Cost–utility of different treatment strategies after the failure of tumour necrosis factor inhibitor in rheumatoid arthritis in the Finnish setting

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Abstract

Objective. To evaluate the cost–utility of different treatment strategies in severe RA after TNF-inhibitor failure.

Methods. The cost-effectiveness of treatment strategies was compared in a group of hypothetical Finnish RA patients. Initially, the patients received either best supportive care (BSC) or one of the following treatments before BSC: adalimumab (ADAL), abatacept (ABAT), etanercept (ETAN), infliximab (INFL) or rituximab (RTX). Further treatments were added to the most cost-effective strategy in a stepwise manner. The analysis was performed on an Excel-based Markov state transition model using the probabilistic approach. The clinical outcomes related to treatments were estimated from published clinical trials. The gained quality-adjusted life-years (QALYs) were estimated based on Health Utilities Index (HUI-3) and disease severity scores (HAQ). The resource use and costs were obtained from the Finnish treatment practice, one published study, the Finnish Unit Cost list and Finnish Medicine Tariffs.

Results. Treatment with RTX was more effective and less costly than treatment with ADAL, ABAT or ETAN after TNF-inhibitor failure. An additional QALY gained with RTX costs 30 248 euros compared with BSC. The incremental cost-effectiveness ratios (ICERs) are 50 941, 50 372, 36 121 and 67 003 euros per QALY gained for adding ADAL, ETAN, INFL and ABAT to the RTX strategy, respectively. According to the cost-effectiveness acceptability frontier (CEAF), only BSC or treatments with RTX or RTX followed by INFL should be considered after TNF-inhibitor failure, if willingness to pay is between 0 and 50 000 euros per QALY gained.

Conclusions. Treatment with RTX is a cost-effective treatment strategy in RA patients in Finland.

Key words: Abatacept, Adalimumab, Cost-effectiveness analysis, Infliximab, Etanercept, Rheumatoid arthritis, Rituximab, TNF-inhibitor.

Introduction

RA is a progressive, chronic, systemic autoimmune disorder that has the potential to cause joint destruction and functional disability. RA decreases the patient’s quality of life (QoL) significantly. Based on a recent publication [1], the annual quality-adjusted life years lost (QALYs-loss) due to RA has been estimated to be 2.69 QALYs per 1000 people (using EQ-5D) in Finland. RA is associated with an increased risk of death, and the life expectancy for RA patients has been 3–4 years shorter than in the general population [2]. The prevalence of RA is ~0.8% in Finland [3].

The treatment of RA in Finland is aimed at remission of the disease and maintenance of normal functioning and QoL [4]. Treatment is usually initiated with traditional DMARDs (tDMARDs). According to statistics of pharmaceutical use in Finnish RA patients, the most commonly prescribed tDMARDs in 2005 were MTX (20 922 users), SSZ (17 718 users) and HCQ (14 871). Gold products (4752), LEF (3438 users), AZA (2252 users), CSA (1401 users) [5] and biologic treatments [3371 users of etanercept (ETAN), anakinra and adalimumab (ADAL) in 2007; 2167 users in 2005] [6] (SII: Statistics on Medicine) were

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used less frequently; credible user data for infliximab (INFL) could not be obtained.

Generally, rituximab (RTX) or abatacept (ABAT) is considered as an option for those RA patients who do not tolerate or who do not get an adequate response to other treatments, including at least one TNF-inhibitor therapy. This study aims to evaluate the cost-utility of different treatment strategies after treatment failure with one TNF-inhibitor in a Finnish setting.

The treatment strategies considered in this evaluation are initiated with another TNF-inhibitor (ETAN + MTX, ADAL + MTX and INFL + MTX), ABAT + MTX or RTX + MTX and their cost-utility is compared with the best supportive care (BSC). For the study purposes, BSC is defined as treatment with intramuscular gold followed by CSA and MTX. When the biological treatment fails, the patients receive either BSC or they are further treated with another biological treatment before BSC. The cost-effectiveness of these treatment strategies is estimated step by step in order to evaluate the cost-effectiveness of adding further treatments to these patients.

The model framework is consistent with the current Finnish treatment practice, since the patients initiating biologic treatments have usually already been treated with tDMARDs (including combination with SSZ, MTX and HCO), LEF + MTX and either ETAN + MTX or ADAL + MTX. The reason for favouring these injectable TNF-inhibitor products over INFL infusions lies in the Finnish health care financing system, where pharmaceuticals purchased in hospitals are financed by municipalities and pharmaceuticals purchased from pharmacies are financed by the Social Security Institution of Finland. As the municipalities face pressure to contain health care costs, the use of INFL is discouraged. However, all relevant treatment options after TNF-inhibitor failure are assessed in this study to achieve international comparability and to openly assess the current practice.

