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ORIGINAL RESEARCH

Economic Benefit from Improvements in Quality of Life with Upadacitinib: Comparisons with Tofacitinib and Methotrexate in Patients with Rheumatoid Arthritis

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ABSTRACT

Introduction: To compare the economic benefit of upadacitinib combination therapy versus tofacitinib combination therapy and upadacitinib monotherapy versus methotrexate monotherapy from improvements in health-related quality of life (HRQOL) in patients with rheumatoid arthritis (RA).

Methods: Data were analyzed from two trials of upadacitinib (SELECT-NEXT and SELECT-MONOTHERAPY) and one trial of tofacitinib (ORAL-Standard) that collected HRQOL measurements using the Short Form 36 (SF-36) Health Survey in patients with RA. Direct medical costs per patient per month (PPPM) for patients receiving upadacitinib 15 mg once daily and methotrexate were derived from observed SF-36 Physical (PCS) and Mental Component Summary (MCS) scores in the SELECT trials using a regression algorithm. Direct medical costs PPPM for patients receiving tofacitinib 5 mg twice daily were obtained from a published analysis of SF-36 PCS and MCS scores observed in the ORAL-Standard trial. Short-term (12–14 weeks) and long-term (48 weeks) estimates of direct medical costs PPPM were compared between upadacitinib and tofacitinib and between upadacitinib and methotrexate.

Results: Over 12 weeks, direct medical costs PPPM were $252 lower (95% CI $72, $446) for upadacitinib-treated patients versus tofacitinib-treated patients. Medical costs PPPM at weeks 24 and 48 and cumulative costs over the entire 48-week period (difference $1759; 95% CI $1162, $2449) were significantly lower for upadacitinib than for tofacitinib. Over 14 weeks, direct medical costs PPPM were $399 lower (95% CI $158, $620) for patients treated with upadacitinib monotherapy compared with those treated with methotrexate alone. Direct medical costs at week 48 and cumulative costs over the entire 48-week period (difference $2044; 95% CI $1221, $2846) were significantly lower for upadacitinib monotherapy compared with methotrexate alone.

Conclusion: In the short and long term, upadacitinib combination therapy versus tofacitinib combination therapy and upadacitinib monotherapy versus methotrexate

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monotherapy were associated with significantly lower direct medical costs for patients with RA. ***Trial Registration***: ClinicalTrials.gov identifier, NCT02675426, NCT02706951, and NCT00853385.

Keywords: Healthcare costs; Health-related quality of life; Methotrexate; Rheumatoid arthritis; Tofacitinib; Upadacitinib

Key Summary Points

Why carry out this study?

The economic burden of rheumatoid arthritis (RA) to both patients and society is high.

Healthcare costs are not often collected as outcomes in clinical trials of RA treatments.

Patient-reported outcomes, such as the Short Form 36 (SF-36) Health Survey, are frequently collected in clinical trials to assess health-related quality of life from the patient perspective and may provide a means to evaluate the economic benefit of various RA treatments.

What was learned from the study?

On the basis of improvements in health-related quality of life in the short and long term, combination therapy with upadacitinib 15 mg once daily was associated with significantly lower direct medical costs than combination therapy with tofacitinib 5 mg twice daily in patients with moderate to severe RA.

In addition, upadacitinib 15 mg once daily monotherapy was associated with significantly lower direct medical costs than methotrexate monotherapy for patients with moderate to severe RA.

Estimates of healthcare expenditures using the patient-reported outcome SF-36 may improve our understanding of the economic implications of different RA treatment strategies.

