Cost-effectiveness simulation model of biologic strategies for treating to target rheumatoid arthritis in Germany

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Abstract

Objectives

The treatment of active rheumatoid arthritis (RA) usually requires different therapeutic options used sequentially in case of an insufficient response (IR) to previous agents. Since there is a lack of clinical trials comparing biologic treatment sequences, simulation models might add to the understanding of optimal treatment sequences and their cost-effectiveness. The objective of this study was to assess the cost-effectiveness of different biologic treatment strategies in patients with an IR to anti-TNF agents, based on levels of disease activity from the German public payer's perspective.

Methods

A cost-effectiveness sequential model was developed in accordance with local RA treatment strategies, using DAS28 scores as dichotomous effectiveness endpoints: achieving remission/no remission (RS/no RS) or a state of low disease activity (LDAS/no LDAS). Costs were estimated using resource utilisation data obtained from a large observational German cohort. Advanced simulations were conducted to assess the cost-effectiveness over 2 years of four sequential biologic strategies composed of up to 3 biologic agents, namely anti-TNF agents, abatacept or rituximab, in patients with moderate-to-severe active RA and an IR to at least one anti-TNF agent.

Results

Over two years, the biological sequence including abatacept after an IR to one anti-TNF agent appeared the most effective and cost-effective versus (vs.) use after two anti-TNF agents (€633 vs. €1,067/day in LDAS and €1,222 vs. €3,592/day in remission), and vs a similar sequence using rituximab (€633 vs. €728/day in LDAS and €1,222 vs. €1,812/day in remission). The sequence using a 3rd anti-TNF agent was less effective and cost-effective than the same sequence using abatacept (€2,000 vs. €1,067/day in LDAS and €6,623 vs. €3,592/day in remission). All differences were statistically significant ($p<0.01$).

Conclusions

The results suggest that in patients with an IR to at least one anti-TNF agent, biologic sequences including abatacept appear more efficacious and cost-effective than similar sequences including rituximab or only cycled anti-TNF agents.

Key words

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

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Received on June 2, 2012; accepted in revised form on October 22, 2012.

Funding: the study was funded by an unrestricted grant from Bristol-Myers Squibb.

Competing interests: A. Beresniak, S. Merkesdal, K. Krüger, C. Baerwald, and H. Zeidler have received expert honoraria from Bristol-Myers Squibb for participating in the working meetings;
A.S. Neubauer is an employee of Bristol-Myers Squibb;
D. Dupont was an employee of Bristol-Myers Squibb at the time of model development and until October 2009.

Background

Burden of illness studies in Rheumatoid Arthritis RA have been conducted in various countries and were reviewed by Rosery *et al*. in 2005 (1). Costs of RA in Germany have been published by Ruof *et al*. in 2003 (2), Hülsemann *et al*. in 2005 (3) and 2006 (4), and Huscher *et al*. in 2006 (5). RA is estimated to affect about 0.5 to 1% of the German population with significantly higher incidence rates among women, patients over 50, and low-income groups (6). Given that there is no cure for RA, this chronic condition is associated with a significant medical and economic burden for patients and society. Current estimates of RA-related direct medical costs in Germany vary from €3815 per patient-year to €4737 a year (2, 5).

RA patients experience different levels of intensity, duration and frequency of disease activity which makes it challenging to choosing an optimal treatment strategy. The chronic and progressive nature of the disease also highlights the importance of "treating to target" to achieve a state of low disease activity (LDAS) or ideally remission (RS). This requires to individualise treatment regimens, to optimise dosing, to combine therapies and if needed, to use biologic therapies based on the level of disease activity and response to previous treatments.

