Cost-effectiveness of early treatment of ACPA-positive rheumatoid arthritis patients with abatacept

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Abstract

Objective

Studies have reported that the presence of elevated anti-citrullinated protein antibodies (ACPA)/RF levels, together with joint erosions, is associated with higher disease burden in terms of disability and mortality in rheumatoid arthritis (RA). Abatacept has been shown to be effective in this patient population with favourable comparative data against adalimumab. However, few studies have investigated the cost-effectiveness of abatacept in this population to similar treatments such as TNFs. The objective of the study was to compare the cost-effectiveness of abatacept to adalimumab as a first bDMARD in ACPA-positive RA patients who failed treatment with methotrexate (MTX) in Germany.

Methods

A decision tree model was used to estimate the cost-effectiveness, from a payer's perspective, of different treatment sequences in RA over a two year time frame. The effectiveness criteria were defined as achieving the treatment target measured by the Disease Activity Score 28 (DAS28(CRP)<2.6; "remission"). A treatment switch to a different biologic as 2nd line and 3rd line bDMARD was allowed – in case of not achieving remission with therapy – every 6 months over a two year time period. Effectiveness data was based on randomised controlled trials (RCT) identified by an updated previous systematic literature search by the Institute for Quality and Efficiency in Health Care (IQWiG). Costs of medication and other direct medical costs were considered. Cost-effectiveness of RA treatment was investigated in ACPA-positive patients and presented as overall costs per day in remission.

Results

For ACPA-positive patients, treatment strategies including early treatment with abatacept had lower total costs per clinical outcome compared to later use. Treatment sequences starting with abatacept resulted in lower costs per day in remission (mean 330 €/day, range 328–333 €/day) compared to sequences starting with adalimumab (mean 384 €/day, range 378–390 €/day). Choice of the second or third biologic in the treatment sequences appears to have little impact on the costs per outcome.

Conclusion

The results of this analysis suggest that in ACPA-positive RA patients treatment with abatacept appears to have lower costs per response (remission) compared to treatment with adalimumab as a first bDMARD.

Key words

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

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Introduction

In Germany there are currently approximately 540,000 patients who suffer from rheumatoid arthritis (RA) (1). The treatment of this chronic disease is not only a medical, but also an economic challenge. New medication options could however improve the situation. Conventional options for RA treatment include nonsteroidal anti-inflammatory drugs, corticosteroids and traditional disease-modifying anti-rheumatic drugs (DMARDs). In case of insufficient response to DMARD therapies patients become candidates for biologic therapies (bDMARDs) such as the anti-tumour necrosis factor-alpha (anti-TNF) agents adalimumab (ADA), etanercept (ETA) and infliximab (INF), or other biologic agents such as abatacept (ABA) and rituximab (RTX) (2).

In RA, relapse rates were recently confirmed to be associated with Anti-citrullinated protein antibodies (ACPA) status (3). Treatment for patients with higher risk of disease progression, such as ACPA-positive patients may need to be more intensive than by DMARDs alone (4-7). Early treatment with abatacept may therefore offer benefits for patients with high risk (8).

From a decision making perspective it is important to consider the cost-effectiveness of different biologic treatment strategies with treatment switches after an insufficient response to prior therapies. In 2013 Beresniak *et al*. proposed a 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 insufficient response to prior anti-TNF agents (2). Based on this work an analogous modelling approach was taken to test the hypothesis, that early treatment with abatacept will improve outcomes in relation to costs as compared to adalimumab as a first bDMARD in a patient population with increased risk (ACPA-positive patients). Considering new evidence of ACPA status for the treatment of RA patients, especially from the AMPLE trial (4), multiple arms of complex therapeutic strategies were compared in terms of cost-effectiveness from a public payer's perspective in Germany. Current effectiveness data identified by a systematic literature search by the Institute for Quality and Efficiency in Health Care (IQWiG) – updated by a systematic update search – was implemented in the model in order to evaluate the cost-effectiveness of different RA treatment strategies.

Materials and methods

A cost-effectiveness-analysis (CEA) in the health care sector is a special form of economic analysis that compares the relative costs and outcomes of different treatment strategies. It can help allocating a fixed health budget between interventions in order to derive implications for the optimal treatment mix in such a way as to maximise health in a society (9). Therefore it can deliver important results to assist making both medical and allocation decisions. To gain these results an appropriate model must be developed and filled with costing and effectiveness data.

