

Treatment of moderate rheumatoid arthritis with different strategies in a health resource-limited setting: a cost-effectiveness analysis in the era of biosimilar

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Abstract

Objective

This paper aims to explore the cost-effectiveness of reduced doses or discontinuation of etanercept biosimilar (Yisaipu) in patients with moderately active rheumatoid arthritis (RA).

Methods

A discrete event simulation model was developed to project lifetime medical costs and quality-adjusted life-years (QALYs) in moderately active RA. Strategies starting with Yisaipu 50 mg/week for nine months following Yisaipu 50 mg/week, 25 mg/week or MTX maintenance were compared. Resource consumptions related to RA were estimated from the perspective of the Chinese health care system. An endpoint of the American College of Rheumatology (ACR) response was used to estimate the utility scores. Uncertainty in model parameters was analysed by sensitivity analyses.

Results

When using ACR as an endpoint for determining successful treatment, strategies starting with Yisaipu 50 mg/week for nine months following Yisaipu 50 mg/week or 25 mg/week maintenance showed the greatest number of QALYs gained (nearly 11.9 and 11.3 with or without rituximab after the failure of Yisaipu, respectively). If decision makers use a threshold of 3×the per capita GDP of China or Shanghai City in 2012, then the strategies most likely to be cost-effective are initial treatment with Yisaipu 50 mg/week for nine months following MTX maintenance and Yisaipu 25 mg/week maintenance, respectively. Results were sensitive to the cost of Yisaipu.

Conclusion

The analysis indicates that, in China, replacing branded etanercept with Yisaipu is likely to be a cost-effective strategy in patients with moderately active RA.

Key words

cost-effectiveness analysis, disease-modifying anti-rheumatic drugs, health related quality-of-life, rheumatoid arthritis, etanercept biosimilar

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Received on November 18, 2013; accepted
in revised form on June 5, 2014.

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Introduction

Rheumatoid arthritis (RA), with a prevalence rate unmet of 0.2% to 0.37% in China (1, 2), is a systemic autoimmune disease that causes chronic inflammation of the joints and tendons resulting in progressive bony erosions and joint damage. Disability and premature mortality caused by RA have substantial socioeconomic implications (3). Disease-modifying anti-rheumatic drugs (DMARDs), especially biologic agents, are often recommended for treating RA (4). Tumour necrosis factor (TNF) inhibitors (etanercept, adalimumab and infliximab) are becoming popular in patients with severe and active RA for their favourable efficacy and safety profile (4-6). However, because biological treatments are expensive compared with traditional DMARDs (tDMARDs), they are restricted to be used after failure of one or more tDMARDs including methotrexate (MTX), generally more than two, especially in health resource limited setting.

The PRESERVE trial investigated whether the response to treatment with conventional doses of the biologic etanercept plus MTX in patients with moderately active RA despite methotrexate treatment would be sustained when doses of etanercept were reduced or withdrawn (7). After a 36-week therapy with 50 mg etanercept plus methotrexate every week, 72% patients with low disease activity were randomly assigned (1:1:1) to one of three treatment groups: 50 mg etanercept plus methotrexate, 25 mg etanercept plus methotrexate, or placebo plus methotrexate. At week 88, 82.6% and 79.1% patients given 50 and 25 mg etanercept had low disease activity, respectively. Meanwhile, only 43% patients given placebo had low disease activity ($p < 0.0001$ for both doses vs. placebo). No substantial difference was noted between the 50 mg and 25 mg regimens. The findings from the PRESERVE study are encouraging. The major conclusion is that low disease activity in patients with RA can be more effectively maintained with a combination of MTX and conventional or reduced doses of etanercept. Although the obvious cost consequences could be concluded, there is still no

evidence related to the economic outcomes of using biological agents in patients with moderately active RA, who are treated with conventional therapy, which represents a common situation in clinical practice (8).

As a biosimilar or intended copy of etanercept, Yisaipu has been approved for treatment of rheumatoid arthritis (RA) in a number of countries (9). The cost of Yisaipu is nearly one-fourth of branded etanercept in China, which leads to significant cost savings for patients and the insurance system (10). Results of two trials indicated that Yisaipu in combination with MTX shows excellent efficacy in reducing disease activity, improving function and slowing down radiographic progression through 24 weeks as branded etanercept. Yisaipu also well tolerated in patients with rheumatoid arthritis in China (11, 12). Based on expert opinion, nearly three-fourths of the biotherapy market in RA has been occupied by Yisaipu in China.

Given the considerable disease burden of RA in China, and increasingly limited healthcare resources, it is necessary to include long-term efficiency criteria when selecting therapies for RA. To this end, it is necessary to examine the economic outcomes of a potential future strategy involving relatively cheap etanercept biosimilar treatment to target in moderately active RA with dose-reduction when remission is achieved in a Chinese setting.

