Cost-utility of tofacitinib in the treatment of moderate-to-severe rheumatoid arthritis in France: a multi-state Markov model analysis

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Abstract

Objective

This study aimed to evaluate the cost-effectiveness of introducing tofacitinib in second-line therapies after methotrexate failure for rheumatoid arthritis in France.

Methods

Using a Markov model, we simulated a cohort of 10,000 patients based on literature data to compare various treatment strategies. The reference strategy included the four classes of biologics commonly used in France (TNFi, tocilizumab, abatacept, rituximab). The trial strategies additionally included tofacitinib at different introduction positions. The cycle duration was set at 6 months, and the time horizon was a lifetime. The data for severe adverse effects were sourced from the ORAL Surveillance study.

Results

Compared to the reference strategy, introducing tofacitinib is a dominant strategy, regardless of its introduction position. Introducing it as the first-line treatment results in the greatest cost savings (€1,679 per patient) while increasing quality-adjusted life years (QALYs) by 0.29. According to the one-way sensitivity analysis, the discount rate and the cost of TNFi were the two variables that most influenced costs, while the change in HAQ score and the discount rate were the two variables that most influenced QALYs.

Conclusion

Our study represents the first assessment of the cost-effectiveness of tofacitinib in France and incorporates the latest adverse effects reported in the literature. It reinforces previously obtained results from other countries. Our study has some limitations, mainly related to the use of data from clinical trials. Our analysis is limited to severe adverse effects, and their cost is extrapolated from the average hospitalisation cost. The estimated costs are therefore underestimated for chronic diseases such as cancer.

Key words

tofacitinib, rheumatoid arthritis JAK inhibitor, cost effectiveness

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Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterised by inflammation of the joints, leading to pain, swelling, and joint damages. The treatment landscape for RA has evolved significantly over the years, with the advent of biologic therapies offering substantial benefits to patients (1-3). However, these biologic therapies come with a substantial financial burden due to their high cost. For instance, a six-month course of treatment with adalimumab can amount to thousands of euros in France, in stark contrast to methotrexate, which costs merely tens of euros for the same duration (4). Despite the availability of various treatments, a subset of patient remains difficult to treat, necessitating the exploration of new therapeutic options (5).

One such novel treatment is tofacitinib, a Janus kinase inhibitor (JAKi), with a distinct mechanism of action (6). Tofacitinib has demonstrated its effectiveness by outperforming placebo treatment (7) and showing non-inferiority to adalimumab (6). This positions it as a viable alternative to biologic therapies. One of its notable benefits is its oral administration, offering greater convenience for patients. While the cost-effectiveness of tofacitinib has been demonstrated in several countries (8-10), its cost-effectiveness in the French population have not been evaluated yet.

In 2022, the Oral Rheumatoid Arthritis Trial (ORAL) Surveillance study raised concerns about the safety profile of tofacitinib in older patients. This study highlighted an increased risk of major cardiovascular events and cancers, in individuals aged 65 years and above (11). Consequently, these new findings have led to several changes; the marketing authorisation of tofacitinib has been modified to be recommended only for individuals over 65 years old when there is no alternative therapeutic option. The French Society of Rheumatology recommends evaluating the cardiovascular risk and thromboembolic disease before starting JAK inhibitors (12). This increased risk of major cardiovascular events and cancers have not been taken into account in previous cost-utility analyses.

Through a multi-state Markov model incorporating the most recent results of large tofacitinib randomised controlled trials, we aimed to evaluate the cost-effectiveness of introducing tofacitinib in second-line therapies after methotrexate (MTX) failure for RA in France. This study will provide valuable insights into the economic implications of tofacitinib use in the French RA population.

Methods

Model overview

A multi-state Markov cohort model was constructed from the perspective of the French healthcare system using R software (v. 4.2.3) with heemod (v. 0.15.1) and ICEinfer (v 1.3) packages (13-16). The decision to employ a Markov model in this study was primarily driven by the availability of data, especially the absence of patient-level variability data, which rendered microsimulation unfeasible. Markov models enhance transparency in the analysis, offering a clear, comprehensible framework that simplifies the representation of disease progression over time. The cohort size was fixed to 10,000 virtual patients. The model cycle length was 6 months, with a lifetime horizon (until 99% patients die). A half cycle correction was built into the analysis, to account for the fact that events and transitions can occur at any point during the cycle (17). Each Markov state was represented by one treatment line. We assumed all treatment were administered with MTX. Patients involved in the model had had an inadequate response to MTX and entered the model with biologic disease-modifying anti-rheumatic drugs (bDMARD) or JAKi for first-line treatment. Cohort characteristics (Supplementary Table S1) were based on a phase 3b/4, double-blind, randomised controlled trial involving 1152 patients with RA to compare efficacy of tofacitinib with tumour necrosis factor inhibitors (TNFi) (6).

