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EXTENDED REPORT

Personalised treatment using serum drug levels of adalimumab in patients with rheumatoid arthritis: an evaluation of costs and effects

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ABSTRACT

Objective To evaluate the cost-effectiveness of personalised treatment for rheumatoid arthritis (RA) using clinical response and serum adalimumab levels.

Methods A personalised treatment algorithm defined, based on clinical (European League Against Rheumatism) response and drug levels at 6 months, whether adalimumab treatment should be continued in a specific dose or discontinued and/or switched to a next biological. Outcomes were simulated using a patient level Markov model, with 3 months cycles, based on a cohort of 272 adalimumab-treated patients with RA for 3 years and data of patients from the Utrecht Rheumatoid Arthritis Cohort. Costs, clinical effectiveness and quality adjusted life years (QALYs) were compared with outcomes as observed in usual care and incremental cost-effectiveness ratios were calculated. Analyses were performed probabilistically.

Results Clinical effectiveness was higher for the cohort simulated to receive personalised care compared with usual care; the average difference in QALYs was 3.84 (95 percentile range −8.39 to 16.20). Costs were saved on drugs: €2 314 354. Testing costs amounted to €10 872. Mean total savings were €2 561 648 (95 percentile range −3 252 529 to −1 898 087), resulting in an incremental cost-effectiveness ratio of €666 500 or €646 266 saved per QALY gained from a societal or healthcare perspective, respectively. In 72% of simulations personalised care saved costs and resulted in more QALYs, in 28% it was cost saving with lower QALYs. Scenario analyses showed cost saving along with QALYs gain or limited loss.

Conclusions Tailoring biological treatment to individual patients with RA starting adalimumab using drug levels and short-term outcome is cost-effective. Results underscore the potential merit of personalised biological treatment in RA.

INTRODUCTION

In the majority of patients with rheumatoid arthritis (RA) biological therapeutics are highly effective in suppressing disease activity.[1–5] However, costs of these drugs are high and have become a concern for doctors and policy makers with the increasing (chronic) use. Hence, there is a societal pressure to reduce the financial burden of these drugs.

Treatment with biologicals is currently based on the principle of 'one size fits all', despite the large variation in pharmacokinetics between patients. These differences in pharmacokinetics are related to the efficacy of the drug. Therefore, to reach adequate response rates in the majority of patients, the registered dose is an overtreatment in a substantial proportion of treated patients. This can be extrapolated from dose finding or registration trials of biologicals: a significant number of patients achieve clinical response with dosages lower than the registered dose of the drug and these response rates are higher as compared with placebo. This kind of overtreatment is not unique for biologicals; however, it has enormous financial consequences. Although drug levels (DLs) are related to the efficacy of the drug and can be measured adequately, measurement of DL (ie, therapeutic drug monitoring, TDM) is currently not routinely incorporated in daily practice.

Pharmacokinetics of biologicals can be influenced by multiple factors like comedication, inflammation, drug dosing or body mass index. However, immunogenicity has the most profound effect on pharmacokinetics. The development of antidrug antibodies (ADAbs) has a negative impact on the clinical effect of treatment with tumour necrosis factor (TNF)-inhibitors since it results in lowered DL.[6–9] Drugs in complex with ADAb will not be biologically active since the ADAbs are directed to the antigen binding site.[10] This mechanism leads to decreased functional DL and consequently to an impaired treatment response.

In case of unsatisfactory response, dose escalation of the TNF-inhibitor can be considered. This decision is nowadays based on clinical response. Literature demonstrates that the rationale for dose increase remains questionable since in most cases, the additional clinical effect is only marginal or even lacking.[11 12]

Whether in a selected group of patients with low DL and without detectable ADAb dose escalation will be effective remains unclear. Moreover, whether patients with very low or undetectable DL and good treatment response could discontinue their biological has not been studied either.

In our own data,[13] we observed high DLs (defined as >12 mg/L) in a third of the adalimumab treated patients with RA. These DLs exceed the levels that are needed for optimal clinical benefit.[13] This overtreatment is a waste of healthcare resources and might be associated with an increased risk of adverse events, although there is no literature available to

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confirm this. In these patients the biological might still be equally effective when administered in a lower dose.