### Methods

#### Model structure

The evaluation was performed on a Microsoft Excel-based microsimulation Markov model [7], in which the life-time treatment outcomes (i.e. life-time costs and benefits) were simulated for identical, hypothetical RA patient cohorts. The cohorts consist of 3000 patients (which we assumed to be the number of potential RA patients in Finland), 33% male and 67% female, with an average age of 48 (s.d. 10) years [8] and an average HAQ score of 1.9 (s.d. 0.58) at baseline [9]. The model is run 1000 times using the transition probabilities in Table 1 to obtain probabilistic sensitivity analysis (PSA) results. The modelling ends when the patients have turned 100 years or died.

The cycle length of the model is 6 months and transitions between health states can occur once every cycle. After the first cycle, the response status of the patients is evaluated and non-responders are switched on to the next treatment in succession. The responders’ response status is evaluated using the American College of Rheumatology criteria (ACR20/ACR50/ACR70), after which they continue the same treatment for a predefined time period (Table 1). After this time period, the patients are assumed to relapse, lose all benefits of treatment (their condition returns to the same level as it was before the treatment) and switch on to the next treatment.

| Drug       | Time on treatment, years | ACR20 | ACR50 | ACR70 | No response | Source               |
|------------|-------------------------|-------|-------|-------|-------------|----------------------|
| RTX + MTX  | 3.75\(^a\)              | 0.27  | 0.17  | 0.13  | 0.43        | Cohen et al. [9]*    |
| ETAN + MTX | 2.50\(^b\)              | 0.29  | 0.22  | 0.14  | 0.35        | Weinblatt et al. [16]*|
| ADAL + MTX | 2.50\(^b\)              | 0.21  | 0.16  | 0.18  | 0.46        | Keystone et al. [17]*|
| INFL + MTX | 2.50\(^b\)              | 0.24  | 0.20  | 0.08  | 0.47        | Maini et al. [18]*   |
| ABAT + MTX | 3.75\(^c\)              | 0.32  | 0.11  | 0.11  | 0.46        | Genovese et al. [33]*|
| GOLD       | 2.00\(^d\)              | 0.17  | 0.04  | 0.01  | 0.78        | Assumption\(^e\)     |
| CSA        | 4.50\(^f\)              | 0.17  | 0.04  | 0.01  | 0.78        | Assumption\(^f\)     |
| MTX        | 0.17                    | 0.04  | 0.01  | 0.78          | Weighted average of the studies marked with asterisk |

\(^a\)Keystone et al. [32] report that 48% of patients withdrew from RTX over four courses of treatment. It was assumed that five courses of RTX were given (9 months apart) summing to 3.75 years. This figure is likely to be an underestimate, because it includes patients who dropped out at the first cycle, i.e. actually belong to the non-responder group of our model. \(^b\)Estimated based on the results shown in Fig. 2 of article by Duclos et al. [34]. Since the time on treatment in our study measures the time on treatment for responders only, we increased the length of treatment by the proportion of patients who dropped out early (to ~33 months). Because the study also reported a hazard ratio of 2.17 for continuing the first compared with second treatment, we took 2.5 years as an estimate for the treatment length. \(^c\)Assumed to be equal to RTX. \(^d\)Bendix and Bjelle [35]. \(^e\)According to Hurst et al. [36], the efficacy of gold and MTX is similar (−0.33 annualized HAQ area units for MTX compared with −0.38 for gold). \(^f\)Median use 75 months (6.25 years) in the study by Marra et al. [37]. On the other hand, in a study by Carpentier et al. [38], the overall continuation rate was 50% after 36 months (3 years). Thus, 4.5 years is used.
QoL effects

The model uses patients’ HAQ scores in the estimation of the patient’s QoL [7, 10–12]. In the first cycle, the baseline HAQ score (1.9) is assumed to change in response to changes in the patients’ response status: −0.1, −0.45, −0.85 and −1.11 for non-responders, ACR20, -50 and -70, respectively [9]. After the first cycle, the patients’ condition is assumed to deteriorate with time. The patient’s HAQ score increases gradually by 0.065 for MTX [11] and by 0.017 for all other treatments [13] every cycle. QoL is estimated on the basis of the formula provided by Bansback et al. [11]: QoL (HUI-3) = 0.76 − 0.28 × HAQ + 0.05 × Female. QoL is extended at the patient level to quality-adjusted survival measured as QALYs by multiplying QoL with the time spent in the respective QoL.