Model design

A decision tree model was developed to compare the costs and the effectiveness expressed in clinical outcomes defined for different RA treatment strategies. For the comparison of the cost-effectiveness of different RA treatment strategies it is necessary to define the possible sequential therapeutic strategies over a specific time frame. As shown in Figure 1 the time horizon for the model is 2 years which is divided into 4 treatment periods of 6 months each. If the response (RS) to the given agent is adequate in one period then this agent will be given in the following treatment period once again. If there is no response (no RS) or just inadequate response the agent will be switched in the following treatment period. The first treatment period (0–6 months) always starts with the most commonly used DMARD methotrexate (MTX). The model assumes that the response to MTX is inadequate in period 1, so it focuses on MTX inadequate responders. After the first treatment period with MTX the therapy will be modified and a biologic treatment – abatacept (ABA) or adalimumab (ADA) – will be added in

period 2. Depending on whether there is response, the biologic agent will be maintained or switched in period 3 and 4 (see Fig. 1). According to this sequential treatment logic a selected bunch of different treatment strategies is analysed (see Table I). Thereby the variety of common therapies for MTX inadequate responders is represented appropriately. There are 3 sequences starting in period 2 with adalimumab after an inadequate response to MTX and 5 with abatacept. This reflects that the possible applications of abatacept are very variable. The model was built in MS-Excel®, utilising the @Risk plugin tool v. 5.5 for probabilistic analysis (Palisade Software).

Cost components

Costs were based on the "Hannover Costing Study" published by Ruof (2, 10-12). According to the Hannover Costing Study all direct medical costs consisting of medical resource utilisation items like specialist visits, hospitalisation, surgery (inpatient and outpatient), rehabilitation and medication costs were included and estimated per 6-months intervals. Since the study uses the public payer perspective, indirect costs were not considered in the model.

The costs for the medical resource utilisation items were calculated for the conditions "response"(RS) and "no response"(no RS), because the costs for medical resources are higher in average when there is no response to the given medical agent (2, 10). The Hannover Costing Study was carried out in 2008 so the cost data had to be updated to the year 2016 in order to maintain current values. To update the cost data from the year 2008 to 2016 the inflation rate for the sector "health" in Germany provided by Eurostat was used (increase by inflation rate of 6.7%). The costs per 6 months are shown in Table II. Key costs drivers were surgery and physiotherapist visits.

The medication costs per 6 months were calculated based on the 2016 price list "Lauer-Taxe" and recommended dosing according to the particular summary of product characteristics (SmPC). Infusion costs were included where required (RTX: 103.12 €; INF: 284.10 €). The costs for the medical agents (inclusive infusion costs) in 2016 are shown in Table II. Due to the short time-horizon of 2 years no cost increase and no discount rates were applied.

