An Economic Evaluation of Tofacitinib Treatment in Rheumatoid Arthritis: Modeling the Cost of Treatment Strategies in the United States

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ABSTRACT

BACKGROUND: Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA). Tofacitinib is approved in the United States for use in adults with moderately to severely active RA and an inadequate response or intolerance to methotrexate.

OBJECTIVES: To (a) evaluate, using an economic model, the treatment costs of an RA strategy including tofacitinib, compared with adalimumab, etanercept, certolizumab and tocilizumab biologic RA treatment strategies, which are commonly prescribed in the United States, and (b) assess the economic impact of monotherapy and combination therapy in patients who had an inadequate response to methotrexate therapy (MTX-IR analysis) and to combination therapy in patients who had an inadequate response to a tumor necrosis factor inhibitor (TNF-IR analysis).

METHODS: A transparent, Excel-based economic model with a decision-tree approach was developed to evaluate costs over a 1- and 2-year time horizon. The model compared tofacitinib 5 mg twice a day (BID) either as monotherapy or in combination with MTX with similarly labeled biologic therapies. Response to treatment was modeled as American College of Rheumatology (ACR) 20/50/70 response. ACR20 represented clinical response and determined whether patients continued therapy. ACR response rates at 6-month intervals were sourced from prescribing information and safety event rates from a published meta-analysis. Following an adverse event or a lack of response to treatment, it was assumed that 75% of patients switched to the next line of treatment (first to abatacept and then to rituximab). The perspective was that of a U.S. payer. Costs were reported in 2015 U.S. dollars and included drug wholesale acquisition costs, monitoring, drug administration, and treatment for minor and serious adverse events. The patient population eligible for treatment was based on the total number of members (i.e., RA and non-RA) in a payer organization; members with RA treated with biologic therapies were estimated using epidemiological data. Sensitivity analyses were conducted to explore the impact of varying key parameters, including treatment-switching probability, product rebate, major rates of adverse drug reaction, and ACR20 rates, on the model outcomes.

RESULTS: Tofacitinib combination therapy after MTX failure was associated with the lowest cost per member per month (PMPM) over a 2-year time frame at $5.53, compared with $6.49 for adalimumab, $6.43 for etanercept, $5.95 for certolizumab, and $5.89 for tocilizumab. Similar savings were observed when all biologics were administered as monotherapy. Tofacitinib combination therapy was also associated with the lower PMPM cost compared with adalimumab combination therapy in the TNF-IR analysis. Tofacitinib was also among the lowest cost per ACR20 responder in each analysis. Sensitivity analyses demonstrated that tofacitinib would potentially be cost saving even in the least optimistic scenarios.

CONCLUSIONS: This analysis suggests that tofacitinib 5 mg BID following MTX failure is a lower cost per patient treatment option when used either as monotherapy or combination therapy, compared with adalimumab, etanercept, certolizumab and tocilizumab biologic regimens. Tofacitinib + MTX in TNF-IR patients was also predicted to be a lower-cost treatment option compared with adalimumab + MTX and was associated with the lowest cost per ACR 20/50/70 responder.

What is already known about this subject

- Rheumatoid arthritis (RA) causes a substantial health care and economic burden in direct costs (i.e., medical expenditures) and indirect costs (i.e., lost earnings).
- Biologic disease-modifying antirheumatic drugs (DMARDs) have been shown to be cost-effective in modeling analyses.

What this study adds

- Per member per month (PMPM) cost and cost per American College of Rheumatology (ACR) responder economic assessment over 1-2 years demonstrated that tofacitinib combination therapy after methotrexate (MTX) failure was associated with the lowest cost PMPM over a 2-year time frame, compared with adalimumab, etanercept, certolizumab, and tocilizumab.
- Tofacitinib administered as monotherapy after MTX failure was also associated with the lowest cost PMPM over a 2-year time frame, compared with adalimumab strategy, etanercept strategy, certolizumab strategy, and the tocilizumab strategy.
- Tofacitinib combination therapy in tumor necrosis factor inhibitor inadequate responder patients was also associated with a lower PMPM cost, compared with adalimumab combination therapy.

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease that affects an estimated 1.5 million patients in the United States.[1,2] It is characterized by inflammation of the synovial membranes, which causes joint swelling, stiffness, and tenderness, and leads to progressive erosion and destruction of cartilage and bone tissue in the affected joints. Wrists, fingers, knees, feet, and ankles are the most commonly affected joints.[3,4]

RA causes a substantial health care and economic burden in direct costs (i.e., medical expenditures) and indirect costs (i.e., lost earnings). According to the 2012 Healthcare Cost and Utilization Project (HCUP) Nationwide Inpatient Survey, U.S. patients with RA accounted for $374 million in total hospital charges, with a mean charge of $41,000 per patient.[5] The majority of hospital stays were by women and patients aged ≥45 years.[5] Further, costs attributable to RA are expected to increase because of the aging of the population and increases in obesity and physical inactivity. An analysis of Medical Expenditures Panel Survey (MEPS) data found that in the United States, from 1997 to 2005, total medical care expenditure for adults with arthritis and other rheumatic conditions increased by more than 40%, from $252 billion to $352 billion.[6]

The goals of treatment are to control disease activity, improve physical functioning and quality of life, and inhibit progression of structural damage throughout the course of the disease.[7] Treatment of RA is typically initiated with nonsteroidal anti-inflammatory drugs and/or low-dose glucocorticoids, with the introduction of conventional (nonbiologic) disease-modifying antirheumatic drugs (cDMARDs), typically methotrexate, as quickly as possible after diagnosis.[7-9] If methotrexate or other cDMARD treatments do not adequately control disease activity, a biologic agent (bDMARD), usually a tumor necrosis factor (TNF) inhibitor, is typically added to the regimen. If anti-TNF therapy does not elicit an adequate response, it is common to switch the bDMARD either to a bDMARD with a different mechanism of action, or from one TNF inhibitor to another.[7,10] In the United States, intraclass switching of anti-TNF agents is common within clinical practice—over 94% of rheumatologists (based on 428 completed surveys) reported switching patients from one TNF inhibitor to another because of inadequate response or side effects.[11]

There is a need for new therapeutic options in RA, since not all patients respond to the currently available treatments (primary nonresponders), or they lose response over time (secondary nonresponders).[12] One such option is tofacitinib, an oral Janus kinase inhibitor for the treatment of RA. It is approved in the United States for use in adults with moderately to severely active RA who also have an inadequate response or intolerance to methotrexate.[13] Tofacitinib is orally administered and may be prescribed as monotherapy or in combination with methotrexate or other cDMARDs. The recommended dose is 5 mg twice daily.[13]

The efficacy and safety of tofacitinib 5 mg and 10 mg twice daily as monotherapy or in combination with cDMARDs has been demonstrated in phase 2, phase 3, and long-term extension studies in patients with moderately to severely active RA.[14-18] In the 12-month trials, American College of Rheumatology (ACR) response rates in XELJANZ (tofacitinib)-treated patients were consistent at 6 and 12 months.