Current options for RA include non-steroidal anti-inflammatory drugs, corticosteroids and traditional disease-modifying anti-rheumatic drugs (DMARDs). However, when the effectiveness of these agents decreases as the disease progresses or when patients experience significant adverse events, treatment regimens must be adjusted. The traditional treatment pyramid includes the use of more potent agents if patients fail to respond to initial therapy (7, 8). In case of insufficient response to DMARD therapies, patients become candidates for biologic therapies, such as anti-tumour necrosis factor-alpha (anti-TNF) agents (etanercept (ETA), adalimumab (ADA) and infliximab (INF), or other biologic agents, abatacept (ABA), rituximab (RTX), each class of agents presenting a distinct mechanism of action. Although anti-TNF agents are frequently used sequentially in case of an insufficient response (IR) or intolerance to a first anti-TNF agent, this practice is not supported by robust clinical nor health economics evidence. A recent study proposed an original algorithm to early predict potential response to anti-TNF agents (9), suggesting the importance of sequential treatment strategies for identified non responders. Moreover, as most of clinical trials focus on a single treatment (10-13), they do not compare multiple arms of complex therapeutic strategies such as sequential biologic treatments. And while the costs of sequential DMARDS therapies were published by Schädlich *et al*. in 2005 (14), most recent cost-effectiveness studies in RA (15, 16) do not take into account biologic treatment switches, making it difficult to compare full treatment sequential strategies from a decision making perspective. Hence, even though the use of biologic switches represents the general medical practice, there is a lack of scientific evidence to compare overall costs and effectiveness of such strategies. Given the importance of treating to target, this approach is based on achieving either remission or LDAS as effectiveness endpoints. A similar approach was used to assess cost-effectiveness of sequential biological strategies in Canada (17), France (18), Italy (19), Finland (20) and Spain (21). This paper proposes a similar modelling approach to evaluate the effectiveness, costs and cost-effectiveness of different sequential biologic treatment strategies for managing moderate-to-severe RA in Germany, in patients with an IR to prior anti-TNF agents.

Methods

Given the scarcity of head-to-head clinical trials, there is a need to use decision analytic models to assess and compare expected costs and effectiveness of different RA biologic strategies used in sequence, using previous studies of RA treatment cost estimates. This approach is aligned with the *Outcome Measures in Rheumatology Clinical Trials* (OMERACT) recommendations to model realistic therapeutic sequences (22), particularly when comparative clinical trials do not exist. Hence,

evaluating the cost-effectiveness of a therapy within a therapeutic sequence may identify the most clinically suitable population for a new medicine, and the most effective and cost-effective treatment sequence (22). A model is a mathematic formula linking different variables to generate results relevant to a given environment based on local medical practices. A cost-effectiveness model is classically composed of a framework structure populated with costing and effectiveness data. Best modelling practices suggest that data populating a model should be based on relevant costs and existing published clinical data at the time of model development (23). RA model assumptions should also be validated by expert clinicians according to their current medical practice in a given country. Specific to RA, results generated by such modelling approach provide unique information on the expected effectiveness, overall costs and cost-effectiveness of different biologic strategies to assist medical decision-making as well as resource allocation decisions.

Cost-effectiveness model design

This model compares the costs of biologic treatment sequences from the perspective of the German health authorities over a 2-year horizon, with effectiveness expressed in clinical outcomes defined as disease activity scores. This time horizon was selected not to have to speculate about the hypothetical long-term efficacy (*e.g.* beyond the 2-year efficacy data available at time of model development) (10, 12, 24). The target population defined for this model consists of patients suffering of moderate-to-severe RA and with an IR to at least one anti-TNF agent. Results were generated using DecisionPro 4.1 programming software in Dscript language and were expressed for one single hypothetical patient. Extensive probabilistic sensitivity analyses were carried out using Monte Carlo simulations.