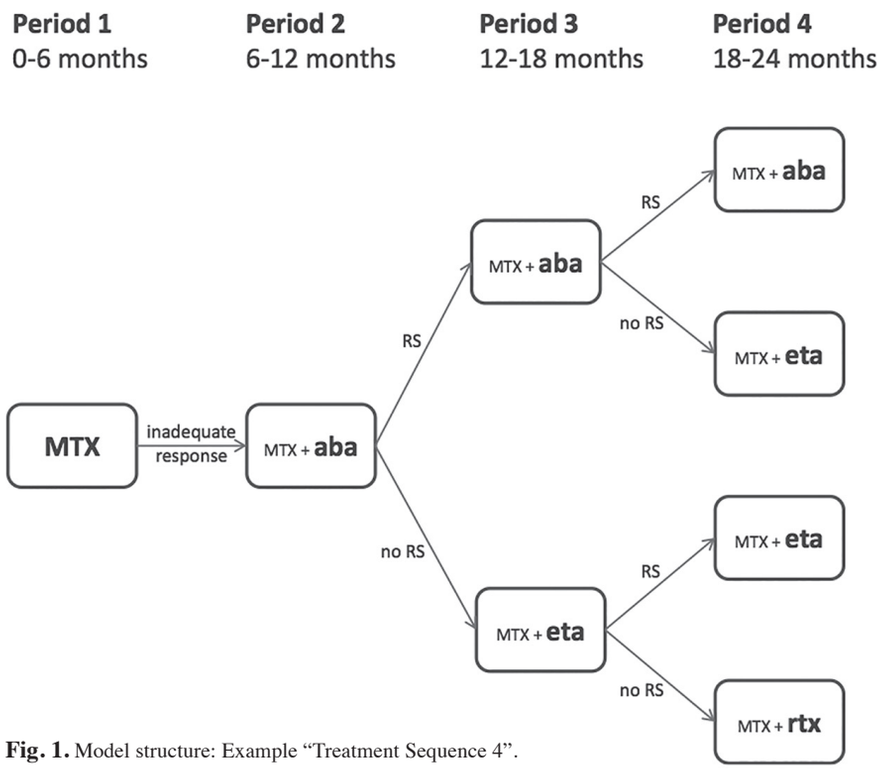

Fig. 1. Model structure: Example "Treatment Sequence 4".

Table I. Model structure: Treatment Sequences.

No.	Treatment sequence if no RS	ADA *vs*. ABA
1	MTX - ADA - ETA - ABA	first
2	MTX - ADA - ABA - ETA	biologic
3	MTX - ADA - RTX - ETA	ADA
4	MTX - ABA - ETA - RTX	
5	MTX - ABA - RTX - ETA	first
6	MTX - ABA - ADA - ETA	biologic
7	MTX - ABA - ADA - RTX	ABA
8	MTX - ABA - ETA - INF	

MTX: methotrexate; ADA: adalimumab; ETA: etanercept; ABA: abatacept; INF: infliximab; RTX: rituximab.

Effectiveness criteria

The effectiveness criteria were defined as achieving low disease activity ("remission", "RS") – according to routine clinical practice – measured by the Disease Activity Score 28 (DAS28 (CRP) <2.6). Probabilities for "remission" were determined via a systematic literature search. In 2013, the IQWiG executed a broad systematic literature search due to a rheumatology assessment (13). On the basis of IQWiG's systematic literature search a systematic update search was performed in December 2015 to ensure an updated database for the decision tree model. The search was for randomised controlled trials (RCT) to provide information with a high grade of validity. The identified literature included among other RCT the results from the AMPLE trial and therefore new evidence about ACPA status for the treatment of RA patients (4).

In Table III the response probabilities and the corresponding sources are shown which were identified by the systematic literature search.. The overall response, *i.e*. without differentiation between ACPA-positive and

Table II. Model inputs I: Costs for medical resources and medication costs.

Costs for medical resources	Total costs per 6 months (2016)*
Response	4,816.01 €
No response	7,599.24 €
Medication costs (including infusion costs)	
Abatacept	9,046.03 €
Adalimumab	10,723.44 €
Etanercept	10,719.46 €
Infliximab	8,698.05 €
Methotrexate	27.63 €
Rituximab	7,650.08 €

*Cost data was updated from 2008 to 2016 with the inflation rate for the sector "health" in Germany in the amount of 6.7%.

Table III. Model inputs II: Summary of effectiveness probabilities.

Biologic agent	%RS	Source
ACPA-pos: ABA after MTX	47%	AMPLE (4)
General: ABA after MTX	20%	IQWiG 2013 (13)
ACPA-pos: ADA after MTX	42%	AMPLE (4)
General: ADA after MTX	16%	IQWiG 2013 (13)
ETA after MTX	16%	IQWiG 2013, O'Dell 2013 (13), (14)
ABA after 1st/2nd biologic	13%	IQWiG 2013, Manders 2015 (13), (15)
ADA after 1st/2nd biologic	12%	assumption of ADA=ETA (16)
ETA after 1st/2nd biologic	12%	IQWiG 2013, O'Dell 2013(*) (13), (14)
INF after 1st/2nd biologic	12%	assumption of INF=ETA(13), (16)
RTX after 1st/2nd biologic	8%	IQWiG 2013 (13)

*adjusted for effectivity differences 1st biologic *vs*. second biologic based on data in (13)
MTX: methotrexate; ADA: adalimumab; ETA: etanercept; ABA: abatacept; INF: infliximab; RTX: rituximab.