Using this knowledge and TDM in daily practice results in a more rational, personalised treatment strategy. This could lead to more optimal treatment responses, less adverse events and an optimal use of scarce healthcare resources. Algorithms combining clinical response and DL testing have been proposed.[14–19] One algorithm was retrospectively evaluated in a cohort of patients with RA and showed a higher probability of achieving clinical response in patients that had treatment decisions according to the algorithm, compared with patients that had discordant decisions.[19] In gastroenterology, a model analysis has been performed, comparing an empirical and test-based strategy in infliximab-treated patients with Crohn's disease.[20] The test-based strategy appeared to be cost-effective. A modelling analysis evaluating the health and economic impact of different approaches is an appropriate step in exploring the possibilities for tailored treatment with biologicals of individual patients. Therefore the objective of the current study was to evaluate the cost-effectiveness of different approaches to personalised treatment, based on clinical response and DL, in patients with RA treated with adalimumab.

METHODS

Patients and measurements

Two hundred and seventy-two patients with RA starting adalimumab treatment were consecutively included at the Department of Rheumatology, Jan van Breemen Research Institute | Reade, Amsterdam, The Netherlands. Trough adalimumab DL and disease activity was measured at baseline and 4, 16, 28, 40 and 52 weeks of treatment and every 6 months thereafter for 3 years. For details on the DL ELISA, see online supplementary appendix I. This observational study was approved by the medical ethics committee of the Jan van Breemen Research Institute | Reade and Slotervaart hospital. All patients gave written informed consent. Disease activity was measured using the Disease Activity Score for 28 joints (DAS28).[21] Treatment response was defined according to the European League Against Rheumatism (EULAR) response criteria.[22] Details of the cohort can be found in an earlier publication.[6]

Treatment protocol for 'personalised treatment' with biologicals

A treatment protocol for personalised care based on EULAR response and DL at 6 months was defined prior to the current analysis (figure 1). In patients responding well to adalimumab (EULAR good or moderate response) and with a low DL (<5 mg/L), treatment with adalimumab was discontinued. This was deemed appropriate since a meaningful clinical effect of this low DL was not expected.[13] If an 'appropriate' DL (5–12 mg/L) was reached in these patients, adalimumab was continued and a DL over 12 mg/L indicated a reduction in the frequency of administration of adalimumab (instead of once every other week, once in 3 weeks).

In patients not achieving EULAR response at 6 months with appropriate or high DL (>5 mg/L), a biological with another mechanism of action was started. The rationale of switching to a biological with another mode of action in patients not responding to a TNF-inhibitor despite adequate DL is that this drug type is probably not suitable for their (type of) disease.[15 23 24] If a low DL (<5 mg/L) was present in these patients, they were switched to a second TNF-inhibitor. Most likely, these patients have low DL due to ADAb formation. We previously showed that response to a second TNF-inhibitor in these patients is similar to the response of anti-TNF naive patients to their first TNF-inhibitor.[23 24]

Cut-offs for DL were derived from a concentration-effect curve of adalimumab-treated patients with RA after 6 months of treatment.[13]

Health economic model

In order to translate the clinical results, as observed in our cohort, to quality adjusted life years (QALYs), and costs and to simulate outcomes for the above defined treatment protocol a so called Markov (or Health state) model was used. In a Markov model (individual) patients are allowed to change between different severities of the disease (health states) over time. This is a very suitable model type for a chronic fluctuating disease like RA. Health states were based on observed disease activity, defined as remission (according to ACR/EULAR 2011 criteria),[25] DAS28 remission (DAS28 <2.6), low disease activity (2.6≤DAS28<3.2), moderate disease activity (3.2≤DAS28≤5.1) and high disease activity (DAS28>5.1). A cycle length of 3 months was used in line with often-used monitoring schemes for RA and the time horizon of the analysis was 3 years. To define progression of the disease over time we simulated progression of functional limitations (health assessment questionnaire; HAQ) over time. To simulate this we used the relation between (cumulative) disease activity and progression of