INTRODUCTION

Healthcare costs associated with rheumatoid arthritis (RA) are high and are likely attributable to the high symptom burden [1–4]. The Short Form 36 (SF-36) Health Survey is a generic measure commonly used to assess health-related quality of life (HRQOL) as reported by the patient [5–9]. The SF-36 has been used to show that RA has a substantial negative impact on HRQOL, particularly with regard to physical function compared with the general, healthy population and in patients with other diseases [7–9]. Treatment-related improvements in disease activity are associated with improvements in disability, pain, and fatigue, which are reflected as an improvement in HRQOL [10–13]. Janus kinase (JAK) inhibitors, such as tofacitinib and upadacitinib, have been shown to significantly reduce disease activity and improve HRQOL in patients with RA [14–21]. Higher healthcare resource use and medical costs are observed in patients with an inadequate response to targeted immunomodulator therapy compared with those who do respond well to therapy [12]. Significant differences in direct costs have been reported for different levels of disease activity, with higher costs associated with higher states of disease activity [11]. Lower costs are likely related to reductions in healthcare resource use resulting from effective treatment, which is in turn associated with improvements in HRQOL. This suggests that measuring improvement in HRQOL may be a useful proxy to estimate reductions in healthcare resource use and costs.

Healthcare costs are not typically collected as outcomes in clinical trials. Estimates of healthcare expenditures based on patient-reported outcomes may help improve our understanding of the economic implications of different RA treatment strategies. For example, HRQOL (as measured by SF-36) has been used to predict the medical expenditures of clinical trial participants receiving RA treatment [22] based on a published algorithm [23]. Using this algorithm-based approach, we estimated the economic benefit of treatment with upadacitinib, tofacitinib, and methotrexate from improvements in

HRQOL. Specifically, we compared the estimated medical expenditures (including costs of medical services and other prescribed medications) between upadacitinib combination therapy and tofacitinib combination therapy, upadacitinib combination therapy and placebo, and between upadacitinib monotherapy and methotrexate monotherapy in patients with RA.

METHODS

Data Sources

SELECT-NEXT (NCT02675426) was a phase 3, randomized clinical trial investigating the safety and efficacy of upadacitinib versus placebo among patients with moderate to severe RA despite prior treatment with conventional systemic disease-modifying antirheumatic drugs (csDMARDs) [24]. In SELECT-NEXT, patients were randomly assigned to either upadacitinib 15 mg QD, upadacitinib 30 mg QD, or placebo while remaining on csDMARDs. Patients in the placebo group were randomly assigned to switch to either upadacitinib 15 mg QD or upadacitinib 30 mg QD after 12 weeks.

SELECT-MONOTHERAPY (NCT02706951) was a phase 3, randomized clinical trial comparing the safety and efficacy of upadacitinib monotherapy versus methotrexate monotherapy in patients with moderate to severe RA, despite treatment with methotrexate [25]. Patients were randomly assigned to upadacitinib 15 mg QD, upadacitinib 30 mg QD, or were continued on their previous dose of methotrexate as a blinded study drug for 14 weeks followed by upadacitinib 15 mg or 30 mg per prespecified randomization assignment.

ORAL-Standard (NCT00853385) was a phase 3, randomized clinical trial investigating the clinical efficacy of tofacitinib compared with placebo in patients with RA on background methotrexate [26]. Patients were randomly assigned to receive tofacitinib 5 or 10 mg orally BID, adalimumab 40 mg subcutaneous injection self-administered once every 2 weeks, or placebo. Patients in the placebo group switched to either tofacitinib 5 or 10 mg BID at 3 months if they were considered non-responders or at 6 months.

Ethics

The current study is a secondary analysis of clinical trial data. The original trials were conducted in accordance with the ethical principles that have their origin in the current Declaration of Helsinki and are consistent with International Conference on Harmonization Good Clinical Practice (ICH GCP) and Good Epidemiology Practices (GEP), and applicable regulatory requirements. Data were de-identified and comply with the patient requirements of the Health Insurance Portability and Accountability Act. The confidentiality of records that could identify patients within the database has been protected, respecting the privacy and confidentiality rules in accordance with applicable regulatory requirements.