Model structure

Advanced simulation models represent a type of decision trees which allow computing variable distributions. The present simulation comprises eight separate models simulating four defined biologic sequences (each using up to three different biologic agents) in patients with an IR to a first anti-TNF agent. The effectiveness criteria were defined as achieving remission or a state of low disease activity, as confirmed by the DAS scores. Because of the large number of possible treatment sequences, a decision was made to assess and compare the main biologic treatment strategies available at time of model development, as defined in the following treatment sequences:

Sequence A: adalimumab→abatacept→etanercept
Sequence B: adalimumab→rituximab→etanercept
Sequence C: adalimumab→etanercept→abatacept
Sequence D: adalimumab→etanercept→infliximab

The model which runs over 2 years uses four 6-months treatment periods, as published by Russel *et al*. in Canada (17), Saraux *et al*. in France (18), Cimmino *et al*. in Italy (19) and Beresniak *et al*. in Spain (21). This also reflected German clinical practice at the time of model development, where biologic therapies could be switched after 6 months in case of an IR to the previous biologic agent. Adalimumab was chosen as the first biologic agent for each sequence because it had the highest market shares based on a prescription database for Germany (IMS DPM) at the time of model simulation. However, given that the model focuses on patients with an IR to at least one anti-TNF agent, all sequences assume an IR to a first anti-TNF agent. Hence, the results of the sequences relative to each other are not dependent on the choice of this first biologic agent. Sequences A (shown in Figure 1) and B assume 100% IR to a first anti-TNF agent (here ADA), followed by a switch to either ABA or RTX, followed by a potential third biologic agent (ETA) in case of further IR. Sequences C and D assume 100% IR to two anti-TNF agents (namely, ADA and ETA), then a switch to a third biologic agent, either ABA or infliximab (INF). The model assumes that each new biologic option introduced in the sequence is maintained as long as the clinical response (DAS score) is deemed adequate. The model therefore assumes using up to 3 biologic agents, and considers a return to DMARDS therapy in case of IR to three successive biologic agents.

To manage uncertainty, and as per best practice in economic modelling, 5000 Monte-Carlo simulations generated mean values and standard deviations of the three model outputs: costs, effectiveness (days in LDAS/RS), and average cost-effectiveness over 2 years. Monte Carlo simulations consist of a class of computational algorithms that rely on repeated random sampling to compute their results. This approach, also called the "probabilistic sensitivity analysis", allows screening all possible values of a given parameter according to a defined distribution shape and to recalculate the results. For the purpose of this study, it was possible to construct distribution shapes from confidence intervals of resource utilisation and from published effectiveness DAS data when standard deviations were presented. Therefore, the model was able to construct distributions of results which are presented with their standard deviations (SD). Statistical tests (2 groups mean tests with known variances deducted from cost-effectiveness SD) were performed to calculate po-

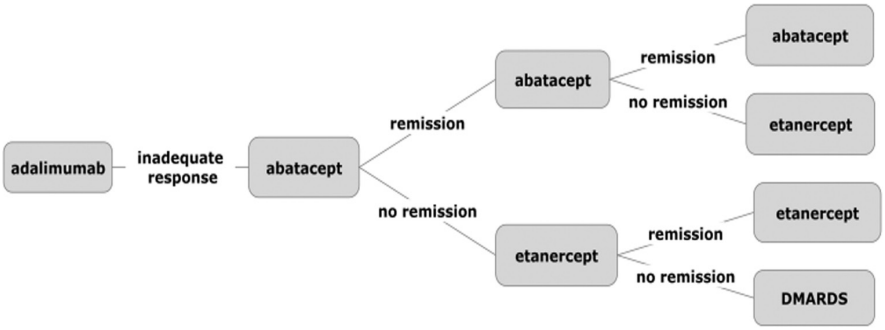

Fig. 1. Sequence A model structure with remission as effectiveness endpoint.

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

Biologic agent		%LDAS	Source
Abatacept after IR to anti-TNF therapy	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 anti-TNF therapy	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 anti-TNFtherapy	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 anti-TNF therapy	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

tential significant differences between cost-effectiveness ratios of treatment strategies.