The purpose of this study was to compare, from a U.S. payer perspective, the treatment costs of an RA strategy that included tofacitinib with biologic RA treatment strategies that included adalimumab, etanercept, certolizumab, and tocilizumab, which are commonly prescribed in the United States. The study also assessed the economic impact of monotherapy and combination therapy in patients who had an inadequate response to methotrexate therapy (MTX-IR analysis) and the economic impact of combination therapy in patients who had an inadequate response to a TNF inhibitor (TNF-IR analysis). This model was developed to establish the clinical and economic value of tofacitinib and the key comparator products to the medical and payer community with an interest in a simple and short-term view of the associated treatment costs of a product.

■ Methods

Patients

Tofacitinib and bDMARDs were evaluated in patients with moderately to severely active RA in 2 patient populations, MTX-IR and TNF-IR patients.

The number of patients eligible for tofacitinib and other treatments was estimated based on the size of the health care organization, the prevalence rate of RA, and the proportion of patients on bDMARDs. For the base case, the organization size was assumed to be constant, at 1 million members, for the course of the model, where the rate of patients leaving the organization and patients joining the organization was assumed to be equal. The Rochester Epidemiology Project provides the most recent evidence on the prevalence rate of RA in the United States, which is estimated at 0.72%.[2] Myasoedova et al. (2010) carried out a U.S. RA incidence report from Olmsted County, Minnesota.[2] The study authors applied this rate to the U.S. population more generally; therefore, this rate is likely to be reflective of the wider U.S. population. The proportion of RA diagnosed patients (87%), DMARD-treated patients (57%), cDMARD and bDMARD combination treated patients (37%), and first TNF inhibitor failure rate (40%) were obtained from IMS LifeLink Health Plan Claims Database, a U.S. health plan insurance claims database containing Medicaid, Medicare, and commercially insured patient data on 64 million unique patients between 2007 and 2011, representing 70% of the commercially insured population.

Model Structure and Comparators

An economic model was constructed in Microsoft Excel (Microsoft, Redmond, WA) with the objective of evaluating the costs of treating patients with, and the number of patients responding to, tofacitinib and a number of the most commonly prescribed agents in the United States for RA, including etanercept, adalimumab, certolizumab, and tocilizumab. Selected comparator agents were self-injectable to allow for a more appropriate comparison to tofacitinib. Each comparator included in the model was reflective of the licensed dosage in

FIGURE 1   Model Diagrams for MTX-IR and TNF-IR Analyses

A. MTX-IR Analysis

B. TNF-IR Analysis

Note: Tofacitinib and biologics in the MTX-IR analysis are modeled either as monotherapy or in combination with MTX.

ABT = abatacept; ACR = American College of Rheumatology; ADA = adalimumab; ADR = adverse drug reaction; bDMARD = biologic disease-modifying antirheumatic drug; BID = twice per day; EOW: every other week; ETN = etanercept; MTX = methotrexate; MTX-IR = methotrexate inadequate response; TNF-IR = tumor necrosis factor inhibitor inadequate response.

| TABLE 1 | Treatment Sequences |

A. MTX-IR Patients[a]

	Treatment	Comparator 1	Comparator 2	Comparator 3	Comparator 4
First line	Methotrexate	Methotrexate	Methotrexate	Methotrexate	Methotrexate
Second line	Tofacitinib	Adalimumab	Certolizumab	Etanercept	Tocilizumab
Third line	Abatacept	Abatacept	Abatacept	Abatacept	Abatacept
Fourth line	Rituximab	Rituximab	Rituximab	Rituximab	Rituximab

B. TNF-IR Patients[b]

	Treatment	Comparator			
First line	Methotrexate	Methotrexate			
Second line	Etanercept	Etanercept			
Third line	Tofacitinib	Adalimumab			
Fourth line	Abatacept	Abatacept			
Fifth line	Rituximab	Rituximab			

Note: Sequences are analyses from the point of convergence. In the MTX-IR model, methotrexate is not modeled explicitly; in the TNF-IR model, methotrexate and etanercept are not modeled explicitly.
[a]Treatments administered either as monotherapy or in combination with methotrexate.
[b]All biologic treatments administered in combination with methotrexate.
MTX-IR = methotrexate inadequate responder; TNF-IR = tumor necrosis factor inhibitor inadequate responder.

terms of clinical efficacy, safety, and costs. The model used a decision tree structure, with treatment nodes corresponding to treatment response outcomes for a cohort of patients. Cost and clinical outcomes were evaluated within model cycles of 6 months. These analyses modeled the patient pathway in the short term (over a 1- and 2-year time horizon). The model evaluated a treatment sequence of 3 lines of therapy. In the model, patients switched from one bDMARD to another based on the proportion that achieved an inadequate treatment response or experienced a major adverse drug reaction (ADR). The ACR20 response, a validated primary endpoint in RA clinical trials, was used as a proxy for adequate response to treatment,[19] which was assessed at 6 months after treatment initiation. The proportion of patients who switch if either of these events occurred was estimated to be 75%, based on an analysis of individual study data identified in a mixed treatment comparison of efficacy, safety and treatment withdrawals in a number of trials for RA.[20] Figure 1 presents a representation of the model structure.

Table 1 presents the treatment sequences evaluated in the analysis. In the MTX-IR scenarios, all patients entered the model having had an inadequate response to methotrexate. Patients then started treatment on either tofacitinib or a bDMARD, specifically adalimumab, etanercept, certolizumab, or tocilizumab. Treatments were administered either as monotherapy or in combination with methotrexate (combination therapy). Methotrexate as first-line therapy was not modeled explicitly (i.e., patient response, safety, and related costs for this treatment line were not included in the model), since it was common to all treatment arms; instead, the model evaluated the new treatment sequence after MTX-IR (second line in Table 1A, from tofacitinib, adalimumab, certolizumab, etanercept, and tocilizumab).

In the TNF-IR analysis, patients entered the model having had an inadequate response to etanercept. Patients then started treatment on either tofacitinib or adalimumab combination therapy. This sequence was selected because etanercept and adalimumab are among the most commonly prescribed TNF inhibitor agents in the United States. Adalimumab is recommended by the United Kingdom's National Institute for Health and Care Excellence as a treatment option after TNF inhibitor failure.[21] The TNF-IR analysis did not model methotrexate and etanercept explicitly but evaluated the treatment sequences after TNF-IR (third line in Table 1B, from tofacitinib and adalimumab).

The subsequent sequence of treatment has been assumed to be identical across all treatment sequences. ACR guidelines recommend that if disease activity remains moderate or high despite use of a single TNF inhibitor, a non-TNF bDMARD should be used over another TNF inhibitor.[7] Patients failing tofacitinib or bDMARD lines of therapy in the model (failing second-line therapy in the MTX-IR analysis or third-line therapy in the TNF-IR analysis) were therefore assumed to switch to abatacept. Following abatacept failure, patients then switched to rituximab combination therapy. Patients on abatacept and rituximab therapy were modeled as being in a TNF-IR population, given that these treatment options followed another bDMARD in the modeled treatment sequences. Rituximab was modeled as combination therapy in all scenarios, in line with the label.[22]

Efficacy and Safety

The efficacy estimates of treatments were defined based on the ACR20 response rate at 6 months (Table 2). Estimates of the proportion of patients achieving ACR20 response were