We used the same discount rate for costs and QALYs. According to the French National Authority for Health (HAS), the annual discount rate should be 2.5% for time horizons less than 30 years, and then it decreases to 1.5% (18).

Table I. Treatment sequence.

Sequence	First-line treatment	Second-line treatment	Third-line treatment	Fourth-line treatment	Fifth-line treatment
Reference	TNFi	Tocilizumab	Abatacept	Rituximab	-
Intervention 1	Tofacitinib	TNFi	Tocilizumab	Abatacept	Rituximab
Intervention 2	TNFi	Tofacitinib	Tocilizumab	Abatacept	Rituximab
Intervention 3	TNFi	Tocilizumab	Tofacitinib	Abatacept	Rituximab
Intervention 4	TNFi	Tocilizumab	Abatacept	Tofacitinib	Rituximab
Intervention 5	TNFi	Tocilizumab	Abatacept	Rituximab	Tofacitinib

TNFi: tumour necrosis factor inhibitor.

Treatment sequences

The current clinical practice in France is based on the European Alliance of Associations for Rheumatology (EULAR) and Société Française de Rhumatologie (SFR) recommendations (1, 2), the order of prescribing bDMARDs is not fixed. We established a reference treatment sequence without Tofacitinib, by selecting an agent with a different mode of action from the previous one after each failure, reflecting current practice (1, 2, 19, 20). This sequence includes, in order: TNFi, Tocilizumab, Abatacept and Rituximab. The trial sequences include adding tofacitinib at different positions (Table I).

After all active treatments failed, a palliative therapy state was maintained until death. This state was simulated as patients being treated with another TNFi not prescribed previously, considering that in France there are enough bDMARDs available for patients to try new therapies until their death.

Based on the reference treatment sequence, we developed the model presented in Figure 1.

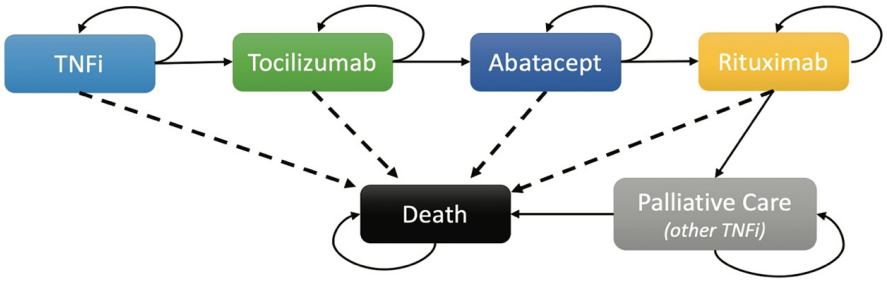

Fig. 1. Markov model for reference treatment sequence. TNFi: tumour necrosis factor inhibitor

Treatment effect and treatment switch

The discontinuation probability was estimated as the probability of patients who switched from one treatment to another. For the first cycle of each state, the discontinuation probability was measured as American College of Rheumatology criteria (ACR) response rate (21). Patients remained in treatment if they reached at least ACR20 response. Otherwise, they switched into the next treatment. For subsequent cycles, the probability of switching was based on the probability of still being under treatment at 5 years and having a ACR20 response (Table II). All efficacy and utility data used in this article are derived from previously published clinical trials (6, 11, 22–27), summarised in Supplementary Table S2. For treatments used after the failure of TNFi, the studies evaluated the efficacy of the respective treatment following TNFi failure. To account for the adverse effects, efficacy, and utility identified by Yttergerg *et al*. in patients over 50 years old treated with tofacitinib or TNFi, we used data from Yttergerg *et al*. when the patients were over 61 years old (average age of the study) (11).

