Cost Effectiveness and Resource Allocation

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Cost-effectiveness analysis of Tocilizumab compared to Adalimumab in the treatment of severe active rheumatoid arthritis in Iran

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Abstract

Background and objective This study aimed to determine the cost-effectiveness of Tocilizumab (TCZ) compared with Adalimumab (ADA) in patients with Rheumatoid Arthritis (RA), who had not responded to methotrexate (MTX), from a societal perspective in Iran.

Method To conduct the cost-utility analysis, using an individual microsimulation Markov model, a hypothetical cohort of 1,000 patients was evaluated over a lifetime horizon. The efficacy and safety of each treatment were estimated using the American College of Rheumatology (ACR) criteria to determine the continuation or switching of treatment every six months. Treatment responses were captured based on Health Assessment Questionnaire (HAQ) scores and mapped into utility values to determine QALY gained for each treatment. All direct and indirect costs associated with the disease and perspective were included according to societal perspective. Deterministic and Probabilistic sensitivity analyses were performed to assess the robustness of the model.

Results The result of the study estimated that TCZ is a more cost-effective treatment option, with a probability of 76%. TCZ was associated with a higher cost ($6,990 versus $6,608) and higher QALYs gained (4.24 versus 3.95) compared to ADA with an incremental cost-effectiveness ratio (ICER) of USD 1,301, which is below the willingness-to-pay threshold of 1,448 USD in Iran.

Conclusion This study provides convincing evidence of the cost-effectiveness of TCZ compared to ADA in the treatment of active severe RA in Iran.

Keywords Cost-utility analysis, Economic evaluation, Quality-adjusted life years, Health economics, Biological treatments, Health economics and outcome research

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Background

Rheumatoid Arthritis (RA) is a prevalent immune system and provocative disease that causes pain, swelling, stiffness, dynamic joint damage, and other systemic effects [1]. In 2020, around 17.6 million people with RA were diagnosed worldwide, representing the age-standardized global prevalence rate of 208·8 cases per 100,000 population, and a 14·1% increase since 1990. The prevalence of RA in Iran was reported to be 89 in 100,000 in 2020, with women being more likely to be affected than men [2]. On the other hand, the financial burden of RA in Iran was estimated at $ 3.7 billion PPP in 2019 [3].

The purpose of treating RA is to reduce the severity of joint damage, deformity, and changes in joint shape that can lead to disability and even premature death [4]. Treatment of RA includes medication, physical or occupational therapy, patient education, weight management, and if necessary surgical procedures [5]. Under the American College of Rheumatology (ACR) guidelines, the first approach to RA treatment usually involves the use of conventional disease-modifying antirheumatic drugs (cDMARDs). Of these medications, methotrexate (MTX) is usually the most commonly recommended. If MTX is not tolerated, other cDMARDs may also be considered. In patients with more severe RA (lasting six months or longer), a biologic DMARD (bDMARDs) is often added to the usual treatment [6].

Recent research indicates that discontinuation of certain agents is common due to various reasons such as intolerance or inadequate efficacy [7]. While tumor necrosis factor-alpha (TNF-α) inhibitors are often the first choice for eligible patients, other bDMARDs have shown comparable effectiveness when used alongside MTX after cDMARDs fail in RA treatment [8]. Tocilizumab (TCZ), a humanized monoclonal antibody targeting the interleukin-6 receptor, has demonstrated efficacy in treating moderate-to-severe active RA in adults who do not respond adequately to TNF-α inhibitor therapy [9, 10].

The ADACTA trial compared the efficacy of adalimumab (ADA) and TCZ in RA patients who could not continue MTX treatment. Results from this 24-week, multicenter, double-blind trial showed that TCZ monotherapy was more effective in alleviating RA symptoms compared to ADA monotherapy [11].

Apart from efficacy, safety, and patient adherence, considering the cost of treatment is crucial. RA is a chronic condition that can impose significant economic burdens on patients, both directly and indirectly, due to lifelong treatment requirements. Previous studies have shown that drug expenses make up a considerable portion of direct RA-related costs [3]. Thus, choosing the most cost-effective therapeutic approach in this era is essential. Hence, this study aims to assess the cost-effectiveness of TCZ monotherapy compared to ADA monotherapy in severe active RA patients who are eligible for bDMARDs and are unable to continue MTX.

Method

Model structure

In this study, we utilized a microsimulation Markov model to assess the cost-utility of TCZ compared to ADA in managing RA using TreeAge 2022 software as shown in Fig. 1. Our analysis focused on a hypothetical cohort of 1,000 patients with severe active RA and inadequate responses to MTX.

To conduct the cost-utility analysis, we considered treatment outcomes and costs associated with TCZ (8 mg/kg intravenously every 4 weeks) monotherapy versus ADA (40 mg subcutaneously every other week) monotherapy from a societal perspective. Given the chronic nature of RA, we employed a lifetime horizon to encompass all relevant costs and outcomes [12].

Based on ACR criteria, patients were evaluated every six months to determine treatment continuation or transition. The ACR criteria, including ACR20, ACR50, and ACR70, serve as standardized measures for assessing treatment efficacy in RA studies [1, 13, 14]. Our model incorporated variations in disease severity using the Health Assessment Questionnaire (HAQ) scores, a commonly used patient-reported instrument in musculoskeletal disorders [15].

Each level of response in terms of ACR20, ACR50, and ACR70, corresponds to a change in the HAQ disability score. On the other hand, a decrease in HAQ score indicates improvement in RA symptoms [14]. Patients who are categorized as initial responders, continue treatment, while non-responders transit to the next treatment option. In the case of treatment failure, patients receive palliative care, with disease severity assumed to increase consistently over time [16, 17].