TABLE 2 ACR Response Rates at 6 Months

Product	Monotherapy				Combination Therapy			
	ACR20 (%)	ACR50 (%)	ACR70 (%)	Source	ACR20 (%)	ACR50 (%)	ACR70 (%)	Source
MTX-IR Patients								
Tofacitinib	69.0	42.0	22.0	Fleischmann et al. 2012[14]	50.0	32.0	14.0	Van der Heijde et al. 2013[18]
Adalimumab	46.0	22.0	12.0	Van de Putte et al. 2004[23]	63.3	39.1	20.8	Keystone et al. 2004[24]
Etanercept	59.0	41.0	15.0	Moreland et al. 1999[25]	71.0	39.0	15.0	Weinblatt et al. 1999[26]
Certolizumab	46.0	23.0	6.0	Fleischmann et al. 2009[27]	59.0	37.0	21.0	Keystone et al. 2008[28]
Tocilizumab	70.0	40.0	25.0	Dougados et al. 2013[29]	51.0	25.0	11.0	Kremer et al. 2011[30]
Rituximab	N/A	N/A	N/A	N/A	51.0	27.0	12.0	Cohen et al. 2006[31]
Abatacept	50.0[a]	20.0[a]	10.0[a]	Genovese et al. 2005[32]	50.0	20.0	10.0	Genovese et al. 2005[32]
TNF-IR Patients								
Tofacitinib					51.0	37.0	16.0	Burmester et al. 2013[16]
Adalimumab					48.2	21.2	6.8	Degraded data from Keystone et al. 2004[24]
Rituximab					51.0	27.0	12.0	Cohen et al. 2006[31]
Abatacept					50.0	20.0	10.0	Genovese et al. 2005[32]

Note: Response was dependent on whether the therapy was administered with methotrexate (monotherapy or combination therapy) and whether the therapy was given to patients who had an inadequate response to methotrexate or to first-line bDMARD.
[a]There were no monotherapy data available for abatacept, so it was assumed that the rates were equivalent to that of combination therapy.
ACR = American College of Rheumatology; bDMARD = biologic disease-modifying antirheumatic drug; MTX-IR = methotrexate inadequate responder; N/A = not available; TNF-IR = tumor necrosis factor inhibitor inadequate responder.

TABLE 3 Degradation Method to Elicit Adalimumab TNF-IR ACR Response

Parameter	ACR20	ACR50	ACR70
Odds ratios (95% CI) for responders			
First time TNF inhibitor switcher	0.54 (0.38-0.76)	0.42 (0.27-0.65)	0.28 (0.14-0.55)
Second time TNF inhibitor switcher	0.42 (0.23-0.78)	0.42 (0.20-0.86)	0.50 (0.19-1.32)
Degradation of adalimumab MTX-IR ACR response rates			
Adalimumab MTX-IR rate	63.3%	39.1%	20.8%
Degradation process			
Odds of response	172.5% (= 63.3% ÷ [100% - 63.3%])	64.2% (= 39.1% ÷ [100% - 39.1%])	26.3% (= 20.8% ÷ [100% - 20.8%])
Adjusted odds	93.1% (= 172.5% × 0.54)	27.0% (= 64.2% × 0.42)	7.4% (= 26.3% × 0.28)
Degraded rates (adjusted probabilities)	48.2% (= 93.1% ÷ [100 + 93.1%])	21.2% (= 27.0% ÷ [100 + 27.0%])	6.8% (= 7.4% ÷ [100 + 7.4%])

Source: 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 CORRONA registry.[35]
Note: Odds ratios are presented for ACR response in patients with an inadequate response to a TNF inhibitor compared with TNF inhibitor-naïve patients and the method by which the adalimumab ACR20 response in MTX-IR patients was adjusted to estimate response in TNF-IR patients.
ACR = American College of Rheumatology; CI = confidence interval; MTX-IR = methotrexate inadequate responder; TNF-IR = tumor necrosis factor inhibitor inadequate responder.
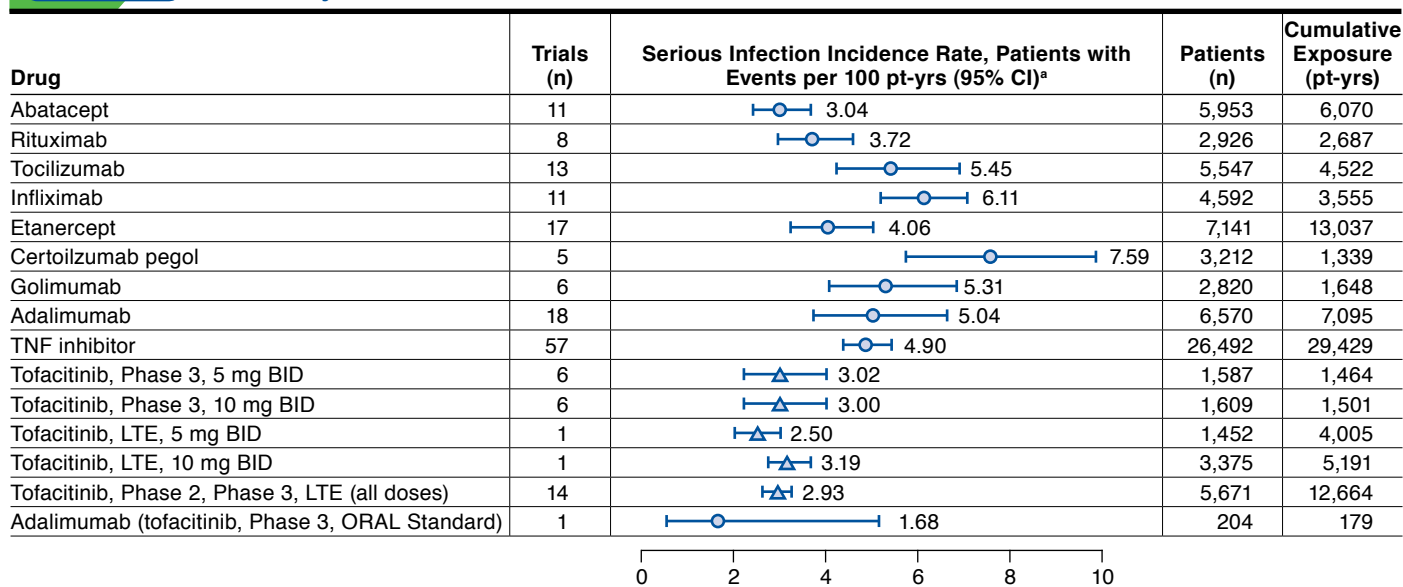
obtained from randomized controlled trial evidence reported in U.S. prescribing information (USPI).[14,18,23-32] Response to treatment was also dependent on previous cDMARD or bDMARD use, with a lower rate of ACR20 response in patients with a previous inadequate response to a bDMARD, as reflected in appropriate trial data evidence reported in the USPIs. ACR20 response is defined as a 20% improvement in tender and swollen joint counts from baseline, and a 20% improvement from baseline in 3 of the 5 remaining ACR-core set measures, which include patient and physician global assessments, patient pain, disability (as measured using the Health Assessment

Questionnaire), and an acute phase reactant (either erythrocyte sedimentation rate or C-reactive protein).[33] It was assumed that if ACR20 was achieved at 6 months, then it was maintained while the patient continued on the line of therapy.[34]

There were no randomized controlled trials for the efficacy of adalimumab in TNF-IR patients; therefore, TNF-IR responses have been estimated from adalimumab MTX-IR responses. The MTX-IR responses were degraded based on odds ratios estimated by Greenberg et al. (2012) in a study that examined treatment response rate of RA patients in the Corrona US RA registry who were undergoing second-line and third-line

