Common Drug Review
Pharmacoeconomic Review Report

January 2018

Drug	tofacitinib (Xeljanz) tablets
Indication	Tofacitinib, in combination with methotrexate (MTX), is indicated for reducing the signs and symptoms of rheumatoid arthritis (RA) in adult patients with moderately to severely active RA who have had an inadequate response to MTX. In cases of intolerance to MTX, physicians may consider the use of Xeljanz (tofacitinib) as monotherapy.
Listing request	Patients with moderately to severely active rheumatoid arthritis in a similar manner to the tumour necrosis factor (TNF) alpha inhibitors.
Manufacturer	Pfizer Canada Inc.

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in rheumatology who provided input on the conduct of the review and the interpretation of findings.

Redactions: Confidential information in this document has been redacted at the request of the manufacturer in accordance with the *CADTH Common Drug Review Confidentiality Guidelines.*

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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ABBREVIATIONS

ACR	American College of Rheumatology
CDR	CADTH Common Drug Review
CUA	cost-utility analysis
DMARD	disease-modifying antirheumatic drug
HAQ	Health Assessment Questionnaire
IV	intravenous administration
MTC	mixed-treatment comparison
MTX	methotrexate
QALY	quality-adjusted life-year
RA	rheumatoid arthritis
SC	subcutaneous administration
TNF	tumour necrosis factor

SUMMARY

1. BACKGROUND

Tofacitinib (Xeljanz) is the first in a new class of antirheumatic drugs called Janus kinase inhibitors. Tofacitinib, in combination with methotrexate (MTX), is indicated for reducing the signs and symptoms of rheumatoid arthritis (RA) in adult patients with moderately to severely active RA who have had an inadequate response to MTX. In cases of intolerance to MTX, physicians may consider the use of tofacitinib as monotherapy.[1]

The recommended dose of tofacitinib is 5 mg twice daily. The manufacturer submitted a price of $23.0965 per 5 mg tablet ($46.19 daily).

The manufacturer is requesting reimbursement of tofacitinib for patients with moderately to severely active RA in a similar manner to the tumour necrosis factor (TNF) alpha inhibitors.

2. SUMMARY OF THE ECONOMIC ANALYSIS SUBMITTED BY THE MANUFACTURER

The manufacturer submitted a cost-minimization analysis comparing tofacitinib 5 mg twice daily with the biologics adalimumab, etanercept, golimumab, infliximab, abatacept, certolizumab pegol, tocilizumab, anakinra, and rituximab.[2] The assumption of similar efficacy and safety of tofacitinib 5 mg twice daily to other biologics was primarily based on the ORAL Standard 1064 study[3] (versus adalimumab) as well as manufacturer-funded Bayesian mixed-treatment comparisons (MTCs) (versus other biologics).[4-10]

The manufacturer-submitted MTCs compared the efficacy and safety of tofacitinib 5 mg and 10 mg twice daily (in monotherapy or in combination with a disease-modifying antirheumatic drug [DMARD]) with other biologics in adult patients who were inadequate responders to DMARDs or to TNF inhibitors.[5,10,11] Among the outcomes of interest in the MTCs were the American College of Rheumatology (ACR) response: ACR 20, ACR 50, and ACR 70;[5,9,10] Health Assessment Questionnaire–Disability Index (HAQ-DI);[5,10] and Disease Activity Score in 28 joints;[10,12] as well as withdrawals and adverse events.[10,12] The manufacturer's MTCs suggested that there were no significant differences between tofacitinib and biologics in terms of efficacy and safety for all outcomes stated above for both monotherapy and combination therapy with a DMARD. The analysis was conducted from the Canadian public payer perspective over a two-year time frame. Only drug acquisition costs were considered, and these were obtained from the Ontario Exceptional Access Program.[13] Administration costs for injectable drugs were not included.