Materials and methods

Model overview

A discrete event simulation model was developed to estimate the health benefits and economic outcomes by considering the baseline characteristics of individual patients and the incurred events and outcomes during the lifetime horizon (13, 14). The model created a number of identical patients to simulate the disease course of each patient under specific treatments and generated data on the economic and health profiles at discrete time points until death.

The main components of the model consist of entities, states and events. An entity is a patient with moderately active RA with a set of attributes which influence the simulation outcomes.

Funding: This work was supported by grants from Shanghai Hospital Association (no. 201002022), the National Natural Sciences Foundation of China (no. 81373209; no. 30671946; no. 81072469) and Shanghai Natural Sciences Foundation (no. 09ZR1417600).

Competing interests: Liang-jing Lu has received consulting fees and payment for lectures and presentations from Wyeth/Pfizer, Abbott, Roche, and Shanghai CP Guojian Pharmaceutical Co., Ltd. (CPGJ). Bin Wu informs that his institution has received financing from CPGJ to build the model.

The other authors have declared no competing interests.

States in the model were characterised by the trend of HAQ change and treatments. For the treatments, a patient can be in certain treatment-related states, which indicate whether the patient is receiving the certain treatment.

Events in the model were classified as 1) HAQ-related events, and 2) HAQ-neutral events. HAQ-related events consist of: 1) HAQ decrease for response, 2) HAQ rebound for the withdrawal of the current drug, and 3) HAQ increase for disease worsening. HAQ neutral events consist of: 1) severe adverse events of the current treatment, 2) patient visit to a rheumatologist, 3) switching to a new treatment, and 4) all-cause death. After each event, a patient's health profile is updated, resulting in a new set of probabilities for future events. For competing events, the patient will incur the event to which the sampled time is shortest. Our models explored 9 competing strategies for moderate RA, as shown in Figure 1. No biological therapy would be included in tDMARD strategy (strategy 1), which might be the reference strategy. The biosimilar, Yisaipu, which replaced etanercept, would be used as 1st-line therapy in strategies 2–9. After the failure of 1st-line TNF-blocking agents, rituximab would be used as 2nd-line treatment (strategies 2–5). When all potential biological therapies have failed, tDMARD would be used until death.

For each strategy, we generated identical cohorts of 100,000 patients according to the health profile of patients, which were derived from the PRESERVE trial, in which the disease activity score in 28 joints (DAS28) of the cohort was more than 3.2 and less 5.1 despite treatment with methotrexate (7). The patients were 48.4 years old on average and they had an HAQ score of 1.1 at the baseline. The characteristics of the patients in the PRESERVE trials were comparable to the Chinese RA population (15).

Using the model, we projected the quality-adjusted-life-years (QALYs) and the health resource consumption of each strategy from the perspective of the Chinese healthcare system. The primary outcome was the incremental cost per QALY gained (ICER). Costs and outcomes were discounted by an annual rate of 3%.

Treatment effect and withdrawal

In order to estimate utility values for the different strategies used in the model, the American College of Rheumatology (ACR) response rates were used as the measure of efficacy. After receiving one treatment, patients might be in one of four kinds of responses: no response, ACR20, ACR50, or ACR70 response. Those with a response equal to or higher than ACR20 would remain on treatment until withdrawal, whereas

those with no response would move to the next treatment in the sequence.

As a biosimilar or 'intended copies' of branded etanercept, the clinical efficacy data of Yisaipu were drawn from the randomised controlled trials of branded etanercept treatment in RA patients (11, 12). The impact of clinical efficacy would be evaluated in sensitivity analyses. The clinical efficacy data of etanercept were drawn from the RCTs conducted in patients with moderate to severe RA. Data from the phase III PRESERVE clinical trial were analysed to estimate the rate of HAQ score change based on the ACR response during the initial treatment with 50 mg etanercept plus MTX for nine months and the following period of maintenance treatment with 50 mg etanercept plus MTX, 25 mg etanercept plus MTX and MTX alone, respectively (7). The key model parameters are presented in Table I.

The long-term probability of withdrawal for TNF- α therapy was taken from the eight years of surveillance of clinical practice in the nationwide Danish DANBIO registry (16). To extrapolate the probability of withdrawal beyond the follow-up period, two-parametric Weibull survival models were used to fit the data extracted from the drug survival rate curves (17).