Mortality

The probability of death in each cycle is the mortality rate by sex and age group in France (28), in 2020, weighted by the excess mortality associated with the progression of RA. This weighting was done using data from Michaud *et al*., who evaluated the relationship between the Health Assessment Questionnaire (HAQ) scale and all-cause mortality in patients with RA (29) (Suppl. Table S3).

Quality Adjusted Life Years

The effectiveness of the model was expressed as quality-adjusted life-years (QALYs) and was calculated by mapping the HAQ scores onto the EuroQoL-5D (EQ-5D) utility values. This mapping was performed using the formula from Lee *et al*. (30):

$$EQ\text{-}5D = 0.7793 - (0.2529 \times HAQ) - (0.0380 \times HAQ^2) + (0.031 \times female) + (0.001 \times RA\ duration)$$

The HAQ scores associated with each health state was derived from previous clinical trials (11, 23, 24, 27). The evolution of the HAQ score at 6 months in the palliative care state is based on a Phase III trial evaluating the effectiveness of a second anti-TNF after the failure of the first anti-TNF therapy (26). The longitudinal evolution of the HAQ score over time is based on a study of 18,485 patients from the prospective American National Data Base cohort, with a follow-up of up to 11 years (31). This study demonstrated an annual increase of 0.8% in the HAQ score when patients were treated with biologic therapies. This increase was similar among the different biologic therapies.

Cost

The economic perspective of our study was focused on the healthcare system, indirect costs were not taken into account (like work time and household production lost). The costs we considered included treatment costs, costs associated with adverse effects, and follow-up costs.

The treatment costs were derived from the public database of medications and the Official Journal of the French Republic for treatments listed under Article L.162-22-7 of the Social Security Code. The price considered was the biosimilar drug. In the absence of biosimilar drugs

Table II. Input parameters. HAQ: Health Assessment Questionnaire.