3. KEY LIMITATIONS

3.1 Limitations with the Mixed-Treatment Comparisons

As stated in Appendix 7 of the CADTH Common Drug Review (CDR) clinical report, in inadequate responders to DMARDs, it seems reasonable to conclude that there is a lack of statistically significant differences in the efficacy and safety of tofacitinib compared with other biological response modifiers at week 12, especially when comparing combination therapies. However, the results of the comparisons between monotherapies and combination therapies have greater limitations to interpretation because the link between these populations was based on a single study. Further, given the differences in rescue therapy protocols between the studies, 24-week results should be interpreted with caution. For the MTC in the inadequate response to TNF inhibitors populations, key limitations were the limited number of trials available and the heterogeneity between trials. In summary, for both patients who were inadequate responders to DMARDs or who were inadequate responders to TNF inhibitors, the comparative efficacy and safety of tofacitinib with that of other biologics beyond 12 weeks is uncertain.

3.2 Overestimation of the Cost of Intravenous Tocilizumab

In the calculation of the cost of the comparator intravenous (IV) tocilizumab at a dose of 4 mg/kg every four weeks, using patient weight of 70 kg, the manufacturer used the price of the 400 mg vial ($896) as the total cost of the 280 mg dose of tocilizumab IV despite the availability of vials of 80 mg ($179) and 200 mg ($448) of tocilizumab, which would have resulted in a total cost of $627 for 280 mg of tocilizumab IV every four weeks. The difference in cost per dose ($269) resulted in an overestimation of the total annual costs of tocilizumab IV and therefore underestimated the total incremental costs of tofacitinib when compared with tocilizumab.

3.3 Differential Cost in Patients With Lower Weight

For the biologics that are dosed based on weight, the manufacturer considered only a weight of 70 kg or 100 kg, except for abatacept, for which a weight of < 60 kg was assessed. In a reanalysis, CDR considered a broader range of weights (50 kg, 70 kg, and 101 kg) to better assess the differential cost of tofacitinib compared with biologics (see Table 2, Appendix 1).

4. ISSUES FOR CONSIDERATION

Since the tofacitinib CDR submission, a subsequent-entry biologic, infliximab (Inflectra), has received a positive listing recommendation by the Canadian Drug Expert Committee. A CDR reanalysis of costs in year 1 and subsequent years including this comparator is presented in Tables 1 and 2.

The approved dose for tofacitinib in Canada is 5 mg twice daily;[1] however, an increased dose of 10 mg twice daily had been studied in clinical trials for tofacitinib.[3,14-23] Although the 10 mg twice daily dose is not approved in Canada, the clinical expert indicated the possibility that tofacitinib dosing will reach 10 mg twice daily, thereby increasing potential costs associated with tofacitinib use.

The manufacturer did not include the administration costs associated with injectable drugs — e.g., infusion costs — for the comparator treatments. The inclusion of administration costs does not change the direction of the results but enhances the differences in costs, associating tofacitinib with more cost savings compared with other treatments.

5. RESULTS/CONCLUSIONS

At the current daily cost of $46.19 ($16,872 annually), and using an average patient weight of 70 kg, based on CDR reanalyses, tofacitinib is expected to result in cost savings ranging from $495 to $6,829 in the first year of treatment when compared with adalimumab, certolizumab pegol, etanercept, golimumab, infliximab (Remicade), anakinra, abatacept, and two courses of rituximab. When compared with the subsequent-entry biologic infliximab (Inflectra), with tocilizumab IV 4 mg/kg every two weeks, and with tocilizumab administered subcutaneously (SC) every two weeks, tofacitinib 5 mg tablets are expected to result in incremental costs ranging from $1,272 to $8,718 in the first year of treatment.

The ability of tofacitinib to result in cost savings is affected by patient weight and escalated dosing regimens: in a 50 kg patient, tofacitinib was more expensive than most weight-based biologics (except infliximab) when used at a dose of up to 10 mg/kg and more expensive than tocilizumab SC using a weekly dosing regimen. However, in a patient of 101 kg, tofacitinib was less expensive than most biologics except tocilizumab IV at a dose of 4 mg/kg every four weeks.