The health outcomes were assessed in terms of QALY gained. The costs are collected in Iranian Rial currency but all costs were presented in US dollars (USD) with an exchange rate of USD 1 = 290,000 Iranian Rials (Table 1). According to the literature, both costs and QALYs were discounted at a rate of 5.8% [18]. The final result was presented as an incremental cost-effectiveness ratio (ICER), which was then compared against the Iranian willingness-to-pay (WTP) threshold range of 1 Gross Domestic Product (GDP) per capita, which was 1,448 USD [19].

Model inputs

Clinical efficacy & safety

ADACTA is a head-to-head clinical trial that has provided valuable insights into the efficacy and safety of TCZ and ADA showcasing significant reductions in patient pain and disease progression [11]. Hence, data on the

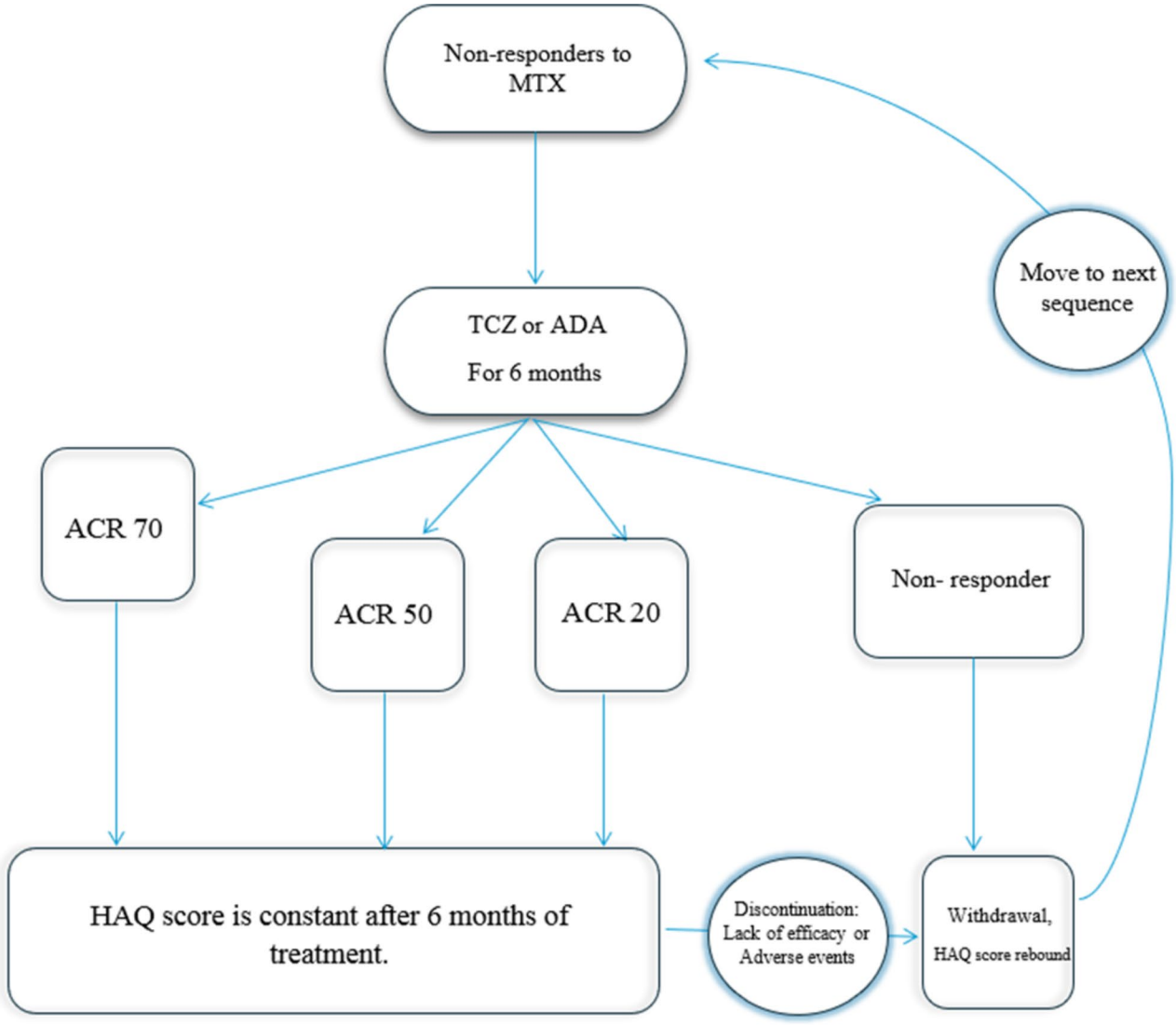

Fig. 1 Overview of the RA lifetime model. Abbreviations: ACR, American College of Rheumatology; ADA, Adalimumab, HAQ, Health Assessment Questionnaire; MTX, methotrexate; TCZ, Tocilizumab

proportion of patients achieving ACR 20/50/70 for each treatment sequence were obtained from the ADACTA trial, as presented in Table 2. ACR response rates, categorized as cumulative categories in clinical trials, signify patients' improvement from baseline. Those achieving at least a 20% improvement were classified as ACR20, 50% as ACR50, and 70% as ACR70. The calculation of the proportion of patients in each response category excluded rates from higher ACR groups. Non-responders, who failed to achieve ACR20, were identified within six months or upon withdrawal progressed to subsequent treatments in the predefined sequence [26, 27].

A previous study showed that the number of patients who experienced serious adverse events did not differ significantly between TCZ and ADA treatments [29]. Therefore, potential adverse effects were not considered in our model like in a similar study [14].

Mortality

The mortality rate in RA correlates with disease severity, suggesting that treatments improving disease severity may positively impact mortality rates. We determined mortality rates by incorporating the association between initial mortality rates and HAQ scores reported by Wolfe et al. [30]. Additionally, mortality rates were adjusted for RA-associated disability using Iranian lifetable estimates. Finally, we applied an equation similar to the previous RA model to estimate RA-specific mortality rates [30, 31].