Mortality

At every cycle of the model, the patients can die of natural causes. The model applies an elevated mortality risk (RA risk multiplier 1.33) [12] to average Finnish life tables [14] since the risk of death in RA patients is higher than in the average population [2, 15].

Transition probabilities

The transition probabilities needed in the model are estimated on the basis of response rates in the same manner as was done in Kielhorn et al. [7]. The response rates are taken from published randomized controlled clinical trials [9,16–19] that reported the ACR response rates at 6 months and that had a common comparator treatment (MTX) that enables indirect comparison of the efficacies (an adjusted indirect comparison). The method used for indirect comparison is presented in Appendix 1 (available as supplementary data at Rheumatology Online) and the obtained transition probabilities are shown in Table 1.

Resource use and costs

The initiation of the first biologic treatment in Finland necessitates a screening procedure (e.g. chest X-ray, mantoux test and antibody tests) to evaluate the safety of the initiation for the patients and an application for reimbursement status for pharmacy products. As the initiation of another biologic treatment does not require the same protocol, these costs are omitted from our model for all products. However, it is assumed that patients need to visit a specialized nurse to get instructions on how to inject ADAL or ETAN also at the initiation of the second injectable product.

All patients in the model are assumed to follow a standard protocol. The patients starting the treatment visit a specialized physician [secondary care outpatient visit (OPV)] at initiation and 3 and 6 months after initiation. Thereafter, the OPVs are scheduled once every 6 months. In addition, the patients visit the general practitioner on an average every 6 months. The laboratory values of the patients during treatment are monitored at the initiation of treatment, 1 and 3 months after the initiation and every 3 months thereafter. The costs for health care resources in this standard protocol are shown in Table 2.

### Table 2 Resource use and unit costs [22] in 2008

| Resource | Cost per visit, € | Resource use (s.e.) |
|----------|------------------|---------------------|
| Nurse    | 41.80<sup>a</sup> | RTX, INF, ABAT, CSA, MTX 0 |
|          |                   | ETAN, ADAL, first cycle 1 |
|          |                   | Intramuscular gold Every 4 weeks |
| Outpatient visit (internal diseases)/day unit visit | 190.62 | First cycle 2 |
| General practitioner visit<sup>a</sup> | 44.86 | First cycle 0 |
| Inpatient day (internal diseases), cost/day | 628.26 | 0.0 < HAQ score < 0.5 0.68 (0.07) |
|          |                   | 0.6 < HAQ score < 1.0 2.77 (0.28) |
|          |                   | 1.1 < HAQ score < 1.5 4.12 (0.41) |
|          |                   | 1.6 < HAQ score < 2.0 8.86 (0.89) |
|          |                   | 2.1 < HAQ score < 2.6 10.25 (1.03) |
|          |                   | 2.6 < HAQ score < 3.0 4.56 (0.46) |
| Phone consulting by patient<sup>b</sup> | 18.71 | First cycle 1 |
| Laboratory visit | 4.81 | First cycle 3 |
| Laboratory tests (ESR, FBC, CRP, liver function tests, creatinine and urea) | 16.72 | Later cycles 2 |
| Travelling to primary health care (by patient) | 6.48 | _c |
| Travelling to secondary health care (by patient) | 33.13 | _c |

<sup>a</sup>The unit cost of outpatient visit in the primary health care for rheumatic diseases. <sup>b</sup>The laboratory results informed over phone for the tests 1 month after initiation. <sup>c</sup>Number of journeys varies according to treatment. For example, RTX, ABAT and INFL infusions are given in secondary care facilities, whereas ETAN and ADAL are not. If the infusion date is in the proximity of scheduled OPV, the OPV is assumed to be on the date of the infusion and only one journey to secondary care is assumed.
The costs used for the pharmaceuticals are the most economical prices in the Finnish Medicine Tariff (11/2008) estimated for an average patient (Table 3). The administration cost for RTX, ABAT and INFL is assumed to be equal to the cost of one OPV. This assumption is made since the unit cost of an OPV includes most tests and procedures related to those visits. In addition, one hospital district has given out a cost estimate of one visit at a day unit (infusions in Finland are given in these units) of 170 euros, which is very close to the average unit cost of an OPV. Since intramuscular gold is administered in the primary health care by a nurse, an additional primary health care visit is assumed to cover the administration costs for gold. All patients are assumed to be able to inject themselves with ETAN and ADAL.