Study Design

This economic analysis used individual patient-level data from two trials of upadacitinib (SELECT-NEXT and SELECT-MONOTHERAPY) [24, 25] and aggregate data from one trial of tofacitinib (ORAL-Standard) [26] that collected repeated measurements of HRQOL using SF-36. A published algorithm [23] was used to longitudinally estimate medical expenditures per patient per month (PPPM) as a function of patients' age, sex, and observed SF-36 Physical and Mental Component Summary (PCS and MCS) scores in SELECT-NEXT and SELECT-MONOTHERAPY. The coefficients in the regression algorithm [23] used to estimate direct medical costs in this study are provided in Table S1 in the supplementary material. The original algorithm was fitted using the Short Form 12 (SF-12) Health Survey PCS and MCS scores, but has subsequently been used to predict medical costs based on SF-36 PCS and MCS scores given the strong correlation between SF-12 and SF-36 scores (correlation coefficient ≥ 0.94 for both) [22, 27, 28]. For each patient in SELECT-NEXT and SELECT-MONOTHERAPY, the equation was used to predict

medical spending for each visit that SF-36 responses were collected. Predicted costs at each study visit were then averaged across all patients in each treatment group.

Estimated mean medical expenditures for patients treated with tofacitinib 5 mg twice daily (BID) in ORAL-Standard were obtained from a published study by Rendas-Baum et al. [22]. This study applied the same regression algorithm [23] described in the preceding paragraph to estimate medical costs based on SF-36 outcomes and demographics in ORAL-Standard. Specifically, mean medical costs PPPM and standard errors for tofacitinib 5 mg BID at weeks 0, 4, and 12 were obtained on the basis of the numbers reported in the text and by digitizing the plotted figure that displays medical cost estimates over time by treatment group in ORAL-Standard [22].

Estimated medical expenditures PPPM for patients treated with upadacitinib 15 mg once daily (QD) combination therapy or placebo (csDMARDs alone) in SELECT-NEXT were compared to patients treated with tofacitinib 5 mg BID combination therapy in ORAL-Standard. Estimated medical expenditures PPPM for patients treated with upadacitinib 15 mg QD monotherapy were compared to those treated with methotrexate monotherapy in SELECT-MONOTHERAPY.

Patient-Reported Outcomes

The patient-reported outcome measure used to estimate direct medical costs was SF-36 [5]. The SF-36 instrument is a validated, generic measure designed to capture an individual's perception of health and well-being [29]. The SF-36 questionnaire [5, 9] is self-administered and responses to the questions yield scores for eight domains (physical functioning, physical role functioning, bodily pain, general health perceptions, vitality, social functioning, emotional role functioning, and mental health) and two summary scores (PCS and MCS scores). The PCS and MCS scores are norm-based aggregates of the eight domain scores with a mean of 50 and a standard deviation of 10 for the US general population with higher scores indicating a more favorable health state [30, 31]. SF-36 was measured at weeks 0, 4, 12, 24, and 48 in SELECT-NEXT and at weeks 0, 4, 14, and 48 in SELECT-MONOTHERAPY. PCS and MCS scores were derived from patients' responses to SF-36 at each time point.

Statistical Analyses

Estimation of Direct Medical Costs

Medical costs PPPM at each study visit in SELECT-NEXT and SELECT-MONOTHERAPY were estimated on the basis of patient age, sex, and observed SF-36 PCS and MCS scores using the regression algorithm from Fleishman et al. [23]. The medical expenditures estimated in this study encompassed types of healthcare resource use that were expected to vary according to RA treatment effectiveness, including use of medical services and prescribed medications other than the study treatments. Specifically, based on the cost components considered in the published algorithm [23], direct medical expenditures captured the sum total of payments for hospital inpatient stays, emergency department visits, outpatient and hospital clinic visits, other prescribed medicines, home health visits, medical supplies, and dental providers. Drug acquisition costs of upadacitinib and tofacitinib were not included in the costs derived using the published algorithm, as the algorithm was developed using 2000–2001 Medical Expenditure Panel Survey data.