Mortality

Natural mortality could be incurred by

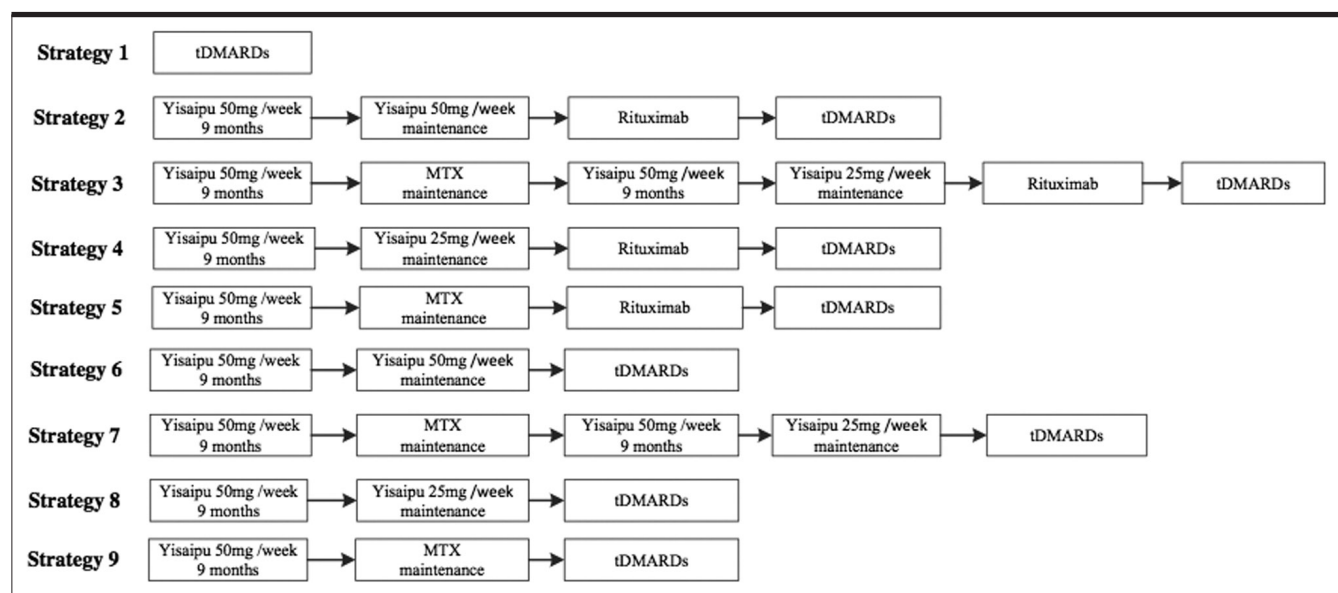


Fig. 1. Simplified treatment strategies in the model.

RA patients at any point on the treatment pathway. The model used a normal life table from the life tables for WHO member states (2011) to adjust mortality risk for patients with RA (1.33 per unit HAQ) (18, 19).

Resource use and unit costs

All costs are reported in 2013 US dollars (\$). The following direct medical cost components were taken into account: drug, monitoring, administration and hospitalisations. The costs were estimated from Chinese healthcare systems. All patients were assumed to be suitable to inject Yisaipu. The recommended dosages of Yisaipu are same as etanercept (50 mg per week). In the real world, the average daily dose of etanercept was 6.07 mg/day, according to the data derived from a large managed care database reported by Ollendorf DA (20). To reflect the actual TNF-antagonist dosage received by patients in clinical practice, we used the daily dosage data to estimate the cost of Yisaipu (strategies containing 50 mg per week). The dosage in patients receiving maintenance treatment with half dosage of Yisaipu would be 25 mg/week (7). The treatment schedule of rituximab is two doses of 1000 mg given 2 weeks apart every 9 months with premedication with methylprednisolone 100 mg *i.v.* before each infusion (16). Based on the recommendations and clinical practice, biological agents are to be given in combination with MTX (4). Costs for physician visit and drug administration are taken from our previously published study (17). Those receiving bDMARD treatments would visit a specialist physician and a general practitioner (GP) once every 6 months (21).

Once the patients received non-biological therapies, health resource usages would be determined by a linear regression line depending on HAQ scores, which was strongly correlated with deterioration of physical function and increase in health resource expenditure (22, 23). Health resource consumption data were collected from a 102 Chinese RA patient cohort with a mean HAQ of 0.8 and a mean disease duration of 2.6 years, who received the non-biological treatment. The consumed health re-

Table I. Key model parameters.

Variable	Value	Distribution	Source
ACR20/50/70 response of etanercept at month 9 (%)	72.8/59.8/27.8	Dirichlet	(7)
ACR20/50/70 response of rituximab at month 6 (%)	51/27/12	Dirichlet	(24)
Withdrawal Etanercept	scale=0.15, shape=0.6275	Weibull	(17)
Rituximab at first and subsequent 6 month (%)	52 and 9	Beta	(17, 24)
MTX at 1 year after 9 months etanercept therapy (%)	70.5	Beta	(7)
Cost (\$)			
Yisaipu per 25 mg	131.6	Fixed	Local charge
Rituximab per 100 mg	635.1	Fixed	(17)

