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RESEARCH ARTICLE

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Targeted therapies and conventional care for the treatment of ankylosing spondylitis in China: a cost-effectiveness analysis based on the network-meta analysis

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Abstract

Objective This study aimed to evaluate the long-term cost-effectiveness of conventional care (CC) and seven first-line targeted therapies marketed in China for the treatment of patients with ankylosing spondylitis (AS)–namely secukinumab, ixekizumab, infliximab, etanercept, adalimumab and golimumab and tofacitinib–from the perspective of the Chinese health care system.

Methods The York model was structured as a 12-week decision tree leading into two Markov models. This study set 1 year as a recurring cycle and a lifetime timeframe for the model. Primary model outcomes included the costs in Chinese yuan (CNY), health outcomes in quality-adjusted life-years (QALYs) and the incremental cost-effectiveness ratio (ICER) under a willingness-to-pay threshold of ¥89,358 (equal to the per capita gross domestic product in China in 2023) per QALY. Parameters in the York model were captured from network meta-analyses and literature including treatment response, short-term disease progression, patient functioning and long-term structural disease progression. Utilities are dependent on indicators such as the BASDAI score, the BASFI score, gender and age. Drug prices were analysed using the median price of the Chinese market from YAOZH net in the basic analysis. Costs and outcomes were discounted at 5.0%. We performed deterministic and probabilistic sensitivity analyses to investigate the robustness of the results. The prices of original drugs and generic drugs were used in the scenario analysis.

Results Compared with CC, the ICER of golimumab was ¥104,217.4/QALY, which is between 1 and 3 times the GDP per capita, while the ICERs of the other six targeted therapies were less than ¥89,358/QALY. The specific economic rank of the targeted therapy was as follows:

secukinumab > ixekizumab > tofacitinib > infliximab > etanercept > adalimumab > golimumab. Treatment response rates such as the BASDAI50, changes in the BASDAI/BASFI scores and the discounting rate were key model drivers. According to the scenario analysis, IL-17 inhibitors were still the most economical intervention when original drugs and generic drugs were used.

Conclusion Targeted therapies are cost-effective treatments for AS. Overall, IL-17 inhibitors were the dominant treatment. The choice of the brand-new prices or generic drug prices can greatly affect economics.

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Keywords Ankylosing spondylitis, Biologicals, Network-meta analysis, Cost-effective

Background

Ankylosing spondylitis (AS) is a chronic, progressive autoimmune disease characterized by the involvement of the sacroiliac joints, spinal bony prominences, paraspinal soft tissues, and peripheral joints (joints located outside the spinal axis) [1]. In China, the prevalence of AS is 0.29% and is increasing, with the prevalence in men being 2.8 times higher than that in women; furthermore, there are approximately 4–5 million patients with AS [2]. The disability caused by AS often occurs in the prime of life, and pain, bed rest, fatigue and other conditions seriously affect the normal work and daily life of patients. Moreover, the cost of treatment and the indirect losses caused by the high rate of disability to the patient's family and even the community have brought a serious economic burden [3].

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the drugs of choice for the treatment of AS, and NSAIDs combined with nonpharmacological interventions (e.g., physiotherapy) constitute conventional care (CC) to alleviate pain among AS patients. However, the long-term use of NSAIDs not only results in poor patient compliance but also increases the risk of gastrointestinal adverse effects. The introduction of biologic and oral targeted therapies has changed the treatment pathway for patients with AS, as reflected in the latest guidelines from the Spondylarthritis International Society [4]. These guidelines that biologics and oral targeted therapies should be considered primarily for patients with persistently high disease activity despite conventional treatments.

Targeted therapies are classified into different types depending on the target of action, such as tumour necrosis factor inhibitors (TNFis), interleukin-17 (IL-17) inhibitors, and Janus kinase (JAK) inhibitors, thus leading to a high number of choices for patients. Among these agents, the biosimilar of the TNFi inhibitor etanercept, named recombinant human tumour necrosis factor-O receptor, was first launched in China in 2006. The imported original infliximab was released a year later. In addition, the JAK inhibitor tofacitinib and the IL-17 inhibitor secukinumab landed on the Chinese market in 2017 and 2019, respectively. To date, there are seven original drugs or generic drugs of targeted therapies available for the treatment of AS on the Chinese market, thus providing patients and clinical treatment with more options.

At present, no studies have evaluated the cost-effectiveness of these seven targeted therapies on the market in China. Therefore, this study aimed to evaluate the cost-effectiveness of conventional care (CC) and seven first-line targeted therapies marketed in China for the treatment of patients with ankylosing spondylitis (AS)–namely, secukinumab, ixekizumab, infliximab, etanercept, adalimumab, golimumab and tofacitinib–from the perspective of the Chinese health system.

By conducting these cost-effectiveness analyses, our study aimed to provide insights into the economic implications of different biotherapeutic interventions for AS in the context of the Chinese market. This information can assist health care decision-makers in optimizing resource allocation and treatment choices.

Methods

Population

The baseline clinical data were derived from the weighted mean of RCTs. Patients with active AS who had not been previously treated with targeted therapies (biologic-naïve patients) and who have inadequate response to NSAIDs therapy were selected for this study. Patients did not differ at baseline ($p > 0.05$). The mean age of the patients was 38.22 years. The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI) scores were 6.49 and 5.60, respectively. The male/female ratio of patients was taken from the epidemiological literature and was 73.68% for males and 26.32% for females [5]. This study did not involve animal or human population research. Clinical data were based on published RCTs, and thus the study did not require approval or ethical review.

