰; and switching thresholds for patients receiving 100% monotherapy or 50% monotherapy and 50% combination therapy with MTX.

The following treatment sequences were analyzed, all of which directly followed MTX:

MTX-IR population

- Tofacitinib→abatacept→rituximab
- ADA→abatacept→rituximab
- ETN→abatacept→rituximab

TNF-IR population

- ADA→tofacitinib
- ETN→tofacitinib
- ADA→ETN→tofacitinib
- ETN→ADA→tofacitinib

MTX as first-line treatment was not modeled explicitly but was common to all treatment arms. A recent real-world analysis found that approximately 55% of patients receiving TNFi were on combination therapy with a concomitant csDMARD, and 45% were on TNFi monotherapy within 12 months post-index.¹³ For each treatment sequence, 2 therapy scenarios were modeled: all patients (100%) received monotherapy, or 50% received monotherapy and 50% received combination therapy with MTX. Treatment switching to the next replacement therapy was permitted based on the proportion of patients who achieved an adequate treatment response as measured by ACR20 and ACR50 response or experienced a major adverse drug reaction (ADR), with each ACR threshold informing separate analyses. Based on literature, and regardless of switching threshold selected, it was estimated that, of the patients who did not respond to treatment, 75% switched therapy due to lack of response or an ADR.²¹

Efficacy and Safety

ACR response rates at 6-month intervals were derived from randomized controlled trial (RCT) data reported in U.S. prescribing information.^{18,22} Inputted efficacy, safety, and costs were reflective of the licensed dosage of the drugs. No rates were available for ADA in the TNF-IR (after MTX) population, so MTX-IR rates were degraded with odds ratios estimated for ACR20 and ACR50 of 0.54 and 0.42 for first-time TNFi switchers and 0.42 and 0.42 for second-time TNFi switchers.¹⁶ After 6 months, the assumed response was maintained over the course of the model. Treatment response was dependent on previous csDMARD or bDMARD use, with a lower rate of ACR20 response for bDMARD-IR patients. Rates of major ADRs were sourced from a meta-analysis,²³ and proxy ADRs were derived from RCT evidence reported in U.S. prescribing information, as shown in the previously published model.^{18,19} Pneumonia was a proxy major ADR, selected as the most commonly reported serious infection for patients with RA, and upper respiratory tract infection was selected as the most commonly reported minor ADR.^{18,19} ADR rates were placebo adjusted and assumed the same when monotherapy rates were 100% or 50%.

Resource Use and Unit Costs

The model included direct medical costs or costs relevant to health care payers. Drug costs were from January 2017; costs for tofacitinib and each comparator were calculated based on wholesale acquisition costs and approved dosing schedule.²⁴ Other costs were from 2016, and no costs were inflated. All costs are presented in 2017 USD. The model did not include dose escalation or adherence, so it does not reflect any dose escalation that may be experienced in the real world. Unit costs were taken from national databases and cost sources.^{3,24,25} Resource utilization, comprising drug monitoring, administration (e.g., physician visits), and treatment for ADRs, was estimated based on ACR guidelines.²⁶ Major ADR cost was \$9,227.00, which included urgent care hospitalization and 2 outpatient follow-up visits.³ Minor ADR cost was \$213.52, which included 1 primary care physician visit and a 7-day course of amoxicillin clavulanate.^{24,25}

Economic endpoints comprised (a) total 2-year costs (including drugs, drug monitoring, drug administration, and ADR costs); (b) cost per member per month (PMPM); and (c) cost per ACR20 and ACR50 responder. Economic endpoints in the TNF-IR (after MTX) population were analyzed with and without 20% rebates for ADA and ETN (0% for tofacitinib). This model was validated by an independent health economist at York Health Economics Consortium, who performed quality control and assurance on the model.