Effectiveness criteria

According to routine clinical practice and RA treatment guidelines, the objective of RA treatment is to control or stop disease progression and to quickly achieve a level of low disease activity, or ideally remission, as assessed by the Disease Activity Score measured on 28 joints (DAS28). The following clinical endpoints were therefore defined as the effectiveness criteria for the purpose of this cost-effectiveness study: remission state (RS) DAS28 score <2.6, and low disease activity state (LDAS) DAS28 score ≤3.2. For patients not achieving RS or LDAS, they were considered in a state of moderate-to-high disease activity state (HDAS) DAS28 score >3.2. In line with these categories, the percentage of patients achieving either RS or LDAS was derived from clinical trials including long-term extension studies where applicable (10, 12). The model assumed that if one patient failed to improve after three biologic options, that patient would be maintained on DMARDS with a residual effectiveness of achieving RS and LDAS estimated at respectively 1% and 5%. Effectiveness probabilities and relevant data sources for each strategy are summarised in Table I and II.

As main effectiveness outcomes of the present model, the "expected" number of days in RS or in LDAS were calculated for each sequence over the complete 2-years time horizon (Table IV) using the following formula:

$$N = \sum [Sr_i * 180]$$

N= expected number of days in therapeutic success (RS or LDAS)

Sr= Success rate (Remission rate or LDAS rate) over 6 months

i = 6 months treatment period

This approach assumed sustained efficacy over 6 months and comparable patient populations between clinical data sources, which was confirmed by similar population characteristics between pivotal clinical trials such as the ATTAIN (12) and the REFLEX (11, 13) trials.

Costing data

Cost-related data were derived from the database of the "Hannover Costing Study" published by Ruof (3, 4). For the purpose of the present model, the costs estimates were calculated for the three defined DAS28-categories. Medi-

Table III. Frequency of medical resource utilisation used (mean + SD) according to three disease activity categories RS, LDAS and HDAS and estimated average reimbursement for each item (in Euros).

Medical resource utilisation item	RS (n =71)	LDAS (n=39)	HDAS (n=227)	Item average reimbursement (2008)
Specialist visits	3.5 (4.2)	3.8 (5.1)	3.8 (5.2)	47.55 €
GPvisits	3.6 (6.2)	4.8 (8.8)	3.8 (6.6)	36.50 €
Lab tests (blood)	4.2 (2.3)	5.4 (4.0)	5.8 (5.0)	19.41 €
Lab tests (urine)	3.3 (2.4)	3.4 (2.2)	3.8 (4.2)	4.90 €
Rx, thorax	0.5	0.5	0.5	8.88 €
Rx, hands	0.9 (1.2)	1.0 (1.0)	1.1 (1.2)	11.10 €
Rx, feet	0.9 (1.0)	0.9 (1.0)	1.0 (1.1)	11.10 €
Rx, hip	0.14 (0.5)	0.2 (0.6)	0.3 (0.8)	68.82 €
Rx, knee	0.14 (0.5)	0.3 (0.7)	0.3 (0.8)	68.82 €
Ultrasound	0.4 (1.3)	0.4 (1.0)	0.7 (1.4)	8.33 €
Physiotherapist visits	5.5 (15.2)	8.2 (12.8)	8.6 (18.8)	88.25 €
Hospitalisation, without surgery	0.03 (0.2)	0 (0)	0.05 (0.3)	2,469.60 €
Surgery, outpatient	0.08 (0.4)	0.05 (0.3)	0.09 (0.4)	356.87 €
Surgery, inpatient	1.0 (3.6)	0.7 (3.0)	1.6 (4.6)	3,147.20 €
Surg., inp., synovect.	0.01 (0.4)	0.03 (1.0)	0.03 (0.9)	2,203.00 €
Surg., inp., hip	0 (0)	0 (0)	0.03 (0.6)	6,630.00 €
Surg., inp., knee	0.03 (0.8)	0 (0)	0.03 (0.7)	7,173.00 €
Aids	0.1 (0.4)	0.3 (0.7)	0.4 (0.8)	90.00 €
Orthesis	1.0 (4.2)	1.4 (4.8)	1.3 (4.4)	89.63 €
Radiosynoviorthese	0	0	0.25	55.32 €