Parameters	Value	95% CI	Distribution (parameters**)	Source
Transition probability at 6 months				
Tofacitinib	0.269	0.225, 0.315	Beta (101, 275)	(6)
Tofacitinib (elderly)	0.287	0.264, 0.311	Beta (403, 999)	(11)
TNFi	0.290	0.246, 0.336	Beta (112, 274)	(6)
TNFi (elderly)	0.290	0.267, 0.314	Beta (401, 981)	(11)
Tocilizumab	0.500	0.425, 0.575	Beta (85, 85)	[22]
Abatacept	0.496	0.435, 0.557	Beta (127, 129)	(23)
Rituximab	0.490	0.433, 0.547	Beta (146, 152)	(24)
Transition probability for subsequent cycles				
Tofacitinib	0.114	0.106, 0.122	Beta (787, 336)	(6)
Tofacitinib (elderly)	0.168	0.155, 0.174	Beta (1212, 243)	(11)
TNFi	0.072	0.065, 0.079	Beta (112, 274)	(25)
TNFi (elderly)	0.164	0.158, 0.178	Beta (1219, 232)	(11)
Tocilizumab	0.106	0.099, 0.113	Beta (804, 392)	(22)
Abatacept	0.090	0.075, 0.107	Beta (127, 81)	(23)
Rituximab	0.110	0.099, 0.123	Beta (343, 122)	(24)
HAQ changes at 6 months, mean (SD)				
Tofacitinib	- 0.52 (0.031)	-0.524, -0.516	Truncated normal (0.031, 0.002)	(6)
Tofacitinib (elderly)	-0.50 (0.02)	-0.502, -0.498	Truncated normal (0.02, 0.001)	(11)
TNFi	- 0.54 (0.031)	-0.544, -0.536	Truncated normal (0.031, 0.002)	(6)
TNFi (elderly)	-0.46 (0.02)	-0.462, -0.458	Truncated normal (0.02, 0.001)	(11)
Tocilizumab	-0.39 (0.02)	-0.394, -0.386	Truncated normal (0.02, 0.002)	[22]
Abatacept	- 0.45 (0.03)	-0.454, -0.446	Truncated normal (0.03, 0.002)	(23)
Rituximab	-0.4 (0.6)	-0.469, -0.331	Truncated normal (0.6, 0.035)	(24)
Palliative care	- 0.2 (0.45)	-0.251, -0.149	Truncated normal (0.45, 0.026)	(26)
Rate of HAQ progression for later cycles, mean (SD)				
Tofacitinib	0.004 (0.00075)	0.004, 0.004	Normal (0.00075, 0.00001)	(31)
TNFi				
Tocilizumab				
Abatacept				
Rituximab				
Palliative care				
Drug acquisition costs* for 6 months				
Tofacitinib	4457.00	2674.2, 4457.00	Fixed	(4)
TNFi	4937.11	3702.83, 4937.11	Fixed	(4)
Tocilizumab	5370.82	3222.49, 5370.82	Fixed	(4)
Abatacept	5370.82	3222.49, 5370.82	Fixed	(4)
Rituximab	2823.91	2823.91, 2117.93	Fixed	(42)
Palliative care	4937.11	3702.83, 4937.11	Fixed	(4)
Day hospitalisation	372.09		Fixed	(43)
Laboratory testing* for 1 year, mean (SD)				
First year	269 (122)	85.59, 557.29	Gamma (4.86, 55.33)	(34)
Later year	303 (126)	108.63, 597.02	Gamma (5.78, 52.40)	(34)
Imaging* for 1 year, mean (SD)				
First year	51 (39)	4.74, 151.57	Gamma (4.74, 151.57)	(34)
Later year	63 (65)	1.30, 240.03	Gamma (0.94, 67.06)	(34)
Physicians consultation* for 1 year, mean (SD)				
First year	224 (118)	55.60, 509.36	Gamma (3.60, 62.06)	(34)
Later year	269 (125)	82.52, 565.42	Gamma (4.63, 58.09)	(34)
SAEs costs* per event, mean (SD)				
Tofacitinib	3441.76 (4059.33)	25.00, 14766.03	Gamma (0.72, 4787.71)	(43)
Tofacitinib (elderly)	3437.61 (3259.04)	119.86, 12183.43	Gamma (1.11, 3089.75)	(43)
TNFi	3586.90 (2993.34)	235.20, 11430.95	Gamma (1.44, 2498.00)	(43)
TNFi (elderly)	3389.53 (4200.49)	15.35, 15201.40	Gamma (0.65, 5205.48)	(43)
Tocilizumab	3476.24 (3427.62)	96.24, 12741.15	Gamma (1.03, 3379.68)	(43)
Abatacept	3266.44 (5297.22)	0.38, 18727.13	Gamma (0.38, 18727.13)	(43)
Rituximab	3216.77 (2645.87)	224.32, 10131.01	Gamma (1.48, 2176.29)	(43)
Palliative care	3389.53 (4200.49)	15.35, 15201.40	Gamma (0.65, 5205.48)	(43)

SAEs: serious adverse events, TNFi: TNF inhibitor.
*costs in €; **parameters for gamma and beta distributions are (α, β), parameters for normal distribution are (mean, standard error).

(for tofacitinib, tocilizumab and abatacept), we considered the price of the reference medication. Multiple TNFi medications are used in routine practice, so the price used was calculated as the weighted average of the different molecules used by patients with RA in the French cohort ESPOIR ("*Etude et Suivi des Polyarthrites Indifférenciées Récentes*") cohort (32). The costs for 6 months of treatment are reported in Table II. Except for rituximab, the studied medications are administered via subcutaneous injection, often using a pre-filled pen. Patients self-administer the injection at home, and we did not consider any additional costs for the injection. However, rituximab must be administered intravenously. This injection is performed during a day hospitalisation. The cost of this hospitalisation was added to the treatment cost.

The adverse events we considered were serious adverse events (SAEs), defined as events leading to death, posing a life-threatening situation, requiring hospitalisation, or prolonging an existing hospital stay. They are systematically reported and published comprehensively on ClinicalTrials.gov. For each reported SAE, we associated the average cost of hospitalisation for that event, which is freely available from the national cost study conducted by ATIH (33). Then, we calculated the weighted average cost of SAEs for each treatment (Table II).

The follow-up costs include the costs of laboratory tests, imaging, and medical consultations. These costs were estimated by Chevreul *et al*. using data from the ESPOIR cohort (34). These costs are expressed in euros for the year 2007.

Analyses

To compare the sequences, we calculated the incremental cost-effectiveness ratio (ICER) in euros per QALY gained. The confidence interval of the ICER was then estimated using the bootstrap method based on the data generated from the probabilistic sensitivity analysis. This method involves generating 1,000 samples of the same size as the initial sample. The 95% confidence interval is determined empirically and represents the narrowest interval containing 95% of the generated data.