ACPA-negative patient populations, of abatacept as first biologic agent after an inadequate response to MTX was 20% and of adalimumab 16%. For ACPA-positive patients the response rate was 47% for abatacept and 42% for adalimumab. In addition, in the AMPLE trial antibody-positive patients were divided into quartiles, Q1-Q4, representing increasing antibody concentrations. Depending on the quartiles the response probabilities varied for Q1-Q4 between 40% and 52% for abatacept and between 36% and 51% for adalimumab (4). For the second respectively subsequent biologic agent after an inadequate response to abatacept or to adalimumab there was no differentiation available between ACPA-positive and ACPA-negative patients. Response rates varied between 8% and 13% depending on the agent in the sequence (Table III).

The main effectiveness outcome of the model was the number of days in RS which was calculated for each treatment sequence with the help of the mentioned response probabilities over a 2-year time frame. To manage uncertainty Monte Carlo simulations were done with 10,000 runs. The simulations generated values for costs, effectiveness and cost-effectiveness, which was displayed as overall costs per day RS.

Results

The overall costs over 2 years for ACPA-positive patients were lower for patients starting with abatacept as first biologic agent compared to patients with treatment sequences starting with adalimumab. For the treatment sequences starting with abatacept the range was 54,774–57,231€ and the mean 55,990€. The range for patients with first biologic agent adalimumab was 57,749–59,459€ and the mean 58,668€. In Figure 2 the overall costs over 2 years for all analysed treatment sequences are shown.

The medication costs were an important cost driver. However, the other costs for medical resources had almost the same impact depending on the treatment sequence. On the average, the treatment sequences starting with abatacept had both lower medication costs and lower costs for medical resources which resulted in lower overall costs compared to treatment sequences with adalimumab as first biologic agent. That was on the hand because the patients had a better response to abatacept compared to adalimumab and therefore lower costs for medical resources. On the other hand the medication costs for abatacept were also slightly lower than for adalimumab.

The sequences based on an early treatment with abatacept had not only lower costs but also a higher effectiveness relating to days spent in remission. The range of the treatment sequences starting with abatacept was 166 to 172 days in remission, the mean was 169. For the treatment sequences starting with adalimumab the range was 148 to 156 days in remission with mean 153 days. The results for effectiveness expressed as number of days in remission are shown in Figure 3.

Treatment sequences starting with abatacept were more cost-effective regarding overall costs per day RS compared to sequences starting with adalimumb due to the lower costs and more days in remission. Resulting in costs per day in remission in a range of 328 €/day to 333 €/day (mean 330 €/day) for abatacept sequences compared to a range of 378 €/day to 390 €/day (mean 384 €/day) for adalimumab sequences. The results for overall costs per day attaining treatment target (remission) are shown in Figure 4.

The results in Table IV show for ACPA-positive patients that treatment strategies including early treatment with abatacept had lower total costs per clinical outcome compared to later use. However the choice of the second or third biologic in the treatment sequences appeared to have little impact on the costs per outcome. There were only small differences between the treatment sequences which had etanercept, rituximab or adalimumab as second biologic after abatacept. The outcome was al-