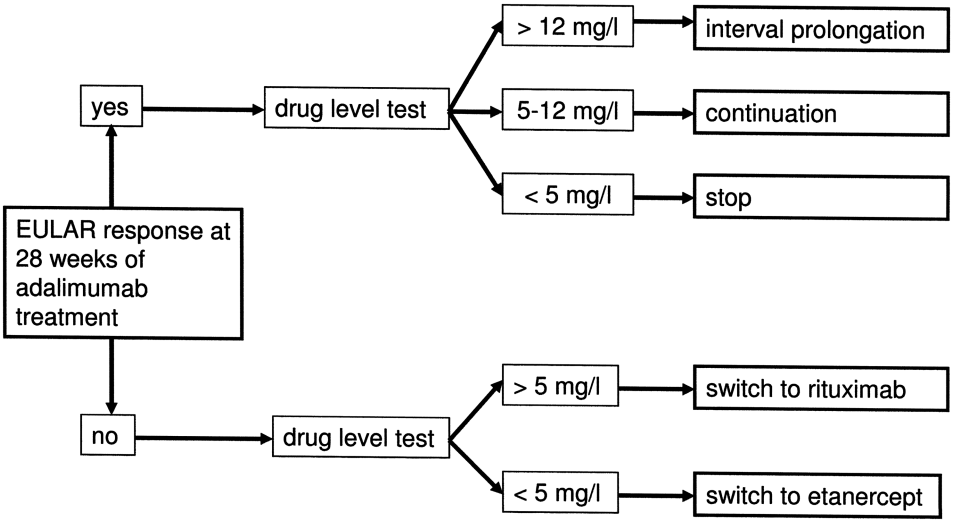

Figure 1 Treatment protocol for personalised treatment with adalimumab based on European League Against Rheumatism (EULAR) response and serum drug level. Dosing of treatment options mentioned in the algorithm: Interval prolongation: adalimumab once every 3 weeks; continuation: adalimumab every other week; rituximab: two times 1000 mg iv with 2 weeks in between, repetition of this regimen in case of flare of disease activity, at least 6 months after initial dosing; etanercept: 50 mg subcutaneous weekly.

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functional limitations according to a regression function estimated in data from the Utrecht Rheumatoid Arthritis Cohort (URAC) study group (n=1034 patients) and the HAQ observed in patients at baseline. URAC included follow-up data from this cohort and pragmatic trial data of patients with (early) RA.[26]

Observed usual care

The observed DAS28 over time was used to calculate outcomes for the usual care group. For this purpose missing 3 months observations on DAS28 and biological use (according to protocol or loss to follow-up) were imputed using single imputation (see online supplementary appendix II). One hundred and forty-eight patients (54.4%) had completed follow-up information.[6]

Personalised care

To simulate personalised care, biological treatment was defined at 6 months according to the above defined treatment protocol. The personalised care cohort was simulated based on the observed DAS28 scores over time, applying changes in DAS28 (ie, the treatment effect) when treatment as defined by the algorithm differed from the observed treatment over time. When patients discontinued adalimumab and did not start another biological in usual care, for example because of side effects, it was assumed that this would also be the case in personalised care.

Definition of treatment effect in the model

To estimate to what extent the different protocol steps affected disease activity, longitudinal regression with DAS28 over time as outcome variable was used. In the cohort data, per step in the treatment algorithm patients treated according to the algorithm (by coincidence; physicians were not aware of DL) were compared with patients treated with other treatments not according to the algorithm, accounting for patients' disease activity at 6 months and other prognostic variables (age, gender and rheumatoid factor status). Based on the result of this analysis and clinical expertise, treatment effects (the difference in DAS28 between patients on a specific treatment according to algorithm and another treatment) were defined (see online supplementary appendix III).

Costs

Data on direct medical and productivity costs were derived from an earlier study within the URAC study including 332 patients with RA with average disease duration of 7 years.[26 27] in which data on disease activity and functional disability were also collected.

The cost of DMARDs was excluded in the current study, since these costs were added separately according to the observed treatment or treatment according to the protocol.

Quality adjusted life years

QALYs are life years weighted by the utility (general health related quality of life, ranging from 0 to 1) they are spent in. Utility was calculated based on the EuroQol-5 dimension questionnaire. Data were derived from the URAC study.[26 27]

Model calculations

Model calculations were performed probabilistically, meaning that 5000 recalculations of the model (simulations) were used to obtain average outcomes and the uncertainty therein. In each simulation a cohort of 272 patients was drawn with resampling (ie, some patients in the cohort might be selected twice in a certain recalculation of the model) to account for population uncertainty. For the treatment effects in each simulation a value was used according to distributions (mean DAS28 change with SE). For costs and utility, values were sampled (with replacement) from the (external) costs and utility data stratified according to the patients DAS28 (health states) and HAQ values (quintiles).

Costs and effects were discounted at 4% and 1.5% per year, respectively, according to the Dutch guidelines.[28]

Scenario analyses

Several scenario analyses regarding the definition of personalised treatment and its effects were performed.