Equation 1: RA-specific mortality rate

Table 1 Key model parameters

Item	Value	Distribution
• Patient characteristics [14, 20, 21]		
Age (y), mean (SD)	60 (13.4)	Normal
Body weight (kg), mean (SD)	77 (3.8)	Normal
Starting HAQ score, mean (SD)	1.65 (0.168)	Normal
Disease duration, mean (SD)	6.1 (0.8)	Normal
Sex: female, %	80	Normal
• HAQ score change by ACR response levels (6 months), mean (SD) [14, 20]		
Non-responder	−0.11 (0.056)	Normal
< ACR20	−0.44 (0.056)	Normal
ACR20-50	−0.76 (0.092)	Normal
ACR > 70	−1.07 (0.179)	Normal
Palliative care	0.03 (0.005)	Normal
• Hospital days per year by HAQ score, mean [14]		
0.0–0.5	0.26	-
0.6–1.0	0.13	-
1.1–1.5	0.51	-
1.6–2.0	0.72	-
2.1–2.5	1.86	-
2.6–3.1	4.16	-
• Probability of Nonresponse [1, 22]		
ADA	0.5	Beta
ETC	0.29	Beta
RTX	0.49	Beta
TCZ	0.34	Beta
• Proportion of lack of efficacy [23–25]		
ADA	15%	-
ETC	30%	-
RTX	40%	-
TCZ	18%	-
• Other inputs		
Cost discount rate	5.8%	-
Utility discount rate	5.8%	-

Table 2 ACR Response Rates in 6 months

Absolute ACR Response Rates at 6 Months (Percent)					Reference
ACR score	ACR < 20	20 < ACR < 50	50 < ACR < 70	ACR > 70	
Tocilizumab	34	18	15	33	[11]
Adalimumab	50	22	10	18	[11]
Etanercept	29	32	24	15	[28]
Rituximab	49	24	15	12	[26]

$$RA\ specific\ mortality\ rate = general\ mortality \times\ 1.33^{HAQ}$$

Health-related quality of life

The HAQ, utilized to evaluate patients' functional and physical conditions, with a lower score indicating improved functional and physical status, plays a crucial role in predicting mortality probability, quality of life, hospitalization, treatment discontinuation, and costs. Discontinuing treatment results in the HAQ score reverting to baseline until the next treatment cycle. Patients entering the model had an average baseline HAQ score of 1.6. The change in HAQ score by ACR response level is detailed in Table 1. We utilized regression equations to convert HAQ into Utility, mapping data onto EQ-5D [32–34] (Eq. 2).

Equation 2: EQ-5D utility scores based on HAQ scores.

$$EQ-5D = \begin{cases} 1\ if\ \ y > 0.883 \\ y\quad otherwise \end{cases}$$

$$\begin{aligned}&\boldsymbol{where}\ \boldsymbol{y} = 0.967 - 0.115 \times \boldsymbol{HAQ}\\&-0.036 \times \boldsymbol{HAQ}^2 - 0.484 \times \frac{\boldsymbol{VASpain}}{100}\\&+0.019 \times \frac{\boldsymbol{Age}-54.32}{10} + 0.006 \times \left(\frac{\boldsymbol{Age}-54.32}{10}\right)^2\\&-0.047 \times \boldsymbol{male} + 0.030 + 0.011\end{aligned}$$

Resource utilization and costs

Considering the societal perspective, all direct and indirect costs associated with the disease, including medication, diagnosis, hospitalization, follow-up care, rehabilitation, transportation, and productivity loss, were captured. Unit costs were sourced from national databases and country-specific tariffs and then converted to represent costs per 6-month cycle, as outlined in Table 3. Patient costs were calculated by averaging weighted expenses from both private hospitals (20%) and public ones (80%). Similarly, outpatient costs were determined by averaging weighted expenses from the private sector (35%) and public (65%) based on Iranian National Health Accounts. In addition to direct medical costs, the model accounts for transportation costs and productivity loss from a societal perspective. Productivity loss costs were estimated based on the minimum daily wage in Iran, which was 7.5 USD. The main reason for productivity loss in RA is patients' hospitalization, which could happen in any disease state. When a patient is hospitalized, the cost of productivity loss is applied to the model as the minimum daily wage of an employee in 2022 in Iran multiplied by the number of hospitalized days. The number of hospitalized days is mentioned in Table 1.

Transportation costs were calculated considering travel within the city, assuming that patients did not require travel to other cities due to the widespread availability of medical facilities and healthcare providers throughout the country.

Sensitivity analysis

To address uncertainties in the study, both deterministic and probabilistic sensitivity analyses were conducted to examine the robustness of the model results. A tornado diagram was generated to illustrate the sensitivity levels of parameters, ranging from most to least sensitive within a ± 20% interval. This involved systematically altering critical parameters to assess their impact on the model's outcomes.

In order to assess the uncertainty of all parameters simultaneously, a probabilistic sensitivity analysis (PSA) was conducted using a second-order Monte Carlo simulation. It was assumed that the baseline HAQ, patients' age at onset, and HAQ decline related to ACR response followed a normal distribution. Furthermore, all costs were incorporated into the model using a gamma distribution, while probabilities were represented in the form of a beta distribution.