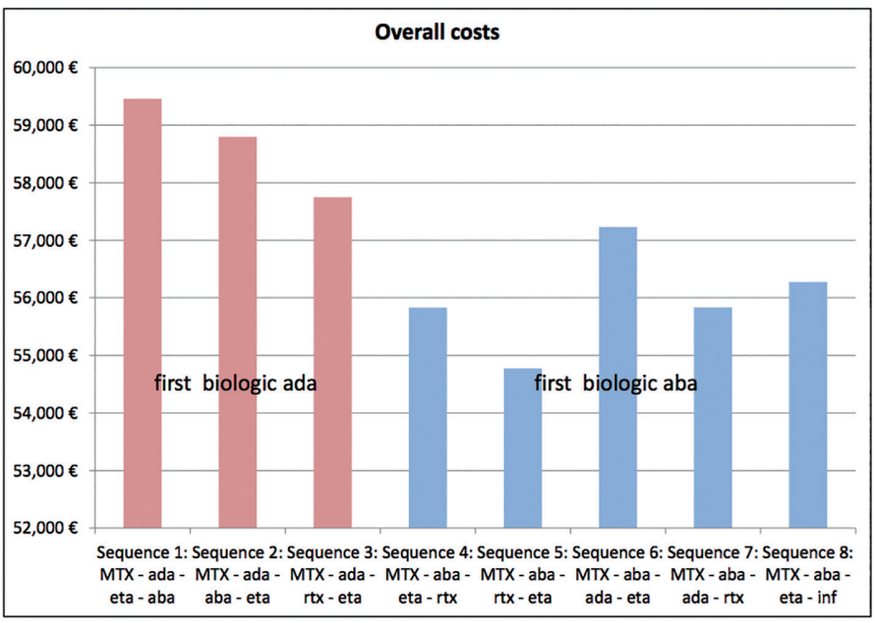

Fig. 2. Overall costs per patient.

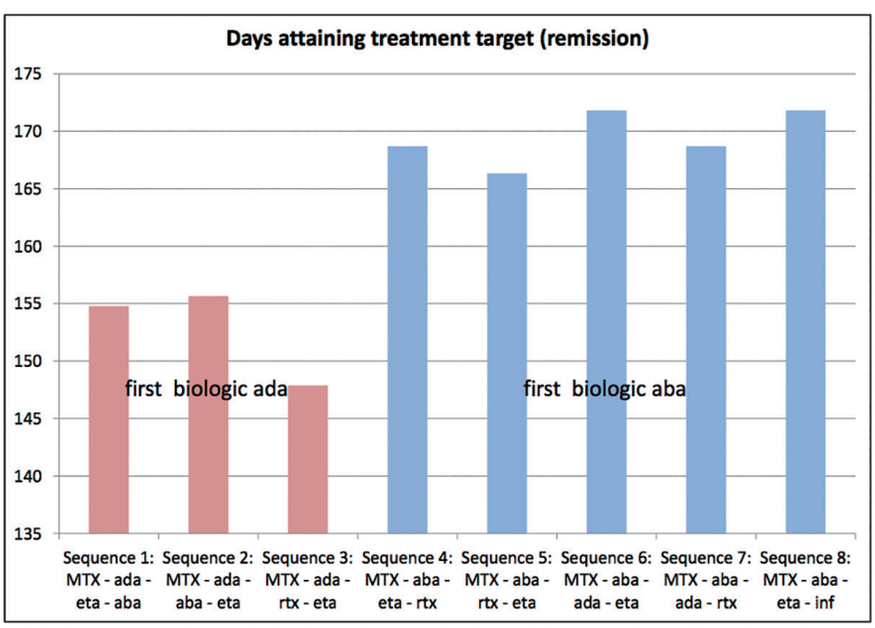

Fig. 3. Days attaining remission (DAS28<2.6) per patient.

ways better compared to treatment sequences starting with adalimumab as first biologic irrespective of the second or third biologic.

Discussion

The results of this cost-effectiveness model based on published clinical evidence and up to date cost data indicate that in ACPA-positive RA patients an early treatment with abatacept has lower costs, is more efficacious in reference to the number of days spent in remission and finally cost-effective regarding costs per day in remission compared to treatment sequences starting with adalimumab as first biologic. These results were obtained from a 2-year economic model filled with effectiveness RCT data for APCA-positive RA patients which was identified by an updated, systematic search with the IQWiG search method and German cost data.

Various RCTs were included to obtain the necessary information and thus diverse patient populations with different characteristics are incorporated in the model (see Table III). This is a limitation, because there is no full matching of patient characteristics and some characteristics may even vary significantly. However, all RCTs were identified by the same systematic search strategy with the same in- and exclusion criteria which helps to avoid such bias. Also, the approach taken to populate the effectiveness data is common practice in economic modelling. For ACPA-positive patients with the first biologic evidence was primarily based on a directly comparative study between abatacept and adalimumab, the AMPLE study (4).

There are several studies and models that deal with cost-effectiveness concerning the treatment of rheumatoid arthritis. Methods applied for a German context include cost per responder (17), cost per responder for treatment strategies (2), (15) and cost-utility analyses (18-20). For abatacept there are numerous international cost-effectiveness studies (21), some of which also investigated Germany (2). In our model sequential treatment strategies and costs per clinical outcome were investigated based on systematic literature reviews, focusing on ACPA-positive patients. To the best of our knowledge, there has not been a comparable study comparing the cost-effectiveness of biologics for ACPA-positive patients in a German setting before.