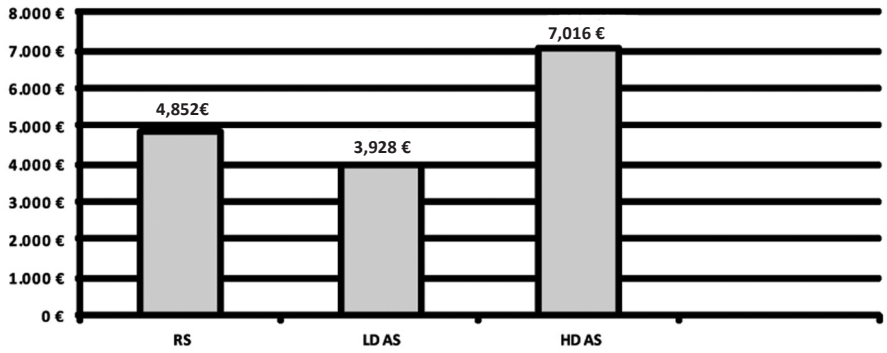

Fig. 2. Total medical resources used in rheumatoid arthritis in Euros over a 6-month period per disease activity category.
(Remission state: RS, Low Disease Activity state: LDAS, High Disease Activity state: HDAS) excluding biologic drug costs).

cal resource utilisation was weighted using 2008 average stationary Disease Related Groups (DRG) and ambulatory services reimbursements. Table III summarises the cost domains covered, the resource utilisation in physical units and the associated costs. As a first step, direct medical costs (excluding biologic drugs cost) were calculated per disease activity categories. The direct medical costs estimated for each of the defined DAS28-categories RS, LDAS and HDAS are represented in Figure 2. For patients achieving RS, costs were estimated at €4,852 (SD=13487) per 6 months. For patients achieving LDAS, costs were estimated at €3,928 (SD=8566) per 6 months. For patients achieving HDAS, costs were estimated at €7,016 per 6 months (SD=11813). Key costs drivers were hospitalisation and surgery.

As a second step, biologic costs were added to run the eight cost-effectiveness models (4 biologic treatment sequences using two outcomes, LDAS and RS). RA medication costs were calculated using the national tariff (Table V). Biologic drug costs were calculated based on the 2008 price lists and recommended dosing. The average dose for infliximab was estimated at 4mg/kg, based on a publication from Zink *et al*. (25). All direct medical costs were estimated per 6-month intervals. Assuming a sustained DAS28 response at each 6-month period, and based on emerging evidence at the time of model development, the re-treatment interval was set at 6 months for rituximab (26, 27). Since the study uses the public payer perspective, indirect costs were not considered in the model.

Results

Using RA management medical costs, cost of biologic therapies and published effectiveness data, the model generated for *each full* sequence, the overall treatment costs over 2 years, the expected number of days in RS or LDAS, and the cost-effectiveness expressed in cost per day in RS or LDAS. Results are summarised in Table IV.

Achieving low disease activity state (LDAS)

Sequence A (which included the use of ABA after an IR to ADA) appeared significantly ($p<0.01$) more efficacious over 2 years (102 days in LDAS) when compared to a similar Sequence B which included RTX (82 days in LDAS). Total costs over 2 years were estimated at €64,907 for Sequence A and at €60,050 for Sequence B. Hence, corresponding mean cost-effectiveness ratios showed significantly lower costs ($p<0.01$) per day in LDAS for Sequence A which included ABA after an IR to ADA (€633), as compared to Sequence B which included RTX (€728).

Sequence C (which included the use of ABA after an IR to two anti-TNF agents, ADA, then ETA) appeared significantly ($p<0.01$) more efficacious over 2 years (64 days in LDAS) compared to a similar Sequence D which included a third anti-TNF agent (INF) (32 days in LDAS). Total costs over 2 years were estimated at €64,221 for Sequence C and at €64,531 for sequence D. Again, corresponding mean cost-effectiveness ratios showed significantly lower costs ($p<0.01$) per day in LDAS for Sequence C, which included ABA after ADA and ETA (€1,067) compared to Sequence D which used three successive anti-TNF agents (€2,000).

Table IV. Effectiveness and cost-effectiveness of the biologic sequences simulated.