Interventions and comparators

This study aimed to assess the cost-effectiveness of different treatment options for ankylosing spondylitis (AS). The analysis included a total of seven targeted therapies as interventions. These interventions included four TNFis (etanercept, adalimumab, infliximab, and golimumab), two IL-17 inhibitors (secukinumab and ixekizumab) and one JAK inhibitor (tofacitinib). In this study, the original drugs and generic drugs of seven targeted therapies were included at the same time. The detailed information is shown in (supplementary material Table S2.)

To evaluate the cost-effectiveness, we compared each targeted therapy intervention with conventional care (CC), which served as the comparator. In the target population, the intervention group would use targeted therapies such as biologics, and when targeted therapies fail, they would switch to conventional care, while the control group will continue to use conventional care until death. Furthermore, pairwise comparisons were conducted

among the biotherapeutic interventions themselves to assess their cost-effectiveness. In the absence of head-to-head clinical trials of targeted therapies, this study the utilized the results of Network-Meta Analysis (NMA) in order to achieve indirect comparison between targeted therapies (supplementary material Table S1). BASDAI 50 model inputs were informed by a NMA of BASDAI 50 scores, with the timepoint of BASDAI 50 score taken as the primary endpoint of the relevant trial, provided this was between weeks 12 and 16. Since responder and non-responder baseline changes in BASDAI and BASFI scores during the initial treatment period were not reported separately in the clinical trials, the changes in these two indicators for TNFi responders and non-responders in this study were derived from previously published pharmacoeconomic studies. [6–8]

Model structure

This study used the York model established by the National Institute for Health and Care Excellence (NICE) in the UK [9], which is based on a systematic evaluation of the efficacy, safety and economics of TNFis. The model fully considers disease progression, incorporates the impact of adverse events on health outcomes, and has been used many times internationally to assess the economics of AS treatment. The model is cycled every year, thus simulating the patient's life. Since AS is a chronic disease requiring long-term or even lifelong medication, the study was set to be lifelong, and 40 years was taken as the model cycle time based on the difference between the baseline mean age and the Chinese life expectancy [10]. The cost year was 2023, and costs and outcomes were discounted by 5% [11]. The model was constructed in Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA).

As shown in Fig. 1, the York model is a 12-week decision tree model combined with the Markov model. Patients treated with targeted therapies were entered into separate Markov models based on their improvement in BASDAI score sat week 12. If a patient achieves BASDAI50 (50% reduction in BASDAI score from baseline), they will enter a three-state Markov model as a responder to the targeted therapy. In the Markov targeted therapy (Fig. 1a), the patient enters the intervention maintenance state, wherein the patient continues to be treated with the targeted therapy. These patients will then receive CC if

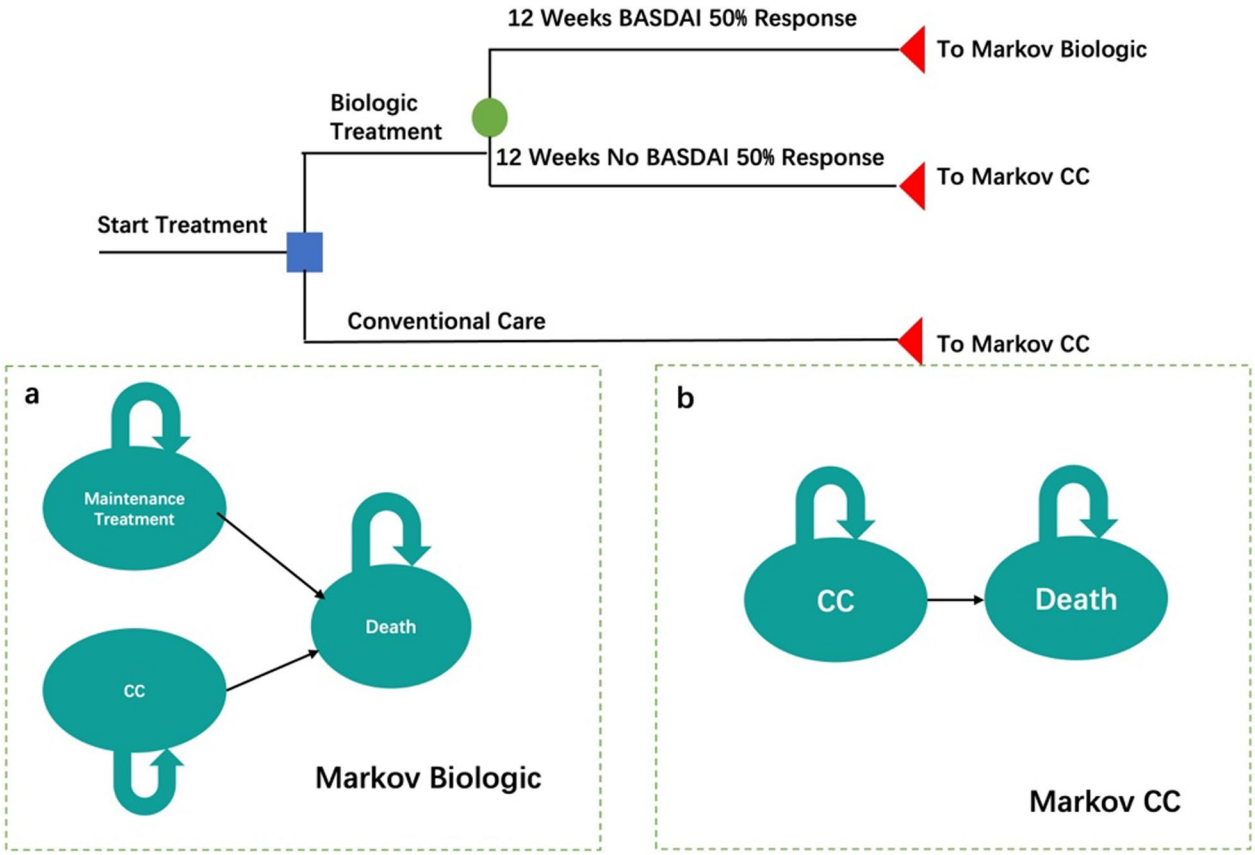

Fig. 1 York model

the targeted therapies fail. They can progress directly to the death state in both the targeted therapies treatment state and the CC treatment state in Markov biology. If the patient does not reach BASDAI50, they will go directly to the CC state as nonresponders. In Markov CCs, patients may remain there or go to the death state. Patients in the control group went directly to the conventional treatment state in the Markov CC, where they will enter the death state.