The inpatient treatment is estimated on the basis of HAQ score (Table 2), which reflects the disease severity. The relationship between HAQ scores and inpatient days in this study comes from a Swedish 5-year follow-up study of 116 consecutive RA patients [10]. These Swedish estimates are used since there is only very limited published information of this relationship for Finland. A Finnish study by Laas et al. [20] reported that there were altogether 395 inpatient days in a year for 96 patients who had an average HAQ score of 1.37. This gives an average number of inpatient days of 4.11, which is the same as in the Swedish study [10].

Production losses due to RA are excluded from the analysis, since patients with similar characteristics to our patient population are usually retired in Finland. In a study by Puolakka et al. [21], the yearly productivity losses were on an average 22,000 euros already at HAQ score 1 (average salary recommended for estimation of productivity losses in Finland is 24,309 euros [22]).

Analyses

Base-case analyses. The cost–utility of different treatment alternatives is evaluated on the basis of the incremental cost-effectiveness ratios (ICERs). Treatments are compared in a stepwise manner: at first step, all alternative treatments are compared with BSC and at subsequent steps, other treatments are added to the treatment/treatment sequence having the smallest ICER in the previous step. The results are also depicted as the cost-effectiveness efficiency frontier using a cost-effectiveness plane.

Based on the probabilistic approach, the uncertainty related to decision making is explored by presenting a cost-effectiveness acceptability frontier (CEAF) [23]. In contrast to the conventional multinomial cost-effectiveness acceptability curves (mCEAC) [23–25], which presents the probability that a treatment is the most cost-effective of all treatments at different willingness to pay (WTP) per QALY gained levels, CEAF demonstrates which of the treatments should be adopted because it results in the highest expected net benefit for a given WTP. This is related to the fact that in the case of skewed distributions of net benefit, the treatment with the highest probability of being cost-effective is not always the treatment with the highest expected net benefit [26]. The net benefit is calculated conventionally as the total cost minus the QALYs multiplied by the WTP.

All analyses are done from the Finnish societal perspective, in which the productivity losses are usually excluded. All costs are estimated without VAT and adjusted to the 2008 price level using the health care price index published by Statistics Finland (transformation coefficient for year 2006: 1.0942). All costs and outcomes are discounted by a 3% annual rate as recommended by the Finnish authorities.

Sensitivity analyses. Multiple one-way sensitivity analyses are performed to evaluate the effect of assumptions made in the absence of conclusive data for some necessary variables. In the sensitivity analyses, the values of the following variables are altered: average time period for treatments (figures from Kielhorn et al. [7] used); 4.25 years for RTX + MTX, ETAN + MTX, ADAL + MTX and ABAT + MTX (ABAT + MTX was not assessed in Kielhorn et al. and we therefore assumed the same length as for RTX + MTX);
2.46 years for INFL + MTX; 1.7 years for CSA; 3.85 years for gold, length of RTX treatment cycle (6 months; 12 months), HAQ score—resource use relationship (inpatient days 4.11 regardless of HAQ; 10% increase in inpatient days for HAQ > 1.6), QoL estimates (negative QALYs allowed; QALYs estimated with [27]: QoL (EQ-5D) = 0.86 – 0.20 × HAQ) and discount rate (0%). Because the costs of outpatient (retail prices) and inpatient (wholesale prices) pharmaceuticals differ significantly in the Finnish system, we also report a sensitivity analysis using the wholesale prices for ETAN (251.80 euros/dose) and ADAL (543.77 euros/dose) to improve the international generalization of the results.

**Results**

**Base-case analyses**

The results of the base-case analyses are shown in Table 4 and Fig. 1. When the patients are given only BSC for their RA, the average total treatment costs, according to our model, are 85 714 euros and the patients gain on an average 2.69 QALYs during their remaining

| Scenario | Treatments | Average cost, € | Average QALYs | ICER vs BSC | ICER vs the smallest ICER in the previous scenario |
|----------|------------|----------------|---------------|-------------|--------------------------------------------------|
| 0        | BSC        | 85 714         | 2.69          |             |                                                  |
| 1        | RTX → BSC  | 106 921        | 3.39          | 30 248      |                                                  |
|          | ADAL → BSC | 111 195        | 3.19          | 50 941      |                                                  |
|          | ETAN → BSC | 112 546        | 3.22          | 50 372      |                                                  |
|          | INFL → BSC | 102 558        | 3.15          | 36 121      |                                                  |
|          | ABAT → BSC | 127 580        | 3.31          | 67 003      |                                                  |
| 2        | RTX → ADAL → BSC | 128 053 | 3.79 | 38 235 | 52 021<sup>a</sup> |
|          | RTX → ETAN → BSC | 130 258 | 3.83 | 38 938 | 52 698<sup>a</sup> |
|          | RTX → INFL → BSC | 120 946 | 3.77 | 32 621 | 37 013<sup>a</sup> |
|          | RTX → ABAT → BSC | 142 335 | 3.91 | 46 367 | 68 100<sup>a</sup> |
| 3        | RTX → INFL → ADAL → BSC | 141 541 | 4.14 | 38 329 | 54 701<sup>b</sup> |
|          | RTX → INFL → ETAN → BSC | 143 686 | 4.18 | 38 785 | 54 836<sup>b</sup> |
|          | RTX → INFL → ABAT → BSC | 155 493 | 4.26 | 44 466 | 70 616<sup>b</sup> |