In the first scenario analysis EULAR good response was used instead of moderate response. In scenario 2, abatacept instead of rituximab was assumed for patients switching to a non-TNF-inhibiting biological. In scenario 3 an extra decrement in utility (0.05) and increase in costs (€500) for (eg, toxicity of) non-TNF-inhibiting biological was assigned per cycle. In scenario 4, the assumptions of scenarios 2 and 3 were combined and scenario 5 combined the assumptions of scenarios 1, 2 and 3. In scenario 6, the cut-offs for DL were set stricter to 2 mg/L and 2–12 mg/L, and scenario 7 combined scenarios 1 and 6. In scenario 8, costs and effects were not discounted for the base case analysis.

For statistical analyses SAS V.9.1.3 and SPSS V.15 were used and for health economic modelling Excel 2007 was used.

RESULTS

Patient characteristics of the cohort of patients with RA starting adalimumab treatment are described in table 1.

Course of disease activity and HAQ over time

Due to the fact that some treatment steps, that is, low-dose adalimumab and stop adalimumab in patients responding, were not observed in usual care, the limited data and confounding by indication, analysis results could only partly be used and assumptions needed to be made for treatment effects of the personalised care algorithm. These assumptions are presented in online supplementary appendix III.

Disease activity in the personalised care group was lower (from 6 months on) as compared with usual care and progression of functional disability (HAQ) was also less, although marginally (see online supplementary appendixes IV and V).

Table 1 Characteristics of patients starting adalimumab treatment (n=272)

Baseline variables	
Female, n (%)	219 (81)
Rheumatoid factor, n (%)	195 (72)
Age, mean (SD)	54 (12)
Erosive disease, n (%)	201 (74)
Methotrexate use, n (%)	202 (74)
Prednisone use, n (%)	91 (34)
Prior biological use, n (%)	75 (28)
DAS28, mean (SD)	5.2 (1.2)
HAQ, mean (SD)	1.32 (0.68)
Utility, mean (SD)	0.59 (0.15)
6 months follow-up	
Adalimumab concentration, mg/L (IQR)	
Total population	10 (4.6–14.8)
Responders	10.9 (6.2–15.7)
Non-responders	7.4 (1.5–11.9)

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Biological use

In the usual care group, the proportion of patients using adalimumab gradually decreased over time and the use of other biologicals increased. Up to 10% of patients stopped using a biological (figure 2A).

Figure 2B shows drug use over time with personalised care. The proportion of patients on adalimumab regular dose decreased considerably more compared with usual care and approximately 30% of patients continued adalimumab in a lower dose at 6 months. Up to 25% stopped biological use.

Cost effectiveness results

Table 2 represents the costs and QALYs for the 272 patients starting adalimumab treatment according to usual care or these patients starting adalimumab treatment according to personalised care over 3 years. Noticeably, the largest cost savings for the personalised care treatment algorithm concerned medication costs (mainly due to the dose reduction or biological stop-treatment steps). The incremental cost effectiveness ratio was −€666 541 per QALY gained using the societal perspective.

The cost effectiveness plane (figure 3) shows the results from the 5000 simulations. Most of the simulations (72%) were in the south-east quadrant (ie, cost savings and more QALYs for personalised care; dominant) and 28% of the simulations fall in the south-west quadrant (ie, cost savings with less QALYs).

Given that a small loss in QALYs is acceptable with costs savings that are higher or equal to the willingness to pay (WTP; the maximum amount one is willing to pay) for a QALY gained, the probability of cost-effectiveness is close to 100% irrespective of WTP up to €250 000 (acceptability curve not shown).

Cost-effectiveness results for the different scenario analyses are presented in table 3. Scenarios in which we consider