Estimated costs PPPM were inflation-adjusted to 2020 United States (US) dollars using the medical care component of the Consumer Price Index [32]. The long-term medical cost PPPM estimation was conducted separately for SELECT-NEXT and SELECT-MONOTHERAPY over a 48-week period. In each treatment group, total medical costs were estimated over the short term (12 or 14 weeks) and long term (48 weeks) based on the longitudinal trend in monthly medical costs, assuming linear improvement between study visits. The week 0–4, week 4–12, week 12–24, and week 24–48 averages were calculated as the simple average of the medical cost PPPM estimates at weeks 0 and 4, weeks 4 and 12, weeks 12 and 24, and weeks 24 and 48, respectively.

Average medical costs PPPM over the entire week 0–48 period represent the weighted average of the week 0–4, week 4–12, week 12–24, and week 24–48 averages.

Total 12-week medical costs were estimated in each treatment group by multiplying average monthly medical costs during week 0–12 by the number of months within a 12-week period (based on a conversion of 4.33 weeks per month). Total 48-week medical costs were estimated in each treatment group by multiplying average monthly medical costs during week 0–48 by the number of months within a 48-week period (based on a conversion of 4.33 weeks per month).

Medical cost PPPM estimates and corresponding standard errors for tofacitinib (based on SF-36 PCS and MCS measurements in ORAL-Standard) at weeks 0, 4, and 12 were extracted from Rendas-Baum et al. [22], and were then inflation-adjusted to 2020 US dollars. Cost estimates for tofacitinib were reported only up to week 12 in the Rendas-Baum publication [22], and were therefore imputed at weeks 24 and 48 using last observation carried forward.

Statistical Comparisons

The 95% confidence intervals (CIs) for cost differences between groups were based on 1000 iterations of bootstrapping for upadacitinib and comparator groups in SELECT-NEXT and SELECT-MONOTHERAPY and 1000 simulations of medical costs for tofacitinib using the visit means and standard errors reported by Rendas-Baum et al. [22]. Statistical comparisons were conducted between upadacitinib 15 mg QD and placebo in SELECT-NEXT and tofacitinib 5 mg BID in ORAL-Standard, and between upadacitinib 15 mg QD and methotrexate in SELECT-MONOTHERAPY. All statistical analyses were conducted using SAS 9.4 software (SAS Institute Inc., Cary, NC).

RESULTS

Key Analysis Variables

Across the treatment groups of the SELECT-NEXT, ORAL-Standard, and SELECT-MONOTHERAPY studies, mean age ranged from 53.0 to 55.3, percentage of female patients ranged from 75.1% to 85.3%, and mean SF-36 PCS and MCS scores ranged from 33.1 to 33.4 and 39.8 to 46.5, respectively, at baseline (Table 1). The visit means of SF-36 PCS and MCS scores used in the medical cost estimation based on the SELECT-NEXT and SELECT-MONOTHERAPY clinical trials are presented in Table 2.

Medical Cost Estimates: Upadacitinib Combination Therapy Versus Tofacitinib Combination Therapy Versus csDMARDs Alone

As shown in Fig. 1, average medical costs PPPM were lower in upadacitinib-treated patients compared with tofacitinib-treated patients over week 0–4 ($977 vs $1042, respectively), week 4–12 ($795 vs $899, respectively), week 12–24 ($725 vs $871, respectively), week 24–48 ($673 vs $871, respectively), and week 0–48 ($731 vs $890, respectively). Cumulative estimated direct medical costs PPPM were $252 lower (95% CI $72, $446) over 12 weeks and $1759 lower (95% CI $1162, $2449) over 48 weeks in patients treated with upadacitinib compared with those treated with tofacitinib (Table 3).

Average medical costs PPPM were lower in upadacitinib-treated patients compared with those in the placebo group (csDMARDs alone) over week 0–4 ($977 vs $1007, respectively), week 4–12 ($795 vs $992, respectively), week 12–24 ($725 vs $982, respectively), week 24–48 ($673 vs $982, respectively), and week 0 to 48 ($731 vs $992, respectively). Cumulative estimated direct medical costs PPPM were $455 lower (95% CI $220, $697) over 12 weeks and $2884 lower (95% CI $2005–$3904) over 48 weeks in upadacitinib-treated patients compared with the placebo group (csDMARDs alone).

