Assessing the cost-effectiveness of biologic agents for the management of moderate-to-severe rheumatoid arthritis in anti-TNF inadequate responders in Italy: a modelling approach

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Abstract

Objective

The objective of this study is to assess cost-effectiveness of different biologic strategies in patients with moderate-to-severe active RA after an insufficient response to anti-TNF agents within the context of the Italian healthcare system.

Methods

Simulation models were developed allowing for potential biologic therapy switch at each 6-month time point in case of an insufficient response to the previous biologic agent. Biologic treatments included etanercept, abatacept, adalimumab, rituximab or infliximab. Effectiveness criteria for these models were defined as achieving a state of low disease activity (LDAS) [DAS28 ≤3.2] or remission (RS) [DAS28<2.6]. Monte-Carlo simulations were performed for each sequence to manage data variability.

Results

The biologic treatment sequence using abatacept after an insufficient response to a first anti-TNF agent appeared significantly more efficacious over 2 years (102 days in LDAS) compared to rituximab (82 days in LDAS). The sequence using abatacept after 2 anti-TNF agents appeared significantly more efficacious (63 days in LDAS) compared to using a third anti-TNF agent (32 days in LDAS). Mean cost-effectiveness ratios showed significantly lower costs per day in LDAS with abatacept used after one anti-TNF agent (€376) compared to rituximab (€456). The sequence using abatacept after 2 anti-TNF agents was also more cost-effective (€642 per day in LDAS) versus a sequential use of anti-TNF therapies (€1164 per day in LDAS). All comparisons were confirmed when using the remission effectiveness criteria.

Conclusion

The results of this health economics modelling study suggest that the biologic treatment sequence using abatacept after an insufficient response to a first anti-TNF agent appears significantly more effective and cost-effective versus a similar sequence using rituximab for achieving remission or LDAS. The results also indicate that in the case of an insufficient reponse to 2 anti-TNF agents, abatacept appears more effective and cost-effective than using a 3rd anti-TNF agent.

Key words

cost-effectiveness, modelling, rheumatoid arthritis, abatacept, rituximab

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Introduction

Rheumatoid arthritis (RA) is a systemic, chronic inflammatory disease that leads to joint damage and bone destruction and causes serious functional disability. Although RA prevalence in the general population is estimated at 1%, several studies revealed somewhat lower RA prevalence rates in southern Europe (0.3%–0.7%) (1). In Italy, prevalence rates fall on the lower spectrum of this distribution with a range of 0.33%–0.46%, with women being affected four times more than men (2, 3). Because of the chronic and progressive nature of the disease, it is associated with a considerable socioeconomic burden (4). Typical long-term medical resource utilisation costs include medical visits, hospitalisations, laboratory tests, imaging, physical therapy and adaptive aids. As RA progresses, patients experience increasing functional impairment and reduced quality of life that may lead to work disability and lost wages (5), which in turn contribute to significant indirect costs estimated to be twice as high as direct costs (6).

The goal of RA treatment is to achieve and maintain a remission or a state of low disease activity to limit or prevent further joint damage. Given the progressive nature of the disease, there is a need for regular re-evaluation of patient status and adjustment of therapeutic regimens in case of an insufficient response or intolerance to the previous therapy. Traditional treatment options usually include non-steroidal anti-inflammatory drugs, corticosteroids or traditional Disease-Modifying Anti-Rheumatic Drugs (DMARDs). When DMARDs are no longer effective due to disease progression or in case of toxicity, biologic agents may be considered (7). These biologic agents include anti-tumour necrosis factor (anti-TNF) drugs, such as etanercept (eta), adalimumab (ada) and infliximab (inf) which are available in Italy. Clinical evidence suggests that anti-TNF-α therapies are similarly effective in RA patients irrespective of the agent administered (8). For patients not responding to anti-TNF therapies, there are new agents available, such as abatacept (aba), a selective T-cell co-stimulation modulator, and rituximab (rtx), a B-cell targeted biologic agent, each having a different mechanism of action from anti-TNF agents. Both agents were studied in vast randomised controlled trials and shown to be effective after an insufficient response to DMARDs, including at least one anti-TNF agent (9, 10). These new treatment options address significant unmet medical needs. In addition, there are no randomised controlled clinical trials confirming the efficacy of successive use of anti-TNF strategies in anti-TNF inadequate responders. In fact, most observational studies reveal a reduced effectiveness following each anti-TNF switch in case of an insufficient response to a previous anti-TNF agent - a practice increasingly associated with significant drug costs and potentially sub-optimal therapeutic results (11). A recent literature review estimated the effectiveness and cost-effectiveness of these treatment options. However, these analyses were limited by a lack of head-to-head clinical trials and analysed only a subset of therapeutic sequences (12). In Italy, this lack of clinical trials is somewhat compensated with the introduction of a new Italian database tracking real-world effectiveness and safety for the three available anti-TNF agents during the first three years of treatment (13). Hence, there is only limited data that can be used to assess comparative clinical efficacy of different biologic therapies and to support robust cost-effectiveness analyses (14). The main reason for the lack of comparative clinical data for different biologic strategies used in sequence is the prohibitive costs of implementing such complex clinical trials involving a very large number of patients in the long term. In addition, there are ethical concerns about exposing patients to potentially sub-optimal treatment patterns in the long term. In the absence of large-scale head-to-head clinical trials comparing sequential treatment strategies, and given the need to compare efficacy and cost-effectiveness of new biologic therapies *versus* existing treatment options, advanced simulation models offer a useful method for assessing complex treatment strategies.