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TABLE 1 Number of ACR20/50 Responders and Predicted Costs over 2 Years for MTX-IR Patients, with Switch Criteria Based on ACR20/50 Responses Without Rebate^a

	100% Monotherapy (n = 1,321)			50% Monotherapy and 50% Combination Therapy (n = 1,321)		
	Tofacitinib→ABA→RTX	ADA→ABA→RTX	ETN→ABA→RTX	Tofacitinib→ABA→RTX	ADA→ABA→RTX	ETN→ABA→RTX
A. Switch Criteria Based on ACR20 Response						
Responders, n						
ACR20	1,086	917	1,012	1,007	967	1,046
ACR50	617	404	623	581	506	605
Total 2-year costs, \$	149,677,072	172,449,974	177,640,640	151,347,506	175,635,131	180,289,525
Drug costs	144,274,723	166,187,200	172,165,870	144,767,326	169,010,029	174,341,811
Administration costs	3,127,826	4,369,427	3,745,342	3,442,784	3,815,019	3,345,974
Monitoring costs	1,471,559	774,279	744,797	2,327,175	1,668,332	1,610,240
ADR costs	802,963	1,119,068	984,631	810,221	1,141,752	991,499
Cost PMPM, \$	6.24	7.19	7.40	6.31	7.32	7.51
Cost per, \$:						
ACR20 responder	137,810	188,141	175,595	150,283	181,678	172,416
ACR50 responder	242,738	426,805	285,115	260,496	347,203	297,946
B. Switch Criteria Based on ACR50 Response						
Responders, n						
ACR20	1,290	1,118	1,164	1,175	1,146	1,225
ACR50	693	480	681	654	584	683
Total 2-year costs, \$	148,742,827	165,074,100	171,623,677	150,164,185	168,551,333	172,742,731
Drug costs	141,596,905	156,950,623	164,710,210	141,891,304	160,029,667	164,914,514
Administration costs	4,959,095	6,231,257	5,157,437	5,116,195	5,616,377	5,093,419
Monitoring costs	1,372,056	839,134	794,029	2,338,011	1,829,155	1,772,708
ADR costs	814,771	1,053,085	962,001	818,674	1,076,134	962,089
Cost PMPM, \$	6.20	6.88	7.15	6.26	7.02	7.20
Cost per, \$:						
ACR20 responder	115,316	147,687	147,475	127,825	147,021	141,059
ACR50 responder	214,500	343,751	252,146	229,687	288,667	253,044

Note: These data are based on a previously published economic model analyzing tofacitinib as a second-line treatment in MTX-IR patients.¹⁹ The previously published model was updated according to recent medication price increases and expanded to include switching criteria, as shown in this table.

^aThis table shows the number of ACR20/50 responders and costs PMPM and per ACR responder for MTX-IR patients receiving tofacitinib 5 mg BID as second-line treatment directly after MTX, compared with ADA and ETN, without rebates.

ABA=abatacept; ACR=American College of Rheumatology; ADA=adalimumab; ADR=adverse drug reaction; BID=twice daily; ETN=etanercept; MTX=methotrexate; MTX-IR=methotrexate-inadequate responder; PMPM=per member per month; RTX=rituximab.

Sensitivity Analyses

Sensitivity analyses with cost PMPM at 2 years were performed for rebate, switching probability, ACR20/50 response rate at 6 months, major ADR rate per 6 months, and ACR20/50 scenario analysis. Variables were increased up to 20% for all except ACR20/50 scenarios, for which ACR rates were varied up to 50%.

Results

In the MTX-IR (after MTX) patient population, based on ACR20 response criteria, irrespective of 100% or 50% monotherapy, the lowest total 2-year costs and cost PMPM were observed for patients receiving tofacitinib as second-line therapy versus either ADA or ETN as second-line therapy (Table 1A). Similarly, based on ACR50 response, tofacitinib as second-line therapy showed the lowest total 2-year costs and PMPM costs versus ADA and ETN (Table 1B).