Medical Cost Estimates: Upadacitinib Monotherapy Versus Methotrexate Monotherapy

As shown in Fig. 2, average medical costs PPPM were lower in upadacitinib-treated patients compared with methotrexate-treated patients

Table 1 Key variables at baseline

Variable	SELECT-NEXT[a,b]		ORAL-Standard[a,c]	SELECT-MONOTHERAPY[a]	
	Upadacitinib 15 mg QD (n = 221)	Placebo (n = 221)	Tofacitinib 5 mg BID (n = 204)	Upadacitinib 15 mg QD (n = 217)	Methotrexate (n = 216)
Age (years), mean ± SD	55.3 ± 11.5	56.0 ± 12.2	53.0 ± 11.9	54.5 ± 12.2	55.3 ± 11.1
Female, %	82.4	75.1	85.3	80.2	82.9
SF-36 PCS, mean ± SD	33.4 ± 7.4	33.1 ± 7.7	33.1 ± 7.7	33.3 ± 7.9	33.3 ± 7.3
SF-36 MCS, mean ± SD	45.9 ± 10.9	46.5 ± 11.7	39.8 ± 11.6	44.1 ± 11.3	45.1 ± 11.0

BID twice daily, *MCS* Mental Component Summary, *PCS* Physical Component Summary, *QD* once daily, *SF-36* 36-Item Short-Form Health Survey

[a] Patients were on stable background csDMARD therapy

[b] Percentages were calculated on non-missing and non-unknown values

[c] Variables from Rendas-Baum et al. [22]

over week 0–4 ($977 vs $1040, respectively), week 4–14 ($802 vs $950, respectively), week 14–48 ($710 vs $919, respectively), and week 0–48 ($751 vs $936, respectively). Cumulative estimated direct medical costs PPPM were $399 lower (95% CI $158, $620) over 14 weeks and $2044 lower (95% CI $1221, $2846) over 48 weeks in patients treated with upadacitinib monotherapy compared with those treated with methotrexate alone (Table 3).

DISCUSSION

Fatigue and morning stiffness can be very burdensome to patients with RA [33–35] and studies have demonstrated that these symptoms substantially reduce HRQOL and productivity in patients with RA [36–40]. The SF-36 PCS and MCS scores, which are also commonly reported measures of HRQOL in clinical trials, were used as a proxy to estimate medical cost savings in the current study. In an adjusted analysis of administrative claims analysis, patients with RA who did not respond to targeted immunomodulator therapy had significantly higher all-cause and RA-related hospital admissions, outpatient visits, and prescription fills than patients who responded to therapy [41]. This increase in healthcare resource use was associated with significantly higher all-cause and RA-related medical costs (approximately 1.3-fold increase for each) in patients who did not respond to therapy compared with those who did respond, and patients who experience stiffness and/or fatigue use more healthcare resources and have higher medical costs than those who do not have these symptoms [41]. Thus, treatments that alleviate RA symptoms and improve HRQOL may decrease use of healthcare resources and thereby decrease associated medical costs.

Three JAK inhibitors (tofacitinib, baricitinib, and upadacitinib) have been approved by the European Medicines Agency [42–44] and US Food and Drug Administration [45–47] for the treatment of moderate to severe RA. All three JAK inhibitors have been approved for use as monotherapy or in combination with a csDMARD such as methotrexate. Although there are no studies comparing these three JAK inhibitors directly, they have been studied in direct head-to-head studies with adalimumab [48–50]. Results obtained in the head-to-head trials with adalimumab suggest that the individual JAK inhibitors may have unique efficacy profiles. Knowledge of the comparative efficacy of tofacitinib, baricitinib, and upadacitinib may assist physicians in determining which JAK inhibitor to use for the treatment and management of RA in their patients and may also be helpful in determining the economic value of a

Table 2 Observed SF-36 PCS and MCS scores by visit in the SELECT-NEXT and SELECT-MONOTHERAPY clinical trials