<sup>a</sup>Compared with RTX + MTX → BSC in scenario 1. <sup>b</sup>Compared with RTX + MTX → INFL + MTX → BSC in scenario 2.

**Fig. 1** The cost-effectiveness efficiency frontier (CEEF) represents the most efficient choices among the compared treatment strategies. The average costs and QALYs gained with BSC are given in the origin.
lifetime. In Fig. 1, the efficiency frontier depicts the most efficient choices (and their respective ICERs) among the compared treatment alternatives: the most efficient strategy is to use RTX + MTX → BSC or, if the WTP of 37 013 euros per QALY gained is not too much, RTX + MTX → INFL + MTX → BSC treatment strategies after TNF-inhibitor failure.

In detail, adding a second biologic treatment after TNF-inhibitor failure increases the average treatment costs by 16 843–41 866 euros and gives 0.46–0.70 additional QALYs compared with BSC alone, depending on which biologic treatment is chosen. The most cost-effective choice is RTX + MTX with an ICER of 37 013 euros per QALY gained, which is lower than those of either INFL + MTX (36 121 euros), ETAN + MTX (50 372 euros), ADAL + MTX (50 941 euros) or ABAT + MTX (67 003 euros). Treatment with RTX + MTX dominates ETAN + MTX, ADAL + MTX and ABAT + MTX, as it is less costly and more effective. Compared with INFL + MTX, the cost of an additional QALY with RTX + MTX is 18 585 euros.

When a third biologic treatment is added after RTX + MTX, the average treatment costs increase further by 14 024–35 414 euros and result in 0.38–0.52 additional QALYs, depending on which treatment comes next. Compared with treatment with RTX + MTX (→ BSC), the ICERs of adding biologic treatment range from 37 013 (INFL + MTX) to 68 100 (ABAT + MTX) euros per QALY gained. Compared with giving INFL + MTX as the third biologic treatment, an additional QALY with ADAL + MTX, ETAN + MTX and ABAT + MTX costs 260 197, 145 658 and 151 562 euros, respectively.

In case a fourth biologic treatment is added after INFL + MTX, the average treatment costs increase further by 20 595–34 547 euros and 0.38–0.49 additional QALYs are gained. Compared with treatment with RTX + MTX → INFL + MTX → BSC, the additional QALY with ETAN + MTX costs 54 836 euros, with ADAL + MTX 54 701 euros and with ABAT + MTX 70 616 euros. Compared with ETAN + MTX and ADAL + MTX, an additional QALY with ABAT + MTX costs 158 411 and 123 775 euros, respectively. Please note that ETAN + MTX and ADAL + MTX are not compared with each other, since one of them is assumed to have been used previously.

If the WTP for an additional QALY gained is ~50 000 euros, the results of the incremental cost-effectiveness analyses performed successively for each treatment indicate that the treatment succession should include only RTX + MTX and INFL + MTX. However, if the analyses are performed for treatment sequences (compared with BSC), the ICERs remain ~50 000 euros even for those treatment sequences that include all possible biologic treatments.

The patients in the model die shortly after their 75th birthday. Currently, the life expectancy in Finland is 82.9 years for a newborn girl and 75.9 years for a newborn boy [14]. When these expectancies are weighted, according to the proportion of males and females in the model, the obtained average life expectancy in Finland is 80.6 years. Compared with this, the patients in the model die ~5 years earlier. This is quite close to the 3–4 years shorter life expectancy in RA patients reported in Finland [2].