Results

Base case analysis

According to the model's projections (Table 4), the total costs over a lifetime horizon for the TCZ and ADA were estimated at $6,990 and $6,608 per patient, respectively. Furthermore, the average quality-adjusted life years (QALYs) gained for TCZ treatment were 4.24, compared to 3.95 for ADA. From a societal perspective, TCZ incurred an additional cost of $382 per patient but

Table 3 Cost inputs

Cost Item	Description	Unit cost $	Total cost ($ 6 months)	Distribution
Treatment-related costs				-
TCZ	162 mg every other week	42.3	544.45	-
ADA	40 mg every other week	34.5	500.4	-
ETC	50 mg SC Once weekly	25.1	648.8	-
RTX	1000 mg IV, repeat after 2 weeks	128.3	574.3	-
Palliative care	weighted mean costs of cDMARDs, prednisolone, and celecoxib	NA	48.44	-
Diagnostic examination				
Laboratory tests: LFT and CBC	Every 2 months	8.46	25.39	-
Bone densitometry	Annually	17.17	8.58	-
Chest X-ray	Annually	5.72	2.86	-
Radiography	Annually	3.43	1.71	-
Tuberculin test	Annually	0.16		-
Other medical Cost				
Hospitalization (per day) (SD)	Based on the HAQ score	31.82 (6.9)	Based on HAQ score	Gamma
Intra-articular corticosteroid	30% of patients on Palliative care	11.73	11.73	-
Mab Infusion	Based on treatment	8.01	Based on treatment	-
Psychotherapist	30% of patients on Palliative care every 3 months	8.15	16.3	-

Abbreviations: ADA, Adalimumab; cDMARDs, conventional Disease-Modifying Antirheumatic Drugs; CBC, Complete Blood Count; ERT, Etanerecpt; HAQ, Health Assessment Questionnaire; IV, Intra Venous; LFT, Liver Function Tests; RTX, Rituximab; TCZ, Tocilizumab

Table 4 Model results

Strategy	Cost ($)	Incr Cost ($)	Eff (QALYs)	Incr Eff (QALYs)	ICER ($/QALYs)
ADA	6,608	382	3.95	0.29	**1,301**
TCZ	6,990		4.24		

Abbreviations: ADA, Adalimumab; TCZ, Tocilizumab

demonstrated a superiority of 0.29 QALY compared to ADA. The Incremental Cost-Effectiveness Ratio (ICER) obtained in this study was $1,301, which falls below the assumed willingness-to-pay threshold of 1 GDP per Capita in Iran, which was 1,448 USD. Consequently, TCZ emerges as a cost-effective treatment option compared to ADA.

Sensitivity analysis

Given that most variables in the model are represented with their distributions, a Probabilistic Sensitivity Analysis (PSA) was conducted with a hypothetical sample size of 1000 to assess the probability of TCZ being the cost-effective option compared to ADA. Being in the first quadrant, TCZ emerges as the cost-effective choice with a probability of 76% (Figs. 2 and 3).

As depicted in the Tornado diagram (Fig. 4), the most sensitive model parameters include the prices of TCZ and ADA, the percentage of patients who respond or do not respond to the treatments, and the lag time to the efficacy of TCZ and ADA. These factors emerged as crucial contributors to the sensitivity of the model, influencing the outcomes to a significant extent, in the range of ±20% changes. The influences of other parameters on the results were almost negligible.

Moreover, given the sensitivity of the model to the prices of both drugs, a two-way sensitivity analysis for these variables was deemed necessary. As illustrated in Fig. 5, ADA could be an alternative to TCZ in terms of cost-effectiveness if its price is reduced.

Discussion

The study conducted a thorough cost-effectiveness analysis comparing TCZ and ADA for treating severe active RA in Iran. By integrating data from the ADACTA study and employing a microsimulation Markov model, the aim was to inform healthcare decision-makers about the economic implications of selecting between these two bDMARDs. The ADACTA clinical trial findings indicated that TCZ outperformed ADA in alleviating severe active RA symptoms in patients eligible for bDMARDs and unable to continue MTX therapy. These findings suggest TCZ, as a promising option for RA patients, offers a viable alternative to ADA. The trial outcomes provide valuable insights into the efficacy of these medications and their potential roles in managing RA [11].

The results of this study have significant implications for healthcare decision-makers tasked with effectively allocating limited resources. By showcasing the cost-effectiveness of TCZ compared to ADA, this study