Sophisticated modelling techniques

thus allow to avoid important logistical and ethical problems of experimental trials by generating valid hypothetical data based on existing clinical evidence, informed expert opinions and simulation of current medical practices in a given country. A modelling approach uses mathematical formulae to generate theoretical data based on clinical evidence and compares various treatment strategies as virtual head-to-head clinical trials. Informative results, such as projected RA treatment costs, effectiveness and cost-effectiveness of various sequential biologic strategies can thus be generated "in silico" (15, 16). The use of simulation modelling in RA treatment is becoming increasingly common in clinical and economic assessments in the US, Canada and Europe (17-19). However, comparative results on effectiveness and cost-effectiveness of treatment regimens generated via simulation are not intended to supplant experimental trials and should be used primarily as decision-making tools in the absence of sufficient clinical evidence.

Table I. Summary of effectiveness probabilities (percentage of patients achieving LDAS).

Biologic agent		%LDAS	Source
Abatacept after IR to 1 anti-TNF agent	Induction – Month 12	18.3%	ATTAIN + LTE study (Genovese 2007)
	Maintenance		
	Month 18	24.2%	ATTAIN + LTE study (Genovese 2007)
	Month 24	28%	ATTAIN + LTE study (Genovese 2007)
Abatacept after IR to 2 anti-TNF agents	Induction – Month 18	24.5%	ATTAIN reanalysis afterIR to 2 anti-TNF agents(EULAR 2008)
	Maintenance		
	Month 24	21.5%	ATTAIN reanalysis afterIR to 2 anti-TNF agents
Anti-TNF agents	Induction – Month 18	11%	REACT trial (Bombardieri 2007)
	Maintenance – Month 24	21.5%	ATTAIN reanalysis afterIR to 2 anti-TNF agents
Rituximab after IR to 1 anti-TNF agent	Induction – Month 12	13%	REFLEX + LTE study (Keystone 2007)
	Maintenance		
	Month 18	25%	REFLEX + LTE study (Keystone 2007)
	Month 24	29%	Keystone (EULAR 2007)
DMARDs	Month 24	5%	Clinical experts opinion

Table II. Summary of effectiveness probabilities (percentage of patients achieving RS).

Biologic agent		%RS	Source
Abatacept after IR to 1 anti-TNF agent	Induction – Month 12	11.1%	ATTAIN + LTE study (Genovese 2007)
	Maintenance		
	Month 18	13.9%	ATTAIN + LTE study (Genovese 2007)
	Month 24	17.1%	ATTAIN + LTE study (Genovese 2007)
Abatacept after IR to 2 anti-TNF agents	Induction – Month 18	8.45%	ATTAIN reanalysis afterIR to 2 anti-TNF agents
	Maintenance – Month 24	14.4%	ATTAIN reanalysis afte IR to 2 anti-TNF agents
Anti-TNF agents	Induction – Month 18	4%	REACT trial (Bombardieri 2007)
	Maintenance – Month 24	14.4%	ATTAIN reanalysis after IR to 2 anti-TNF agents
Rituximab after IR to 1 anti-TNF agent	Induction – Month 12	6%	REFLEX + LTE study (Keystone 2007)
	Maintenance		
	Month 18	13%	REFLEX + LTE study (Keystone 2007)
	Month 24	12%	Keystone (EULAR 2007)
DMARDs	Month 24	1%	Clinical experts opinion

Material and methods

The objective of this cost-effectiveness model was to compare costs, effectiveness and cost-effectiveness of different biologic sequential strategies in Italy in patients with moderate-to-severe active RA (20) and an insufficient response to at least one anti-TNF agent. The study was conducted using the perspective of the public healthcare payer in Italy.