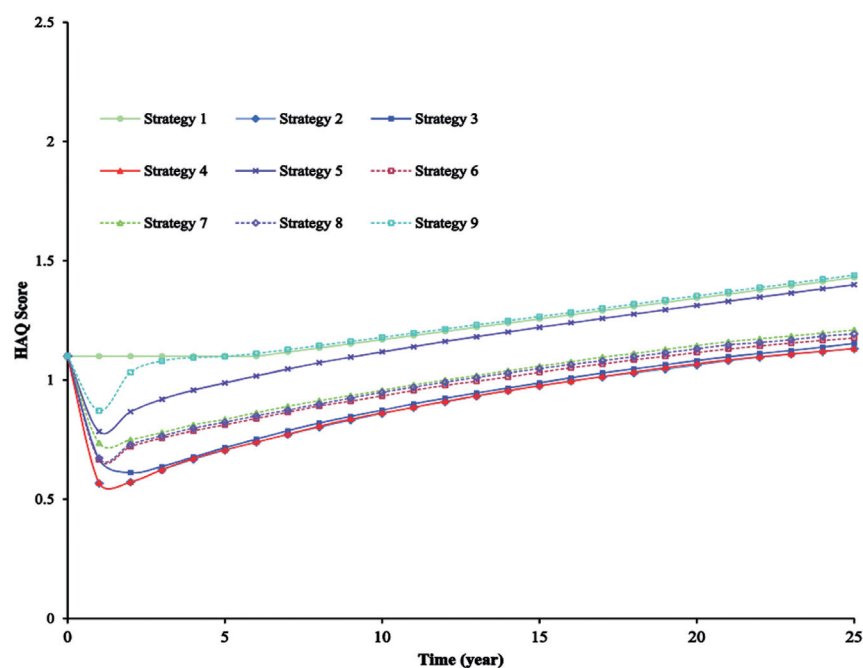


Fig. 2. Estimated changes of HAQ score over time for each strategy.

sources included drug cost, hospitalisation cost, costs for outpatients visits, laboratory tests and ancillary treatment. Based on the centered logistic regression analysis, the expected value of the cost with non-biological therapies could be calculated by the formula: annually cost (\$) = $415 \times \text{HAQ} + 315$ ($p < 0.01$ for HAQ coefficients).

Quality-of-life values

Utility scores are essential for adjusting life expectancy with quality of life and generating QALYs for performing cost-utility analysis. In the current analysis, we assumed HAQ scores had a credible bridge with utility values. Utility values were estimated by patients' HAQ scores using the following linear transformation formula: utility values (EQ-5D) = $0.82 - 0.11 \times \text{HAQ} -$

$0.07 \times (\text{HAQ} \times \text{HAQ})$ ($p < 0.0001$ for all HAQ coefficients) (21). The dropped HAQ score achieved by biological therapy was converted based on ACR response status: 0.13572, 0.44266, 0.66795 and 0.92257 for non-responders, ACR20, ACR 50, and ACR70, respectively (21). For every response to a new treatment, the corresponding HAQ score reduction was applied at the time point of incurring the response event. The reduction was assumed to be equivalent regardless of treatment. Once the treatment is withdrawn, a rebound effect would be incurred, which would result in the HAQ worsening equal to the initial HAQ (25). During the treatment with tDMARDs, a constant progression of disability over time and HAQ-score increases of 0 and 0.017386 per year for the course of the

treatment with tDMARDs lower and higher than 5 years, respectively (26).

Analytical framework

R software environment (version 2.15.2; R Development Core Team, Vienna, Austria) was used for model building, data handling and statistical and output analyses. We reflected uncertainties around the model's key parameters by employing one-way sensitivity and probabilistic sensitivity analyses. Using Monte Carlo simulation, probabilistic sensitivity analysis (PSA) with 1,000 iterations was conducted to determine the joint uncertainty by assigning distributions to all the parameters simultaneously (Dirichlet distributions for ACR responses, lognormal distributions for costs, beta distributions for probability parameters and utilities, normal distributions for patient baseline characteristics and HAQ progression rates). A range of 1-way analyses was performed to examine the key determinants of the robustness of the findings by varying the variables over the ranges. Ranges were sourced from the reported literature or from a range of $\pm 20\%$ of the base-case value when reported data were not available. We used 3×the per capita GDP of China in 2012 (\$18,300) / QALY and 3×the per capita GDP of Shanghai City in 2012 (\$41,400) / QALY as the threshold according to WHO recommendation. (27–29) This recommendation has shown potential for serving as a benchmark for thresholds in the Asian context (30).

Results

Costs and effectiveness

Our model extrapolates that bDMARDs strategies reduced HAQ score, which led to the delay of HAQ score worsening by 2 to 4 years (Fig. 2); these delays have a substantial effect on both costs and utilities by preventing progression in health status.

The simulation results of the base-case analyses are shown in Table II. When the patients received only tDMARD therapy (Strategy 1), the average expected lifetime costs were \$12,735.4 and the remaining average lifetime's gain of life years and QALYs were 23.5 and 9.1, respectively.