In France, there is no fixed threshold set by the French National Authority for Health (HAS) for cost-effective-

ness. Values used in the literature to determine cost-effectiveness are typically €30,000 to €50,000 per QALY gained. Therefore, strategies are considered cost-effective when their ICER falls below this threshold.

Sensitivity analyses

To test the robustness of our results, we conducted two types of sensitivity analyses: deterministic analysis and probabilistic analysis.

The deterministic sensitivity analysis aims to assess the influence of a parameter on the results. We performed a "one-way" analysis where each parameter was individually varied to evaluate its impact. The values used were the bounds of the confidence intervals.

To account for drug acquisition costs changes, we relied on the framework agreement between the Economic Committee for Health Products and pharmaceutical companies (35), which states that the price of a biosimilar drug is set to be less than 40% of the reference drug, and the price of biosimilars can decrease by as much as 15%. In the deterministic sensitivity analysis, reference drugs were tested at price reductions ranging from -40% to 0%, while biosimilars were tested in the range of -15% to 0%. For the discount rate, a zero discount rate and a 4.5% annual discount rate were used, as recommended by the HAS (18).

The probabilistic sensitivity analysis aims to explore the overall statistical uncertainty of the model. The parameters are varied according to their probability distribution, and Monte Carlo simulation is repeated 1,000 times. Gamma distribution was applied to cost distributions. The alpha and beta parameters were determined using the method of moments. Beta distribution was applied to transition probabilities. The alpha and beta parameters were estimated from the number of events and the sample size.

Ethics

The model used in this analysis was based on previously conducted studies; no studies with human participants were performed by any of the authors. Ethics committee approval was not required.

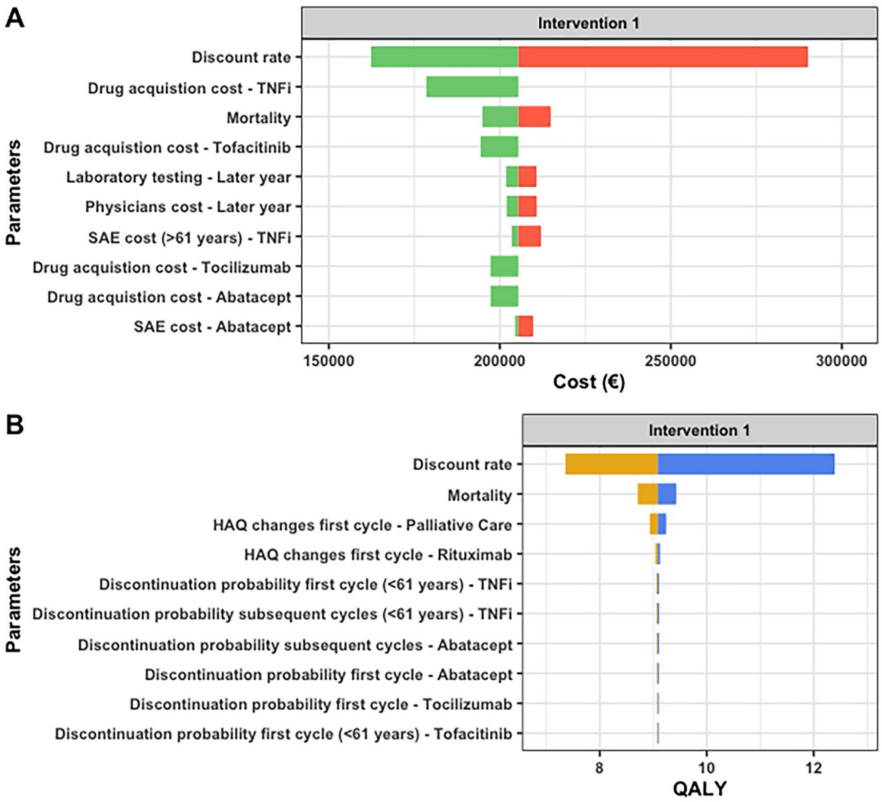

Fig. 2. "Tornado" plot of the one-way sensitivity analysis of the intervention 1.
A: Ten parameters having the most influence on cost. The green bars represent a decrease in costs, while the red bars represent an increase in costs. SAE: serious adverse event.
B: Ten parameters having the most influence on Quality-Adjusted Life Years (QALY). The blue bars represent an increase in QALYs, while the yellow bars represent a decrease in QALYs.