While we built an economic model, it has also clinical relevance. By means of the RCT data the model predicts which treatment strategy is reasonable relating to remission for ACPA-positive RA patients who failed treatment with methotrexate. Although ACPA-positive patients can be classified as severe cases an appropriate treatment strategy can contribute to lower treatment costs when remission is increased. The percentage of days in remission measured by the Disease Activity Score 28 (DAS28 (CRP)<2.6) can be increased with an early treatment with abatacept. Patients in remission have lower costs due to less demand of medical resources than patients with a high disease activity which leads to lower

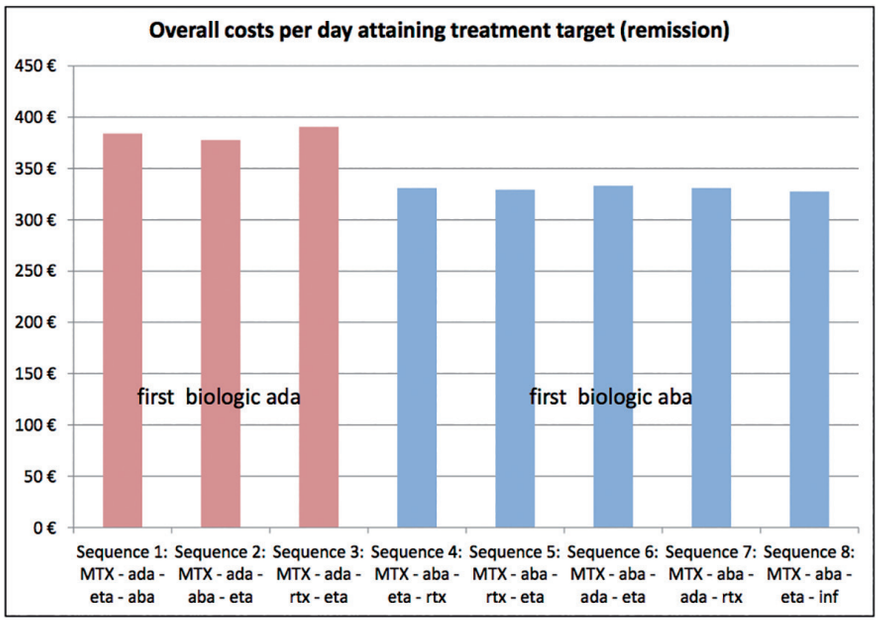

Fig. 4. Overall costs per day attaining remission (DAS28<2.6) per patient.

Table IV. Results overview.

Seq. no.	Treatment sequence	Overall costs	Days attaining treatment target (remission)	Overall costs per day attaining treatment target (remission)
1	MTX - ADA - ETA - ABA	59,459.48 €	154.79	384.13 €
2	MTX - ADA - ABA - ETA	58,796.74 €	155.66	377.72 €
3	MTX - ADA - RTX - ETA	57,748.88 €	147.89	390.49 €
4	MTX - ABA - ETA - RTX	55,831.53 €	168.70	330.95 €
5	MTX - ABA - RTX - ETA	54,774.59 €	166.34	329.29 €
6	MTX - ABA - ADA - ETA	57,230.98 €	171.82	333.09 €
7	MTX - ABA - ADA - RTX	55,834.90 €	168.70	330.97 €
8	MTX - ABA - ETA - INF	56,276.91 €	171.82	327.54 €

overall costs. Therefore, an appropriate treatment strategy is important from a medical as well as from a payer's perspective.