During cycles in the York model, disease progression is reflected by changes in BASDAI and BASFI scores, where BASDAI scores show the degree of disease activity and BASFI scores show changes in the patient's somatic function. Additionally, disease-related costs and patient utility are related to the BASDAI and BASDAI scores. The main hypotheses included in this model are as follows:

(1) Patients are directly switched back to conventional NSAID therapy when they do not respond to a targeted therapy during the intervention.
(2) Targeted therapy responding and nonresponding patients had similar BASDAI and BASFI scores at pretreatment.
(3) The BASDAI score varies only in the initial phase according to whether a person responds and remains unchanged during long-term progression.
(4) The BASDAI and BASFI scores returned to baseline levels when patients moved from the intervention treatment state to the conventional treatment state.

In the scenario analysis, we considered different prices of medicines. The lowest market price (generic price) was used for all interventions in Scenario 1, and the highest market price (originator price) was selected for all interventions in Scenario 2 for simulation.

Clinical data

Treatment response

In the decision tree branch, each targeted therapy was entered into a different Markov model based on its BASDAI50 response at week 12 (Table 1). The BASDAI50 is a commonly used outcome metric in efficacy trials to determine whether a targeted therapy is clinically effective [16]. BASDAI50 responders will be admitted to the Markov Targeted therapies System.

Short-term health outcomes

Short-term health outcomes after the initial 12 weeks of treatment are captured by the BASDAI and BASFI scores, which reflect the effects of different interventions on disease activity as well as patient functioning. Changes in patients' BASDAI and BASFI scores after 12 weeks vary according to the patient's response to different interventions (Table 1).

Long-term health outcomes

In addition to reflecting short-term changes in the BASDAI and BASFI scores in the York model, the model captured the impact of treatment on long-term disease progression.

In patients with AS, patient function changes with age in response to the degree of disease activity and imaging progression, and this change in patient function is reflected by the long-term progression of the BASFI score. They are mainly related to the imaging process, and they are calculated by Eq. 1. In this case, the change in BASFI for a 1-unit change in modified Stoke AS Spine Score (mSASSS) is a fixed value of 0.057 [17], whereas the annual rate of change in mSASSS varies according to the treatment measure. According to the published literature, the annual rate of change in mSASSS is 0.42, which applies to all biologics [18]. Tofacitinib, while not a biologic, is different from NSAIDs and still follows this equation in published health economics studies [8]. In contrast, CC treatment is not considered to delay imaging progression, so the annual rate of change in the mSASSS score is 1.440 during natural disease progression [18].

$$\begin{aligned} &Annual\ rate\ of\ BASFI\ change \\ &= Annual\ rate\ of\ mSASSS\ change \\ &\quad * BASFI\ change\ with\ a\ 1 \\ &\quad - unit\ change\ in\ mSASSS \end{aligned} \tag{1}$$

Withdrawal of targeted therapy

Patients who respond to the initial intervention may be moved from targeted therapies maintenance treatment status to CC status in any subsequent cycle due to withdrawal. The withdrawal rate data for each intervention are shown in Table 1.

Adverse events

Adverse events in this study included tuberculosis and serious infections, which have an impact on both utility value and cost. The annual incidence data for tuberculosis and serious infections were obtained from a Cochrane systematic evaluation of adverse events for biologics and oral targeted therapy [19], and it was assumed that the incidence of tuberculosis and serious infections would be the same for all targeted therapies, at 0.22 and 3.5%, respectively.

Table 1 Parameters in the York model

Items	Mean (Range$_a$)	Distribution	Sources
12-Week BASDAI50			
Etanercept	33.21% (14.92%, 65.89%)	Normal	NMA
Adalimumab	48.97% (24.50%, 59.37%)	Normal	
Infliximab	59.16% (26.00%, 64.10%)	Normal	
Golimumab	51.14% (28.39%, 66.85%)	Normal	
Tofacitinib	38.99% (23.81%, 54.47%)	Normal	
Ixekizumab	43.86% (23.39%, 62.73%)	Normal	
Secukinumab	41.53% (15.21%, 73.77%)	Normal	
CC	19.45% (13.07%, 21.17%)	Normal	
12-Weeks Change from baseline in BASDAI(responder)			
Etanercept	−4.47 (−6.21, −2.74)	Normal	7 8 6
Adalimumab	−4.56 (−5.15, −3.97)	Normal	
Infliximab	−7.94 (−10.05, −5.84)	Normal	
Golimumab	−5.32 (−6.63, −4.00)	Normal	
Tofacitinib	−4.05(−5.54, −2.46)	Normal	
Ixekizumab	−4.14(−4.66, −3.62)	Normal	
Secukinumab	−4.60 (−6.22, −2.98)	Normal	
CC	−3.06 (−3.72, −2.40)	Normal	
12-Week Change from baseline in BASDAI(nonresponder)			
Etanercept	−1.02 (−1.42, −0.63)	Normal	7 8 6
Adalimumab	−1.82 (−2.30, −1.34)	Normal	
Infliximab	−0.81 (−0.91, −0.70)	Normal	
Golimumab	−1.37 (−1.71, −1.03)	Normal	
Tofacitinib	− 0.92 (−1.48, −0.36)	Normal	
Ixekizumab	−1.06(−0.69, −1.43)	Normal	
Secukinumab	−1.01 (−0.65, −1.36)	Normal	
CC	−0.70 (−0.85, −0.55)	Normal	
12-Week Change from baseline in BASFI(responder)			
Etanercept	−3.44 (−4.97, −1.91)	Normal	7 8 6
Adalimumab	−3.15 (−3.67, −2.62)	Normal	
Infliximab	−3.96 (−5.19, −2.74)	Normal	
Golimumab	−4.07 (−5.33, −2.81)	Normal	
Tofacitinib	−3.39 (−4.27, −2.52)	Normal	
Ixekizumab	−3.62(−3.81, −2.81)	Normal	
Secukinumab	−3.75 (−5.20, −2.29)	Normal	
CC	−1.63 (−0.55, −0.26)	Normal	
12-Week Change from baseline in BASFI(nonresponder)			
Etanercept	−0.85 (−0.47, −1.23)	Normal	7 8 6
Adalimumab	−0.78 (−0.90, −0.65)	Normal	
Infliximab	−0.98 (−0.68, −1.28)	Normal	
Golimumab	−0.71 (−0.93, −0.49)	Normal	
Tofacitinib	−0.50 (−1.51, −0.16)	Normal	
Ixekizumab	−1.24 (−1.72, −0.76)	Normal	
Secukinumab	−1.17 (−1.63, −0.72)	Normal	
CC	−0.40 (−0.55, −0.26)	Normal	