Results

Estimated cost-efficacy of treatment strategies

Based on our simulation, the estimated cost per patient in the reference strategy was €207,053.45 for 8.80 QALYs. All of the intervention strategies proved to be dominant. The strategy placing tofacitinib in the first position is the strategy with the best cost-effectiveness ratio. It leads to savings of €1,678.51 while gaining 0.29 QALYs (Table III). With the exception of intervention 2, the confidence intervals of the ICERs are all below the threshold of €30,000 per QALY (Suppl. Fig. S1).

The addition of tofacitinib increases the average time before reaching the palliative state (15.4 to 15.5 vs. 12.6 years in the reference strategy). The time in palliative care is also reduced: 11.7 years in the intervention strategies compared to 14.3 years in the reference strategy (Suppl. Fig. S2, Suppl. Table S4). These changes are consistent with the addition of an additional treatment line.

Deterministic analyses

Figure 2, Supplementary Figures S3 and S4 illustrate the changes in costs and QALYs resulting from variations in parameters within the intervention strategies. Among these parameters, the discount rate stands out as the most influential factor affecting costs. For the first intervention strategy, the cost per patient is estimated at €290,070 with a zero-discount rate and €162,315 with a 4.5% annual discount rate. Additionally, the costs associated with the acquisition of TNFi treatments also exhibit a significant impact, ranging from €178,460 to €205,375.

In terms of QALYs, the discount rate accounts for the most substantial variation, with an estimated 12.39 QALYs per patient for a zero-discount rate and 7.36 QALYs per patient for a 4.5% annual discount rate in the first strategy. The mortality rate is the second most influential variable affecting QALYs, resulting in a variation from 8.71 to 9.43 QALYs per patient. Detailed vari-

Table III. Results of reference and interventions strategies.

Sequence	Cost (€)	QALYs	Incremental Cost (€)	Incremental QALYs	ICER
Reference	207053.45	8.80	–	–	–
Intervention 1	205374.94	9.09	-1678.51	0.29	Dominant
Intervention 2	205698.16	9.10	-1355.29	0.30	Dominant
Intervention 3	206251.58	9.09	-801.87	0.29	Dominant
Intervention 4	206897.52	9.08	-155.93	0.28	Dominant
Intervention 5	206562.62	9.07	-490.83	0.27	Dominant

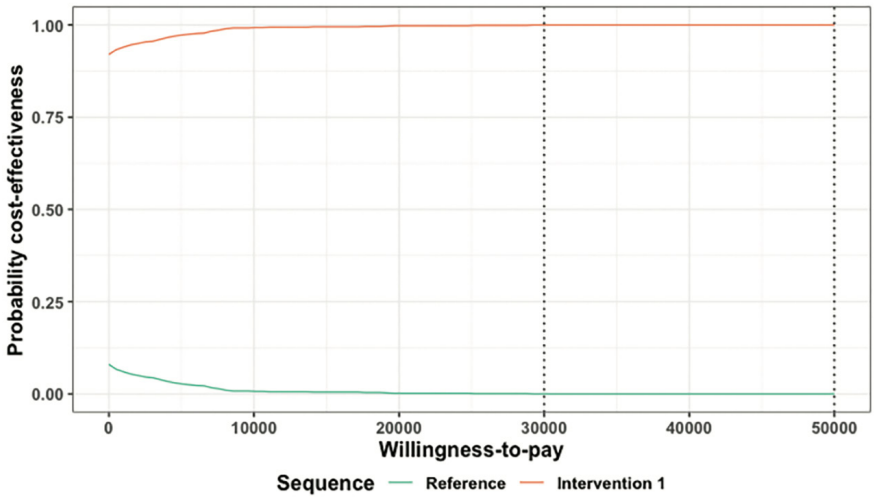

Fig. 3. Acceptability curves from the probabilistic sensitivity analysis of the reference strategy and the first intervention.

ations for each parameter can be found in Supplementary Table S5

Probabilistic analysis

Based on the probabilistic sensitivity analysis, when comparing the intervention strategies to the reference strategy, there is a 100% probability that the interventions are cost-effective at the €30,000 and €50,000 per QALY thresholds (Fig. 3 and Suppl. Fig. S5).