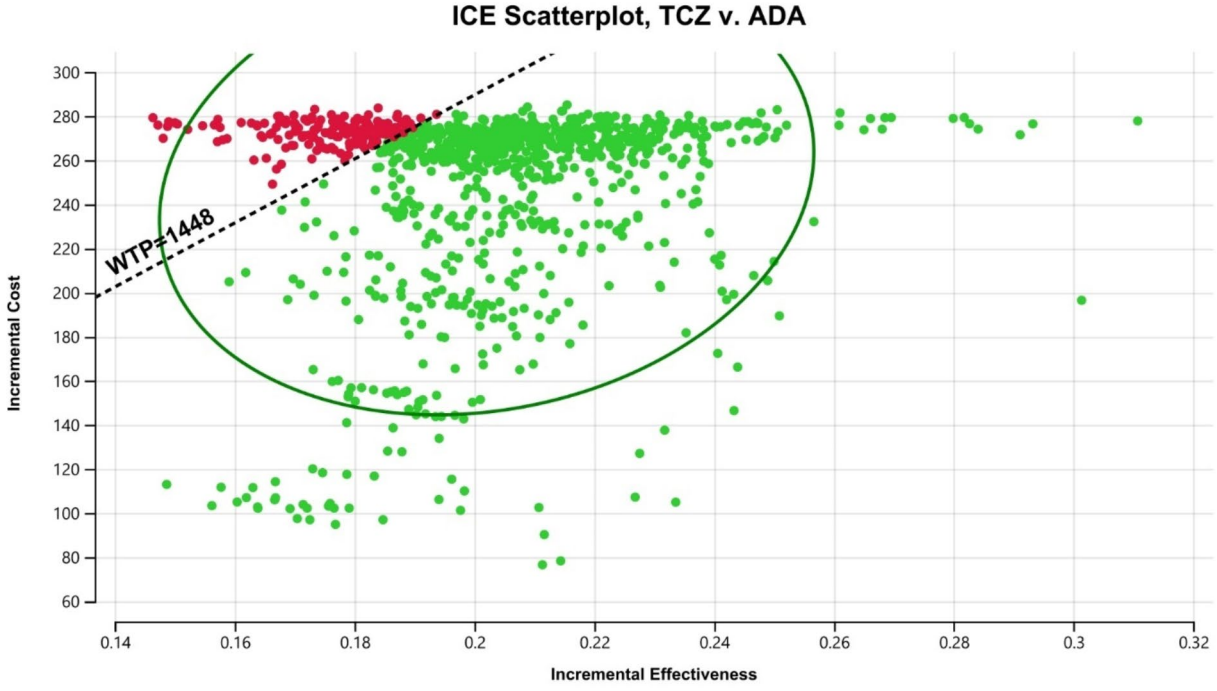

Fig. 2 PSA diagram

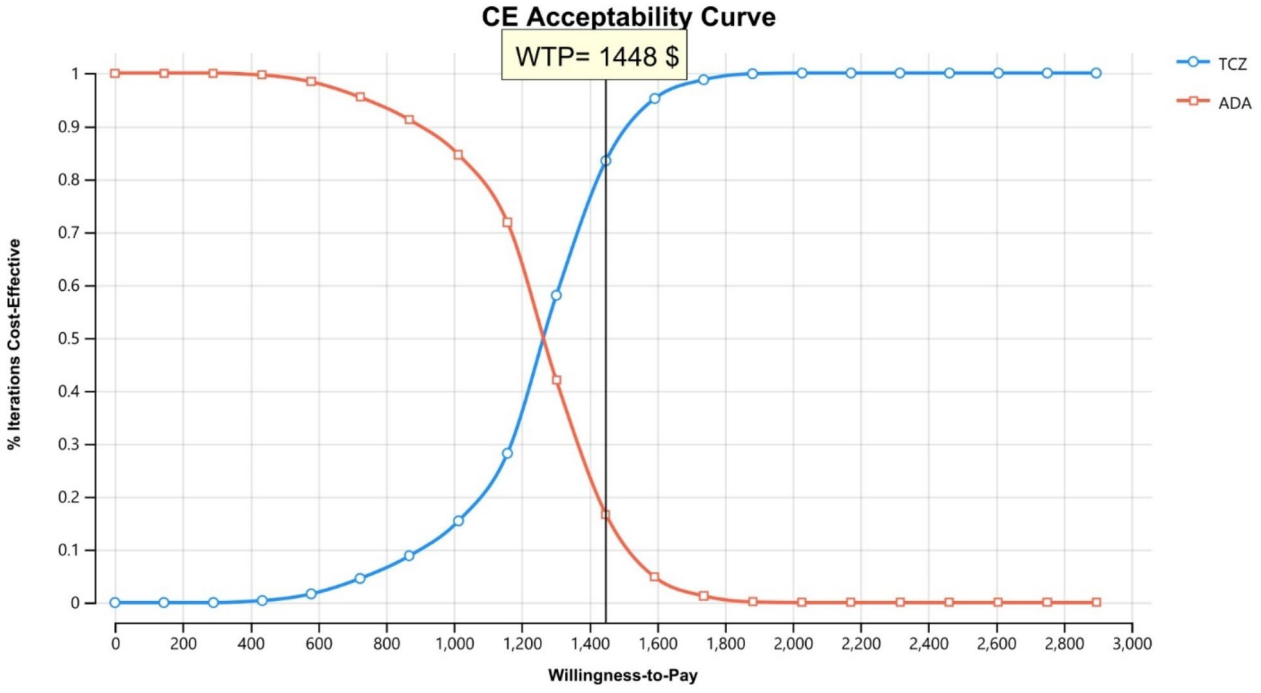

Fig. 3 Acceptability curve

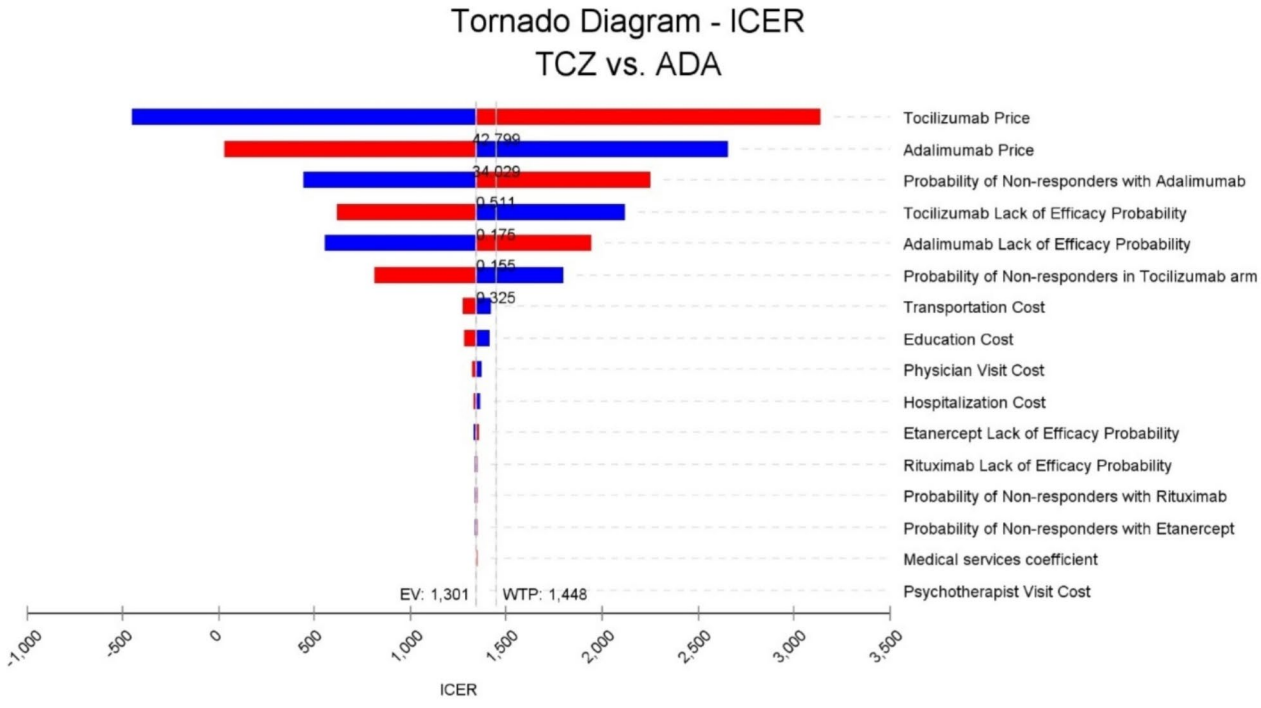

Fig. 4 Tornado diagram

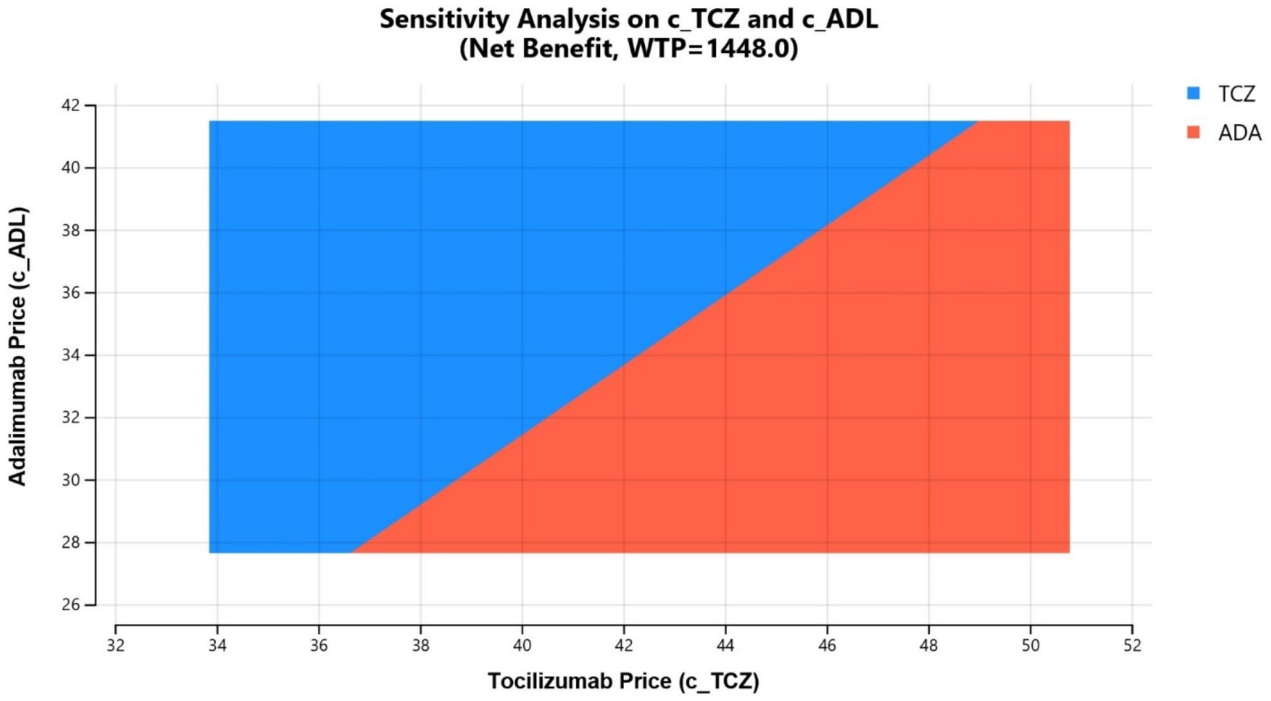

Fig. 5 Two-way sensitivity analysis of the price of Tocilizumab and Adalimumab

provides compelling evidence for TCZ's inclusion in RA treatment strategies in Iran. Results indicate that while TCZ incurs higher costs ($6,990 vs. $6,60), it also yields higher QALYs (4.24 vs. 3.95) compared to ADA. The ICER suggests that TCZ would be a cost-effective option compared to ADA at the Iran willingness-to-pay threshold of 1,448 USD.

The results of this study are consistent with those of the ADACTA trial, demonstrating that TCZ monotherapy is more effective than ADA monotherapy in relieving severe active RA symptoms. These results highlight TCZ's potential as a promising therapeutic option for RA patients unresponsive to first-line treatment, MTX.

Our findings are aligned with similar studies from other countries. An Italian study, for example, demonstrated TCZ's cost-effectiveness when used alongside MTX over a lifetime horizon, highlighting TCZ's suitability both as an initial biologic therapy and as a switch option following anti-TNF-α failure [35]. Additionally, a recent study from Saudi Arabia showed that TCZ significantly improves quality of life and offers favorable economic value relative to ADA and Etanercept, reinforcing TCZ's potential applicability within the healthcare context of Middle Eastern countries [36]. Supporting these results, an economic analysis conducted in the United States also found TCZ (8 mg/kg) to be more effective and cost-efficient than ADA. In particular, TCZ demonstrated greater QALY gains relative to its incremental cost, making it a strong candidate for patients requiring alternatives to MTX. This U.S.-based study underscores TCZ's ability to deliver clinically meaningful health improvements while remaining within acceptable cost-effectiveness thresholds [14].

On the other hand, previous economic evaluation focusing on biological treatments for refractory RA was carried out in Iran and compared the cost-effectiveness of the TCZ plus MTX regimen to the infliximab plus MTX regimen over a 5-year period, suggesting infliximab as a cost-effective and feasible alternative to TCZ in the treatment of RA. However, it's important to note that the short-term time horizon of the study could yield different results if the model were extended to a lifetime horizon. Additionally, the payer perspective used in the study could significantly impact cost calculations [37].