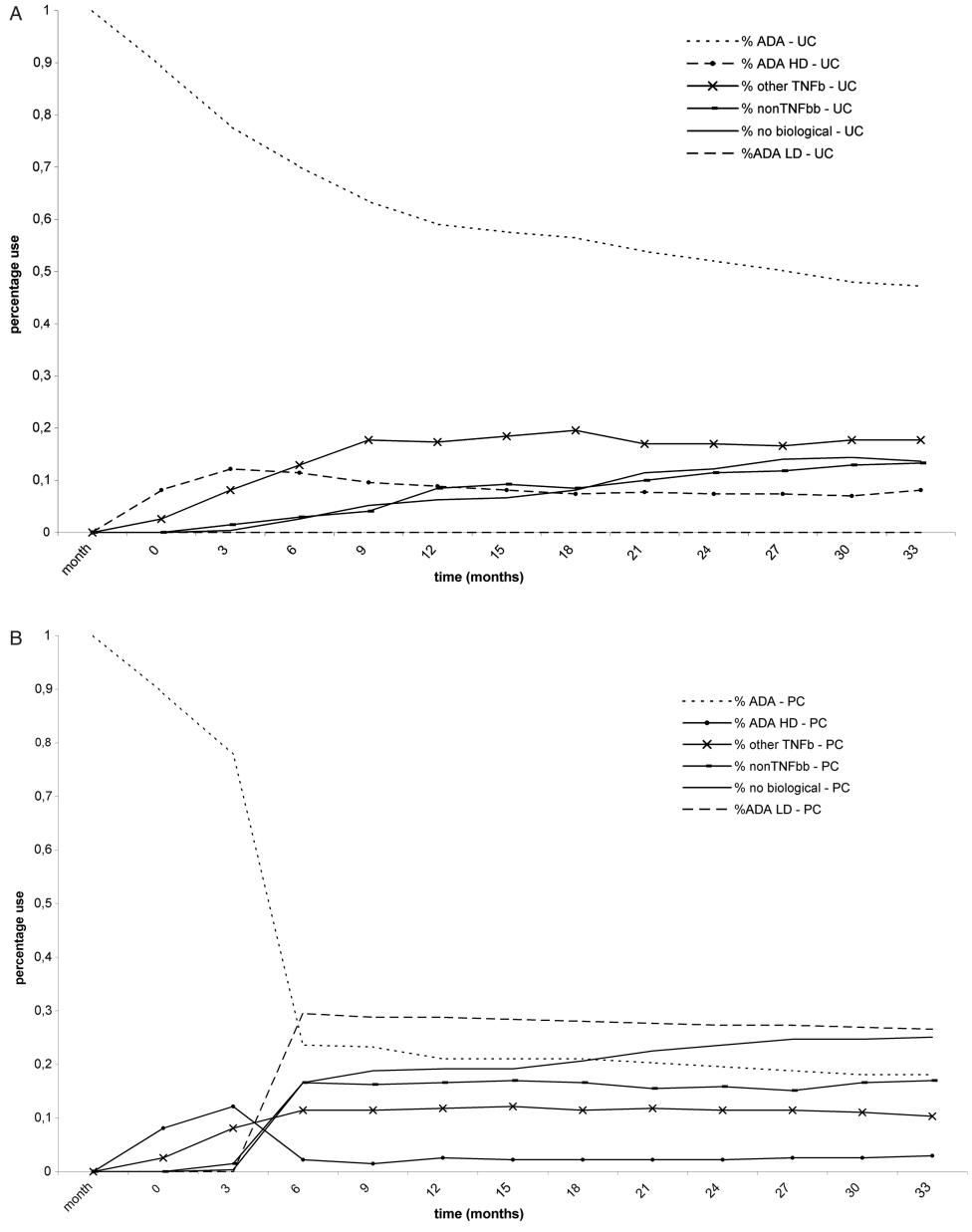

Figure 2 (A) Medication use over time in usual care group. (B) Medication use over time in personalised care group. ADA, adalimumab; ADA HD, adalimumab high dose; TNFb, tumour necrosis factor inhibitor; non-TNFbb, non-tumour necrosis factor inhibiting biological; ADA LD, adalimumab low dose.

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Table 2 Expected Costs, QALYs and ICER over 3 years for the cohort of 272 patients for each treatment approach

Discounted	Usual care (UC)	Personalised care (PC)	Difference (PC-UC) 2.5% to 97.5% CI
Direct costs	€ 4 261 555	€ 4 238 248	−€ 23 307 −€ 56 058 to € 49 346
Productivity costs	€ 1 875 160	€ 1 859 802	−€ 15 357 −€ 225 986 to € 195 370
Drug costs	€ 12 009 964	€ 9 678 572	−€ 2 314 354
Testing costs	€ 0	€ 10 872.52	€ 10 872.52
Total costs	€ 18 028 517	€ 15 466 869	−€ 2 561 648 −€ 3 252 529 to € −1 898 087
QALYs	587.81	591.65	3.84 −8.39 to 16.20
Healthcare ICER			**−€ 646 266/QALY**
Societal ICER			**−€ 666 541/QALY**

Represented values are discounted for costs and effects at 4% and 1.5% respectively. The results represent mean of 5000 simulations.
ICER, incremental cost-effectiveness ratio; PC, personalised care; QALY, quality adjusted life year; UC, usual care.

disutility and extra costs for the non-TNF-inhibiting biologicals, in which we use abatacept instead of rituximab with or without using EULAR good response as response criteria (scenarios 3–5) show a decrease in QALYs next to considerable cost savings. The other scenarios show domination of the personal care strategy in at least 72% of simulations. The savings in the scenarios that result in QALY loss make up for this limited QALY loss up to very high WTP values. The worst QALY loss was observed in scenario 5 where QALY loss amounted to 6.45 QALYs. This can be interpreted as an average loss in utility of 0.008 per patient over the 3 years (ie, 6.45 QALYs divided by 816 patient years) from an average utility of 0.72 in usual care.