### Sensitivity analyses

The robustness of the cost–utility results was tested by performing multiple sensitivity analyses. The results of the one-way sensitivity analyses are shown in Table 5 and PSA is presented in Fig. 2.

| Change | Treatment* | Cost | QALYs | ICER | Change | Treatment* | Cost | QALYs | ICER |
|--------|------------|------|-------|------|--------|------------|------|-------|------|
| Length of treatment according to Kielhorn et al. [7] | BSC | 83 741 | 2.63 | | | | | | |
| | RTX + MTX | 107 319 | 3.44 | 28 972 | | | | | |
| | ADAL + MTX | 126 046 | 3.46 | 51 018 | | | | | |
| | INFL + MTX | 100 630 | 3.11 | 35 320 | | | | | |
| | ABAT + MTX | 130 181 | 3.36 | 63 513 | | | | | |
| Constant resource use based on Finnish data (4.12 inpatient days in all HAQ) | BSC | 62 153 | 2.69 | | No. of inpatient days after HAQ >1.6 | | | | |
| | RTX + MTX | 85 092 | 3.39 | 32 717 | category always 10% larger than | | | | |
| | ADAL + MTX | 88 877 | 3.19 | 53 425 | in the previous category | | | | |
| | ETAN + MTX | 90 448 | 3.22 | 53 118 | | | | | |
| | INFL + MTX | 80 073 | 3.15 | 38 428 | | | | | |
| | ABAT + MTX | 105 294 | 3.31 | 69 044 | | | | | |
| Qol. estimated using Hawthorne et al. [27] | BSC | 85 714 | 6.91 | | Discount rate 0% | | | | |
| | RTX + MTX | 106 921 | 7.50 | 36 228 | | | | | |
| | ADAL + MTX | 111 185 | 7.33 | 60 842 | | | | | |
| | ETAN + MTX | 112 546 | 7.36 | 60 273 | | | | | |
| | INFL + MTX | 102 548 | 7.31 | 42 794 | | | | | |
| | ABAT + MTX | 127 580 | 7.44 | 79 647 | | | | | |
| Wholesale prices | ETAN + MTX | 108 421 | 3.22 | 42 628 | | | | | |
| | ADAL + MTX | 107 332 | 3.19 | 43 218 | | | | | |

*After the biologic treatment, BSC is given.*

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One-way sensitivity analyses. In the first sensitivity analyses, the length of the average treatment period was changed to match those of a similar study by Kielhorn et al. [7]. Using these treatment lengths, the average treatment costs of BSC are 1973 euros lower than in the base-case scenario and 0.06 less QALYs are gained during the remaining life time. The ICERs of this scenario do not change dramatically from the base-case scenario (from €3490 to €957 euros). However, RTX + MTX now dominates only ABAT + MTX, because ETAN + MTX and ADAL + MTX are now both more costly and more effective than RTX. An additional QALY with ETAN + MTX and ADAL + MTX compared with RTX + MTX costs 306 945 and 1 215 418 euros, whereas an additional QALY with RTX + MTX compared with INFL + MTX now costs 19 930 euros.

When the dosing interval of RTX is changed to 6 months and 12 months, the average treatment costs increase and decrease by 11 548 and 5780 euros, respectively. With a 12-month treatment cycle of RTX, RTX + MTX dominates all other treatments and is more effective and less costly. With a 6-month treatment cycle of RTX, RTX + MTX dominates ABAT + MTX and is more effective and more costly than other TNF-inhibitors. An additional QALY with RTX + MTX in this scenario costs 36 209, 35 169 and 67 767 euros compared with ADAL + MTX, ETAN + MTX and INFL + MTX, respectively.

Allowing the QALYs to become negative (i.e. worse than death) decreases the QALYs gained while costs remain the same. The cost–utility results do not change much, because the ICERs become only €24200–45000 euros smaller. Estimating the QoL based on Hawthorne et al. [27] doubles the number of QALYs gained in the model. The relative cost-effectiveness results do not change, and RTX + MTX continues to dominate ADAL + MTX, ETAN + MTX and ABAT + MTX. However, the cost per additional QALY gained with all treatments increases. An additional QALY with RTX + MTX compared with INFL + MTX costs now almost €4200 more than in the base-case scenario (i.e. €22 778 euros).

As expected, changing the discounting rate from 3 to 0% changes the results: all ICERs become clearly smaller (by ~2800–9400 euros). Assuming that the number of inpatient days is not related to the patient’s HAQ scores (always an average 4.12 days/year) decreases the total cost of RA treatment in this patient population. The ICERs for all treatment alternatives compared with BSC increase by ~2000–2700 euros. Similarly, the assumption that the number of inpatient days increases by 10% in each HAQ category when HAQ exceeds the value of 1.5 decreases the total treatment costs. However, the ICERs in this case remain almost unchanged.