FIGURE 2 Meta-analysis for Serious ADRs

Drug	Trials (n)	Serious Infection Incidence Rate, Patients with Events per 100 pt-yrs (95% CI)[a]	Patients (n)	Cumulative Exposure (pt-yrs)
Abatacept	11	3.04	5,953	6,070
Rituximab	8	3.72	2,926	2,687
Tocilizumab	13	5.45	5,547	4,522
Infliximab	11	6.11	4,592	3,555
Etanercept	17	4.06	7,141	13,037
Certoilzumab pegol	5	7.59	3,212	1,339
Golimumab	6	5.31	2,820	1,648
Adalimumab	18	5.04	6,570	7,095
TNF inhibitor	57	4.90	26,492	29,429
Tofacitinib, Phase 3, 5 mg BID	6	3.02	1,587	1,464
Tofacitinib, Phase 3, 10 mg BID	6	3.00	1,609	1,501
Tofacitinib, LTE, 5 mg BID	1	2.50	1,452	4,005
Tofacitinib, LTE, 10 mg BID	1	3.19	3,375	5,191
Tofacitinib, Phase 2, Phase 3, LTE (all doses)	14	2.93	5,671	12,664
Adalimumab (tofacitinib, Phase 3, ORAL Standard)	1	1.68	204	179

0 2 4 6 8 10

Source: Strand V, Ahadieh S, French J, et al. Systematic review and meta-analysis of serious infections with tofacitinib and biologic disease-modifying antirheumatic drug treatment in rheumatoid arthritis clinical trials (http://creativecommons.org/licenses/by/4.0/).[36]
[a]Triangles represent tofacitinib data; circles represent biologic DMARD data.
ADR = adverse drug reaction; BID = twice a day; CI = confidence interval; DMARD = disease-modifying antirheumatic drug; LTE = long-term extension; pt-yr = patient-year; TNF = tumor necrosis factor.

anti-TNF therapy (patients who had previously failed either 1 or 2 bDMARDs).[35] The odds of each level of ACR response in first-time switchers to bDMARDs compared with biologically naïve patients were estimated. Odds ratios and the calculation steps for estimating the degraded ACR responses for adalimumab are presented in Table 3.

Patients were at risk of an ADR throughout the time horizon of the model. The model considered major and minor ADRs. Major ADR rates were identified in a systematic review and meta-analysis around serious adverse events (including serious infections) associated with treatment with bDMARDs in RA clinical trials (Figure 2).[36] The study estimated the incidence rate per 100 patient-years for each safety endpoint, which was then converted to a 6-month probability in the model, thus assuming a constant rate of ADR over the modeling time frame.

Minor ADRs included within the analysis were upper respiratory tract infections (URTIs), the most commonly reported adverse event in RA clinical trials. URTI rates were identified from the pooled clinical study results in the USPIs for each comparator and thus are likely to be reflective of MTX-IR and TNF-IR patient populations and treatment strategies (monotherapy and combination therapy).[22,37-41] In order to take into consideration the variance in minor ADRs in the placebo arms of each of the USPI trials, a naïve adjustment was made, whereby the placebo URTI rate from the USPI for each drug was adjusted to reflect the variation in URTI for the placebo arm in each study. All studies were adjusted to reflect the placebo rate from the USPI for tofacitinib, which was equal to 3.3%.

Rates of serious and minor ADRs were assumed to be the same for combination and monotherapy and in the MTX-IR and TNF-IR patient populations. Major and minor ADR 6-month probabilities are presented in Table 4.

Resource Use and Unit Costs

Costs included in the model were direct medical costs relevant to a health care payer. Unit costs were taken from national databases and cost sources.[5,42,43] The resources required to administer treatment, monitor treated patients, and manage ADRs were estimated based on ACR guidelines.[44] Drug costs, resource use inputs, and unit costs associated with the treatment of major and minor ADRs are shown in Table 5. Costs are denoted in 2015 U.S. dollars.

Drug costs for each comparator over the model time horizon were calculated based on wholesale acquisition cost obtained from RED BOOK Online[42] and the licensed dosing schedule.[22,37-41] No product rebates were applied in the base case analysis. The analysis assumed a semiannual wholesale acquisition cost price increase of 6.9%.

The cost of administering treatments intravenously was that of an infusion in an outpatient setting, and the costs were tied

TABLE 4	Adverse Drug Events[a]		
Product	Major ADR (%)	Minor ADR (%)	Placebo-Adjusted Minor ADR (%)
Tofacitinib	1.50	4.50	4.50
Adalimumab	2.49	17.00	4.32
Etanercept	2.01	13.00	4.18
Certolizumab	3.72	6.00	9.90
Tocilizumab	2.69	6.00	3.30
Rituximab	1.84	2.00	3.77
Abatacept	1.51	5.00	4.40

Sources: Major ADRs: Strand V, Ahadieh S, French J, et al. Systematic review and meta-analysis of serious infections with tofacitinib and biologic disease-modifying antirheumatic drug treatment in rheumatoid arthritis clinical trials.[36] Minor ADRs: U.S. prescribing information for each product.[13,22,37-41]

[a]Rate of adverse drug events are presented at 6 months for each therapy option. ADR = adverse drug reaction.

to the infusion dosing schedule. The cost for subcutaneously administered treatments was that of a single self-injection training session. An initiation visit for the evaluation and management of a new patient and subsequent visits for established patients were incurred for each of the products in the analysis.

Unit costs of monitoring were obtained from the U.S. Medicare fee schedule.[43] The recommended monitoring resources and visit schedule were based on ACR guidelines, which contain recommendations on treatment for RA based on published clinical evidence and clinical expertise.[43]

The cost associated with a patient experiencing a major ADR was estimated to be $9,227, incorporating the cost of treating an episode of pneumonia (the most commonly reported serious infection in RA patients are URTIs) in U.S. hospitals and 2 outpatient visits for follow-up after discharge. The cost of pneumonia was estimated by the Agency for Healthcare Research and Quality and reflects actual expenses incurred by the hospital (e.g., wages, supplies, and utility costs).[5] Minor ADRs were costed at $213.52 and were assumed to be treated with 1 primary care physician visit and a 7-day course of amoxicillin clavulanate, which is a typical assumption for the treatment of URTIs.[42,43]

Model Analysis

Total costs in the overall eligible population were estimated for each of the treatment sequences. Each sequence is described according to the product that distinguishes it from other sequences (i.e., the arm evaluating the sequence with tofacitinib will be referred to as the tofacitinib arm). The primary outcome of the model was the cost per member (specifically, the member of the organization's plan) per month. The secondary outcomes were the total number of ACR20 responders and the cost per ACR20 response.

A series of sensitivity analyses were conducted to assess the sensitivity of the model to changes in parameter estimates, by observing the impact of changing parameter values on the

model results. Parameters considered to be associated with the uncertainty include the treatment switching probability, major ADR probability, ACR20 response rate, and product rebate (up to 20%). Threshold analysis was also conducted for each of these parameters. A 2-way sensitivity analysis included simultaneously varying the rebate level and ACR response rate. Costs reported were those accrued over 2 years.

■ Results

The base case analyses evaluated the treatment costs of tofacitinib in patients with moderately to severely active RA compared with different bDMARDs licensed for use in the U.S. market. In the MTX-IR analysis, these comparators included adalimumab, etanercept, certolizumab, and tocilizumab. In the TNF-IR analysis, tofacitinib was compared with adalimumab. Clinical and cost outcomes were assessed at 1 and 2 years.