In the model a 2-year time frame was chosen. This matches the public payers' perspective because they are bound by budget years. Because of budget restrictions public payers make decisions mostly considering short terms. In addition, a short time frame does not require extrapolating effectiveness data from RCTs, which would introduce additional uncertainty. In the model a treatment period of 6 months is assumed and treatment changes are only allowed after those time segments. This appears clinically plausible because in clinical practice the effectiveness of a treatment is assessed every 3–6 months and the treatment strategy can be changed after the assessment. Furthermore the period length of 6 months has a technical reason in the fact, that most clinical trials report effectiveness data at 6-month time points (2). Overall since a treatment period in the model is 6 months to assess the response to the treatment and if the agent must be switched or not, a model time horizon of 2 years appears appropriate from a medical and an economic point of view. Quality of life is important when investigating treatment strategies. Our model, however, focuses on remission measured by the DAS28, which does not explicitly indicate quality of life values and therefore is a limitation of the approach taken. It was not the scope of the model approach to collect and implement evidence for quality of life of different treatment strategies for RA patients. While cost-utility-analyses extensively consider quality of life and use quality adjusted life years (QALY), this introduces high variability and may lead to divergent results (22). Therefore, the German IQWiG method paper disencourages such economic modeling approaches and proposes to adhere to cost-effectiveness per clinical outcomes, like in our model overall costs per day in remission, instead of applying the QALY concept (23, 15). Using the DAS28 score in our model avoids the variability associated with implementing QALYs or transforming effectiveness outcomes into utilities.

The number of days spent in remission shows to what extent the treatment target was attained. Taking the related costs into consideration, the costs per day spent in remission is a metric, which directly relates to clinical outcomes and it also relates to quality of life for the patient. The results of the model have relevant implications for the public payers as well as for the patients. With an early treatment with abatacept, ACPA-positive patients can achieve up to 24 additional days spent in remission compared to adalimumab and the savings for the public payers are up to 4,700€ per patient over the two year horizon.

Regarding cost-effectiveness, only comparative conclusions can be made within this model. It is possible to decide which of the analysed eight treatment sequences has the lowest treatment costs, the highest effectiveness and the best cost-effectiveness. The model focuses on ACPA-positive RA patients and shows that an early treatment with abatacept is the better option for this patient group in comparison to adalimumab, while choice of second and third biologic has only little impact on results.

Conclusions

The model reveals that an early treatment of ACPA-positive RA patients with abatacept has advantages compared to adalimumab for both the patients and the payers. If patients fail to respond to initial therapy with MTX it is reasonable to add a biologic agent. Using abatacept as a first bDMARD

instead of adalimumab after an insufficient response to MTX, the days spent in remission can be increased. The overall costs drop with attaining the treatment target, because the costs for medical resources decrease when patients are in remission. Ultimately, this leads to increased cost-effectiveness expressed in overall costs per day in remission of abatacept compared to adalimumab for ACPA-positive patients. Therefore an early treatment of ACPA-positive RA patients with abatacept yields benefits regarding quality of care as well as costs.