In the absence of studies assessing RA treatment costs by the level of disease activity in Italy, RA direct medical costs were derived from a standard cost analysis performed with a panel of expert rheumatologists (co-authors of the present paper), having vast clinical experience in RA management in Italy. Four categories of disease activity were defined according to DAS28 (Disease Activity Score 28) thresholds: remission (DAS28<2.6), no remission (DAS28≥2.6), LDAS (DAS28≤3.2) and no LDAS (DAS28>3.2) (21-23).

Resource utilisation was estimated per 6-months intervals considering six RA medical resource items according to the clinical experience of the medical expert panel: medical visits, laboratory tests, hospitalisation, imaging, physical therapy and adaptive aids. Unit costs from the national healthcare provider perspective were collected and simulated using distribution ranges for each item. Sub-simulation costing models were carried out to compute specific distributions for each resource item in order to calculate the total medical direct costs for each disease activity categories (24). Biologic drug costs were calculated separately based on 2008 price lists and the recommended dosing in Italy, then further incorporated in the model.

Treatment success was defined using two clinical endpoints aligned with RA treatment targets: achieving LDAS or remission, as published by Russel *et al*., (25) in Canada and by Saraux *et al*. in France (26). Effectiveness estimates of biologic therapies in anti-TNF inadequate responders were derived directly from published clinical trials at the time of model development, namely, the ATTAIN trial and long-term extension study for abatacept (9, 27), the ReAct open label trial for anti-TNF agents (28) and for rituximab, the REFLEX trial and open-label extension analysis in anti-TNF inadequate responders (10, 29). Effectiveness data expressed in percentage of patients achieving LDAS or remission are respectively presented in Tables I and II.

Re-treatment intervals for rituximab were set at 6 months given that most patients who received additional courses of rituximab in pivotal clinical trials (where the need for repeated courses were at physician's discretion based on specific response criteria), did so 24 weeks after the previous course and none were re-treated sooner than 16 weeks (Rituximab US Product monograph). A 6-month re-treatment interval thus aligns with the rituximab effectiveness data used in this simulation model and allows to project a sustained DAS28 response over time. However, a recent analysis suggests that the DAS28 reduction from baseline with rituximab appears to be intermittent and dependent on re-treatment intervals (30). While a 6-month re-treatment interval is suggested in the literature (31), in daily practice, re-treatment intervals for subsequent rituximab courses remain at the discretion of the physician. Then, assuming comparable patient populations, the percentage of patients achieving LDAS or remission at each simulated 6-month time points was used to populate the model over a 2-year time horizon, as previously published (25) (26). To address potential population variability, the simulation model considers full parameters distributions. The overall effectiveness is then expressed in expected number of days in remission or LDAS for each sequence over 2 years.

Eight advanced simulation models were therefore developed to simulate four biologic sequences using two effectiveness criteria (remission or LDAS).

Sequence A: eta-aba-ada
Sequence B: eta-rtx-ada
Sequence C: eta-ada-aba
Sequence D: eta-ada-inf

Sequences A and B assume an insufficient response to a first anti-TNF agent (eta), while sequences C and D assume an insufficient response to two successive anti-TNF agents (eta and ada). Etanercept was chosen as the first anti-TNF agent because it is the most widely prescribed anti-TNF agent in Italy. A sequence including rtx as the third biologic option was not considered because of a lack of published clinical evidence at the time of model development of rtx remission rate after inadequate response to two anti-TNF agents. Hence, using a 2-year time horizon over four 6-month treatment intervals, four biologic strategies were simulated to reflect the sequential use of biologic agents in case of an insufficient response or intolerance to 1 or 2 anti-TNF agents. The same treatment was maintained as long as it was efficacious (*i.e.* for achieving LDAS or remission), and a decision to switch biologic therapy for an inadequate response to the previous agent was allowed at each 6-months time point.