DISCUSSION

We evaluated the impact on costs-effectiveness of TDM guided clinical decision making in patients with RA starting treatment with adalimumab, compared with usual care. In our model analysis, we showed a substantial reduction in costs of medication if treatment decisions after 6 months of therapy were based on clinical response, and on the results of DL testing. This personalised approach did not lead to large alterations in efficacy of treatment. Scenario analyses also showed saving of costs, however, efficacy was variable.

Biologicals possess a large variation in pharmacokinetics and therefore measuring DL seems appropriate. Measurement of DL is straightforward and the costs are relatively low. Using the variation in pharmacokinetics, treatment with biologicals can be tailored to the individual patient.

Our study indicates that using TDM in a personalised treatment algorithm might indeed be a sensible thing to do. Evidence based algorithms that incorporate TDM are necessary to improve treatment strategies in clinical practice. This study is a first step towards such an evidence-based algorithm.

Some aspects of our study require comment: Although assumptions always need to be made in modelling studies, extensive sensitivity analysis makes the results more reliable.[29] In our analysis we tried to take all important possible scenarios into account, all resulting in acceptable cost-effectiveness results.

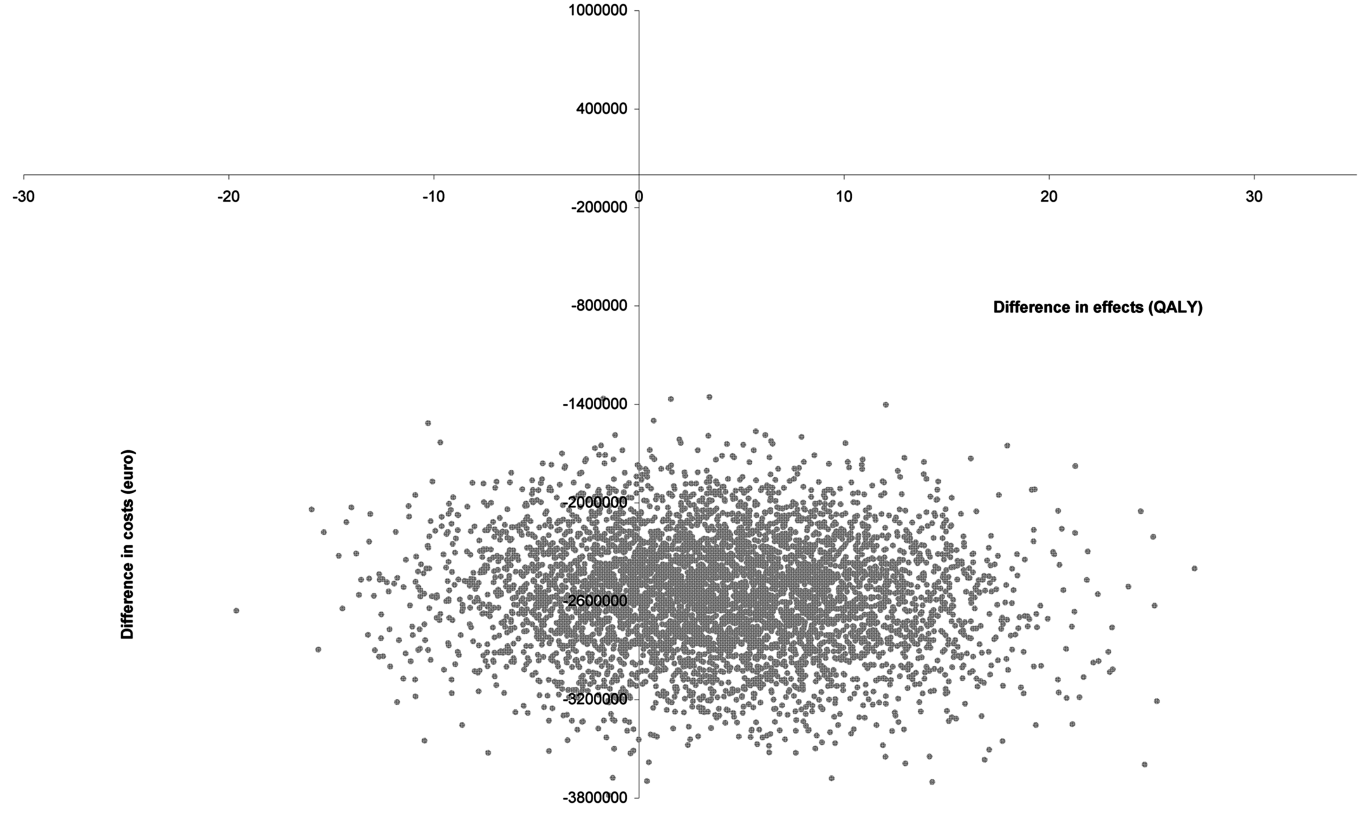

Figure 3 Cost effectiveness plane for the comparison of personalised treatment with usual care.

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In a proportion of patients responding to adalimumab, DLs were low. In these patients, response might not be attributable to the drug, but rather a cause of natural fluctuation of disease. However, whether 5 mg/L will be the optimal cut-off for this treatment step remains a subject of investigation since no validation study of the cut-offs has been performed yet. Therefore scenarios 6 and 7 were additionally performed, using stricter cut-offs. The part of cost savings attributable to this treatment step might therefore be an overestimation since a proportion of those patients will need retreatment with biologicals.

For our treatment algorithm we chose rituximab as the non-TNF-inhibiting biological, because, at least in the Netherlands, this is one of the less costly biologicals. Abatacept or tocilizumab or other biologicals with another mechanism of action will probably also be suitable for this treatment step. Abatacept was used as another example in one of the scenario analysis with still highly cost-effective results. In our algorithm we chose etanercept as a second TNF-inhibitor. This also could have been one of the other TNF-inhibitors. However, patients who developed antibodies to their first anti-TNF agent are more prone to also develop antibodies to their second agent, when this is a therapeutic monoclonal antibody again.[24]