Table II. Base-case simulation results.

Treatments	Costs (\$)	QALY gained	Life year gained	ICERs*	Comments
Strategy 1	12.735	9.09	23.50	–	
Strategy 2	126.171	11.90	26.29	40.333	Dominated
Strategy 3	98.290	11.79	26.16	31.700	Dominated
Strategy 4	101.696	11.90	26.26	31.589	
Strategy 5	55.708	10.22	23.93	37.995	Dominated
Strategy 6	82.860	11.28	25.48	32.021	Dominated
Strategy 7	50.523	11.16	25.45	18.224	
Strategy 8	54.165	11.22	25.39	19.441	
Strategy 9	18.574	9.76	23.50	8.680	

*Addition cost per additional QALY gained in comparison with strategy 1.

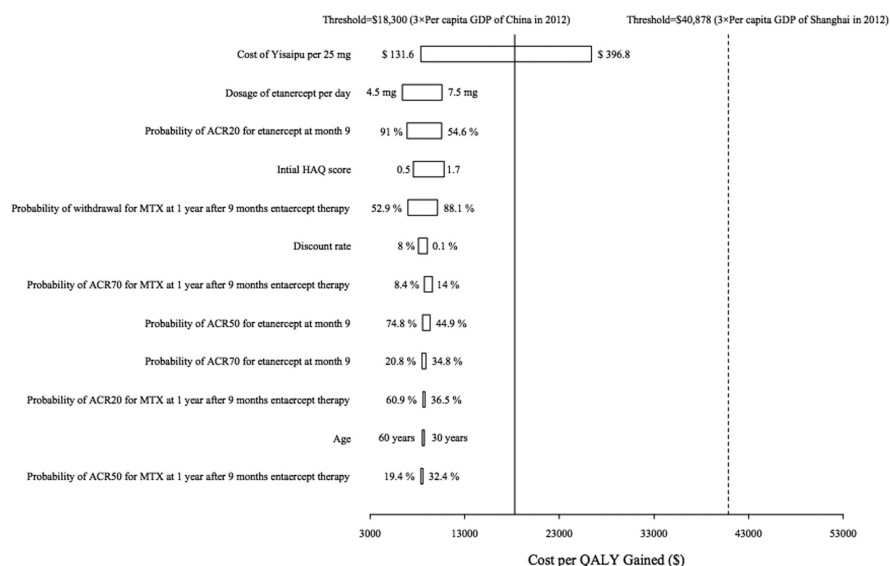


Fig. 3. Tornado diagram representing the cost per QALY gained in one-way sensitivity analysis for Strategy 9 vs. Strategy 1. The width of the bars represents the range of the results when the variables were changed. The vertical dotted line represents the base-case results. HAQ: Health Assessment Questionnaire; ACR: American College of Rheumatology criteria.

In comparison with Strategy 1, the most cost-effective strategy was to use Yisaipu 9 months following MTX maintenance (Strategy 9) with the incremental ICER of \$8,680 per QALY gained, followed by Strategy 7, 8 and 4.

Sensitivity analysis

Figure 3 showed that the result was most sensitive to the cost of Yisaipu. When the branded etanercept (\$396.8 per 25 mg) was used, the ICER exceeded the Chinese threshold of \$18,300 per QALY. Other modelling inputs only had a small impact on the relative results. In the probabilistic analysis, 9 competing strategies were accounted. At the threshold of \$18,300 per QALY gained, Strategy 9 was the preferred and potentially cost-effective strategy (highest expected net monetary benefit and probability of cost-effec-

tiveness ~80%). With the threshold of \$40,878 per QALY gained, Strategy 8 achieved nearly 75% probability of cost-effectiveness (Fig. 4).

Discussion

Our analysis identified the cost-effectiveness strategies in 9 potential competing strategies: Strategy 9, 7, 8 and 4. The four biological strategies in cost-effectiveness efficiency frontier are all based on the etanercept biosimilar (Yisaipu) intervention, which suggests Yisaipu may be an attractive economic option, given the relatively lower cost of biotherapy. In Chinese setting, a threshold of 3×the per capita GDP per QALY is typically applied. When the threshold was \$18,300 per QALY (3×the per capita GDP of China in 2012), Strategy 9 showed the smallest ICER comparing with Strategy 1 in base-case analysis,