Two sets of mathematical formulae were programmed in this model: i) the "expected value" formula based on weighted averages of each branch of the decision tree. The weights are the transition probabilities expressed either in remission rate or LDAS rate at each node; ii) simulations of lognormal distributions using Monte-Carlo techniques.

The concept of "simulation" used in this advanced modelling approach refers to any analytical method managing data with their specific distributions rather than considering a fixed value only, such as the mean. Simulation models use a random number generator to automatically analyse the effect of varying inputs on outputs of the modelled system. Since current medical practices and different treatment sequences are not explicitly documented in RA, simulation models represent the best approach for comparing various strategies by taking into account the uncertainty inherent to these parameters. Lognormal type distributions were programmed for each direct medical costs of managing remission, low disease activity and moderate-to-high disease activity, from mean and the standard deviations. For example, instead of using the mean value of direct medical costs to manage a patient in remission during 6 months, in the model, the log normal distribution constructs a distribution shape from the mean and the standard deviation, then Monte Carlo simulations screen 5000 times potential values along the distribution shape, allowing to calculate the results with standard deviations.

Monte-Carlo simulations (using 5000 iterations of random numbers) were computed for each sequence, allowing to screen all shapes of parameters distributions. This approach is considered a robust sensitivity analysis (probabilistic sensitivity analysis) which is recommended as "best practice" in economic modelling to assess the potential impact of parameters distribution on the results. Then, eight models were developed using 2 different treatment success criteria (remission or LDAS) for each of the 4 defined treatment sequences. Each model generated mean values and standard deviations of costs, effectiveness and mean cost-effectiveness over 2 years. Statistical tests (mean comparisons) were performed to calculate potential significant differences.

Results

Medical costs

Direct medical costs (excluding the cost of biologic therapies which were calculated separately) were estimated per level of disease activity. Direct medical costs were estimated at 1292€ per 6 months (SD= 403) for patients in remission (Fig. 1), at 1333€ per 6 months (SD=403) for patients in LDAS (Fig. 2) and at 5010€ (SD=1120) for patients in moderate-to-high disease activity (Fig. 3). Hence, achieving LDAS or remission was associated with lower medical costs. Higher direct medical costs for patients in moderate-to-high disease activity reflect the higher use of health care services. Key costs drivers were mainly due to hospitalisation.

Total costs, effectiveness and cost effectiveness

Using direct medical costs, the cost of biologic therapies and published effectiveness data for each sequence, 8 simulation models generated the following results, as presented in Table III.

a) Achieving LDAS

Sequence A, representing the use of abatacept after an insufficient response to one anti-TNF agent (eta), appeared significantly ($p<0.01$) more efficacious over 2 years (102 days in LDAS) compared to sequence B which includes rituximab in a similar sequence (82 days in LDAS). Corresponding mean

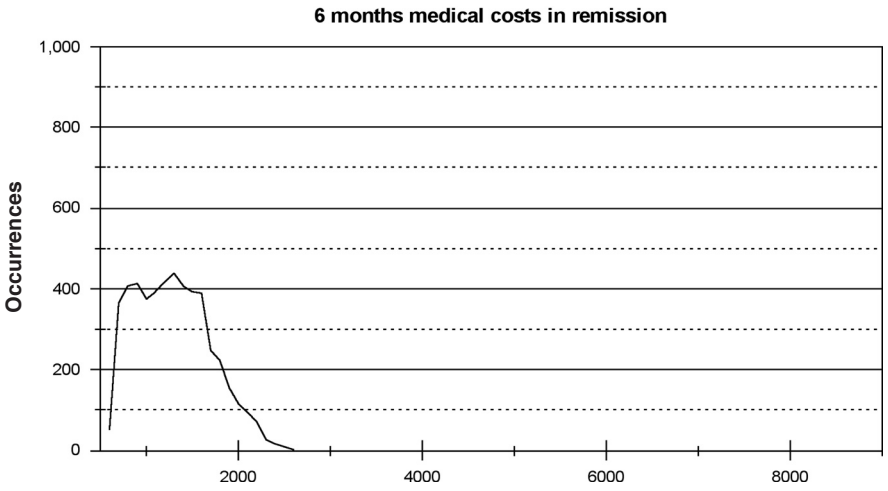

Fig. 1. Medical cost distribution for patients in Remission in € per 6 months (excluding biologic drug costs).