Discussion

Our study evaluated the cost-effectiveness of introducing tofacitinib as a second-line therapy after MTX failure for RA in France. We demonstrated that introducing tofacitinib is cost-effective at a threshold of €30,000 per QALY, regardless of the treatment position. These results were confirmed by considering the 95% confidence interval of the ICER in 4 out of 5 positions tested. The first two strategies are the ones in which patients spend the most time in the tofacitinib state (Suppl. Table S4), which could explain why they are the two most efficient strategies.

We observed that the difference in cost and efficacy between tofacitinib and other treatments was minimal, as they showed similar effectiveness and costs. Nevertheless, adding tofacitinib as an additional treatment is interesting for patients who are difficult to treat with existing therapies.

The cost-effectiveness of tofacitinib has already been demonstrated in other countries, using a cohort Markov cohort (9, 10) as in this study or by conducting microsimulations (8, 36). However, as healthcare practices and costs differ from one country to another, it was necessary to replicate this evaluation using French data.

Our study is the first to consider the adverse effects highlighted in a study conducted by Ytterberg *et al* (11), which represents the worst-case scenario since these increase in adverse effect were not found in the French national health data system ("Systeme National de Donnees de Sante") (37). These findings did not affect the cost-effectiveness of tofacitinib. The incidence of MACE and cancer, as highlighted by Ytterberg, is less than 5%, which is considered economically limited, especially when considering the numerous different serious adverse events reported for each treatment. Additionally, the cost of managing RA remains closely tied to the expenses associated with treatment, even with the inclusion of biosimilar costs in this study.

It is essential to acknowledge some limitations in our study, primarily related to the use of clinical trials that may have been conducted in different countries and not exclusively in France. However, this approach allowed us to gather data on drug's efficacy after the failure of anti-TNF therapies, a critical aspect in real-world clinical practice. Data from clinical trials involve selected patients and which might not be fully representative of real-world patient.

Our study only included direct costs, and incorporating indirect costs would have been relevant given the active nature of the population. Unfortunately, these data were not available.

One limitation of our study is that it did not account for non-serious adverse effects and estimated the cost of serious adverse events based on hospitalisation expenses. This may have led to the underestimation of the overall cost of treatment, especially for patients with chronic conditions who may experience multiple hospitalisations, treatments and follow up over time.

Another limitation is the comparability of patients over time. The studies utilised were published between 2006 and 2022, during which the definition of RA has undergone significant changes. Specifically, the criteria for RA were revised from the 1987 standards to the updated 2010 criteria. The 2010 criteria are noted for their increased sensitivity but decreased specificity (38). As a result, patients included in the most recent studies, particularly those in the ORAL trial, might not have been diagnosed with RA according to the 1987 criteria. This evolution in diagnostic standards complicates direct comparisons of patient populations across different time periods.

The studies we relied on did not include EQ-5D data. Consequently, we conducted a mapping exercise between

HAQ and EQ-5D, utilising a model previously developed from international clinical trials. The algorithm used in this model is a critical factor; alterations to it could significantly impact our findings (39). Therefore, there is a clear need for additional studies aimed at developing a mapping model tailored specifically to the French context. Additionally, in clinical practice, the Disease Activity Score (DAS28) (40) is commonly used to evaluate the impact of RA. However, this measure was also absent from the studies we examined, which led us to adopt ACR20 as an alternative. This may have affected the switching rate of bDMARD and on the cost-effectiveness evaluation of tofacitinib in our simulation compared to what might be observed in the real world.

In conclusion, our study provides valuable insights into the cost-effectiveness of tofacitinib as a second-line therapy for RA patients in France. The marginal difference in cost and efficacy compared to other treatments, combined with its established effectiveness abroad and consideration of adverse effects, supports the integration of tofacitinib as an additional treatment option for difficult-to-treat patients. However, we acknowledge the limitations related to the use of diverse clinical trial data and the exclusion of certain adverse effects from the analysis. Future research should address these limitations to provide a more comprehensive evaluation of tofacitinib's cost-effectiveness and its potential impact on RA management.

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