References

1. ZINK A: Healthcare research in rheumatology. Current state. *Z Rheumatol* 2014; 73: 115-22.
2. BERESNIAK A, BAERWALD C, ZEIDLER H *et al*.: Cost-effectiveness simulation model of biologic strategies for treating to target rheumatoid arthritis in Germany. *Clin Exp Rheumatol* 2013; 31: 400-8.
3. HASCHKA J, ENGLBRECHT M, HUEBER AJ *et al*.: Relapse rates in patients with rheumatoid arthritis in stable remission tapering or stopping antirheumatic therapy: interim results from the prospective randomised controlled RETRO study. *Ann Rheum Dis* 2016; 75: 45-51.
4. SOKOLOVE J, SCHIFF M, FLEISCHMANN R *et al*.: Impact of baseline anti-cyclic citrullinated peptide-2 antibody concentration on efficacy outcomes following treatment with subcutaneous abatacept or adalimumab: 2-year results from the AMPLE trial. *Ann Rheum Dis* 2016; 75: 709-14.
5. ENGELMANN R, MULLER-HILKE B: Antibodies against citrullinated peptides in clinical practice and research. *Z Rheumatol* 2009; 68: 485-90.
6. SEEGOBIN SD, MA MH, DAHANAYAKE C *et al*.: ACPA-positive and ACPA-negative rheumatoid arthritis differ in their requirements for combination DMARDs and corticosteroids: secondary analysis of a randomized controlled trial. *Arthritis Res Ther* 2014; 16: R13.
7. JILANI AA, MACKWORTH-YOUNG CG: The Role of citrullinated protein antibodies in predicting erosive disease in rheumatoid arthritis: a systematic literature review and meta-analysis. *Int J Rheumatol* 2015; 2015: 728610.
8. PIEPER J, HERRATH J, RAGHAVAN S, MUHAMMAD K, VOLLENHOVEN R, MALMSTROM V: CTLA4-Ig (abatacept) therapy modulates T cell effector functions in autoantibody-positive rheumatoid arthritis patients. *BMC Immunol* 2013; 14: 34.
9. WORLD HEALTH ORGANIZATION. WHO GUIDE TO COST-EFFECTIVENESS ANALYSIS. 2003. [Online]. Available: http://www.who.int/choice/publications/p_2003_generalised_cea.pdf [Accessed 18.09.2017].
10. RUOF J, HULSEMANN JL, MITTENDORF T *et al*.: Costs of rheumatoid arthritis in Germany: a micro-costing approach based on healthcare payer's data sources. *Ann Rheum Dis* 2003; 62: 544-9.
11. HULSEMANN JL, RUOF J, ZEIDLER H, MITTENDORF T: Costs in rheumatology: results and lessons learned from the 'Hannover Costing Study'. *Rheumatol Int* 2006; 26: 704-11.
12. HULSEMANN JL, MITTENDORF T, MERKESDAL S *et al*.: Direct costs related to rheumatoid arthritis: the patient perspective. *Ann Rheum Dis* 2005; 64: 1456-61.
13. INSTITUT FÜR QUALITÄT UND WIRTSCHAFTLICHKEIT IM GESUNDHEITSWESEN: Biotechnologisch hergestellte Arzneimittel in der Zweitlinientherapie bei der rheumatoiden Arthritis, IQWiG-Berichte – Nr. 180, Auftrag A10-01, Version: 1.0, Stand: 28.06.2013. 2013. [Online]. Available: https://www.iqwig.de/download/A10-01_Abschlussbericht_Biologika-Zweitlinientherapie-bei-rheumatoider-Arthritis.pdf [Accessed 18.09.2017].
14. O'DELL JR, MIKULS TR, TAYLOR TH *et al*.: Therapies for active rheumatoid arthritis after methotrexate failure. *N Engl J Med* 2013; 369: 307-18.
15. MANDERS SH, KIEVIT W, ADANG E *et al*.: Cost-effectiveness of abatacept, rituximab, and TNFi treatment after previous failure with TNFi treatment in rheumatoid arthritis: a pragmatic multi-centre randomised trial. *Arthritis Res Ther* 2015; 17: 134.
16. CANHAO H, RODRIGUES AM, MOURAO AF *et al*.: Comparative effectiveness and predictors of response to tumour necrosis factor inhibitor therapies in rheumatoid arthritis. *Rheumatology* (Oxford) 2012; 51: 2020-6.
17. GISSEL C, REPP H: Cost per responder of TNF-alpha therapies in Germany. *Clin Rheumatol* 2013; 32: 1805-9.
18. GISSEL C, GOTZ G, REPP H: Cost-effectiveness of adalimumab for rheumatoid arthritis in Germany. *Z Rheumatol* 2016; 75: 1006-1015.
19. JANSEN JP, INCERTI D, MUTEBI A *et al*.: Cost-effectiveness of sequenced treatment of rheumatoid arthritis with targeted immune modulators. *J Med Econ* 2017: 1-12.
20. MERKESDAL S, KIRCHHOFF T, WOLKA D, LADINEK G, KIELHORN A, RUBBERT-ROTH A: Cost-effectiveness analysis of rituximab treatment in patients in Germany with rheumatoid arthritis after etanercept-failure. *Eur J Health Econ* 2010; 11: 95-104.
21. ATHANASAKIS K, PETRAKIS I, KYRIOPOULOS J: Investigating the value of abatacept in the treatment of rheumatoid arthritis: a systematic review of cost-effectiveness studies. *ISRN Rheumatol* 2013; 2013: 256871.
22. BERESNIAK A, RUSSELL AS, HARAOUI B, BESSETTE L, BOMBARDIER C, DURU G: Advantages and limitations of utility assessment methods in rheumatoid arthritis. *J Rheumatol* 2007; 34: 2193-200.
23. INSTITUT FÜR QUALITÄT UND WIRTSCHAFTLICHKEIT IM GESUNDHEITSWESEN: General Methods Version 5.0. 2017. [Online]. Available: https://www.iqwig.de/de/methoden/methodenpapier.3020.html [Accessed 18.09.2017].