The assumptions regarding improvements in disease activity over time with the personalised treatment approach are not directly observed and are based on a combination of analysis results and expert opinion. Therefore we varied the magnitude of the

Table 3 Results of scenario analyses

Scenario	Societal perspective (2.5–97.5% percentile)	Healthcare perspective (2.5–97.5% percentile)
1. EULAR good response		
Cost diff	−€ 1 999 594 (−2 628 427 to −1 376 991)	−€ 1 967 523 (−2 575 581 to −1 378 044)
QALY diff	8.53 (−4.71 to 22.05)	8.53 (−4.71 to 22.05)
ICER	−€ 233 200/QALY	−€ 225 450/QALY
% (Q1,Q2,Q3,Q4)	89, 11, 0, 0	89, 11, 0, 0
2. Abatacept		
Cost diff	−€ 2 475 546 (−3 123 416 to −1 792 839)	−€ 2 585 592 (−3 090 176 to −1 813 623)
QALY diff	3.75 (−8.24 to 16.03)	3.75 (−8.24 to16.03)
ICER	−€ 659 845/QALY	−€ 689 500/QALY
% (Q1,Q2,Q3,Q4)	73, 27, 0, 0	73, 27, 0, 0
3. Utility loss and extra costs for non-TNF-inhibiting biological		
Cost diff	−€ 2 500 298 (−3 168 398 to −1 816 060)	−€ 2 532 520 (−3 139 230 to −1 846 444)
QALY diff	−4.70 (−16.96 to 7.45)	−4.70 (−16.96 to 7.45)
ICER	−€ 531 570/QALY	−€ 538 421/QALY
% (Q1,Q2,Q3,Q4)	23, 77, 0, 0	23, 77, 0, 0
4. Abatacept+utility loss and extra costs for non-TNF-inhibiting biological		
Cost diff	−€ 2 496 757 (−3 184 331 to −1 828 609)	−€ 2 671 528 (−3 126 653 to −1 838 130)
QALY diff	−4.81 (−16.98 to 7.73)	−4.81 (−16.98 to 7.73)
ICER	−€ 519 571/QALY	−€ 530 914/QALY
% (Q1,Q2,Q3,Q4)	22, 78, 0, 0	22, 78, 0, 0
5. EULAR good response+abatacept+utility loss and extra costs for non-TNF-inhibiting biological		
Cost diff	−€ 1 588 478 (−2 233 077 to 169 235)	−€ 1 979 837 (−2 157 080 to−969 718)
QALY diff	−6.45 (−19.98 to 7.58)	−6.45 (−19.98 to 7.58)
ICER	−€ 246 228/QALY	−€ 244 030/QALY
% (Q1,Q2,Q3,Q4)	18, 82, 0, 0	18, 82, 0, 0
6. stricter drug level cut-offs		
Cost diff	−€ 2 198 829 (−2 845 213 to −1 546 767)	−€ 2 051 150 (−2 794 594 to −1 558 940)
QALY diff	4.20 (−8.19 to 16.88)	4.20 (−8.19 to16.88)
ICER	−€ 523 668/QALY	−€ 488 497/QALY
% (Q1,Q2,Q3,Q4)	74, 26, 0,0	74, 26, 0, 0
7. EULAR good response+stricter drug level cut-offs		
Cost diff	−€ 2.090.551 (−2 720 828 to −1 463 210)	−€ 2 108 341 (−2 644 244 to −1 464 647)
QALY diff	10.67 (−4.32 to 26.15)	10.67 (−4.32 to 26.15)
ICER	−€ 196 006/QALY	−€ 174 448/QALY
% (Q1,Q2,Q3,Q4)	92, 8, 0,0	92, 8, 0, 0
8. Undiscounted		
Cost diff	−€ 2 590 772 (−3 275 690 to −1 922 325)	−€ 2 233 283 (−3 220 860 to −1 931 872)
QALY diff	3.69 (−8.33 to 15.78)	3.69 (−8.33 to 15.78)
ICER	−€ 700 751/QALY	−€ 746 602/QALY
% (Q1,Q2,Q3,Q4)	72, 28, 0, 0	72, 28, 0, 0