The comparative efficacy and safety of tofacitinib with that of other biologics beyond 12 weeks is uncertain.

6. COST COMPARISON TABLE

Clinical experts have deemed the comparator treatments presented in Table 1 to be appropriate. Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified. Existing Product Listing Agreements are not reflected in the table and, as a result, the table may not represent the actual costs to public drug plans.

TABLE 1: COST COMPARISON TABLE FOR BIOLOGIC DISEASE-MODIFYING DRUGS FOR RHEUMATOID ARTHRITIS

Comparators	Strength	Dose Form	Price ($)	Recommended Dose	Annual Drug Cost ($)
Tofacitinib (Xeljanz)	**5 mg**	**Tablet**	**23.0965**[a]	**5 mg twice daily**	16,872
Abatacept SC (Orencia)	125 mg/mL	Pre-filled syringe	358.9000	125 mg weekly[b]	18,663[b]
Abatacept IV (Orencia)	250 mg/ 15 mL	Vial	480.4100	Patients < 60 kg: 500 mg Patients 60 to 100 kg: 750 mg Patients > 100 kg: 1,000 mg Initial dose at weeks 0, 2 and 4 then every 4 weeks	Year 1: 20,177[c] Thereafter: 18,736
Adalimumab SC (Humira)	40 mg/ 0.8 mL	Pre-filled syringe or pen	740.3600	40 mg every other week	19,249
Anakinra (Kineret)	100 mg	Pre-filled syringe	47.5814	100 mg daily	17,367
Certolizumab pegol (Cimzia)	200 mg/mL	Pre-filled syringe	664.5100	Year 1: 400 mg at weeks 0, 2, and 4 then 200 mg every 2 weeks	Year 1: 19,271 Thereafter: 17,277
Etanercept (Enbrel)	25 mg	Vial	194.2450	50 mg weekly or two 25 mg doses on same day every week or every 3 or 4 days	20,201
	50 mg/mL	Pre-filled syringe or auto-injector	388.6050		20,207
Golimumab SC (Simponi)	50 mg/ 0.5 mL	Pre-filled syringe or auto-injector	1,520.2100	50 mg monthly	18,243
Golimumab IV (Simponi)	50 mg/ 4 mL	Vial	897.1500[d]	2 mg/kg at weeks 0 and 4, then every 8 weeks thereafter	Year 1: 18,840[ef] Thereafter: 17,494[ef]
Infliximab (Remicade)	100 mg	Vial	987.5600	3 mg/kg at weeks 0, 2 and 6, then every 8 weeks thereafter Depending on clinical response, dose can be increased to 10 mg/kg and/or up to every 4 weeks	Year 1: 23,701[eg] Thereafter: 19,257[eg] 10 mg/kg every 4 weeks: $102,706 annually[e]
Infliximab (Inflectra)	100 mg	Vial	650.0000[h]		Year 1: 15,600[eg] Thereafter: 12,675[eg] 10 mg/kg every 4 weeks: $67,600 annually[e]

Comparators	Strength	Dose Form	Price ($)	Recommended Dose	Annual Drug Cost ($)
Rituximab (Rituxan)	100 mg/10 mL 500 mg/50 mL	Vial	453.1000 2,265.5000	A course consists of 1,000 mg infusions at weeks 0 and 2 1,000 mg in week 0 and 1,000 mg week 2; reassess for retreatment at week 26, no sooner than 16 weeks after previous	18,124 assumes 2 courses Per course: 9,062
Tocilizumab SC (Actemra)	162 mg/0.9 mL	Pre-filled syringe with needle safety device	385.1750[d]	Patients < 100 kg: 162 mg SC every 2 weeks, increasing to weekly based on clinical response. Patients ≥ 100 kg: 162 mg SC weekly	Every two weeks: 10,015 Weekly: 20,029
Tocilizumab IV (Actemra)	80 mg/4 mL 200 mg/10 mL 400 mg/20 mL	Vial	179.2000 448.0000 896.0000	4 mg/kg every 4 weeks followed by an increase to 8 mg/kg based on clinical response	4 mg/kg: 8,154[e] 8 mg/kg: 17,472[e]