Table 1 (continued)

Items	Mean (Range$_a$)	Distribution	Sources
Withdrawal of Targeted therapy			
Etanercept	25.10% (15.30%, 35.00%)	Normal	7
Adalimumab (First year)	13.00% (7.90%, 18.20%)	Normal	
Adalimumab (continued care)	9.30% (5.70%, 13.00%)	Normal	
Infliximab (First year)	2.10% (1.30%, 3.00%)	Normal	
Infliximab (Continued care)	15.70% (9.60%, 21.90%)	Normal	
Golimumab(First year)	13.70% (8.30%, 19.10%)	Normal	
Golimumab (Continued care)	6.60% (4.00%, 9.20%)	Normal	
Secukinumab (First year)	15.20% (9.30%, 21.20%)	Normal	
Secukinumab (continued care)	6.00% (3.60%, 8.30%)	Normal	
Ixekizumab Tofacitinib	11.00% (9.90%, 12.10%)	Normal	
Others			
Discount rate	5% (0%,8%) $_b$	Beta	11
Cost of severe infections(¥)	16,352.17 (14,716.95, 17,987.38)	Gamma	[12]
Costs of tuberculosis(¥)	6028.72(391.30, 11,666,14)	Gamma	[13]
Cost of CC(¥)$_c$ (first 12 weeks)	780.20(702.18,858.22)	Gamma	3
Cost of CC(¥) $_c$ (continued care)	3120.78(2808.7,3432.86)	Gamma	3
Negative Utility of Severe Infection	−0.1560(−0.1872, −0.148)	Beta	[14]
Negative Utility of Tuberculosis	−0.0100(−0.0296, −0.0096)	Beta	[15]

[a] Values in brackets represent 95% confidence intervals.

[b] Range of discount rate is captured from guidelines [11].

[c] The cost of CC fluctuates within 10%.

Mortality

Patients can enter the death state at both the intervention maintenance state and the conventional treatment state in the Markov model. The baseline mortality data (0.737%) in the model were obtained from the *China National Bureau of Statistics* [20], and the mortality rate of AS patients was obtained by multiplying the baseline rate with the AS mortality odds ratio, which was obtained from the published literature; the standardized death ratio for men was 1.63 [9], and that for women was 1.38 [9].

Utility

Health-related quality of life in AS patients has been proven to be dependent on BASDAI scores, BASFI scores, age and sex [7], whereas long-term BASDAI and BASFI scores were captured in the York model. Therefore, this evaluation (Eq. 2) was similarly able to model health state utility using a regression model approach. The negative utility of severe infection or tuberculosis is shown in Table 2.

Table 2 Base-case deterministic cost-effectiveness results (targeted therapies vs. CCs)

	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER
CC	¥80,429	7.55			
Tofacitinib	¥92,904	8.81	¥12,474.6	1.26	9,885.9
Ixekizumab	¥116,486	9.18	¥36,057.2	1.63	22,097.7
Etanercept	¥119,483	8.58	¥39,053.7	1.03	37,909.7
Secukinumab	¥123,551	9.38	¥43,121.7	1.83	23,551.7
Infliximab	¥154,413	9.21	¥73,984.1	1.66	44,441.9
Golimumab	¥294,313	9.60	¥213,884.4	2.05	104,217.4
Adalimumab	¥163,380	9.08	¥82,951.2	1.53	54,127.6

$$\begin{aligned} Utility =& 0:9610 - 0:0442 * BASDAI - 0.0330 \\ & * BASFI - 0.0111 * Sex \\ & [1 = male, 0 = female] + 0:0005 * Age \end{aligned} \quad (2)$$

Cost

The financial burden that patients need to bear includes direct costs and indirect costs. Direct costs include direct medical costs related to disease treatment, such as drug costs, injection fees, examination fees, and hospitalization fees. Indirect costs involve the patient's labor loss due to the AS disease, such as the loss of wages of patients and caregivers. This study calculates direct health care costs based on the Chinese health system perspective, including drug and injection costs, outpatient fees, examination fees, disease-related costs and adverse event costs. Drug and injection costs, outpatient fees and examination fees are defined as initial treatment costs for the first 12 weeks and continued care costs. The median prices of targeted therapies were selected for the base analysis. The prices of drug originators and generics were considered in the scenario analysis. The drug prices were obtained from the Chinese market [21], while the injection costs, outpatient fees and adverse event costs were obtained from the literature (Table 1). The relevant fees for outpatient visits and examinations are from the price list of medical service items for each province in China. In addition, disease-related costs (Eq. 3) and adverse effect treatment costs were included in this study. Disease-related costs (Eq. 3) are dependent upon the extent of disease progression as measured by the BASFI score [9]. The cost parameters are shown in (supplementary material Table S3).