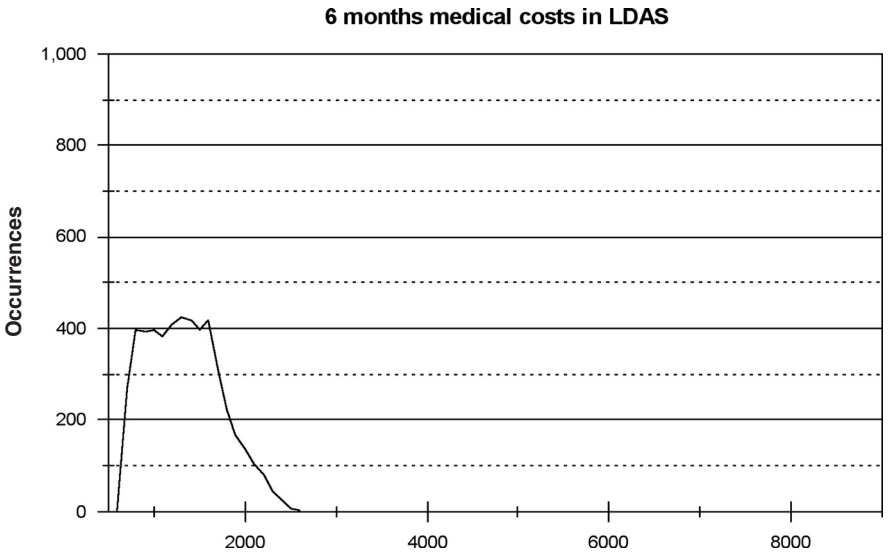

Fig. 2. Medical cost distribution for patients in Low Disease Activity State in € per 6 months (excluding biologic drug costs).

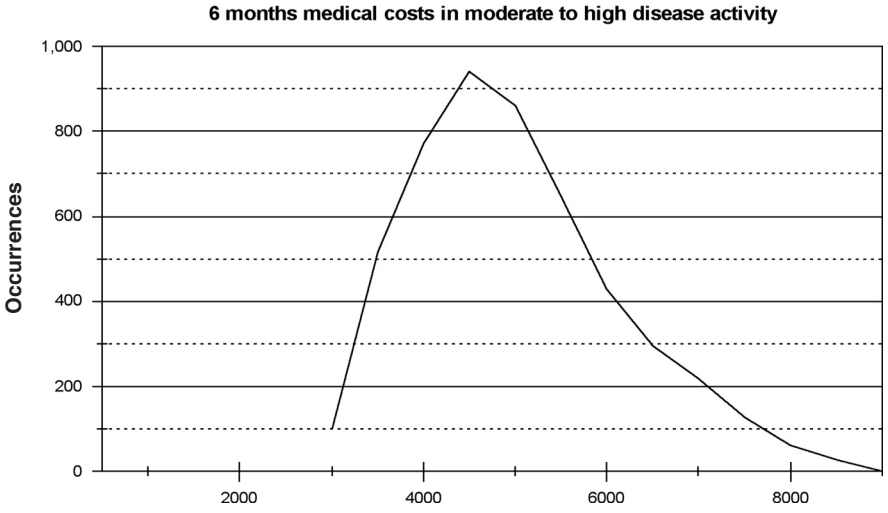

Fig. 3. Medical cost distribution for patients in Moderate to High Disease Activity State in € per 6 months (excluding biologic drug costs).

cost-effectiveness ratios showed significantly lower costs ($p<0.01$) per day in LDAS for sequence A which included abatacept after a first anti-TNF agent (€376) compared to a similar sequence B including rituximab (€456).

Figures 4 and 5 represent cost-effectiveness acceptability curves for sequences A and B. The acceptability curve shows the probability that a sequence strategy is cost-effective given the range of monetary values that a decision-maker might be willing to pay for a unit change in the clinical outcome. The range of maximum monetary values, expressed as Euros per day in LDAS, is given on the *x*-axis. Given a specified value of this 'acceptable' cost-effectiveness ratio (a point on the *x*-axis), the curve shows the probability that the data are consistent with a cost-effectiveness ratio falling below that value (read off the *y*-axis). Figure 4 shows that for about 80% of patients on sequence A (eta-aba-ada), direct treatment costs were estimated at less than 400 Euros per day in LDAS. Figure 5 shows that for sequence B (eta-rtx-ada), only 4% of patients had direct treatment costs estimates at less than 400 Euros per day in LDAS.