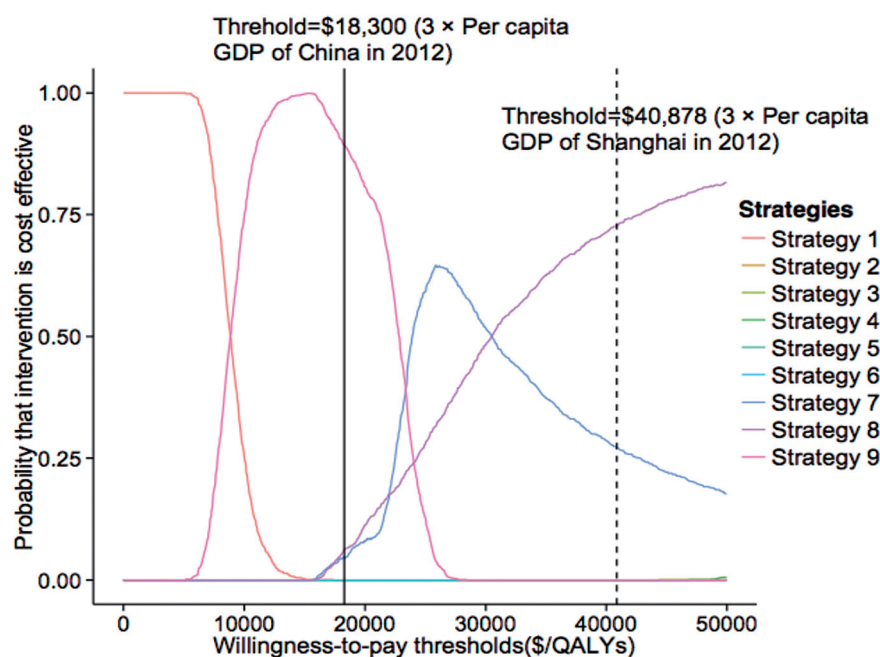


Fig. 4. Cost-effectiveness acceptability curves showing the probability of 15 competing strategies for a range of cost-effectiveness thresholds.

and achieved the greatest probability of cost-effectiveness in probabilistic analysis. This finding indicates that 9-month conventional doses Yisaipu therapy following MTX maintenance might be an acceptable and cost-effective alternative for moderately active RA in a health resource-limited setting. The results were robust to the key parameters except the cost of Yisaipu. The ICER of Strategy 11 against Strategy 1 would be steeply increased and far higher than the threshold of \$18,300/QALY if the price of branded etanercept had been assumed to be applied in the cost of Yisaipu. For those patients living in relatively developed regions of China, reduced doses of Yisaipu with MTX after 9-month conventional doses Yisaipu (Strategy 11) is a potential alternative option. For example, 3×the per capita GDP of Shanghai (\$40,878) is higher than the ICER (\$19,441) of Strategy 8 over Strategy 1. Nearly 75% RA patients receiving Strategy 9 could achieve cost-effectiveness.

In patients with RA, dozens of cost-effectiveness analyses for TNF- α inhibitors as first-line therapy have been reported. In moderate-to-severe RA, etanercept, adalimumab and infliximab plus MTX all showed cost-effective under the thresholds of \$50,000–100,000 from the

perspective of society after tDMARD failure. However, the combination of TNF- α inhibitor with MTX was not cost effective in comparison with first-line MTX therapy in patients with early RA (31). When dose reduction of etanercept was considered in early RA, the cost per QALY gained was nearly \$11,000 over 20 years in Sweden (32). Although these results are not directly comparable due to different perspectives, products and time frames, these analyses suggested that the cost of the agents might be one of the main parameters substantially affected the model output (33). Our findings also showed the results were sensitive to the cost of first-line biological agents, even in situation of a half dose-adjustment in maintenance phase with etanercept. Using branded etanercept in Strategy 9 would lead to about \$26,000 per QALY gained in comparison with Strategy 1, which indicated that Strategy 9 was not cost-effective.

Largely due to the high cost, biological agents should always be prescribed after failure of one or more tDMARDs including MTX. In Europe, nearly 12% of RA patients were received biologic therapy in 2008 (32). In China, because the all biological agents are not covered by society insurance system for their high costs, it could be concluded that

the proportion would be much lower than Europe. As the intended copy and nearly one-fourth of cost of branded etanercept, Yisaipu have been widely used in Chinese clinical practice. By using a Markov model, our previous study found Yisaipu was the most favourable option in patients with moderate-to-severe RA, because its ICER against tDMARD strategy was lower than branded etanercept, adalimumab and infliximab (17). At present, another biosimilar or intended copy of branded etanercept has been investigated in the clinical trials, which could effectively control the disease activity and radiographic progression of RA (34). We look forward to the advent of more cost saving with the uptake of more biosimilar or intended copy for RA treatment.