$$Disease - related\ cost = 143.53 * exp\,(0.213\,x\,BASFI\ score) \quad (3)$$

Model outcomes

The final results of the model in this study included total costs incurred cumulatively after the study timeframe and quality-adjusted life years (QALYs), both calculated at a discount rate of 5%. Incremental cost-effectiveness ratios (ICERs) and incremental net monetary benefits (INMBs) were calculated to compare the economics of different treatment options. According to the World Health Organization (WHO) and *China Guidelines for Pharmacoeconomic Evaluations* [11] recommendations, the willingness to pay (WTP) will be 1–3 times the per capita gross domestic product (GDP) in China in 2023, namely, ¥89,358/QALY–¥268,074/QALY. If the ICER < WTP, then the intervention was cost-effective. INMB > 0 indicates an economical intervention, and the calculation methods for the ICER and INMB are shown in Eqs. 4 and 5.

$$ICER = (C_2 - C_1)/(E_2 - E_1) \quad (4)$$

$$INMB = WTP * (E_2 - E_1) - (C_2 - C_1) \quad (5)$$

Sensitivity analysis

We performed a one-way sensitivity analysis (OWSA) to explore the cost-effectiveness of each regimen when parameters changed between the upper and lower limits, and a tornado diagram was generated to depict the analysis results. We conducted probabilistic sensitivity analysis (PSA) by 1000 iterations of Monte Carlo simulation. We used scatter plots and cost-effectiveness acceptability curves (CEACs) to analyse the economics of targeted therapies at different WTP levels. The range of parameters included in the sensitivity analyses is shown in Table 2. Additionally, since some parameters did not have a reported range, this study selected a 10% fluctuation as the parameter variation range based on reference guidelines and expert opinions.

Scenario analysis

To gain a comprehensive understanding of the pricing dynamics in the Chinese pharmaceutical market, this study conducted scenario analyses based on two specific scenarios. The first scenario focused on the analysis of generic drugs available in the Chinese market for the treatment of AS. By examining the pricing of these generic drugs, we aimed to investigate the pricing strategies employed by pharmaceutical companies for AS generic drugs in China, considering factors such as competition, regulatory requirements, and cost-saving potential. The second scenario involved the analysis of imported innovative drugs, focusing on seven targeted therapies used to treat ankylosing spondylitis (AS) that are available in the Chinese market. Through these two distinct scenarios, our study aimed to provide a comprehensive understanding of the pricing landscape for AS treatments in the Chinese pharmaceutical market, encompassing both imported innovative drugs and generic drugs alternatives.

Results

Base-case results

The results of each targeted therapy compared to the CC and the results of each targeted therapy compared to each other are shown in Tables 2 and 3, respectively. Compared to those for CC, the ICERs for each targeted therapy, except for golimumab, were less than ¥89,358/QALY (1 GDP/QALY), suggesting that they are economical. In

Table 3 Base-case deterministic cost-effectiveness results (comparison of targeted therapies)

Targeted therapy	1 GDP as WTP		
	NMB	$INMB_a$	$Rank_b$
Secukinumab	714.4		1
Ixekizumab	703.7	10.7	2
Tofacitinib	694.2	9.5	3
Infliximab	668.7	25.5	4
Adalimumab	647.9	20.8	5
Etanercept	646.9	1.0	6
Golimumab	563.4	83.5	7
	3 GDP as WTP		
Targeted therapy	NMB	$INMB_a$	$Rank_b$
Secukinumab	2390.4		1
Ixekizumab	2344.0	46.3	2
Infliximab	2315.0	29.1	3
Golimumab	2279.0	36.0	4
Adalimumab	2270.6	8.4	5
Tofacitinib	2268.5	2.1	6
Etanercept	2179.8	88.7	7

[a] INMB is the NMB of the targeted therapies in the row minus the NMB of the targeted therapies in the next row, and an INMB > 0 indicates that the economics of the targeted therapies in the row are greater than those in the next row.

[b] Rank represents the ranking of the economics of the line's targeted therapies among the 7 targeted therapies in descending order, with rank 1 representing the best economics and 7 representing the worst economics.

addition, the ICER of golimumab was less than ¥268,074/QALY (3 GDP/QALY), indicating its comparative affordability. When comparing the seven targeted therapies, IL-17 inhibitors were the most cost-effective treatments, followed by JAK inhibitors and TNFi inhibitors. The results were robust to sensitivity and scenario analyses. The specific economic ranks of the targeted therapies were as follows:

secukinumab > ixekizumab > tofacitinib > infliximab > etanercept > adalimumab > golimumab.

Sensitivity analyses

One-way sensitivity analyses

OWSA was performed for each parameter to obtain a tornado diagram showing different ICERs (supplementary material FigureS1–S7). The tornado plots showed that the key drivers of cost-effectiveness results were the proportion of responders with a 12-week BASDAI 50, the discount rate, the withdrawal rate, and the change in the 12-week responder's BASDAI/BASFI.