	SELECT-NEXT				SELECT-MONOTHERAPY			
	Upadacitinib 15 mg QD[a]		Placebo[b]		Upadacitinib 15 mg QD		Methotrexate[c]	
	n	Visit mean	*n*	Visit mean	*n*	Visit mean	*n*	Visit mean
SF-36 PCS								
Week 0	219	33.4	221	33.1	217	33.3	216	33.3
Week 4	217	39.0	219	36.2	212	39.1	213	35.6
Week 12	213	41.4	213	36.9	–	–	–	–
Week 14	–	–	–	–	203	41.2	202	37.0
Week 24	200	42.8	196	42.5	–	–	–	–
Week 48	179	44.1	186	44.1	168	44.1	184	43.6
SF-36 MCS								
Week 0	219	45.9	221	46.5	217	44.1	216	45.1
Week 4	217	49.0	219	48.2	212	48.1	213	46.8
Week 12	213	50.3	213	48.7	–	–	–	–
Week 14	–	–	–	–	203	49.2	202	47.2
Week 24	200	51.8	196	51.1	–	–	–	–
Week 48	179	51.4	186	51.8	168	50.2	184	49.7

MCS Mental Component Summary, *PCS* Physical Component Summary, *QD* once daily, *SF-36* 36-Item Short-Form Health Survey

[a] In SELECT-NEXT, patients were on stable background csDMARD therapy

[b] In SELECT-NEXT, patients in the placebo group received upadacitinib after week 12; therefore, the medical cost estimation used SF-36 outcomes carried forward from week 12 in the placebo group

[c] In SELECT-MONOTHERAPY, patients in the methotrexate group received upadacitinib after week 14; therefore, the medical cost estimation used SF-36 outcomes carried forward from week 14 in the methotrexate group

particular treatment. Results of a recent network meta-analysis [51] provide insight into the comparative efficacy of these three JAK inhibitors at their approved doses. The meta-analysis compared American College of Rheumatology (ACR)20/50/70 responses and Disease Activity Score 28-joint count C-reactive protein (DAS28-CRP) remission rates (DAS28-CRP < 2.6) at 12 and 24 weeks for the three JAK inhibitors in patients with RA who had an inadequate response to csDMARDs. Although results were not statistically significant between JAK inhibitors, upadacitinib had greater efficacy as measured by ACR responses and clinical remission among the combination therapies (JAK inhibitor + csDMARD) and monotherapies.

The results obtained in our study support those obtained in the network meta-analysis assessing the comparative efficacy of JAK inhibitors and suggest that the economic benefit of these within-class RA treatments can be estimated and compared using patient-reported outcomes reported in clinical trials as a proxy. In our study, medical costs of clinical trial participants receiving treatment for RA were estimated using a previously published algorithm [23] that translates measurements of SF-36 PCS and MCS into an estimate of monthly medical