Sequence C represents the use of abatacept after an insufficient response to two successive anti-TNF agents (eta and ada) and appeared significantly ($p<0.01$) more efficacious over 2 years (63 days in LDAS) compared to sequence D, which included a third anti-TNF (inf) after two anti-TNF agents (32 days in LDAS). Corresponding mean cost-effectiveness ratios showed significantly lower costs ($p<0.01$) per day in LDAS in sequence C, including abatacept after two anti-TNF agents (€642), as compared to sequence D using three successive anti-TNF agents (€1164).

b) Achieving remission

Sequence A, which represents the use of abatacept after an insufficient response to one anti-TNF agent (eta), appeared significantly ($p<0.01$) more efficacious over 2 years (52 days in remission) compared to sequence B which included rituximab in a similar sequence (32 days in remission). Corresponding mean cost-effectiveness ratios showed

Table III. Model results over 2 years (mean and SD: Standard Deviation).

	Total costs in LDAS (€)	Expected number of days in LDAS	Cost-effectiveness (€/LDAS day)	Total costs in remission (€)	Expected number of days in remission	Cost-effectiveness (€/remission day)
Sequence A : eta-aba-ada	38,616 (SD 2,621)	102 (SD 1.1)	376 (SD 25)	38,583 (SD 2,372)	52 (SD 0.2)	741 (SD 45)
Sequence B : eta-rtx-ada	37,667 (SD 2,571)	82 (SD 1.2)	456 (SD 31)	37,686 (SD 2,311)	32 (SD 0.2)	1,158 (SD 71)
Sequence C : eta-ada-aba	38,628 (SD 2,492)	63 (SD 15)	642 (SD 167)	38,522 (SD 2,301)	21 (SD 9)	2,173 (SD 1,144)
Sequence D : eta-ada-inf	37,566 (SD 2,417)	32 (SD 1.3)	1,164 (SD 89)	37,729 (SD 2,234)	9 (SD 0.3)	3,923 (SD 265)

Effectiveness and cost-effectiveness differences between sequences A and B and between C and D are statistically significant ($p<0.01$).

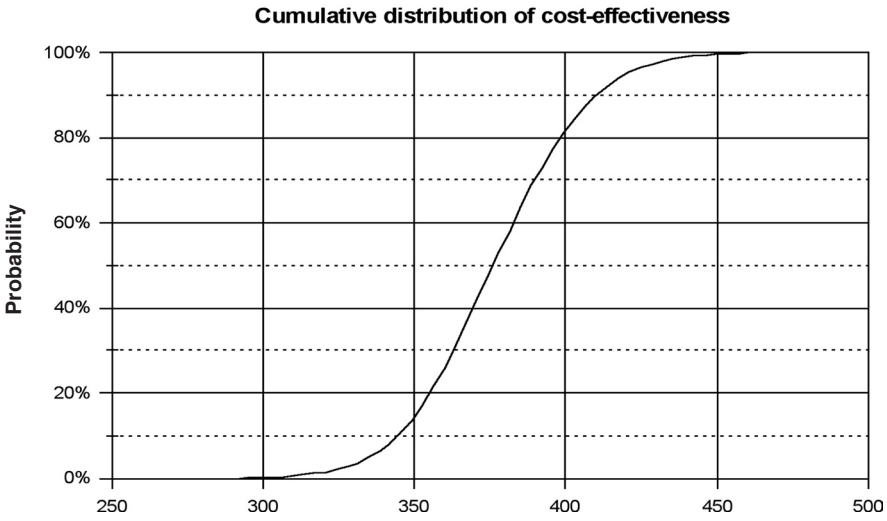

Fig. 4. Cost-effectiveness acceptability curve of sequence A (eta-aba-ada) using LDAS success endpoint (direct treatment costs were estimated at less than 400 Euros per day in LDAS in about 80% of patients).