Using an organization size of 1 million patients, combined with epidemiological data, resulted in an estimated 7,200 patients with RA in the population, of which 6,264 were estimated to have received a diagnosis. Of those diagnosed patients, it was estimated that there were 1,321 RA patients on bDMARDs in the MTX-IR population and 528 RA patients on bDMARDs in the TNF-IR population.

Similar conclusions were observed in the MTX-IR and the TNF-IR analysis. In both patient populations, tofacitinib was associated with the lowest total costs; per member per month (PMPM) cost; and cost per ACR20, ACR50, and ACR70 responders compared with each bDMARD comparator over 1 and 2 years. The cost savings arise mainly because of lower drug and administration costs and ADR treatment costs (because of lower serious ADR rates for tofacitinib compared with adalimumab).

MTX-IR Analysis

Results for the MTX-IR analyses are presented in Table 6. The cost breakdown is presented in Figure 3A-B. For monotherapy treatment options, the cost PMPM for tofacitinib was $5.36, compared with $6.33 for adalimumab, $6.30 for etanercept, $5.88 for certolizumab, and $5.79 for tocilizumab. For combination therapy treatment options, the cost PMPM for tofacitinib monotherapy was $5.53, compared with $6.49 for adalimumab, $6.43 for etanercept, $5.95 for certolizumab, and $5.89 for tocilizumab.

TNF-IR Analysis

Table 7 reports the outcomes for the TNF-IR subpopulation. The cost breakdown is presented in Figure 3C. At 2 years, tofacitinib combination therapy was associated with a cost PMPM of $2.21 and a cost per ACR20 responder of $132,500, compared with a cost PMPM of $2.57 and a cost per ACR20 responder of $157,273 for adalimumab.

TABLE 5   Unit Costs and Resource Use

Product	Unit Cost	Frequency and Administration Mode	Source
Lipid panel	$97.00	Includes: cholesterol, serum, total lipo-protein, direct measurement, high-density cholesterol, and triglycerides Administered 4-8 weeks following initiation of tofacitinib therapy	*Physician's Fee and Coding Guide* (HCPCS code 80061)[43]
Atorvastatin	$0.73 (daily drug cost)	Used while on tofacitinib 20 mg daily Orally administered	RED BOOK Online[42]
Tuberculin or Mantoux test	$30.50	Skin test: tuberculosis, intradermal Administered annually for all biologics	*Physician's Fee and Coding Guide* (HCPCS code 86580)[43]
Chest x-ray	$109.00 (mid-point of cost range $97-$121)	Applied annually for all biologics	*Physician's Fee and Coding Guide* (HCPCS code 71010)[43]
Evaluation and management visit for x-ray	$53.00 (mid-point of cost range $45-$61)	Annually for all biologics	*Physician's Fee and Coding Guide* (HCPCS code 99211)[43]
CBC with differential	$43.00	Blood count: complete (CBC), automated (Hgb, Hct, RBC, WBC, and platelet count). Administered before initiation for all biologics per ACR guidelines	*Physician's Fee and Coding Guide* (HCPCS code 85027)[43]
Hepatic panel test	$61.00	Includes: albumin, bilirubin, phosphatase, alkaline protein, total transferase, alanine aminotransferase, aspartate aminotransferase Administered on initiation for biologics, per ACR guidelines Five in the first 6 months and 2 in next 6 months for methotrexate	*Physician's Fee and Coding Guide* (HCPCS code 80076)[43]
Treatment of pneumonia	$8,853	Treatment for serious ADR	HCUPnet 2012[5]
Outpatient follow-up visit	$187.00 (mid-point of cost range $159-$215)	Costs for 2 visits were applied Treatment for ADR	*Physician's Fee and Coding Guide* (HCPCS code 99214)[43]
Amoxicillin clavulanate	$2.36 (daily cost) (based on $23.60 for 20 tablets)	7-day course; 875 mg tablet every 12 hours Treatment for minor ADR Orally administered	RED BOOK Online[42]
Primary care physician visit	$197.00 (mid-point of cost range $168-$226)	1 visit Treatment for minor ADR	*Physician's Fee and Coding Guide* (HCPCS code 99203)[43]
Initiation visit	$197.00 (mid-point of cost range $168-$226)	At initiation of each biologic therapy	*Physician's Fee and Coding Guide* (HCPCS code 99203)[43]
Subsequent visit	$123.50 (mid-point of cost range $105-$142)	Visit every 3 months	*Physician's Fee and Coding Guide* (HCPCS code 99213)[43]
Training	$95.00 (mid-point of cost range $81-$109)	At initiation of biologic therapies administered as self-injection (etanercept, adalimumab, tocilizumab, certolizumab, and abatacept)	*Physician's Fee and Coding Guide* (HCPCS code 99201)[43]
Infusion	$504.50 (cost per hour) (mid-point of cost range $429-$580)	Tocilizumab: infusion over 1 hour Rituximab: infusion over 3 hours Abatacept: infusion over 1 hour See dosing schedule for applicable biologics	*Physician's Fee and Coding Guide* (HCPCS code 96413)[43]
Abatacept injection	$864.08 (125 mg/mL syringe)	Injection once weekly Self-administered subcutaneous injection	RED BOOK Online[42]
Abatacept vial	$849.44 (250 mg vial)	Loading dose of 3 vials at initiation Administered by intravenous infusion	RED BOOK Online[42]
Adalimumab	$1,898.55 (40 mg/0.8 mL pen injector kit)	40 mg every other week Self-administered subcutaneous injection	RED BOOK Online[42]

TABLE 5	Unit Costs and Resource Use *(continued)*		
Certolizumab	$3,344.59 (400 mg/2 mL syringe kit)	200 mg every 4 weeks Self-administered subcutaneous injection	RED BOOK Online[42]
Etanercept	$932.16 (50 mg/mL syringe)	50 mg once weekly Self-administered subcutaneous injection	RED BOOK Online[42]
Rituximab	$774.07 (10 mg/mL vial)	One infusion of 1 gm, followed by a second infusion of 1 gm after 2 weeks. Course is repeated every 6 months. Administered by intravenous infusion	RED BOOK Online[42]
Tocilizumab	$819.48 (80 mg/mL vial)	One infusion of a 400 mL vial, followed by a subcutaneous injection every week Intravenous infusion and self-administered subcutaneous injection	RED BOOK Online[42]
Tofacitinib	$52.82 (cost per 5 mg tablet)	5 mg twice a day Orally administered	RED BOOK Online[42]

ACR = American College of Rheumatology; ADR = adverse drug reaction; CBC = complete blood count; HCPCS = Healthcare Common Procedure Coding System; Hct = hematocrit; Hgb = hemoglobin; RBC = red blood cell count; WBC = white blood cell count.