IV = intravenous administration; SC = subcutaneous injection.
[a] Manufacturer's submitted price.[2]
[b] Abatacept-naive patients require a single weight-based loading dose of 500 mg, 750 mg, or 1,000 mg IV abatacept, with weekly SC injections to start within one day thereafter, not included in cost.
[c] Assumes 14 doses in year 1 (one dose every four weeks with an additional dose at week 2).
[d] McKesson Canada wholesale price; includes markup (December 2014).[24]
[e] Costs include wastage of unused medication in vial.
[f] Assumes 7 doses in first year and 6.5 per year thereafter.
[g] Assumes 8 doses in first year and 6.5 doses per year thereafter.
[h] Canadian Drug Expert Committee final recommendation for infliximab (Inflectra — Hospira Healthcare Corporation); December 19, 2014.[25] Available from: http://www.cadth.ca/media/cdr/complete/cdr_complete_SE0384_Inflectra_Dec-23-14.pdf.
Source: Ontario Drug Benefit Formulary Exceptional Access Program (December 2014),[13] unless otherwise indicated. Patient weight assumed to be 70 kg. Annual period assumes 52 weeks, 26 × 2 weeks, or 13 × 4 weeks per year.

APPENDIX 1: REVIEWER WORKSHEETS

Summary of Manufacturer's Submission

Drug Product	**Tofacitinib 5 mg**
Treatment	Tofacitinib 5 mg twice daily
Comparator(s)	Adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, anakinra, rituximab, abatacept, and tocilizumab
Study Question	Not specified
Type of Economic Evaluation	Cost-minimization analysis
Target Population	Adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to methotrexate (MTX)
Perspective	Canadian public payer
Outcome(s) Considered	Not specified
Key Data Sources	
Cost	Ontario Drug Benefit, British Columbia PharmaCare Formulary, Alberta Drug Benefit, Manitoba Drug Formulary, Ontario Exceptional Access Program
Clinical Efficacy	Manufacturer-conducted network meta-analyses
Harms	Manufacturer-conducted network meta-analyses
Time Horizon	2 years
Results for Base Case	• Use of tofacitinib is expected to incur additional costs of up to $7,810 annually when compared with rituximab (2 courses), abatacept (in patients with weight less than 60 kg), and tocilizumab (at lower doses) • Tofacitinib is expected to result in cost savings up to $10,117 in the first year (versus abatacept in patients with weight more than 100 kg) and up to $26,069 in consequent years (versus infliximab [Remicade] 5 mg/kg in patients weighing 100 kg

Manufacturer's Results

The manufacturer reported that, based on a patient weight of 70 kg, tofacitinib is less costly than adalimumab, certolizumab, etanercept, golimumab, infliximab (Remicade), and anakinra in terms of first year and subsequent year annual costs. Tofacitinib is expected to result in cost savings of up to $10,117 in the first year and $26,069 in consequent years when compared with adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, anakinra, abatacept (in patients weighing 60 kg and more), and tocilizumab at higher doses. Tofacitinib is expected to be more costly by up to $7,810 annually when compared with abatacept in patients weighing 60 kg or less, rituximab, and tocilizumab using a dose of 4 mg/kg.

CADTH Common Drug Review Results

A cost comparison of tofacitinib with all other biologics, based on a patient weight of 70 kg, is presented in Table 1.

CDR performed a sensitivity analysis for different patient weights (50 kg, 70 kg, and 101 kg) to assess the incremental cost or savings with tofacitinib compared with biologics with weight-based dosing: infliximab, abatacept, and tocilizumab.