Our results should be interpreted carefully due to several limitations. First, the current analysis was conducted from the perspective of health care system and loss of work capacity was not taken into account as an indirect cost. However, because our previous study has showed that the incremental costs of the biological treatment strategies would further decrease when a broader perspective and incorporated the indirect costs associated with lost productivity was applied, we could suggest that using biological therapy might become favourable in moderately active disease (17). It also should be noted that the gained productivity have the potential to compensate for the costs of biologics, but only in patients with early RA who still have jobs (33). Second, although the primary amino acid sequence of Yisaipu was identical to the branded etanercept, the efficacy and safety of the biosimilar comparing with originally licensed biopharmaceutical is still needed to be further investigated in clinical trials. Thus, it is an inevitable limitation that the current analysis absorbed the clinical data of branded etanercept in the Yisaipu based strategies. Fortunately, the results of one-way sensitivity analyses suggested that decreasing the ACR20/50/70 to 80% of branded etanercept could increase the ICERs, but not exceed the threshold. Finally, the current analysis did not evaluate the biologic sequences includ-

ing abatacept, because it is waiting for license from Chinese government. We would update the analysis when it is available in China (35). Nonetheless, because the results of this analysis reflect clinical conditions of RA that are common in China, we believe that the results can serve as important reference points for Chinese decision-makers.

Conclusion

In conclusion, the results of our study provided health economic evidence that the treatment of moderately active RA with reduced doses of Yisaipu based strategies rather than tDMARDs and other biological therapies is associated with cost-effectiveness ratios within the range of efficiency normally accepted in China. The results are relatively robust in sensitivity analyses, and there may be benefit in assessing economic outcomes of medical interventions through head-to-head trial. Our findings are presented for China and as such are not directly transferrable to other regions or countries, particularly those using branded etanercept. However, what is in our opinion valid everywhere is that a strategy of dose reduction would substantially improve economic outcomes.