The impact of the Finnish system, where wholesale prices are used for inpatient pharmaceuticals (RTX, ABAT and INFL) and retail prices for outpatient pharmaceuticals (ADAL and ETAN), was also assessed. In this scenario, RTX + MTX still dominated both ADAL + MTX and ETAN + MTX. However, the ICERs of ADAL + MTX and ETAN + MTX compared with BSC dropped considerably by over 7700 euros.

PSA. The CEAF approach based on PSA is depicted in Fig. 2. According to CEAF, the optimal decision is to use BSC with WTP levels <30 246 euros per QALY gained. RTX + MTX → BSC is the optimal decision with WTP levels between 30 249 and 37 012 euros per QALY gained. RTX + MTX → INFL + MTX → BSC becomes preferable above a WTP level of 37 015 euros per QALY gained.

Furthermore, RTX + MTX → INFL + MTX → BSC becomes a potentially cost-effective (i.e. the probability of cost-effectiveness/highest expected net monetary benefit
exceeds 50%) treatment option with a WTP level of 44 385 euros per QALY gained. None of the treatments achieves potential cost-effectiveness, with WTP levels between 27 961 and 44 384 euros per QALY gained. However, it should be noted that in the multiple comparison presented in Fig. 2, the expected (default) probability of cost-effectiveness is only 7.7% for any treatment (i.e. actually 13 different treatment scenarios are simultaneously being compared in Fig. 2). With a WTP of 30 000 euros per QALY gained, RTX + MTX → BSC has 37.9% and BSC has 36.8% probability of cost-effectiveness and with a WTP of 50 000 euros, RTX + MTX → INFL + MTX → BSC 55.5% probability of cost-effectiveness; these probabilities are significantly higher compared with the default of 7.7% (the probabilities of cost-effectiveness for other treatments are quite similar to or even lower than the default). Thus, given the typical threshold of cost-effectiveness (50 000 euros per QALY gained) and taking uncertainty into account, the optimal treatment seems to be RTX + MTX → INFL + MTX → BSC.

Discussion

We compared the cost–utility of different treatment strategies in the treatment of severe RA after TNF-inhibitor failure. The results indicate that RTX + MTX dominates ADAL + MTX, ETAN + MTX and ABAT + MTX. An additional QALY gained with RTX + MTX costs 30 248 euros compared with BSC and 18 585 euros compared with INFL + MTX. The ICERs are 52 021, 52 698, 37 013 and 68 100 euros per QALY gained for adding ADAL + MTX, ETAN + MTX, INFL + MTX and ABAT + MTX to the RTX + MTX strategy, respectively. According to CEAF, only treatments with RTX + MTX or RTX + MTX followed by INFL + MTX should be considered after TNF-inhibitor failure, if 50 000 euros per QALY gained is used as a WTP threshold. If the objective is to offer potentially cost-effective treatment to RA patients and the threshold is 50 000 euros per QALY gained, only RTX + MTX followed by INFL + MTX should be considered after TNF-inhibitor failure.

According to a systematic review by Chen et al. [28], 10 economic evaluations had been published on the cost-effectiveness of ADAL, ETAN and INFL before February 2005. The studies included in the review reported a large range for the values of ICERs due to varying assumptions and parameters. The base-case ICER was found to be around 30 000 pounds (~33 583 euros) per QALY gained in early RA and 50 000 pounds (~55 972 euros) per QALY gained in late RA [28]. The ICERs for late RA in the review are thus very close to our estimates for ETAN + MTX and ADAL + MTX.

The study by Kielhorn et al. [7] is the only study thus far reporting the cost-effectiveness of RTX in the treatment of RA. The study reports ICERs from 11 601 (12 987 euros) to 14 690 pounds (16 445 euros) per QALY gained for adding RTX + MTX in two different treatment sequences in an almost identical patient population to ours. As the treatments included in the analyses by Kielhorn et al. differ from ours, the comparison of the results is not straightforward. The treatment costs in the study by Kielhorn et al. seem to be somewhat lower than ours (74 535 euros in the secondary analysis that is similar to our sequence, including RTX, INFL and ADAL with costs of 141 541 euros). The potential reasons for these differences cannot be analysed because the exact resource use in Kielhorn et al. [7] is not reported.

There are some limitations that are likely to influence the results of our study. First, the ACR response rates used in our evaluation are mostly collected from trials whose patient populations do not match the population of interest in our study. There were no randomized, controlled clinical trials of the efficacy of the TNF-inhibitors after TNF-inhibitor failure. Therefore, results from trials with TNF-inhibitor-naive patients had to be used as estimates. However, the response rate estimates for RTX + MTX and ABAT + MTX match the population of interest [9, 19]. Similarly, the response rates of BSC treatments (intramuscular gold and CSA) had to be assumed to be identical to MTX due to the absence of relevant reported clinical trials. The BSC assumption, however, does not have a significant impact on the results because the same BSC is included in all strategies.