For a patient weight of 50 kg, in year 1, tofacitinib was more expensive than infliximab (Remicade – Inflectra) at a dose of 3 mg/kg every eight weeks, abatacept, and tocilizumab IV at a dose of 4 mg/kg every four weeks, and tocilizumab SC every two weeks (incremental cost ranging from $1,072 to $11,048). In subsequent years, tofacitinib was less expensive than infliximab (Remicade – Inflectra) at a dose of 10 mg/kg every four weeks and tocilizumab SC weekly (cost savings ranging from $3,157 to $47,319), but more expensive than abatacept and tocilizumab IV at a dose of 8 mg/kg (incremental costs ranging from $4,381 to $5,224).

For a patient weight of 70 kg, in year 1, tofacitinib was more expensive than tocilizumab IV at doses of 4 mg/kg every four weeks (incremental cost of $8,718), tocilizumab SC every two weeks (incremental cost of $6,857), and infliximab (Inflectra) at 3 mg/kg every eight weeks (incremental cost of $1,272), but was less expensive than infliximab (Remicade) at a dose of 3 mg/kg every eight weeks (cost saving $6,829) and abatacept IV (cost saving $3,305). In subsequent years, tofacitinib was more expensive than tocilizumab IV at doses of 8 mg/kg every four weeks (incremental cost of $600) but less expensive than infliximab at a dose of 10 mg/kg every four weeks (cost savings ranging from $42,278 to $72,996) and abatacept IV (cost savings $8,109).

For a patient with weight 101 kg, in year 1, tofacitinib was a cost-saving option compared with infliximab at a dose of 3 mg/kg every eight weeks, with abatacept, and with tocilizumab SC, but was more expensive than tocilizumab IV at a dose of 4 mg/kg every four weeks. In subsequent years, tofacitinib was a less expensive option compared with all biologics with weight-based dosing when using escalated dosing regimens.

TABLE 2: RESULTS OF CADTH COMMON DRUG REVIEW REANALYSIS FOR BIOLOGICS WITH WEIGHT-BASED DOSING

	Total Costs Based on Patient Weight		
	50 kg	70 kg[a]	101 kg
Tofacitinib	**$16,872**		
Year 1			
Infliximab 3 mg/kg (Remicade)[b]	$15,800	$23,701	$31,602
Infliximab 3 mg/kg (Inflectra)	$10,400	$15,600	$20,800
Abatacept IV	$13,451	$20,177	$26,903
Tocilizumab IV 4 mg/kg	$5,824	$8,154	$13,978
Tocilizumab SC	$10,015		$20,029
Subsequent years			
Infliximab[c] (Remicade)	$12,833 to $64,191	$19,257 to $89,868	$25,677 to $141,221
Infliximab[c] (Inflectra)	$8,450 to $42,250	$12,675 to $59,150	$16,900 to $92,950
Abatacept IV	$12,491	$18,736	$24,981
Tocilizumab IV[b]	$5,824 to $11,648	$8,154 to $17,472	$13,978 to $25,626
Tocilizumab SC[b]	$10,015 to $20,029		$20,029

IV = intravenous; SC = subcutaneous.
[a] Patient weight used in manufacturer's base-case analysis — Pharmacoeconomic Evaluation.[2]
[b] Assumes 8 doses in first year and 6.5 doses per year thereafter.
[c] Range values indicate dose escalation was in effect (from 3 mg/kg every 8 weeks to 10 mg/kg every 4 weeks for infliximab, from 4 mg/kg to 8 mg/kg for tocilizumab IV, and from biweekly to weekly for tocilizumab SC).
Note: Annual period assumes 52 weeks, 26 × 2 weeks, or 13 × 4 weeks per year.