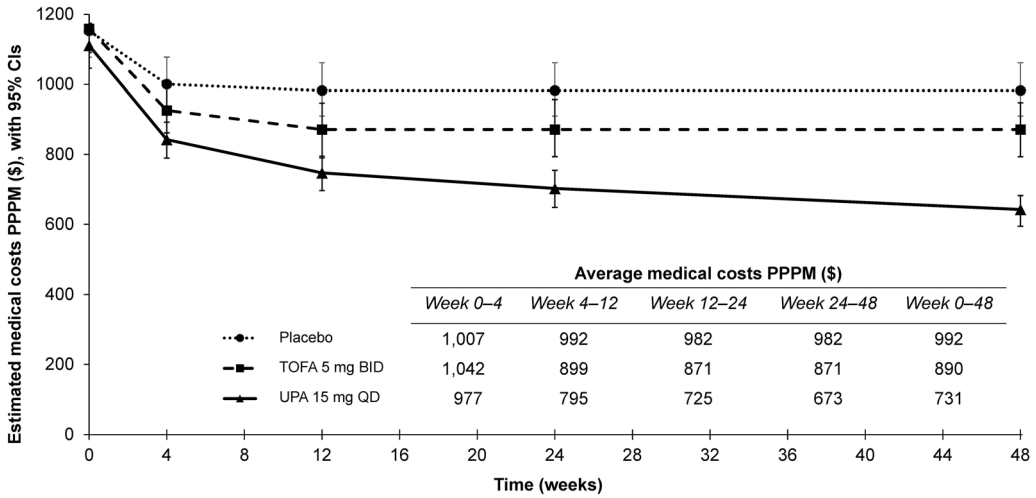

Fig. 1 Estimated long-term direct medical costs PPPM with upadacitinib combination therapy versus placebo or tofacitinib combination therapy. Average monthly medical costs for upadacitinib 15 mg QD and placebo were estimated on the basis of SF-36 PCS and MCS scores from SELECT-NEXT using a published algorithm [23] and are adjusted to 2020 US dollars. Costs and standard errors for tofacitinib 5 mg BID were taken from Rendas-Baum et al. [22]. BID twice daily, MCS Mental Component Summary, PCS Physical Component Summary, PPPM per patient per month, QD once daily, SF-36 36-Item Short-Form Health Survey, TOFA tofacitinib, UPA upadacitinib, US United States

Table 3 Cumulative cost savings over 12/14 and 48 weeks

Treatment	Total 12/14-week medical costs ($)	Difference versus upadacitinib (95% CI) ($)	Total 48-week medical costs ($)	Difference versus upadacitinib (95% CI) ($)
Upadacitinib combination therapy versus placebo or versus tofacitinib combination therapy				
Placebo	2824	455 (220–697)	10,987	2884 (2005–3904)
Tofacitinib 5 mg BID[a]	2621	252 (72–446)	9861	1759 (1162–2449)
Upadacitinib 15 mg QD[a]	2369	–	8102	–
Upadacitinib monotherapy versus methotrexate monotherapy				
Methotrexate	3152	399 (158–620)	10,364	2044 (1221–2846)
Upadacitinib 15 mg QD	2753	–	8320	–

Difference was calculated using additional decimal places for precision and may not match the difference between the rounded 12/14-week or 48-week medical costs displayed above
BID twice daily, *CI* confidence interval, *QD* once daily

expenditure. We compared the estimated cumulative costs over a 48-week period between upadacitinib 15 mg QD and tofacitinib 5 mg BID and found that the estimated long-term costs were significantly lower for upadacitinib than for tofacitinib. We also compared estimated long-term costs for upadacitinib 15 mg QD monotherapy and methotrexate monotherapy