In the TNF-IR (after MTX) patient population, based on ACR20 response criteria without rebates for ADA and ETN and irrespective of whether 100% or 50% monotherapy rates were applied, total 2-year costs and cost PMPM were lower for patients receiving tofacitinib after 1 TNFi versus those receiving tofacitinib after 2 TNFi (Table 2A). Total costs and PMPM costs were lowest for those receiving ADA→tofacitinib irrespective of 100% or 50% monotherapy rates (Table 2A). Costs per ACR20/50 responder criteria were lowest for patients receiving ETN→tofacitinib and were highest for those receiving ADA→ETN→tofacitinib (Table 2A), regardless of 100% or 50% monotherapy.

Similarly, based on ACR50 response criteria without rebates for ADA and ETN, and irrespective of 100% or 50% monotherapy, total 2-year and PMPM costs were lower for patients receiving tofacitinib after 1 TNFi versus those receiving tofacitinib after 2 TNFi. Costs were lowest for those receiving ADA→tofacitinib and

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TABLE 2 Number of ACR20/50 Responders and Predicted Costs over 2 Years for TNF-IR (after MTX) Patients Receiving Tofacitinib 5 mg BID After 1 or 2 TNFi, with Switch Criteria Based on ACR20/50 Responses Without Rebates^a

	100% Monotherapy (n = 1,321)				50% Monotherapy and 50% Combination Therapy (n = 1,321)			
	ADA→ Tofacitinib	ETN→ Tofacitinib	ADA→ETN→ Tofacitinib	ETN→ADA→ Tofacitinib	ADA→ Tofacitinib	ETN→ Tofacitinib	ADA→ETN→ Tofacitinib	ETN→ADA→ Tofacitinib
A. Switch Criteria Based on ACR20 Response								
Responders, n								
ACR20	969	1,052	969	1,049	1,023	1,090	1,023	1,087
ACR50	483	683	536	656	563	649	608	626
Total 2-year costs, \$	170,811,363	176,379,670	181,365,571	183,741,878	173,720,179	178,794,528	182,726,846	185,175,590
Drug costs	166,695,200	172,550,093	177,365,866	179,952,692	168,774,841	174,154,654	177,880,436	180,569,871
Administration costs	1,912,120	1,861,338	1,982,427	1,916,390	1,879,779	1,838,678	1,939,948	1,886,509
Monitoring costs	1,121,543	1,011,773	870,579	820,184	1,956,443	1,835,219	1,742,583	1,669,940
ADR costs	1,082,499	956,466	1,146,698	1,052,612	1,109,116	965,978	1,163,878	1,049,270
Cost PMPM, \$	7.12	7.35	7.56	7.66	7.24	7.45	7.61	7.72
Cost per, \$:								
ACR20 responder	176,186	167,643	187,244	175,113	169,770	164,092	178,703	170,330
ACR50 responder	353,683	258,088	338,355	280,140	308,797	275,412	300,774	296,040
B. Switch Criteria Based on ACR50 Response								
Responders, n								
ACR20	1,199	1,225	1,168	1,234	1,246	1,311	1,219	1,320
ACR50	604	775	665	743	680	766	734	733
Total 2-year costs, \$	165,309,851	171,796,434	178,602,625	179,959,372	168,285,444	172,509,811	180,203,322	180,806,868
Drug costs	160,927,699	167,737,698	174,380,451	175,922,777	162,981,933	167,470,400	175,052,842	175,784,649
Administration costs	2,037,974	1,956,954	2,122,301	2,038,817	2,002,270	1,961,172	2,078,058	2,044,320
Monitoring costs	1,335,497	1,173,842	1,009,764	962,167	2,266,268	2,151,883	1,964,398	1,942,171
ADR costs	1,008,680	927,940	1,090,111	1,035,610	1,034,973	926,355	1,108,023	1,035,729
Cost PMPM, \$	6.89	7.16	7.44	7.50	7.01	7.19	7.51	7.53
Cost per, \$:								
ACR20 responder	137,899	140,188	152,859	145,811	135,076	131,616	147,862	137,019
ACR50 responder	273,541	221,620	268,768	242,234	247,329	225,137	245,438	246,517

^aThis table shows the number of ACR20/50 responders and costs PMPM and per ACR responder for TNF-IR patients receiving tofacitinib 5 mg BID after 1 or 2 TNFi, directly after MTX, without rebates.