These findings are crucial as anti-TNF-α drugs typically serve as the initial treatment option for RA patients qualifying for bDMARDs. Alongside the ADACTA trial and other relevant clinical studies, this research contributes to the growing literature emphasizing favorable clinical and economic outcomes associated with TCZ, a new interleukin-6 receptor inhibitor for severe RA patients.

This study has several limitations, with the most significant being the lack of head-to-head data for the entire treatment sequence. Currently, only the ADACTA trial has examined the monotherapy superiority of one bDMARD over another. However, due to the absence of direct head-to-head data, efficacy data for agents used later in the treatment sequence rely on mixed treatment

comparison results. It is recommended to update these findings as more head-to-head data becomes available. In our base case, we used the rates directly from ADACTA as the most reliable data for direct comparison [11].

While our model had limitations due to reliance on ACR rates and mean change in the HAQ score from baseline, we conducted an analysis based on fairly comparable patient groups at baseline. However, due to limited data, we were unable to evaluate the potential impact of patient variations at baseline. Additionally, it's important to note that the HAQ score may not fully reflect disease severity. Nevertheless, using the HAQ to inform costs and outcomes is a common approach in economic models for RA [40]. The model didn't consider adverse effects from treatment; however, given the similar safety profiles of biologic DMARDs, their inclusion is unlikely to significantly impact results. Adverse effects costs were indirectly reflected through treatment discontinuation, leading to HAQ score increases and subsequent price increases. The model also indirectly accounted for quality of life reduction through HAQ score changes, mapped to the EQ-5D based on data obtained from TCZ clinical trials.

Conclusion

From a societal perspective, TCZ proved to be a cost-effective treatment option compared to ADA with an ICER below the Iranian willingness to pay threshold. Decision-makers can use these results to optimize treatment pathways, improve patient outcomes, and allocate healthcare resources efficiently. However, limitations of the study include dependence on modeled outcomes due to the lack of direct data for the entire treatment sequence, potential variation in patient characteristics not captured in the model, and exclusion of adverse events associated with treatment.

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Author contributions
All authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by YM, SR, NY, and RA. The first draft of the manuscript was written by YM and NY and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Code availability
Not applicable.

Declarations

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Not applicable.

Consent to participate
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Competing interests
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References

1. Claxton L, Jenks M, Taylor M, et al. An economic evaluation of tofacitinib treatment in rheumatoid arthritis: modeling the cost of treatment strategies in the United States. J Manag Care Spec Pharm. 2016;22:1088–102. https://doi.org/10.18553/jmcp.2016.22.9.1088.
2. Black RJ, Cross M, Haile LM, et al. Global, regional, and national burden of rheumatoid arthritis, 1990–2020, and projections to 2050: a systematic analysis of the global burden of Disease Study 2021. Lancet Rheumatol. 2023;5:e594–610. https://doi.org/10.1016/S2665-9913(23)00211-4.
3. Maravic M. Economic burden of rheumatoid arthritis in France. Expert Rev Pharmacoeconomics Outcomes Res. 2006;6:25–32. https://doi.org/10.1586/14737167.6.1.25.
4. Radu AF, Bungau SG. (2021) Management of rheumatoid arthritis: an overview. Cells 10.
5. Callahan LF et al. wiley-exley elizabeth k, mielenz thelma j, (2009) Use of Complementary and Alternative Medicine Among Patients With Arthritis. Prev Chronic Dis Public Heal Res Pract Policy 6:44.
6. Fraenkel L, Bathon JM, England BR, et al. 2021 American College of Rheumatology Guideline for the treatment of rheumatoid arthritis. Arthritis Care Res. 2021;73:924–39. https://doi.org/10.1002/acr.24596.
7. McWilliams DF, Kiely PDW, Young A, Walsh DA. Baseline factors predicting change from the initial DMARD treatment during the first 2 years of rheumatoid arthritis: experience in the ERAN inception cohort. BMC Musculoskelet Disord. 2013;14:153. https://doi.org/10.1186/1471-2474-14-153.
8. Pierreisnard A, Issa N, Barnetche T, et al. Meta-analysis of clinical and radiological efficacy of biologics in rheumatoid arthritis patients naive or inadequately responsive to methotrexate. Jt Bone Spine. 2013;80:386–92. https://doi.org/10.1016/j.jbspin.2012.09.023.
9. Mihara M, Kasutani K, Okazaki M, et al. Tocilizumab inhibits signal transduction mediated by both mIL-6R and sIL-6R, but not by the receptors of other members of IL-6 cytokine family. Int Immunopharmacol. 2005;5:1731–40. https://doi.org/10.1016/j.intimp.2005.05.010.
10. Dougados M, Kissel K, Sheeran T, et al. Adding tocilizumab or switching to tocilizumab monotherapy in methotrexate inadequate responders: 24-week symptomatic and structural results of a 2-year randomised controlled strategy trial in rheumatoid arthritis (ACT-RAY). Ann Rheum Dis. 2013;72:43–50. https://doi.org/10.1136/annrheumdis-2011-201282.
11. Gabay C, Emery P, Van Vollenhoven R, et al. Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial. Lancet. 2013;381:1541–50. https://doi.org/10.1016/S0140-6736(13)60250-0.
12. Aletaha D, Neogi T, Silman AJ, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League against Rheumatism collaborative initiative. Arthritis Rheum. 2010;62:2569–81. https://doi.org/10.1002/art.27584.
13. Lee M-Y, Park S-K, Park S-Y, et al. Cost-effectiveness of Tofacitinib in the treatment of moderate to severe rheumatoid arthritis in South Korea. Clin Ther. 2015;37:1662–e762. https://doi.org/10.1016/j.clinthera.2015.07.001.
14. Carlson JJ, Ogale S, Dejonckheere F, Sullivan SD. Economic evaluation of tocilizumab monotherapy compared to adalimumab monotherapy in the treatment of severe active rheumatoid arthritis. Value Heal. 2015;18:173–9. https://doi.org/10.1016/j.jval.2014.10.013.