Probabilistic sensitivity analyses

PSA was conducted by varying the model parameters simultaneously over 1000 simulations (ICERs were stable at this number of iterations). The results (Fig. 2) showed

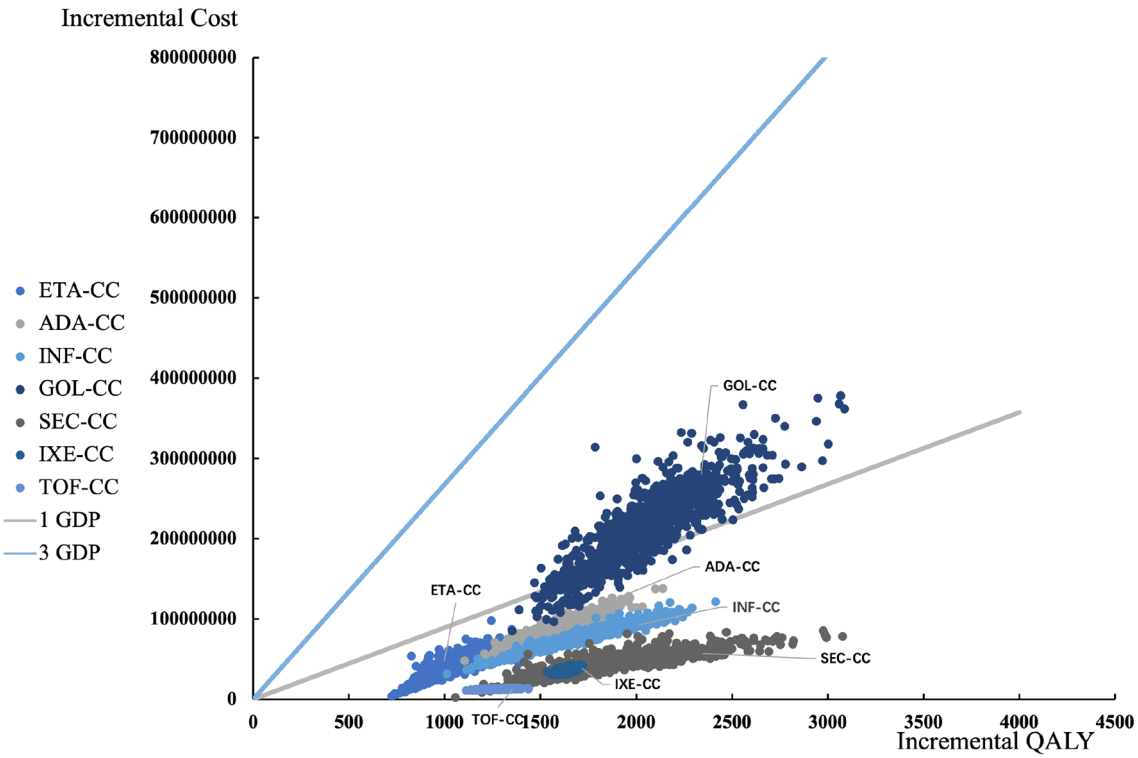

Fig. 2 Base-case probabilistic sensitivity analysis: scatter plot (10,000 iterations)

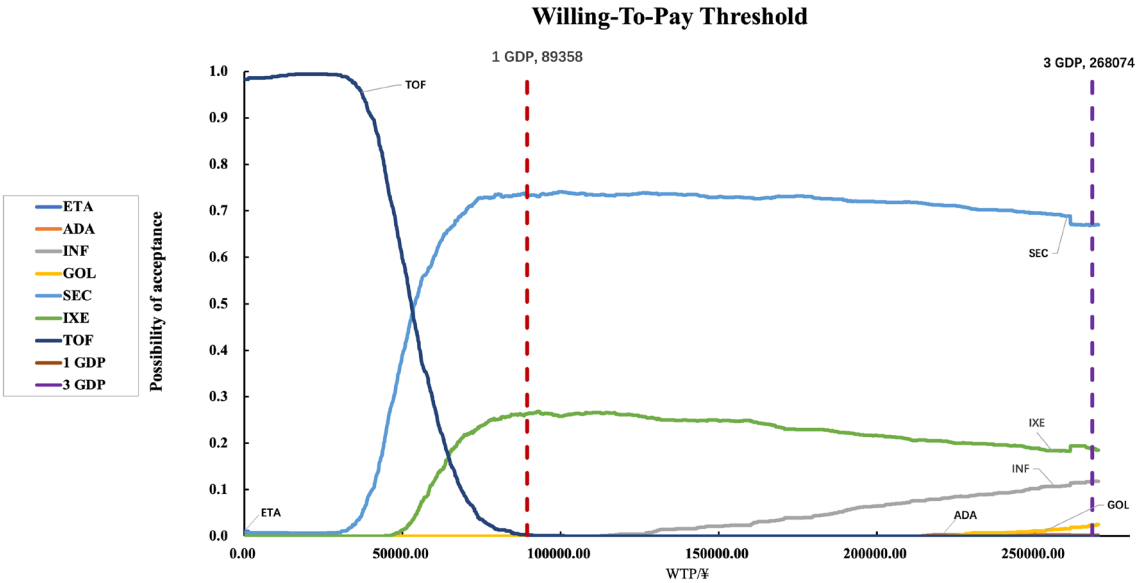

Fig. 3 depicts the cost-effectiveness acceptability curve(CEAC), which showed that when using a range of WTP thresholds of ¥89,358/QALY–¥268,074/QALY gained, Secukinumab was always the most economical option, followed by Ixekizumab. Under the chosen WTP, the probabilities that IL-17 inhibitors had economic advantages over TNFis inhibitors and JAK inhibitors were 99.6% (Secukinumab 71.8% and Ixekizumab 27.8%) and 85.7% (Secukinumab 66.9% and Ixekizumab 18.8%).The acceptance rates of ETA and ADA are close to 0, and there is overlap between the graph and the horizontal axis