ACR=American College of Rheumatology; ADA=adalimumab; ADR=adverse drug reaction; BID=twice daily; ETN=etanercept; MTX=methotrexate; PMPM=per member per month; TNFi=tumor necrosis factor inhibitor; TNF-IR=tumor necrosis factor-inadequate responder.

highest for those receiving ETN→ADA→tofacitinib (Table 2B), irrespective of 100% or 50% monotherapy. Per ACR20 responder, ADA→tofacitinib showed the lowest costs for 100% monotherapy and ETN→tofacitinib the lowest costs for 50% monotherapy, and ADA→ETN→tofacitinib showed the highest costs (Table 2B) regardless of 100% or 50% monotherapy. However, per ACR50 responder criteria, and regardless of 100% or 50% monotherapy, costs were lowest for those receiving ETN→tofacitinib, and costs were highest for those receiving ADA→tofacitinib (Table 2B).

Patients receiving ADA as the single previous TNFi showed lower total 2-year costs and PMPM costs versus ETN (Table 2), based on ACR20 and ACR50 criteria and irrespective of 100% and 50% monotherapy. Although drug monitoring, drug administration, and ADR costs were slightly higher for those receiving ADA→tofacitinib, the higher total 2-year cost for

patients receiving ETN→tofacitinib can be attributed to higher drug costs (Table 2).

With 20% rebates applied for ADA and ETN (0% for tofacitinib) and based on ACR20 and ACR50 responses, including 100% or 50% monotherapy, lowest total 2-year and PMPM costs were observed in patients receiving ADA→tofacitinib and highest total 2-year and PMPM costs were observed for those receiving ETN→tofacitinib. However, irrespective of 100% or 50% monotherapy, the cost differences were somewhat mitigated with similar costs for patients receiving ETN→tofacitinib and ETN→ADA→tofacitinib versus ADA→tofacitinib and ADA→ETN→tofacitinib.

Sensitivity analysis was performed for the treatment sequences, with the output of cost PMPM at 2 years. In MTX-IR patients and TNF-IR patients for monotherapy or combination therapy, tofacitinib was estimated to be cost

saving at 2 years when no rebate was applied to tofacitinib, but up to 20% rebates were applied for comparators. Generally, for ACR20 and ACR50 scenario analyses, as variations in ACR20 and ACR50 responses were increased up to 50%, tofacitinib continued to have a lower cost PMPM for monotherapy and combination therapy. Tofacitinib was estimated to have a lower cost PMPM than comparators when switching probability rate was adjusted up to 20%, and for ACR20 and ACR50 responses when adjusted up to 20% for both monotherapy and combination therapy.