Scenario 1: Use of EULAR good response instead of EULAR moderate response as response criteria for treatment algorithm. Scenario 2: The use of abatacept, a more expensive non-tumour necrosis factor (TNF)-inhibiting biological, instead of rituximab. Scenario 3: Loss in utility and extra costs (eg, regarding toxicity) for non-TNF-inhibiting biologicals. Scenario 4: scenario 2+3. Scenario 5: scenario 1+2+3. Scenario 6: Change cut-off for low drug levels from 5 mg/L to 2 mg/L and for high drug level from 5–12 mg/L to 2–12 mg/L. Scenario 7: scenario 1+6. Scenario 8: Undiscounted values for costs and effects.
Q1 is S-E quadrant, Q2 is S-W quadrant, Q3 is N-W quadrant, Q4 is N-E quadrant of cost-effectiveness plane.
EULAR, European league against rheumatism; ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year.

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clinical effects over a broad range in the probabilistic analysis and results showed a high probability of cost-effectiveness. However, before this algorithm can be implemented in daily clinical practice, the clinical impact of the treatment steps in our algorithm have to be investigated in a randomised clinical trial.

Another assumption was to stop biological treatment in personalised care when this was observed in usual care. We think this was a reasonable assumption given that treatment decisions in daily practice were based on interactions between the treating physician and the patient. Furthermore, no change in clinical effect is assumed since the disease activity as observed is used in those instances.

Costs in this study reflect the current situation in the Netherlands and might not automatically be representative for other countries, especially outside Europe. The external data used to extrapolate clinical data to costs and QALYs was older data but costs were updated to reflect current costs. The main difference is that biologicals are used in a substantial part of patients nowadays. These costs were added separately according to the observed treatment or treatment defined by the algorithm. Since the disease duration and disease activity characteristics of this external population are comparable with the population using the biological, this seemed appropriate.

The time horizon for analysis was just 3 years. However, given the dynamic nature of RA treatment it is questionable whether (clinical) effects of the one-time intervention would be present after this time and we regard this as an appropriate time horizon for the current analysis.

Altogether, our results indicate that using TDM in a patient tailored treatment algorithm is cost saving. However, implementing the proposed treatment algorithm poses a risk of a small loss of efficacy on group level. When there is a certain WTP for gaining a QALY, there is theoretically also 'willingness to accept' an amount of money to save for a QALY to be lost. However this can be different (higher) than the WTP for gaining a QALY.[30 31] Results from our scenario analyses suggest that to limit possible QALY loss, using a stricter definition of response (EULAR good response) and stricter cut-offs regarding DL in the algorithm is the way to go.

CONCLUSION

Tailoring biological treatment to individual patients with RA starting adalimumab using DL tests and short-term outcomes is cost-effective. Although specific for patients starting adalimumab treatment, the results underscore the potential merit of personalised biological treatment in RA.

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