Sequential Biological Strategies	Effectiveness (expected no. of days)		Medical costs (€)		Cost-Effectiveness	
	LDAS	RS	LDAS	RS	LDAS	RS
Insufficient response to a first anti-TNF agent						
A : ADA(IR)-ABA-ETA	102 (1.1)	52 (0.2)	64,907 (23,521)	63,601 (22,978)	633 (230)	1,222 (442)
B : ADA(IR)-RTX-ETA	82 (1.2)	33 (0.2)	60,050 (23,509)	58,952 (33,316)	728 (286)	1,812 (699)
Insufficient response to 2 anti-TNF agents						
C: ADA(IR)-ETA(IR)-ABA	64 (15.0)	22 (9.4)	64,221 (22,071)	63,433 (23,836)	1,067 (476)	3,592 (2'458)
D : ADA(IR)-ETA(IR)-INF	32 (1.4)	10 (0.3)	64,531 (23,626)	63,709 (22,687)	2,000 (740)	6,623 (2'350)

*Strategy A *vs*. Strategy B: $p<0.01$; Strategy A *vs*. Strategy C: $p<0.01$; Strategy C *vs*. Strategy D: $p<0.01$.
Effectiveness is expressed in expected number of "success" days over a 2-year period for each entire sequence. Total costs include disease management and drug costs over a 2-year period for each entire sequence. Cost-effectiveness is expressed as mean cost-effectiveness over 2 years for each entire sequence. Results were calculated based on published clinical trials. Sensitivity analyses were performed using Monte Carlo simulations (n=5000) for each sequence. The numbers in brackets provides the standard deviations (SD).
IR: Insufficient response

Table V. Biologic drug costs and recommended dosages.

	Year 1	Year 2
Abatacept (250 mg vial)		
Estimated number of IV infusions per year[1]	14	13
Estimated number of vials per year[1,2] (per infusion)	42 (3)	39 (3)
Acquisition drug cost per unit [7]	550€	550€
Adalimumab (40 mg syringe)		
Estimated number of s.c. injections per year[3]	26	26
Estimated number of pre-filled syringes per year	26	26
Acquisition drug cost per pre-filled syringe	879€	879€
Etanercept (25 mg vial)		
Estimated number of s.c. injections per year[4]	104	104
Estimated number of vials per year	104	104
Acquisition drug cost per unit	220€	220€
Infliximab (100 mg vial)		
Estimated number of IV infusions per year[5]	8	6,5
Estimated number of vials per year[2]	24	19,5
Acquisition drug cost per unit	836€	836€
Rituximab (500 mg vial)		
Estimated number of IV infusions per year[6]	4	4
Estimated number of vials per year	8	8
Acquisition drug cost per unit	1,868€	1,868€

1. Abatacept dosing: (<60 kg=2 vials, ≥60 kg- ≤100 kg = 3 vials, >100 kg = 4 vials) iv infusion at 2 and 4 weeks after initial infusion, then every 4 weeks. Year 1 = 14 infusions (including loading dose). Year 2 = 13 infusions. For 75 kg = 3 vials (750 mg) per infusion.
2. Assuming 75 kg average body weight.
3. Adalimumab dosing: 40 mg s.c. every other week (26 injections per year).
4. Etanercept dosing: 25 mg s.c. twice weekly (or 50mg once weekly) = 104 injections per year.
5. Infliximab dosing (see Zink *et al*. 2006 Dosisanpassung): assuming 4 mg/kg for the first 3 doses (at week 0, 2 and 6) and 4 mg/kg every 8 weeks thereafter.
6. Rituximab dosing: 2 x 1000 mg IV infusions separated by 2 weeks interval as first treatment course; another treatment course is assumed every 6 months.
7. All unit costs are based on the Rote Liste 2008 and the EBM 2008.