TABLE 3: KEY LIMITATIONS

Identified Limitation	Description	Implication
MTC limitations	For the population of inadequate responders to DMARDs, the limitations include no a priori description of how potential biases and inconsistencies in trial methodology or patient characteristics would be handled, no presentation of the traditional pairwise meta-analyses results to assess consistency between direct and indirect evidence, and no primary efficacy or safety outcomes stated. The results of comparisons between monotherapies and combination therapies have greater limitations to interpretation because the link between these populations was based on a single study. Heterogeneity between trials was also present; e.g., dropout rates in the placebo groups, doses of concomitant MTX, and the reassignment schemes imposed for patients after 12 weeks of treatment (i.e., early escape design). Trials imposed reassignment at 12 weeks, 16 weeks, or (in one case) 22 weeks, and used various statistical imputations and methods to obtain 24-week data. Given this variation, 24-week efficacy and harm outcomes become difficult to interpret. For the population of inadequate responders to TNF inhibitors, a key limitation of the MTCs was the limited number of trials available for the meta-analyses, which raised uncertainty regarding the reliability of the results from the MTCs. Additional analyses, including sensitivity analyses and meta-regressions to address heterogeneity between study methodology and baseline patient characteristics, were not possible due to the limited number of included studies for the population of TNF inhibitor inadequate responders.	There remains some uncertainty over the treatment similarities as perceived from the manufacturer-submitted MTCs, especially for the results at 24 weeks.
Annual cost of tocilizumab is overestimated	In the calculation of the cost of the comparator tocilizumab at a dose of 4 mg/kg every 4 weeks, using patient weight of 70 kg, the manufacturer used the price of the 400 mg vial ($896) as the total cost of the 280 mg dose of tocilizumab despite the availability of vials of 80 mg ($179) and 200 mg ($448) of tocilizumab, which would have resulted in a total cost of $627 for 280 mg of tocilizumab every 4 weeks. The difference in cost per dose ($269) resulted in overestimation of the total annual costs of tocilizumab and therefore underestimated the total incremental costs of tofacitinib when compared with tocilizumab.	Underestimation of the incremental cost of tofacitinib versus low-dose tocilizumab.

APPENDIX 2: SUMMARY OF MANUFACTURER'S COST-UTILITY ANALYSIS

Summary

In addition to the cost-minimization analysis, the manufacturer submitted a cost-utility analysis (CUA) based on a patient-level micro-simulation model of RA progression over time, which compared treatment sequences with tofacitinib to comparator sequences without tofacitinib in the patient care pathway.[26] The comparator sequences looked at current standard of care for RA involving the sequential use of non-biologic and biologic DMARD therapies. As shown in Figure 1, two different scenarios are evaluated: one in which adalimumab is the first biologic used within the sequence (Scenario 1), and one in which etanercept is the first biologic used within the sequence (Scenario 2).

FIGURE 1: TREATMENT SEQUENCES FOR MANUFACTURER'S BASE-CASE SCENARIOS

Table 1: Medication Sequences for Scenario 1

	Treatment Sequence	Comparator Sequence
1st line	Tofacitinib 5 mg +MTX	Adalimumab +MTX
2nd line	Adalimumab +MTX	Etanercept +MTX
3rd line	Etanercept +MTX	Abatacept +MTX
4th line	Abatacept +MTX	Tocilizumab +MTX
5th line	Tocilizumab +MTX	Rituximab +MTX
6th line	Rituximab +MTX	Golimumab +MTX

Table 2: Medication Sequences for Scenario 2

	Treatment Sequence	Comparator Sequence
1st line	Tofacitinib 5 mg +MTX	Etanercept +MTX
2nd line	Etanercept +MTX	Adalimumab +MTX
3rd line	Adalimumab +MTX	Abatacept +MTX
4th line	Abatacept +MTX	Tocilizumab +MTX
5th line	Tocilizumab +MTX	Rituximab +MTX
6th line	Rituximab +MTX	Golimumab +MTX

MTX = methotrexate.
Source: Manufacturer's Submission — Pharmacoeconomic Evaluation, page 4.[26]

The Health Assessment Questionnaire (HAQ) was used to measure a patient's change in RA symptoms; a negative HAQ score change signifies an improvement in RA symptoms. The progression of RA for each patient as he or she goes through each six-month cycle of the model is defined by his or her HAQ score. The HAQ score for a patient in a cycle is based on his or her HAQ score in the previous cycle and the change in HAQ score in the current model cycle. The HAQ score change for any specific medication is divided into short-term, medium-term, and long-term changes. Short-term changes reflect the first six months after treatment initiation. These changes are applied to the first cycle of a new medication. Medium-term HAQ changes apply between six months and 36 months after treatment initiation. Long-term HAQ changes are applied more than 36 months after treatment initiation.