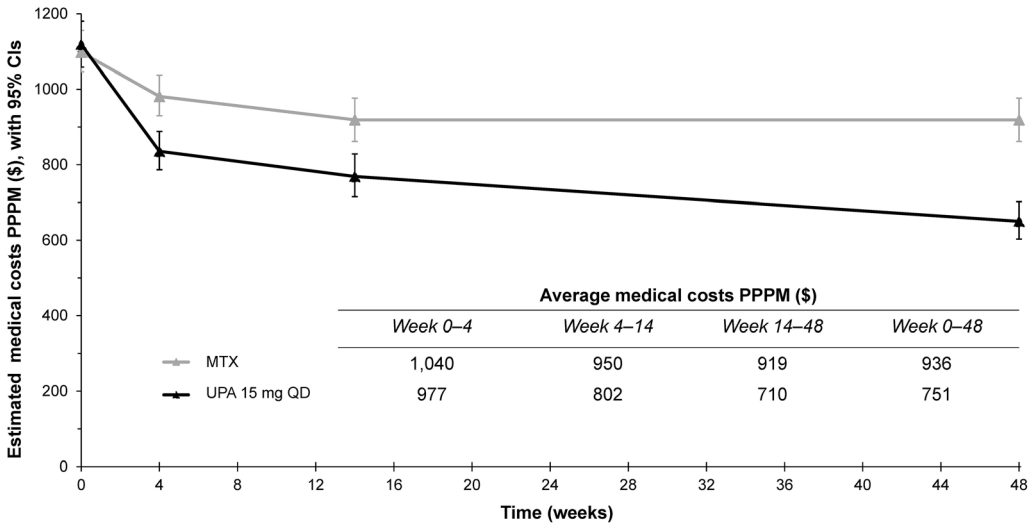

Fig. 2 Estimated long-term direct medical costs PPPM with upadacitinib monotherapy versus methotrexate monotherapy. Average monthly medical costs for upadacitinib 15 mg QD monotherapy and methotrexate monotherapy were estimated on the basis of SF-36 PCS and MCS scores from SELECT-MONOTHERAPY using a published algorithm [23] and are adjusted to 2020 US dollars. MCS Mental Component Summary, MTX methotrexate, PCS Physical Component Summary, PPPM per patient per month, QD once daily, SF-36 36-Item Short-Form Health Survey, UPA upadacitinib, US United States.

and found that the cumulative costs were significantly lower for upadacitinib monotherapy than for methotrexate monotherapy. A recent survey conducted in patients with RA noted that 51% of patients stopped participating in certain activities because of their disease and 72% worried about the impact of RA on HRQOL, suggesting that assessing the effect of treatment on improvement in HRQOL is important in the management of RA [52]. Because SF-36 is often used to assess HRQOL in clinical trials evaluating the therapeutic benefits of RA treatments [53], it is a patient-reported outcome that can be used to help assess the economic implications of within-class RA treatment strategies using results reported in clinical trials.

This study has several important strengths that should be noted. We used phase 3 clinical trial data, which ensures that patients were closely monitored, and that patient-reported outcomes were well measured. This study combined data from multiple sources (including two clinical trials and literature sources) and evaluated the impact of upadacitinib on economic outcomes not directly observed in the trial, but instead based on patient-reported outcome measures from the trials.

Our study has some limitations that need to be kept in mind when interpreting the results. The comparative efficacy data for upadacitinib versus tofacitinib were obtained from two separate clinical trials and are potentially subject to confounding due to cross-trial differences in patient characteristics. However, there were similarities in the inclusion criteria of the trials and the estimates of monthly medical expenditures for upadacitinib and tofacitinib were similar at week 0. Patient-reported outcomes were collected at fixed visits; linear interpolation was used to estimate monthly medical expenditures between consecutive visits in which SF-36 scores were measured. The generalizability of these results may be limited as patients enrolled in the clinical trial may differ from patients in the general population. The published algorithm [23] used in this analysis may not yield accurate predictions of monthly medical expenditures at the individual patient level given that medical spending may be largely driven by a small percentage of high-

spending patients, while the algorithm was developed using all-comers data from the 2000 to 2001 Medical Expenditure Panel Study. Nevertheless, the algorithm was shown to accurately predict mean monthly medical expenditures at the group level. The benefits quantified in this study may be underestimated because of the advancement in clinical management of RA and thus the associated costs since the algorithm was developed. Our analysis does not estimate indirect costs associated with different RA treatments. As a result, this may underestimate the reported benefits as indirect costs resulting from patients' reduced capacity to work are an important component of the overall economic burden of RA [54, 55].

CONCLUSIONS

On the basis of improvements in HRQOL in the short and long term, upadacitinib 15 mg QD was associated with significantly lower direct medical costs than tofacitinib 5 mg BID in patients with moderate to severe RA. In addition, upadacitinib 15 mg QD monotherapy was associated with significantly lower direct medical costs than methotrexate monotherapy in patients with moderate to severe RA. These results provide evidence of the economic benefits of upadacitinib as an important treatment for patients with moderate to severe RA.

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Compliance with Ethics Guidelines. The current study is a secondary analysis of clinical trial data. The original trials were conducted in accordance with the ethical principles that have their origin in the current Declaration of Helsinki and are consistent with International Conference on Harmonization Good Clinical Practice (ICH GCP) and Good Epidemiology Practices (GEP), and applicable regulatory requirements. Data were de-identified and comply with the patient requirements of the Health Insurance Portability and Accountability Act. The confidentiality of records that could identify subjects within the database has been protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirements.

Data Availability. All data generated or analyzed during this study are included in this published article or as supplementary files.

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