TABLE 6	Results of MTX-IR Monotherapy and Combination Therapy				
	Tofacitinib	**Adalimumab**	**Etanercept**	**Certolizumab**	**Tocilizumab**
MTX-IR Monotherapy					
1 year					
Total cost	$60,607,294	$74,368,973	$73,169,567	$67,909,788	$66,396,638
Cost PMPM	$5.05	$6.20	$6.10	$5.66	$5.53
ACR20 responders	1,055	864	971	855	1,059
Cost per ACR20 responder	$57,424	$86,096	$75,335	$79,418	$62,690
2 years					
Total cost	$128,596,040	$151,904,799	$151,268,017	$141,096,133	$139,014,925
Cost PMPM	$5.36	$6.33	$6.30	$5.88	$5.79
ACR20 responders	1,115	967	1,050	960	1,118
Cost per ACR20 responder	$115,286	$157,072	$144,025	$146,919	$124,309
MTX-IR Combination Therapy					
1 year					
Total cost	$63,127,535	$75,726,239	$74,467,450	$68,860,603	$68,503,703
Cost PMPM	$5.26	$6.31	$6.21	$5.74	$5.71
ACR20 responders	900	1,004	1,069	961	903
Cost per ACR20 responder	$70,123	$75,448	$69,676	$71,635	$75,830
2 years					
Total cost	$132,687,087	$155,709,298	$154,258,796	$142,891,347	$141,432,866
Cost PMPM	$5.53	$6.49	$6.43	$5.95	$5.89
ACR20 responders	995	1,075	1,126	1,043	998
Cost per ACR20 responder	$133,311	$119,388	$114,748	$123,492	$132,923

Note: The analysis for this table is based on 1,321 treated patients. The cost PMPM is based on the total number of 1 million organization (plan) members.
ACR = American College of Rheumatology; MTX-IR = methotrexate inadequate responder; PMPM = per member per month.

Sensitivity Analysis

Tofacitinib was estimated to be cost saving compared with the other comparators over a wide range of ACR20 rates (Figure 4). Cost PMPM for tofacitinib compared with the bDMARDs does not overlap even when the ACR20 rate is simultaneously improved by 75% for comparators and decreased by 75% for tofacitinib. As such, there is no threshold value for ACR20 for which tofacitinib is no longer a cost-saving option.

Figure 5 presents the impact of different levels of drug rebates applied to each comparator in each of the analyses. The cost PMPM for tofacitinib when no rebate is applied remains lower than that for adalimumab and etanercept bDMARDs when a 20% rebate is applied. A large rebate for the other comparators was required for tofacitinib to no longer be cost saving. In the MTX-IR combination therapy analysis, the required rebates are approximately 23% for adalimumab, 21% for

TABLE 7	Results of TNF-IR Combination Therapy

	1 Year		2 Years	
	Tofa + MTX	ADA + MTX	Tofa + MTX	ADA + MTX
Total cost	$25,227,134	$30,319,508	$53,022,456	$61,633,990
Cost PMPM	$2.10	$2.53	$2.21	$2.57
ACR20 responders	363	352	400	392
Cost per ACR20 responder	$69,575	$86,164	$132,500	$157,273

Note: For TNF-IR results, all therapies were administered as combination therapy with MTX. The analysis is based on 528 treated patients. The cost PMPM is based on the total number of 1 million organization (plan) members.
ACR = American College of Rheumatology; ADA = adalimumab; MTX = methotrexate; PMPM = per member per month; TNF-IR = tumor necrosis factor inhibitor inadequate responder; Tofa = tofacitinib.

etanercept, 12% for certolizumab, and 12% for tocilizumab, with similar rebates required in the monotherapy analysis. In the TNF-IR analysis, the required rebate for adalimumab was 61%.

A sensitivity analysis evaluating the impact of the probability of switching treatment demonstrated that tofacitinib remains a lower cost option than each comparator, in all scenarios (Figure 6). A threshold analysis suggests that tofacitinib is the lower cost option regardless of the probability of switching treatment.

Varying the probability of major ADRs did not have a large effect on the results (Figure 7). Tofacitinib remained a lower cost option even in pessimistic scenarios, when the rate of serious infections was allowed to increase up to 20% and set to 0% for comparators.

Discussion

The economic impact of tofacitinib compared with a range of bDMARDs approved for use in RA, including adalimumab, etanercept, certolizumab, and tocilizumab, was assessed in 2 populations: in patients who had a previous inadequate response to MTX and in patients after first-line TNF inhibitor treatment failure. The results indicated that tofacitinib was cost saving in MTX-IR and TNF-IR patients compared with other treatment options in a range of scenarios and patient populations. The sensitivity analyses suggested the results were robust to each parameter when evaluated individually. The tofacitinib strategies were associated with substantially lower drug costs, which vastly outweigh the additional costs of monitoring in these scenarios. In particular, the results were robust to the rate of response to treatment, since the key impact of this input was the proportion of patients switching to the next line of therapy. A cost-effectiveness study from a South Korean perspective demonstrated that tofacitinib was cost-effective.[45] However, no published studies evaluating the cost impact of a tofacitinib strategy from a U.S. perspective were identified.

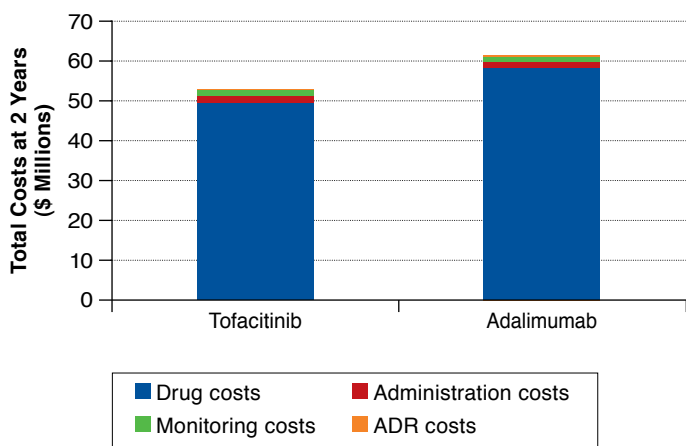| FIGURE 3	Analyses of Total Costs at 2 Years for MTX-IR Monotherapy, MTX-IR Combination Therapy, and TNF-IR Combination Therapy