Table 4 Results of scenario analysis

	Total Costs	Total QALYs	Incremental Costs[a]	Incremental QALYs[a]	ICER	Rank-1GDP[b]	Rank-3GDP[c]
Scenario 1 Generic Drugs price							
Secukinumab	¥96,632.6	9.38	¥22,856.9	1.83	12,483.7	1	1
Ixekizumab	¥116,486.2	9.18	¥36,057.2	1.63	22,097.7	3	2
Tofacitinib	¥79,381.7	8.81	−¥1,047.3[d]	1.26[d]	−830.0	2	5
Adalimumab	¥128,137.3	9.08	¥47,708.3	1.53	31,130.8	4	4
Infliximab	¥154,413.2	9.21	¥73,984.1	1.66	44,441.9	5	5
Etanercept	¥103,286.0	8.58	¥22,856.9	1.03	22,187.4	6	6
Golimumab	¥294,313.5	9.60	¥213,884.4	2.05	104,217.4	7	7
Scenario 2 Brand-new price							
Secukinumab	¥137,586.9	9.38	¥57,157.9	1.83	31,217.9	2	1
Ixekizumab	¥116,486.2	9.18	¥36,057.2	1.63	22,097.7	1	2
Tofacitinib	¥129,308.6	8.81	¥48,879.6	1.26	38,736.2	3	6
Adalimumab	¥182,521.8	9.08	¥102,092.8	1.53	66,618.0	6	5
Infliximab	¥191,876.6	9.21	¥111,447.5	1.66	66,946.0	5	4
Etanercept	¥120,486.2	8.58	¥40,057.1	1.03	38,883.7	4	7
Golimumab	¥294,313.5	9.60	¥213,884.4	2.05	104,217.4	7	3

[a] Using CC as a comparison

[b] (1 GDP as WTP) Rank represents the ranking of the economics of the line's targeted therapies among the 7 targeted therapies in descending order, with rank 1 representing the best economics and 7 representing the worst economics

[c] (3 GDP as WTP) Rank represents the ranking of the economics of the line's targeted therapies among the 7 targeted therapies in descending order

[d] When incremental costs < 0, incremental QALYs > 0 indicate that the intervention is a dominant intervention with lower costs and greater outcomes

that secukinumab, ixekizumab, tofacitinib, infliximab, etanercept, and adalimumab were all cost-effective treatments, with ¥89,358/QALY (1 GDP/QALY) as the WTP, and golimumab was robust, with 3 times the GDP per capita as the WTP. According to the targeted therapies ranking, the results showed that IL-17 inhibitors (secukinumab and ixekizumab) had economically advantageous over the other two agents. When using a range of WTP thresholds of ¥89,358/QALY–¥268,074/QALY gained, secukinumab was always the most economical option, followed by ixekizumab. (Fig. 3).

The straight lines in the graph represent the two WTPs. when the scatter of a drug falls in the lower right of the line it means that the drug is economical compared to CC at that WTP. The larger the area falling on the lower right side, the higher the probability of economy.

Scenario analysis

The results of each scenario analysis are shown in Table 4. In Scenario 1, the prices of generic drugs were considered for four drugs on the Chinese market: etanercept, adalimumab, infliximab, and tofacitinib. Secukinumab remained the most cost-effective intervention, while tofacitinib surpassed ixekizumab in terms of ranking. The four TNFi inhibitors ranked lower in terms of cost-effectiveness, while adalimumab improved the rankings. In Scenario 2, the prices of the originator drugs for all seven targeted therapies were used. The two IL-17 inhibitors remained the most cost-effective interventions, followed by tofacitinib. Notably, the cost-effectiveness of etanercept significantly improved in this scenario.

Overall, the results indicated that IL-17 inhibitors, particularly secukinumab, consistently demonstrated the highest cost-effectiveness across both scenarios. Tofacitinib also had favourable cost-effectiveness, outperforming ixekizumab in Scenario 1. The improved cost-effectiveness ranking of etanercept in Scenario 2 highlighted the impact of considering generic drugs in the evaluation. However, TNFi inhibitors generally had lower cost-effectiveness rankings in both scenarios.

Discussion

In this study, we explored the cost and effect of secukinumab, ixekizumab, tofacitinib, infliximab, etanercept, adalimumab and golimumab in the treatment of AS. The final results showed that secukinumab was the most effective, and the ranking of cost-effectiveness was as follows:

secukinumab > ixekizumab > tofacitinib > infliximab > etanercept > adalimumab > golimumab. As the model predicted, Golimumab is associated with improvements in quality-adjusted life expectancy than other biologics. Nevertheless, the health gains of Golimumab gains were associated with slightly higher direct medical costs, generating ICERs ¥104,217.4/QALY gained that fall well below the defined WTP.

In other countries, scholars have also compared the cost-effectiveness of the aforementioned targeted therapies. Similar to the findings of this study, Dam Kim et al. [22] found that, from the perspective of the South Korean health care insurance payment system, secukinumab and adalimumab were more cost-effective than other targeted therapies. Ron Goeree et al. [14] conducted a study in Canada and demonstrated that, from the perspective of the Canadian health care system, secukinumab was more economically favourable than adalimumab, golimumab, etanercept (originator and generic drugs), and infliximab (originator and generic drugs). Similarly, Paul Emery et al. [7] and Timo Purmonen et al. [23] found that, from the perspective of the UK health care payer and Finnish health care institutions, respectively, secukinumab was more cost-effective than TNF inhibitors and conventional treatments. However, the results reported by Nigel Armstrong et al. [24] and Borse et al. [25] contradicted the findings of this study, indicating that golimumab was more cost-effective than traditional treatments for the long-term treatment of AS. Additionally, two studies [26, 27] reported economic outcomes comparing adalimumab, etanercept, and infliximab. The results showed that in Spain, the UK, and the United States, the treatment costs ranked from low to high were as follows: etanercept, adalimumab, and infliximab. This differs from the findings of this study regarding the cost-effectiveness of these targeted therapies in the Chinese context.