Discussion

TNF cycling is common among patients with RA; however, response and remission outcomes can be diminished for patients switching TNFi versus biologic-naïve patients,¹⁶ and treatment sequences, including TNFi switches, can have cost implications. Recent refinement of treat-to-target guidelines recommends regular adjustment of therapy until the desired therapeutic target of low disease activity or remission is achieved²⁷; however, the cost implications of this approach are not yet known. Previous evaluation showed that tofacitinib 5 mg BID following MTX failure may be a lower cost treatment option versus ADA, ETN, certolizumab, and tocilizumab.¹⁹ However, a comparison of the economic effect of second-line tofacitinib after MTX failure and with tofacitinib following 1 or 2 TNFi had not been previously investigated. In a recent U.S. health care claims study, more patients were shown to switch to a second TNFi compared with a non-TNFi, and these patients had lower 1-year RA-related and total health care costs, largely attributed to increased physician office visits for non-TNFi-treated patients.²⁸ In addition, patients who cycle TNFi have been shown to be more likely to switch to a third-line bDMARD.¹³ In contrast to these studies, the analysis presented here specifically focuses on tofacitinib as second-, third-, or fourth-line treatment. However, these analyses identified that lower drug costs for tofacitinib may offset the additional cost of monitoring. In addition, tofacitinib as second-line treatment had lower total 2-year costs, PMPM costs, and costs per ACR20/50 responder criteria versus ETN and ADA and showed lower costs than patients receiving tofacitinib after 1 or 2 previous TNFi. For TNF-IR (after MTX) patients, tofacitinib treatment after a single previous TNFi showed lower total 2-year costs, PMPM costs, and lower costs per ACR20/50 responder versus patients receiving 2 previous TNFi, regardless of 100% or 50% monotherapy. Once 20% rebates were applied for ADA and ETN using the ACR20/50 response criteria, total 2-year and PMPM cost differences were somewhat mitigated, although ADA→tofacitinib remained the lowest cost option regardless of 100% and 50% monotherapy. Results of sensitivity analyses were consistent across the different treatment scenarios and showed that, generally, tofacitinib was estimated to have a lower cost PMPM when

rebates were applied to comparators, when adjusting for variations in ACR20/50 scenario responses, and for ACR20/50 responses for monotherapy and combination therapy.

A South Korean study of tofacitinib cost-effectiveness showed that the earlier in the treatment sequence tofacitinib was added, the more cost-effective it was for csDMARD-IR patients, from a societal perspective.²⁹ The analyses presented here are consistent with this finding and a previous economic evaluation of tofacitinib versus a range of bDMARDs, which showed that tofacitinib 5 mg BID was a cost-effective treatment option for RA because of lower costs per patient than ADA or ETN, when given as monotherapy or combination therapy in MTX-IR patients, and showed lower costs in TNF-IR (after MTX) patients than ADA plus MTX when administered in combination with MTX.¹⁹

Limitations

There were several limitations associated with this economic evaluation model. Although data were obtained from a base case assumption of 1 million members, disease severity at baseline and disease duration may vary between different patient populations. RA prevalence was obtained from The Rochester Epidemiology Project²; however, these data were obtained from 1 U.S. county, which may limit the generalizability of the data. No epidemiological breakdown was included in the model and differential costs, and ACR response or switching probabilities were not assumed by patient characteristics of gender or age. There were also no data available to robustly evaluate the response to ADA in the TNF-IR (after MTX) population.

This model reports only aggregate estimates of utilization pattern costs; it does not analyze differences between beneficiaries, which can often encompass a wide variation in member demographics and characteristics, benefit designs, and payers. A breakdown of Medicare Advantage or prescription drug benefit beneficiaries was not available, so benefit design and cost exposures were not investigated. Treatment sequences were fixed in a linear method for a limited time horizon, with no available real-world data and, as such, may not truly reflect the clinical setting where the reason for failure may affect the effectiveness or choice of the following therapy.

In addition, not every available comparator was modeled; the focus was specifically on the 2 most frequently prescribed comparators. Other than ACR20 and ACR50, important clinical outcomes such as physical function and disability were not investigated; however, the clinical measures used here reflect how treatment decisions are made. Treatment costs were based on a range of rebates that may not reflect the actual costs to payers. Efficacy and minor ADR rates were based on data from RCTs that were not performed contemporaneously and could result in population differences that were not adjusted for in this model.

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Conclusions

In this economic model, predicted total 2-year costs and PMPM costs were lowest when tofacitinib 5 mg BID was administered as second-line treatment after MTX. For TNF-IR (after MTX) patients, lowest predicted total 2-year costs and PMPM costs were observed when tofacitinib 5 mg BID was administered after 1 TNFi versus 2 TNFi in patients with RA, and ADA→tofacitinib remained the lowest cost option when 20% rebates were applied for ETN and ADA. A treatment strategy with introduction of tofacitinib early in the sequence, as either second- or third-line therapy after MTX, may be a lower-cost treatment option when compared with fourth-line introduction of tofacitinib, after cycling through 2 TNFi following MTX.