A. MTX-IR Monotherapy
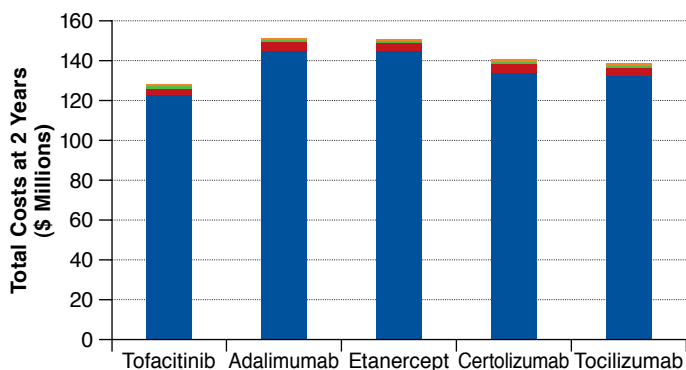
B. MTX-IR Combination Therapy

C. TNF-IR Combination Therapy

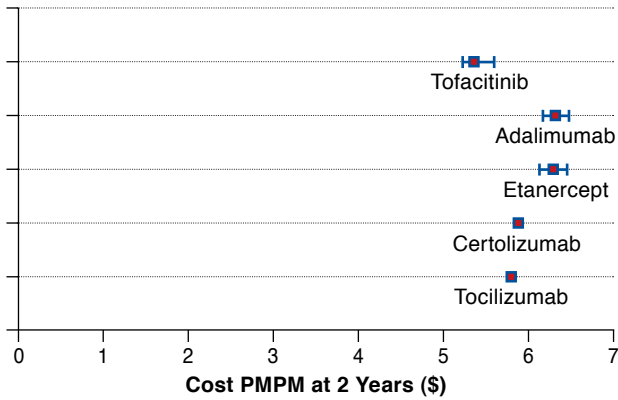*ADR = adverse drug reaction; MTX-IR = methotrexate inadequate responder; TNF-IR = tumor necrosis factor inhibitor inadequate responder.*
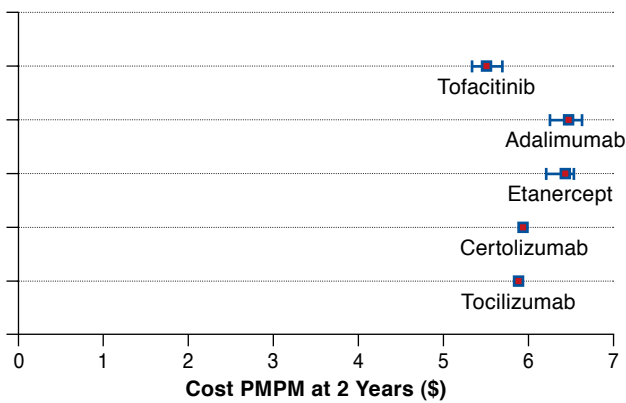
FIGURE 4 Sensitivity Analyses: Varying ACR Response Rates
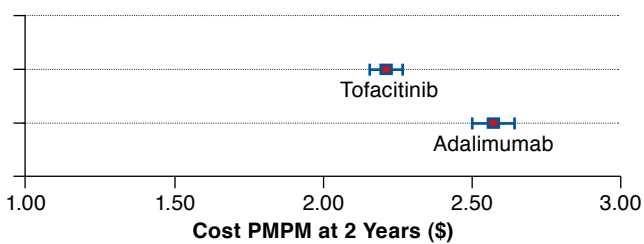
A. MTX-IR Monotherapy

B. MTX-IR Combination Therapy

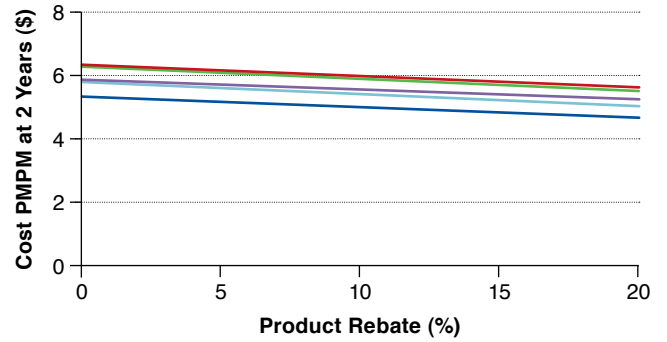
C. TNF-IR Combination Therapy

Note: Impact on model outcomes are shown when varying the ACR20 response rates for tofacitinib and adalimumab. Base case results (the cost PMPM for tofacitinib, adalimumab, and etanercept, respectively) represented by the red squares, with values corresponding to increased ACR20 rates by ±75% represented by the horizontal bars.
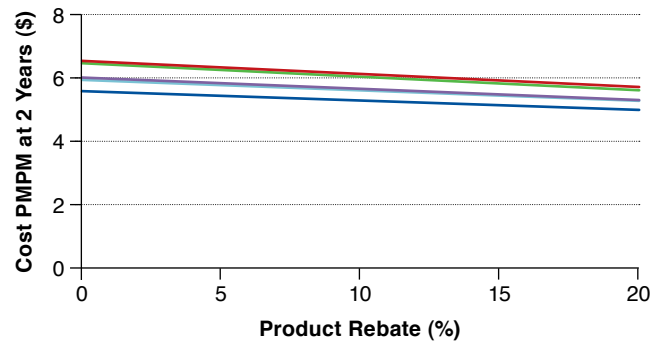*ACR = American College of Rheumatology; MTX-IR = methotrexate inadequate responder; PMPM = per member per month; TNF-IR = tumor necrosis factor inhibitor inadequate responder.*

FIGURE 5 Sensitivity Analyses: Level of Rebate

A. MTX-IR Monotherapy

B. MTX-IR Combination Therapy

C. TNF-IR Combination Therapy
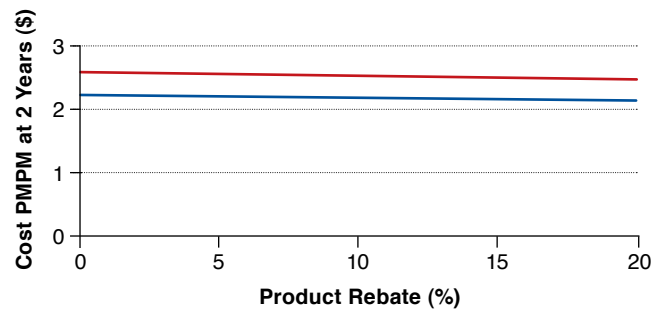
Note: The impact of applying varying levels of product rebate on the model results is shown here. The colored lines represent the cost PMPM for each therapy, with different levels of rebate applied.
MTX-IR = methotrexate inadequate responder; PMPM = per member per month; TNF-IR = tumor necrosis factor inhibitor inadequate responder.

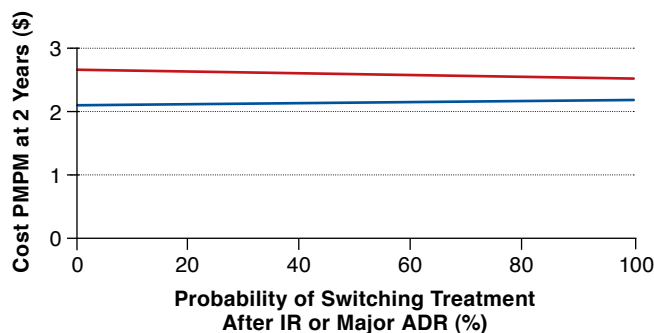**FIGURE 6** *Sensitivity Analyses: Treatment Switching*

A. MTX-IR Monotherapy
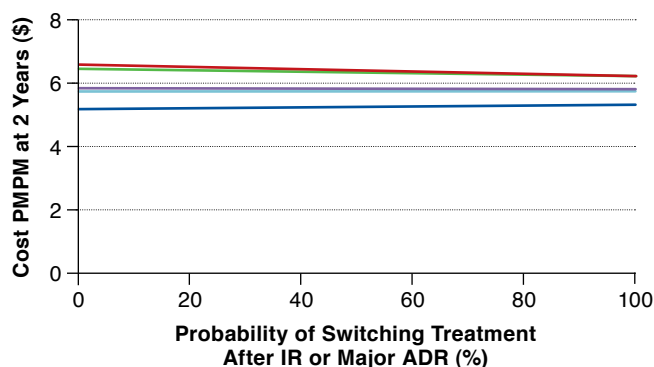
B. MTX-IR Combination Therapy
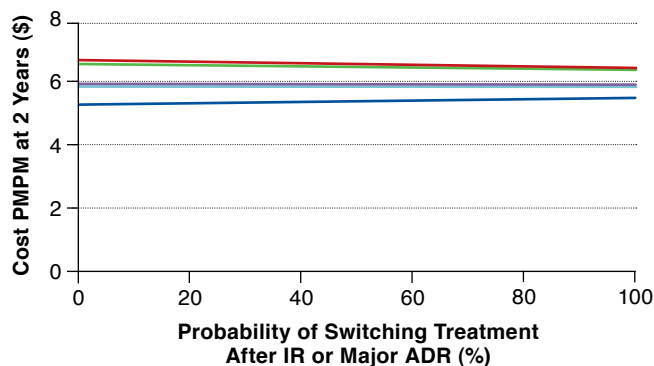
C. TNF-IR Combination Therapy

Legend: Tofacitinib, Adalimumab, Etanercept, Certolzumab, Tocilizumab

Note: The impact of varying the treatment switching probability on the model result is shown here.
ADR = adverse drug reaction; IR = inadequate response; MTX-IR = methotrexate inadequate responder; PMPM = per member per month; TNF-IR = tumor necrosis factor inhibitor inadequate responder.