The results for the economics of targeted therapies in the base analysis were relatively stable in the OWSA and PSA, but there was a large change in the ranking of targeted therapies in the scenario analysis due to drug price. In clinical practice for the treatment of ankylosing spondylitis (AS), IL-17 inhibitors, TNFi inhibitors and JAK inhibitors are the first-line treatment recommended by the guidelines. Although IL-17 inhibitors are new biologics, they present the best cost-effectiveness due to their moderate price and good clinical effects. TNFi inhibitors as early to enter the market, although the prices are higher, but due to the longer market time, there may be a certain price advantage or more alternatives, such as adalimumab. The development and marketing of biosimilar drugs has also alleviated the impact of drug price on the financial burden of patients to a certain extent.

It is worth noting that in China, price factors have a great impact on the results of cost-effectiveness studies. In recent years, generic drugs and volume-based purchasing (VBP) policies have emerged as crucial factors influencing drug prices. The development and promotion of generic drugs have been key strategies for ensuring affordable health care. Generic drugs are produced

after the patent protection of brand-name drugs expires, allowing other pharmaceutical manufacturers to produce and sell these lower-cost alternatives. The Chinese government has actively encouraged the production and use of generic drugs to increase the accessibility and affordability of medications for its vast population. In Scenario 1, where the prices of four drugs were based on their generic equivalents in the Chinese market, we observed a shift in the economic ranking of the interventions. This highlights the potential cost-effectiveness of utilizing generic alternatives in health care systems. Adalimumab exhibited the most significant variation in cost-effectiveness rankings across the two scenarios. The underlying reason for this disparity lies in the timing of Adalimumab's entry into the Chinese market and subsequent reductions in the price of generic drugs. The originator drug, being introduced earlier, established a higher price point, while the generic drugs, which entered the market later, underwent significant price reductions to compete with the originator.

Another factor that affects drug prices is volume-based purchasing (VBP) policy. Recognizing the need to control rising health care costs and ensure access to affordable medications, China has implemented centralized VBP in recent years. VBP was expanded nationwide with the aim of reducing drug prices and using accredited generic drugs for branded drug substitutes [28]. This policy involves the centralized selection and procurement of drugs for public hospitals and health care institutions. Through a competitive bidding process, a limited number of manufacturers are chosen to supply drugs at negotiated prices. The price of tofacitinib for its generic versions has substantially decreased under the influence of VBP. The price reduction of tofacitinib generics compared to that of the originator drug reached an impressive decrease of nearly 95%. From Scenario 1, it can be observed that tofacitinib, when considering the price of generic drugs, has gained a significant advantage in terms of cost-effectiveness compared to ixekizumab, primarily due to the impact of VBP on price reduction.

However, this study has several limitations. Firstly, this study analysed only biologic-naïve patients, but in the real world, IL-17 inhibitors combined with JAK inhibitors are currently used more often in patients for whom TNFis are ineffective. This population was not included in this study due to the lack of parameters. Secondly, the disease-related cost and the health utility regression equation in the utility calculation are all referenced from foreign literature, which may be different from the actual disease level of the Chinese population. Further local studies are needed to improve the applicability of the results to the Chinese population. Thirdly, this study chose the health care system perspective as the research perspective. Considering the indirect losses caused by the high rate of disability to the AS patients and their families, choosing a social perspective can allow for a more comprehensive analysis and comparison. However, there is currently a lack of high-quality data reports on indirect costs of AS patients, such as productivity loss, so this study ultimately chose a health care system perspective. We look forward to subsequent studies with multi-regional, large-sample, high-quality data on the indirect burden of AS to explore the disease burden of AS.

Conclusion

In this study, we showed that the effectiveness of treatments was ranked as follows: secukinumab > ixekizumab > tofacitinib > infliximab > etanercept > adalimumab > golimumab. Although golimumab has the most favourable outcomes, secukinumab remains the most cost-effective option due to its low price. It is expected that these regimens may be more widely adopted when the price of these drugs drops and the WTP threshold increases in the future.

Abbreviations

AS	Ankylosing spondylitis
CC	Conventional care
NSAIDs	Nonsteroidal anti-inflammatory drugs
TNFi	Tumor Necrosis factor α inhibitor
IL-17	Interleukin-17 inhibitors
JAK	Janus kinase inhibitors
NMA	Network-meta analysis
NICE	National institute for health and care excellence
GDP	Gross domestic product
CNY	Chinese Yuan
BASDAI50	50% reduction in BASDAI score from baseline
DMARDs	Disease-modifying antirheumatic drugs
mSASSS	Modified stoke AS spine score
GC	Glucocorticoid
ADA	Adalimumab
ETA	Etanercept
GOL	Golimumab
IFX	Infliximab
RCT	Randomized controlled trial
BASDAI	Bath ankylosing spondylitis disease activity index
BASFI	Bath ankylosing spondylitis functional index
ASAS	Assessment in ankylosing spondylitis international society
QALY	Quality adjusted life year
ICER	Incremental cost effectiveness ratio
INMBs	Incremental net monetary benefits
WHO	World health organization
WTP	Willingness to pay
OWSA	One-way sensitivity analysis
PSA	Probabilistic sensitivity analysis
CEACs	Cost-effectiveness acceptability curves
VBP	Volume-based purchasing

Supplementary Information

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Supplementary file 1.

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Author contributions
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Declarations

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Not applicable.

Consent for publication
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Competing interests
The authors declare that no conflict of interest exists concerning this paper.

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