Authors

LINDSAY CLAXTON, MMath, and MATTHEW TAYLOR, MSc, York Health Economics Consortium, University of York, United Kingdom. ARIF SOONASRA, PharmD, and JEFFREY A. BOURRET, PharmD, Pfizer, Collegeville, Pennsylvania. ROBERT A. GERBER, PharmD, Pfizer, Groton, Connecticut.

AUTHOR CORRESPONDENCE: Lindsay Claxton, MMath, Centre for Reviews and Dissemination, University of York, York YO10 5DD, United Kingdom. Tel.: +44 1904 321048; E-mail: lindsay.claxton@york.ac.uk.

DISCLOSURES

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A previous iteration of the data reported in this manuscript (before adjustment for recent drug price increases) was presented at the Academy of Managed Care Pharmacy 28th Annual Meeting and Expo; April 19-22, 2016; San Francisco, CA.

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REFERENCES

1. Helmick CG, Felson DT, Lawrence RC, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I. *Arthritis Rheum*. 2008;58(1):15-25.
2. Myasoedova E, Crowson CS, Kremers HM, Thorneau TM, Gabriel SE. Is the incidence of rheumatoid arthritis rising? Results from Olmsted County, Minnesota, 1955-2007. *Arthritis Rheum*. 2010;62(6):1576-82.

3. Agency for Healthcare Research and Quality. Healthcare Cost and Utilization Project (HCUP). National and regional 2012 estimates on hospital use for all patients from the HCUP Nationwide Inpatient Sample (NIS). National statistics—principal diagnosis only. ICD-9-CM 714.0. 2015. Available at: <http://hcupnet.ahrq.gov/>. Accessed June 1, 2018.
4. Birnbaum H, Pike C, Kaufman R, Marynchenko M, Kidolezi Y, Cifaldi M. Societal cost of rheumatoid arthritis patients in the U.S. *Curr Med Res Opin*. 2010;26(1):77-90.
5. Singh JA, Saag KG, Bridges SL Jr. et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. *Arthritis Rheumatol*. 2016;68(1):1-26.
6. Smolen JS, Landewé R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis*. 2014;73(3):492-509.
7. Grabner M, Boytsov NN, Huang Q, Zhang X, Yan T, Curtis JR. Costs associated with failure to respond to treatment among patients with rheumatoid arthritis initiating TNFi therapy: a retrospective claims analysis. *Arthritis Res Ther*. 2017;19(1):92.
8. Gomez-Reino JJ, Carmona L. Switching TNF antagonists in patients with chronic arthritis: an observational study of 488 patients over a four-year period. *Arthritis Res Ther*. 2006;8(1):R29.
9. Agarwal SK, Glass RJ, Shadick NA, et al. Predictors of discontinuation of tumor necrosis factor inhibitors in patients with rheumatoid arthritis. *J Rheumatol*. 2008;35(9):1737-44.
10. Finckh A, Simard JF, Gabay C, Guerne PA. Evidence for differential acquired drug resistance to anti-tumour necrosis factor agents in rheumatoid arthritis. *Ann Rheum Dis*. 2006;65(6):746-52.
11. Rubbert-Roth A, Finckh A. Treatment options in patients with rheumatoid arthritis failing initial TNF inhibitor therapy: a critical review. *Arthritis Res Ther*. 2009;11(Suppl 1):S1.
12. Sullivan SD, Alfonso-Cristancho R, Carlson J, Mallya U, Ringold S. Economic consequences of sequencing biologics in rheumatoid arthritis: a systematic review. *J Med Econ*. 2013;16(3):391-96.
13. Harnett J, Wiederkehr D, Gerber R, Gruben D, Koenig A, Bourret J. Real-world evaluation of TNF-inhibitor utilization in rheumatoid arthritis. *J Med Econ*. 2016;19(2):91-102.
14. Cannon GW, DuVall SL, Haroldsen CL, et al. Clinical outcomes and biologic costs of switching between tumor necrosis factor inhibitors in U.S. veterans with rheumatoid arthritis. *Adv Ther*. 2016;33(8):1347-59.
15. Fleischmann R, Goldman JA, Leirisalo-Repo M, et al. Infliximab efficacy in rheumatoid arthritis after an inadequate response to etanercept or adalimumab: results of a target-driven active switch study. *Curr Med Res Opin*. 2014;30(11):2139-49.
16. Greenberg JD, Reed G, Decktor D, et al. A comparative effectiveness study of adalimumab, etanercept and infliximab in biologically naive and switched rheumatoid arthritis patients: results from the US CORONA registry. *Ann Rheum Dis*. 2012;71(7):1134-42.
17. Gottenberg JE, Brocq O, Perdriger A, et al. Non-TNF-targeted biologic vs a second anti-TNF drug to treat rheumatoid arthritis in patients with insufficient response to a first anti-TNF drug: a randomized clinical trial. *JAMA*. 2016;316(11):1172-80.
18. XELJANZ (tofacitinib) tablets for oral administration. Pfizer. Revised May 2018. Available at: <http://labeling.pfizer.com/ShowLabeling.aspx?id=959>. Accessed May 31, 2018.
19. Claxton L, Jenks M, Taylor M, et al. An economic evaluation of tofacitinib treatment in rheumatoid arthritis: modeling the cost of treatment strategies in the United States. *J Manag Care Spec Pharm*. 2016;22(9):1088-102. Available at: <https://www.jmcp.org/doi/10.18553/jmcp.2016.22.9.1088>.