References

- DAI SM, HAN XH, ZHAO DB, SHI YQ, LIU Y, MENG JM: Prevalence of rheumatic symptoms, rheumatoid arthritis, ankylosing spondylitis, and gout in Shanghai, China: a COPCORD study. *J Rheumatol* 2003; 30: 2245-51.
- ZENG QY, CHEN R, DARMAWAN J *et al.*: Rheumatic diseases in China. *Arthritis Res Ther* 2008; 10: R17.
- SCHOELS M, WONG J, SCOTT DL *et al.*: Economic aspects of treatment options in rheumatoid arthritis: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. *Ann Rheum Dis* 2010; 69: 995-1003.
- SMOLEN JS, LANDEWÉ R, BREEDVELD FC *et al.*: EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. *Ann Rheum Dis* 2010; 69: 964-75.
- SMOLEN JS, ALETAHA D, KOELLER M, WEISMAN MH, EMERY P: New therapies for treatment of rheumatoid arthritis. *Lancet* 2007; 370: 1861-74.
- KLARESKOG L, CATRINA AI, PAGET S: Rheumatoid arthritis. *Lancet* 2009; 373: 659-72.
- SMOLEN JS, NASH P, DUREZ P *et al.*: Maintenance, reduction, or withdrawal of etanercept after treatment with etanercept and methotrexate in patients with moderate rheumatoid arthritis (PRESERVE): a randomised controlled trial. *Lancet* 2013; 381: 918-29.
- MIOSEC P: Rheumatoid arthritis: still a chronic disease. *Lancet* 2013; 381: 884-6.
- DORNER T, STRAND V, CASTANEDA-HERNANDEZ G *et al.*: The role of biosimilars in the treatment of rheumatic diseases. *Ann Rheum Dis* 2013; 72: 322-8.
- SCHEINBERG MA, KAY J: The advent of biosimilar therapies in rheumatology--"O brave new world". *Nat Rev Rheumatol* 2012; 8: 430-6.
- HU D, BAO C, CHEN S *et al.*: A comparison study of a recombinant tumor necrosis factor receptor:Fc fusion protein (rhTNFR:Fc) and methotrexate in treatment of patients with active rheumatoid arthritis in China. *Rheumatol Int* 2009; 29: 297-303.
- WU QJ, ZHANG ZL, LI ZB *et al.*: An open-label, multicentric clinical trial to evaluate the efficacy and impact on bone metabolism of recombinant human tumor necrosis factor-alpha receptor II IgG Fc fusion protein with methotrexate in active rheumatoid arthritis: 24-week clinical and radiographic results from ReABLE study. *Zhonghua Yi Xue Za Zhi* 2010; 90: 2481-5.
- KARNON J, STAHL J, BRENNAN A *et al.*: Modeling using discrete event simulation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--4. *Value Health* 2012; 15: 821-7.
- BERESNIAK A, DUPONT DM, BECKER JC, MERKESDAL S: Interest of modelling in rheumatoid arthritis. *Clin Exp Rheumatol* 2012; 30: S96-101.
- LU LJ, BAO CD, DAI M *et al.*: Multicenter, randomized, double-blind, controlled trial of treatment of active rheumatoid arthritis with T-614 compared with methotrexate. *Arthritis Rheum* 2009; 61: 979-87.
- HETLAND ML, CHRISTENSEN U, TARP U *et al.*: Direct comparison of treatment responses, remission rates, and drug adherence in patients with rheumatoid arthritis treated with adalimumab, etanercept, or infliximab: results from eight years of surveillance of clinical practice in the nationwide Danish DANBIO registry. *Arthritis Rheum* 2010; 62: 22-32.
- WU B, WILSON A, WANG FF *et al.*: Cost effectiveness of different treatment strategies in the treatment of patients with moderate to severe rheumatoid arthritis in china. *PLoS One* 2012; 7: e47373.
- Life tables for WHO Member States. http://www.who.int/healthinfo/statistics/mortality_life_tables/en/. Accessed 2012 September 18.
- BARTON P, JOBANPUTRA P, WILSON J, BRYAN S, BURLS A: 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 - Introduction. *Health Technol Assess* 2004; 8: 1-91.
- OLLENDORF DA, KLINGMAN D, HAZARD E, RAY S: Differences in annual medication costs and rates of dosage increase between tumor necrosis factor-antagonist therapies for rheumatoid arthritis in a managed care population. *Clin Ther* 2009; 31: 825-35.
- SOINI EJ, HALLINEN TA, PUOLAKKA K, VIERVAARA V, KAUPPI MJ: Cost-effectiveness of adalimumab, etanercept, and tocilizumab as first-line treatments for moderate-to-severe rheumatoid arthritis. *J Med Econ* 2012; 15: 340-51.
- KOBELT G, EBERHARDT K, JONSSON L, JONSSON B: Economic consequences of the progression of rheumatoid arthritis in Sweden. *Arthritis Rheum* 1999; 42: 347-56.
- YELIN E, WANKE LA: An assessment of the annual and long-term direct costs of rheumatoid arthritis: the impact of poor function and functional decline. *Arthritis Rheum* 1999; 42: 1209-18.
- KEYSTONE EC, COHEN SB, EMERY P *et al.*: Multiple courses of rituximab produce sustained clinical and radiographic efficacy and safety in patients with rheumatoid arthritis and an inadequate response to 1 or more tumor necrosis factor inhibitors: 5-year data from the REFLEX study. *J Rheumatol* 2012; 39: 2238-46.
- BRENNAN A, BANSBACK N, REYNOLDS A, CONWAY P: Modelling the cost-effectiveness of etanercept in adults with rheumatoid arthritis in the UK. *Rheumatology (Oxford)* 2004; 43: 62-72.
- GORDON P, WEST J, JONES H, GIBSON T: A 10 year prospective followup of patients with rheumatoid arthritis 1986-96. *J Rheumatol* 2001; 28: 2409-15.
- List of Chinese administrative divisions by GDP per capita. http://en.wikipedia.org/wiki/List_of_Chinese_administrative_divisions_by_GDP_per_capita. Accessed October 28, 2011.
- EICHLER HG, KONG SX, GERTH WC, MAVROS P, JONSSON B: Use of cost-effectiveness analysis in health-care resource allocation decision-making: how are cost-effectiveness thresholds expected to emerge? *Value Health* 2004; 7: 518-28.
- MURRAY CJ, EVANS DB, ACHARYA A, BALTUSSEN RM: Development of WHO guidelines on generalized cost-effectiveness analysis. *Health Econ* 2000; 9: 235-51.
- ZHAO FL, YUE M, YANG H, WANG T, WU JH, LI SC: Willingness to pay per quality-adjusted life year: is one threshold enough for decision-making?: results from a study in patients with chronic prostatitis. *Med Care* 2011; 49: 267-72.
- SCHOELS M, WONG J, SCOTT DL *et al.*: Economic aspects of treatment options in rheumatoid arthritis: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. *Ann Rheum Dis* 2010; 69: 995-1003.
- KOBELT G, LEKANDER I, LANG A, RAFFEINER B, BOTSIOS C, GEBOREK P: Cost-effectiveness of etanercept treatment in early active rheumatoid arthritis followed by dose adjustment. *Int J Technol Assess Health Care* 2011; 27: 193-200.
- VAN DEN HOUT WB: Deficiencies in current evaluations of the cost-effectiveness of biologic agents for RA. *Nat Clin Pract Rheumatol* 2009; 5: 78-9.
- CHEN XX, DAI Q, HUANG AB *et al.*: A multicenter, randomized, double-blind clinical trial of combination therapy with Anbainuo, a novel recombinant human TNFR:Fc fusion protein, plus methotrexate versus methotrexate alone or Anbainuo alone in Chinese patients with moderate to severe rheumatoid arthritis. *Clin Rheumatol* 2013; 32: 99-108.
- BERESNIAK A, BAERWALD C, ZEIDLER H *et al.*: Cost-effectiveness simulation model of biologic strategies for treating target rheumatoid arthritis in Germany. *Clin Exp Rheumatol* 2013; 31: 400-8.