15. Bruce B, Fries JF. The Stanford Health Assessment Questionnaire: a review of its history, issues, progress, and documentation. J Rheumatol. 2003;30:167–78.
16. Brennan A. Modelling the cost-effectiveness of etanercept in adults with rheumatoid arthritis in the UK. Rheumatology. 2004;43:62–72. https://doi.org/10.1093/rheumatology/keg451.
17. National Institue for Health and Clinical Excellence Guideline. (2016) Tocilizumab and abatacept for rheumatoid arthritis not previously viously treated with DMARDs or after con conventional DMARDs only have failed. NICE Clin Guidel 1–81.
18. Daneshmand A, Jahangard E, Abdollah-Milani M. A time preference measure of the social discount rate for Iran. J Econ Struct. 2018;7. https://doi.org/10.1186/s40008-018-0127-x.
19. Bertram MY, Lauer JA, De Joncheere K, et al. Cost-effectiveness thresholds: pros and cons. Bull World Health Organ. 2016;94:925–30. https://doi.org/10.2471/BLT.15.164418.
20. Institute for Clinical and Economic Review (ICER). Targeted Immune modulators for rheumatoid arthritis. Effectiveness & Value; 2017. Inst Clin Econ Rev ES19.
21. Lee MY, Park SK, Park SY, et al. Cost-effectiveness of Tofacitinib in the treatment of moderate to severe rheumatoid arthritis in South Korea. Clin Ther. 2015;37:1662–e16762. https://doi.org/10.1016/j.clinthera.2015.07.001.
22. 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. Arthritis Res Ther. 2015;17:362. https://doi.org/10.1186/s13075-015-0880-2.
23. Fleischmann R, Mysler E, Hall S, et al. Efficacy and safety of tofacitinib monotherapy, tofacitinib with methotrexate, and adalimumab with methotrexate in patients with rheumatoid arthritis (ORAL strategy): a phase 3b/4, double-blind, head-to-head, randomised controlled trial. Lancet. 2017;390:457–68. https://doi.org/10.1016/S0140-6736(17)31618-5.
24. Klareskog L, van der Heijde D, de Jager JP, et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial.[see comment]. Lancet. 2004;363:675–81. https://doi.org/10.1016/S0140-6736(04)15640-7. S0140673604156407 [pii].
25. Cohen SB, Emery P, Greenwald MW, et al. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. Arthritis Rheum. 2006;54:2793–806. https://doi.org/10.1002/art.22025.
26. Cohen SB, Emery P, Greenwald MW, et al. Rituximab for rheumatoid arthritis refractory to anti–tumor necrosis factor therapy: results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. Arthritis Rheum. 2006;54:2793–806. https://doi.org/10.1002/art.22025.
27. Emery P, Breedveld FC, Hall S, et al. Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. Lancet. 2008;372:375–82. https://doi.org/10.1016/S0140-6736(08)61000-4.
28. Weinblatt ME, Kremer JM, Bankhurst AD, et al. A trial of Etanercept, a recombinant tumor necrosis factor receptor:fc Fusion protein, in patients with rheumatoid arthritis receiving methotrexate. N Engl J Med. 1999;340:253–9. https://doi.org/10.1056/nejm199901283400401.
29. Sung YK, Lee YH. Comparison of the efficacy and safety of tocilizumab, sarilumab, and sirukumab in comparison with adalimumab as monotherapy in patients with active rheumatoid arthritis: a bayesian network meta-analysis of randomized controlled trials. Int J Clin Pharmacol Ther. 2021;59:618–26. https://doi.org/10.5414/CP204017.
30. Wolfe F, Michaud K, Gefeller O, Choi HK. Predicting mortality in patients with rheumatoid arthritis. Arthritis Rheum. 2003;48:1530–42. https://doi.org/10.1002/art.11024.
31. Barton P, Jobanputra P, Wilson J, et al. The use of modelling to evaluate new drugs for patients with a chronic condition: the case of antibodies against tumour necrosis factor in rheumatoid arthritis. Health Technol Assess (Rockv). 2004;8. https://doi.org/10.3310/hta8110.
32. Pennington B, Davis S. Mapping from the health assessment questionnaire to the eq-5d: the impact of different algorithms on cost-effectiveness results. Value Heal. 2014;17:762–71. https://doi.org/10.1016/j.jval.2014.11.002.
33. Hernández Alava M, Wailoo A, Wolfe F, Michaud K. The relationship between EQ-5D, HAQ and pain in patients with rheumatoid arthritis. Rheumatol (United Kingdom). 2013;52:944–50. https://doi.org/10.1093/rheumatology/kes400.
34. Hernández Alava M, Wailoo AJ, Ara R. Tails from the peak district: adjusted limited dependent variable mixture models of EQ-5D questionnaire health state utility values. Value Heal. 2012;15:550–61. https://doi.org/10.1016/j.jval.2011.12.014.
35. Diamantopoulos A, Benucci M, Capri S, et al. Economic evaluation of tocilizumab combination in the treatment of moderate-to-severe rheumatoid arthritis in Italy. J Med Econ. 2012;15:576–85. https://doi.org/10.3111/13696998.2012.665110.
36. Alotaibi AM, Albahdal AS, Abanmy N, et al. Health-related quality of life of patients with rheumatoid arthritis on tocilizumab, adalimumab, and etanercept in Saudi Arabia: a single-center cross-sectional study. Front Pharmacol. 2023;14:1–8. https://doi.org/10.3389/fphar.2023.1299630.
37. Hashemi-Meshkini A, Nikfar S, Glaser E, et al. Cost-effectiveness analysis of Tocilizumab in comparison with Infliximab in Iranian rheumatoid arthritis patients with inadequate response to tDMARDs: a Multistage Markov Model. Value Heal Reg Issues. 2016;9:42–8. https://doi.org/10.1016/j.vhri.2015.10.003.

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