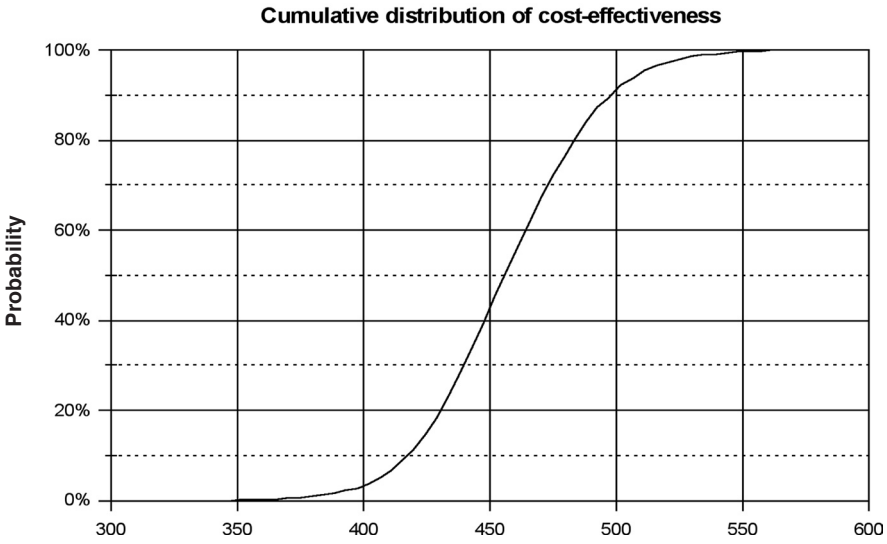

Fig. 5. Cost-effectiveness acceptability curve of sequence B (eta-rtx-ada) using LDAS success endpoint (direct treatment costs were estimated at less than 400 Euros per day in LDAS in about 4% of patients).

significantly lower costs ($p<0.01$) per day in remission in sequence A which included abatacept after a first anti-TNF agent (€741), as compared to sequence B which included rituximab in a similar sequence (€1158).

Sequence C, which represents the use of abatacept after an insufficient response to two successive anti-TNF agents (eta and ada), appeared significantly ($p<0.01$) more efficacious over 2 years (21 days in remission) compared to sequence D which included a third anti-TNF agent (inf) after two anti-TNF agents (9 days in remission). Corresponding mean cost-effectiveness ratios showed significantly lower costs ($p<0.01$) per day in remission in sequence C which included abatacept after two anti-TNF agents (€2173) compared to sequence D which used three successive anti-TNF agents (€3923).

Discussion

Long-term management of RA is complex and demands considering different therapeutic options such as DMARDs and biologic agents, and using different therapeutic regimens in a sequential manner in case of an insufficient response to previous therapy. Biologic therapies hold substantial promise for patients. However, due to their significant costs compared to traditional DMARDs, biologic agents tend to be used later in the sequence of treatment – namely, after an insufficient response to one or more traditional DMARDs. Given the chronic and progressive nature of the disease, delaying biologic therapy to a later stage may expose patients to developing irreversible joint damage in the long-term, leading to negative clinical and socio-economic consequences.

As longitudinal multi-arms clinical trials comparing various sequences of biologic agents are impractical, it is critical to estimate the efficacy and public healthcare costs of such clinical interventions. Considering the varied socio-medical environments of different European countries, economic analyses are country-specific and their conclu-

sions do not apply to different health care systems (32). A novel solution to these problems consists of conducting simulations using advanced modelling approaches as detailed in this paper (16). This model's assumptions are limited and based on the most recent clinical evidence, recommended dosing for each treatment option and medical practices in Italy at the time of model development. Combining the clinical evidence with relevant health resource utilisation costs in Italy allows to derive comprehensive and robust (albeit theoretical) comparative results that otherwise would not be available to clinicians and policy-makers.