Data for HAQ change during the first six months of treatment were based on an MTC for the effectiveness of different treatments for moderate to severe RA.[5] Data on medium-term HAQ score changes were derived from various sources.[26] For long-term HAQ change, a value of 0 was assumed for all medications owing to a lack of data.

For both the treatment and the comparator sequence, short-term HAQ change data (i.e., the first six months) were taken from the MTC data from the population with an inadequate response to DMARDs for the initial medication in the sequence. These assumptions were based on all patients entering the model having failed methotrexate monotherapy and being TNF inhibitor-naive. For the comparator sequence, MTC data from the inadequate response to TNF inhibitors were used for all subsequent medications, as patients would have failed on a biologic after the first medication in the sequence (etanercept for Scenario 1; adalimumab for Scenario 2). In the treatment sequence, DMARD inadequate responder short-term HAQ change data were applied to the first two medications (tofacitinib 5 mg), while TNF inadequate responder HAQ change data were used for all subsequent medications in the treatment sequence. This assumption was based on the manufacturer's expectation that patients failing on tofacitinib had similar characteristics to patients who have failed an anti-TNF inhibitor.

Quality of life was estimated by mapping the patient's current HAQ score during each model cycle to Health Utilities Index Mark 3 values. Utility decrements from serious adverse events were obtained from published literature,[26] while decrements from medication injections or infusions were obtained from unpublished research.[26]

Costs of the products were obtained from the Ontario Drug Benefit Formulary,[26] while resource use was based on published literature.[26] The submitted CUA simulates patients over a five-year period and uses the perspective of publicly funded Canadian health care.[26]

Results

The results of Scenario 1 in the base case show that the treatment sequence starting with tofacitinib produces cost savings of $3,973 and 0.134 more quality-adjusted life-years (QALYs) than the comparator sequence starting with adalimumab. Therefore, the tofacitinib sequence is considered to be dominant versus the comparator sequence (less costly, more QALYs). For Scenario 2, the base-case results show that the sequence starting with tofacitinib produces cost savings of $4,394 and 0.09 more QALYs than the comparator sequence that begins with etanercept. Therefore, the tofacitinib sequence is also considered to be dominant versus the comparator sequence. Several sensitivity analyses were conducted that suggest the results are robust.

Limitations

There are a number of limitations to this analysis:

- Use of a sequence of treatments and comparators is less informative because of the very limited clinical trials in which those biologics were used in that specific sequence.[27,28] There are also limited data to support the assumption of treatment duration assigned to each treatment within a defined sequence.
- In the CADTH therapeutic review on Biological Response Modifier Agents for Adults with Rheumatoid Arthritis,[28] an analysis of the use of sequential biologic drugs found that the optimal sequence was adalimumab, followed by golimumab, abatacept, and then rituximab. The sequential use of adalimumab, followed by golimumab, was associated with an incremental cost per QALY of $106,603 when compared with adalimumab alone. The incorporation of additional biologic drugs in the

sequence resulted in steadily increasing incremental cost-effectiveness ratios, indicating that adding treatments to a sequence becomes increasingly less cost-effective as more biologic drugs are used.
- Long-term HAQ change data are lacking, therefore requiring the assumption that, on average, HAQ score did not change for any of the medications in the model.
- The clinical expert for this review had indicated that the probability of using more than four biologic agents or TNF alpha inhibitors in the treatment of a patient with RA is low.

For these reasons, and because the results of the manufacturer-submitted MTCs suggested similar efficacy and safety between tofacitinib and other biologic drugs, the CDR pharmacoeconomic review focused on appraisal of the cost-minimization analysis submitted by the manufacturer.

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