Limitations

The present study demonstrates that tofacitinib may be a cost-saving treatment strategy compared with other strategies. These findings could have implications for managed care organizations as they evaluate benefit design and treatments for RA. However, this model has some limitations to consider. First, this model included a cross-trial efficacy and safety comparison of trials that were not performed contemporaneously. It is possible that the patient populations are not comparable (e.g., different disease severity and disease duration at baseline), although this is unlikely given the similar labels for each product. Rates of treatment response and adverse events may have been influenced by these factors. Rates estimated in a mixed treatment comparison have been published in a conference abstract and were demonstrated to be similar to those in each individual USPI[20]; however, given the lack of detail on methodology in the abstract, it was felt preferable to use data from the USPIs.

Second, there were no available data to represent response to adalimumab robustly in a TNF-IR population. By using the degradation method to adjust the MTX-IR ACR response rates for this comparator, the estimated response rates were more likely to better reflect patients who have switched from another bDMARD, since those who switch are less likely to respond to further lines of treatment.[35] The alternative assumption that response rates are equal for TNF-IR and MTX-IR patients would have likely overestimated the response rate for the TNF-IR patient population, so it was not included in the analysis. Sensitivity analysis around ACR20 rates demonstrated that the model results were robust to this parameter.

Third, the treatment sequence was fixed in a linear method; that is, after either tofacitinib or the bDMARD comparator, patients always moved to abatacept and then to rituximab. However, it is often the case that the reason for failure (e.g., adverse events or loss of effectiveness) may affect the choice of the next therapy. This may also have an effect on the effectiveness of the subsequent treatment. This is the case with patients treated with an initial TNF inibitor who demonstrated no evidence of efficacy after 6 months (primary nonresponders), who stepped through to a second TNF inhibitor. At present, there is little evidence on this issue to be able to consider this effect in the model because RA disease activity is not routinely measured or captured and, as such, was not included in the analysis. It is also difficult to predict the direction of the bias in the results, but it may be that patients would go to the line of therapy deemed to be the most appropriate given their medical histories, and as such, the current estimate of effectiveness in subsequent lines of treatment may underestimate the true impact.
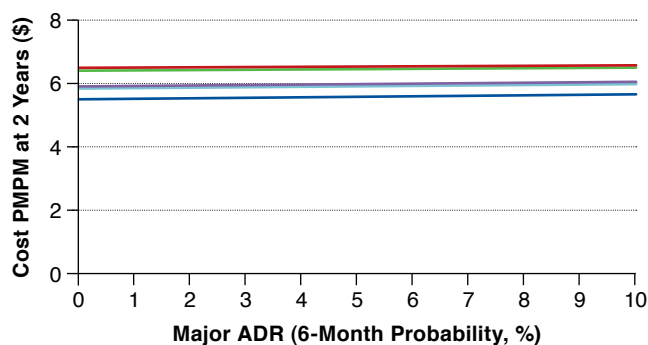
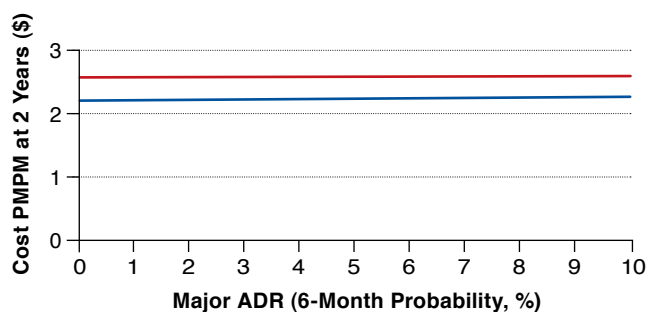FIGURE 7 Sensitivity Analyses: Major ADR Probability

A. MTX-IR Monotherapy
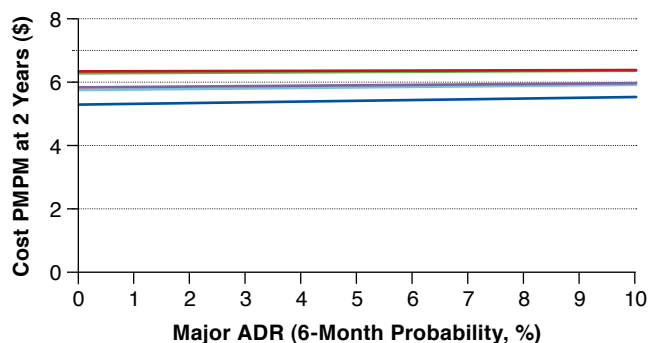
B. MTX-IR Combination Therapy

C. TNF-IR Combination Therapy

Legend: Tofacitinib — Adalimumab — Etanercept — Certolizumab — Tocilizumab

Note: The impact of varying the major ADR probability for each comparator on the model results is shown here.
ADR = adverse drug reaction; MTX-IR = methotrexate inadequate responder; PMPM = per member per month; TNF-IR = tumor necrosis factor inhibitor inadequate responder.

Finally, the models do not include rebates based on market share of the market-leading products nor does the analysis address any share-shift scenarios or actual forecasting growth trends of each agent in the RA category. The introduction of any new innovative therapy at launch will not have the market share necessary to offset managed care rebates of market leaders; yet, formulary decision makers need to assess cost of care per patient beyond quality-adjusted life-years. In addition, the construction of this model was the result of requests by formulary decision makers for a transparent Excel-based model that could be left with them, so they could conduct their own internal scenario planning. The model is provided to customers only after they receive specific training on its design, editable input fields, assumptions, and output fields. This allows for routine updates to the model based on price increases in the market. Some formulary decision makers lack the time or resources to build or constantly update models based on existing evidence and market dynamics. Providing a transparent, Excel-based model that can be used in concert with decision makers' existing resources has been found to be a useful input for their formulary decisions.

■ **Conclusions**

The strategies of tofacitinib as a second-line therapy following the failure of methotrexate and as a third-line therapy following the failure of a TNF inhibitor therapy appear to be a cost-saving treatment strategy based upon the assumptions used within the model.

Tofacitinib 5 mg twice a day following MTX failure is predicted to be a cost-saving treatment option when used either as monotherapy or combination therapy compared with regimens using other bDMARDs. Tofacitinib in TNF-IR patients was also predicted to be cost saving compared with adalimumab. Tofacitinib was associated with the lowest cost per ACR20 response in both patient subpopulations.

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