There are a few aspects of this model worth noting. The first one is the selection of the outcome measure. Most published economic models in RA are cost-utility models (often presented as "cost-effectiveness" models) and use "Quality Adjusted Life Years" (QALY) as subjective outcome measure (33-36). However, the objective validity of the QALY is at the centre of an active scientific debate (37, 38). Importantly, cost-utility analyses use multiple assumptions and concepts which may lead to divergent results. This is because utility scores can vary considerably according to the utility assessment technique used (33, 39, 40). Marra *et al*. (41) showed that utility scores in RA patients derived from indirect methods – the HUI, EQ5D (EuroQol) and SF-6D questionnaires – were statistically significantly different. Similarly, Conner-Spady *et al*. (42) found significant differences in the utility scores from different instruments (EQ5D, SF-6D and HUI) and warned about the validity of their use in cost-utility analyses. In that study, utility scores derived from one technique (Time Trade-off) were significantly different than utility scores derived from another technique (EuroQol questionnaire). Given the variety of utility assessment methods, interpretation of cost-utility results expressed in cost per QALY should be done with considerable caution. Consequently, it appears that real cost-effectiveness analyses expressing results in evidence-based clinical outcomes rather than in QALYs are methodologically more consistent, clinically relevant and reliable for assessing innovative RA treatments (33, 38). Aligned with recommended RA treatment targets, we chose the clinically relevant outcome measures of achieving a state of remission or low disease activity (LDAS). In particular, Welsing *et al*. (43) demonstrated the relationship between a fluctuant disease activity score and radiologic progression in patients with RA. Their study showed that radiologic progression is not linear in individual patients and that fluctuations in disease activity are directly related to changes in radiologic progression. Importantly, their results showed that a fluctuating LDAS and a constant level of high disease activity were associated with similar predictive radiologic damage. Consequently, slowing the progression of joint damage is dependent on having and maintaining a constant LDAS or remission.

Besides the clear relationship between disease activity and progression of joint destruction and functional disability, disease activity is also correlated with overall costs (44-46). Due to these reasons, this innovative cost-effectiveness sequential model is based on the therapeutic goal of achieving and maintaining a sustained DAS28 response over time by either continuing an effective biologic agent or switching to another agent in case of an insufficient response to the previous biologic therapy.

Other types of models are only cost-based, such as "Budget Impact Analyses". This approach is much more simple as it does not take into account any clinical benefit. It is mostly used to estimate the budgetary impact of reimbursing a new drug (47). In contrast, cost-effectiveness models estimate the overall costs and clinical benefits and are used to assess and compare the overall clinical and economic value of different therapies. Such models also suggest to use data across clinical trials, which is always a difficult task as populations and methodologies are not necessarily similar. However, robust meta-analyses are nowadays considered as part of evidence-based medicine and simulation models provide interesting additional techniques to combine and compare data from different sources (clinical trials, literature, reports, observational data, etc.). In the present model, the ATTAIN and REFLEX clinical trials were deemed comparable in terms of patients baseline characteristics (age, gender, disease duration and DAS28 score) (26). Furthermore, potential data variability was managed using probabilistic sensitivity analyses and validated assumptions to integrate data from heterogeneous sources. Because the model is based on Lognormal distribution, which is derived from Normal distributions, similar results could be obtained without Monte-Carlo simulations. However, the added value of Monte Carlo simulations is to generate results with standard deviations, providing interesting information about the uncertainty of results. Hence, simulation approaches provide methodological frameworks allowing to better interpret the conclusions in the context of their specific underlying assumptions.

Since there are a number of modelling studies using different clinical and economic outcomes in RA treatment, there is an effort to standardise these modelling criteria. The Outcome Measures in the Rheumatology Clinical Trials (OMERACT) working group proposed twelve key elements for economic evaluation in RA, including the duration of therapy, clinical outcome measures, valuation of outcomes, therapeutic sequences and others (48). As always, it is important to remember that despite the sophistication and robustness of data generated via modelling approaches, such analyses are not meant to replace clinical trials, real life cohorts, or therapeutic guidelines. Nevertheless, health economic evaluations prove to be most useful and are increasingly used to assess and compare effectiveness and costs of different therapeutic options to assist resource allocation decisions.

Conclusions

This innovative cost-effectiveness simulation model based on the Italian health care system used LDAS and remission as measures of effectiveness to assess and compare therapeutic strategies involving different biologic agents used in a sequential manner for the

treatment of moderate-to-severe RA patients with an insufficient response to at least one anti-TNF agent. The resource utilisation assessment shows that RA imposes a substantial economic burden on the healthcare system and that achieving LDAS or remission is associated with lower RA medical costs. Furthermore, the effectiveness, overall treatment costs and cost-effectiveness vary according to different treatment sequences. This study shows that a treatment sequence using abatacept after one anti-TNF agent appears to be significantly more effective and cost-effective *versus* a similar sequence using rituximab, as well as when using abatacept after two anti-TNF agents *versus* a third anti-TNF agent for achieving LDAS or remission. Advanced simulation models based on clinical evidence and medical practices offer a promising approach for comparing costs, effectiveness and cost-effectiveness of complex sequential biologic strategies for the management of moderate-to-severe active RA in Italy.

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