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20. Felson DT, Anderson JJ, Boers M, et al. American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum.* 1995;38(6):727-35.
21. Vieira MC, Wallenstein GV, Bradley JD, et al. Tofacitinib versus biologic treatments with and without methotrexate in patients with active rheumatoid arthritis who have had an inadequate response to traditional disease modifying anti-rheumatic drugs - a network meta-analysis. *Ann Rheum Dis.* 2012;71(Suppl 3):375 [Abstract FRI0185]. Available at: http://ard.bmj.com/content/71/Suppl_3/375.1. Accessed May 5, 2018.
22. U.S. Food and Drug Administration. FDA approves Xeljanz for rheumatoid arthritis. Press release. November 6, 2012. Available at: <https://wayback.archive-it.org/7993/20161022200148/http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm327152.htm>. Accessed May 5, 2018.
23. Strand V, Ahadieh S, French J, et al. Systematic review and meta-analysis of serious infections with tofacitinib and biologic disease-modifying anti-rheumatic drug treatment in rheumatoid arthritis clinical trials. *Arthritis Res Ther.* 2015;17:362.
24. Truven Health Analytics. RED BOOK Online. 2017. Available at: <http://truvenhealth.com/Products/Micromedex/Product-Suites/Clinical-Knowledge/REDBOOK>. Accessed May 5, 2018.
25. InGauge Healthcare Solutions. *Physicians' Fee & Coding Guide 2015*. Atlanta, GA: InGauge; 2015.
26. Saag KG, Teng GG, Patkar NM, et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. *Arthritis Rheum.* 2008;59(6):762-84.
27. Smolen JS, Breedveld FC, Burmester GR, et al. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. *Ann Rheum Dis.* 2016;75(1):3-15.
28. Baser O, Ganguli A, Roy S, Xie L, Cifaldi M. Impact of switching from an initial tumor necrosis factor inhibitor on health care resource utilization and costs among patients with rheumatoid arthritis. *Clin Ther.* 2015;37(7):1454-65.
29. Lee MY, Park SK, Park SY, et al. Cost-effectiveness of tofacitinib in the treatment of moderate to severe rheumatoid arthritis in South Korea. *Clin Ther.* 2015;37(8):1662-76.