Achieving remission (RS)

Sequence A (which included the use of ABA after an IR to ADA) appeared significantly ($p<0.01$) more efficacious over 2 years (52 days in RS) when compared to a similar Sequence B which included RTX (33 days in RS). Total costs over 2 years were estimated at €63,601 for Sequence A and at €58,952 for Sequence B. Hence, corresponding mean cost-effectiveness ratios showed significantly lower costs ($p<0.01$) per day in remission for Sequence A which included ABA after an IR to ADA (€1,222), as compared to Sequence B which included RTX (€1,812).Sequence C (which included the use of ABA after an IR to two anti-TNF agents, ADA, then ETA) appeared significantly ($p<0.01$) more efficacious over 2 years (22 days in RS) compared to a similar Sequence D which included a third anti-TNF agent (INF) (10 days in RS). Total costs over 2 years were estimated at €63,433 for Sequence C and at €63,709 for Sequence D. Again, corresponding mean cost-effectiveness ratios showed significantly lower costs ($p<0.01$) per day in remission for Sequence C which included ABA after ADA and ETA (€3,592), compared to Sequence D which used three successive anti-TNF agents (€6,623).

Discussion

The results of this cost-effectiveness model based on published clinical evidence suggest that in patients with moderate-to-severe RA and an IR to one anti-TNF agent, the sequential biologic strategy including abatacept as second biologic option appears to be significantly more efficacious and cost-effective compared to the similar sequence using rituximab. After an IR to two anti-TNF agents, the sequential biologic strategy including abatacept as a third biologic agent appears more efficacious and cost-effective *versus* a

similar sequence using cycled anti-TNF agents only. Three factors contribute to the better cost-effectiveness of abatacept. First, the results are driven by the efficacy reported in clinical trials (DAS28 endpoints). Secondly, given that patients in remission or LDAS have lower medical management costs than patients in moderate-to-high disease activity, this is reflected in the overall treatment costs estimated for achieving therapeutic success. Thirdly, the higher success rates offset any difference in biologic drug costs.

One of the most important issues in the creation of valid medico-economic models is the use of clinical effectiveness endpoints that are clinically meaningful and consistent across different settings. Selecting objective and consistent clinical outcomes allow defining clinical effectiveness of a given treatment more accurately and comparing across different treatment strategies for a specific patient population. Given that the goal of RA treatment is to achieve LDAS or RS, as measured by the DAS28 score, these clinical endpoints appeared to be the most relevant effectiveness criteria for the purpose of conducting this cost-effectiveness analysis. Using a dichotomous approach of achieving success or no-success (RS/no RS or LDAS/no LDAS) as demonstrated by the DAS28 scores, also appeared more clinically meaningful because these endpoints reflect clinical practice in Germany as well as "treat to target" RA guidelines. However, as for the Health Assessment Questionnaire HAQ, given that the DAS28 is an "ordinal score" (all degrees are not equal), it would be methodologically incorrect to calculate cost-effectiveness ratios such as cost per unit of DAS28 or cost per unit of HAQ, even though such approaches using the HAQ are frequently published (28).

One major advantage of adopting success cut-off points is that success or failure measures are generally more easily interpretable than continuous measures. Such cut-off points avoid the need of using continuous scales to compute effectiveness endpoints. The dichotomous approach also requires fewer assumptions than other modelling approaches and appears more methodologically robust as published in other countries (17-21).

The model assumes a 6-month treatment period prior to allowing a potential switch to the next biologic agent in case of IR. This assumption is based on the fact that most clinical trials report effectiveness data at 6 months time points. Furthermore, the model also applies by default a 6-month re-treatment interval for rituximab given that only 6 months efficacy data was published at time of model development (13). Hence, it is important to note that this approach assumes sustained 6-month efficacy for rituximab, and does not account for the risk of potential RA flares between rituximab re-treatments. Not adjusting for this might underestimate the potential clinical benefits associated with the sustained efficacy demonstrated with abatabept. Furthermore, longer re-treatment intervals for RTX in this model (*e.g.* 9 months instead of 6 months) would not significantly impact the model results, as this would concern very few patients in the final branches of the model. This was confirmed in a similar cost-effectiveness analysis conducted in France where both 6 and 9 months re-treatment intervals assumptions were modelled for RTX given as second biologic option in patients with an insufficient response to at least one anti-TNF agent. This analysis showed that altering RTX re-treatment intervals from 6 to 9 months did not significantly impact the model results (18). This is also because for the RTX 9-month re-treatment interval simulation, the model assumed a sustained effectiveness with RTX during the period between 6 and 9 months. However, an analysis of the DAS-28 reduction from baseline with RTX rather suggests a potential intermittent DAS-28 response beyond 6 months (29). Hence, given the possibility of reactivation of RA symptoms between RTX re-treatments given at 9-month intervals, a 6-month re-treatment interval for RTX was deemed appropriate. Finally, the model assumes that a potential RS or LDAS is sustained over the entire 6-month treatment period. These assumptions could be further discussed but they appeared to be consistent with medical practices in Germany, as validated with the expert panel. Furthermore, the time horizon of the model is limited to 2 years in order to reflect the data available at the time of model development. Hence, no long term effectiveness assumptions were made, as is it often the case in published "lifetime" cost-effectiveness models in RA (30).

Even if the relationship between DAS scores and costs has been established, the DAS score does not capture all aspects of Quality of Life (QOL) improvement. This is why we would recommend that such evidence be considered separately, to its full merit. Furthermore, it is not the purpose of one clinical indicator to capture all the dimensions of life, so QOL dimensions should be collected separately using appropriate validated instruments. Many published "cost-utility" (cost/QALY) models (often presented under the label of "cost-effectiveness" analyses) consider the use of Quality Adjusted Life Years (QALY) as effectiveness criteria in order to take into account both the Quality of Life and the survival perspectives (15, 31). Not only the QALY approach is not recommended in Germany, but such approach reveals to be inconsistent in RA (31). This is because the results are directly dependent on how the utility scores are derived, explaining why these studies often lead to divergent results (31-34). The advantage of cost-effectiveness models using clinical effectiveness outcomes (such as DAS scores) from published clinical trials is that the effectiveness criteria are not further transformed into utilities. Hence, classic cost-effectiveness assessments (cost/clinical outcome achieved or per medical event avoided) generate more transparent and consistent results (18). In addition, no significant relationship has been established between DAS and survival rates (34), as most clinical trials do not contain adequate power or follow up on differentiate mortality benefits in RA with one intervention *versus* another. This explains why most economic models have not included mortality as a treatment-specific con-

sequence (22, 35). This cost-effectiveness analysis does not use a societal perspective but the perspective of the public payer in Germany. In such case, the results do not take into account the reported favourable impact of biologic therapies on indirect costs. As indirect costs related to RA are substantial and are estimated to be 2-3 times as high as direct costs, the results of this economic evaluation are likely to be understated. Finally, a frequent concern about cost-effectiveness models is that most publications seem to support the product of the study sponsor, suggesting a potential publication bias such as for publications of clinical trials. As they are used to inform and optimise resource allocation decisions, cost-effectiveness models should always define the assumptions and conditions where a therapeutic strategy is found to be cost-effective, which should also be in line with medical practices. Any model assuming very hypothetical clinical practices or theoretical outcomes should be considered with caution, as for any scientific studies.

Conclusions

Using the outcomes LDAS or remission defined by DAS28-scores to compare sequential biologic strategies in patients with moderate-to-severe RA and an IR to at least one anti-TNF agent, this model reveals differences in overall effectiveness treatment costs and cost-effectiveness regarding the defined treatment sequences. The results show that the sequential biologic strategy using abatacept after an IR to one anti-TNF agent appears to be more effective and cost-effective than the same sequence using RTX in this patient population. For patients with an IR to two anti-TNF agents, the results show that the sequential biologic strategy using abatacept appears to be more effective and cost-effective than the same sequence using a third anti-TNF agent instead. These results also revealed to be statistically significant.

Future modelling approaches should confirm these results as further comparative data of biological treatment strategies in RA and long-term evidence become available.

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