There is some evidence that the response rates used in our study for TNF-inhibitors may overestimate the efficacy of TNF-inhibitors. For example, a register-based study by Hyrich et al. [29] showed that only 36–42% of patients who switch their original TNF-inhibitor to another due to inefficacy experience, an improvement of at least 0.22 U in their HAQ scores. This improvement is even less than that related to the ACR20 response in our study (~0.45) [9]. Also, the follow-up studies by Buch et al. [30] and van der Bijl et al. [31] give similar results. For example, the ACR20 level response was obtained by 38% of the ETAN-treated patients with a previous treatment failure with INFL [30] compared with the 71% estimate used in our study. Similarly, the ACR20 level response was obtained by 46% of ADAL patients with previous treatment failure with INFL [31] compared with the 63% estimate in our study. Therefore, ~60% of the users of second TNF-inhibitor may in fact be non-responders, although the estimates used in our study are ~30–40%.

Since we found no research evidence describing the actual changes in the HAQ scores of RA patients during the treatment periods, we had to assume that the patients' condition deteriorates at a certain rate during the treatment. The rate used was 0.065 per cycle for MTX and 0.017 for other treatments, which have also been used in another similar study [7]. This assumption is likely to simplify the reality, because the rate may differ between various treatments. At least for RTX + MTX and ABAT + MTX, the patients' condition may even improve in time. In studies by Keystone et al. [32] and Genovese et al. [33], the number of patients obtaining ACR responses increased after 6 months of treatment.

Another related factor that affects the results in our study is the length of the average treatment period. Our study used 3.75 years as an estimate for RTX + MTX and ABAT + MTX and 2.5 years for TNF-inhibitors. Since there
are no conclusive data available on these figures, they may well be over- or underestimates of the treatment length in real life. The treatment length for TNF-inhibitors in our study is based on a study by Duclos et al. [34], who reported the treatment continuation for all TNF-inhibitor users (regardless of product and whether it was first or second) in one treatment centre.

According to Duclos et al. [34], ~50% of TNF-inhibitor users had discontinued to use after 2 years and 60% after 3 years. In our model, the early stoppers belong to the non-responder group and, therefore, we increased the length of treatment by the proportion of patients who dropped out early (to ~33 months). Since the study also reported a hazard ratio of 2.17 for continuing the first compared with the second treatment, we took 2.5 years as an estimate for the treatment length. For RTX + MTX, the treatment length was taken from a clinical trial, which may overestimate the length of average treatment in a real life setting. However, to keep the estimate conservative, we did not make the assumption for RTX that patients who discontinued early would belong to the non-responder group (33% of patients discontinued after the first cycle [32]). Similar treatment length to that for RTX + MTX was assumed for ABAT + MTX. In sensitivity analyses, we took the treatment lengths from the study by Kielhorn et al. [7]. Changing the lengths of treatment with ETAN + MTX and ADAL + MTX did not change the results of the analysis dramatically. RTX + MTX no longer dominated ETAN + MTX or ADAL + MTX, but the cost for an additional QALY gained with ETAN + MTX and ADAL + MTX was as high as 337 033–1 215 418 euros.

There were certain uncertainties in the evaluation of resource use in our study. The model estimates inpatient costs based on resource use that is determined according to the patient’s HAQ score. Because there were no available data on this relationship for Finland, the relationship between HAQ scores and resource use in Finland was assumed to be identical to that in Sweden [10]. Even though Finland and Sweden are geographically and culturally very similar, there may be differences in the organization of health care. However, the differences may not be great. According to a study by Laas et al. [20], the resource use for patients with an average HAQ score of 1.37 in Finland was the same as that reported in the Swedish study [10]. This assumption was also further explored in the sensitivity analysis and was found to be insignificant.

A further uncertainty, related to the cost estimates in our study, is due to the fact that the outpatient costs were not included separately in the model. This was done to prevent potential double-counting when separate, drug-specific administration and monitoring costs are already in the model. The model includes the costs of surgical procedures only to the extent that their cost is reflected in the unit cost of an average inpatient day in Finland. In essence, the potential differences in the need for surgical procedures between the various treatments are conveyed through the differences in obtained HAQ scores, which are used to estimate the number of inpatient days. The effects of surgical procedures were omitted from the evaluation, since the estimation of their benefits in terms of HAQ improvements would have made the model extremely complex.

The base-case results of our study may not be readily generalized to other countries with health care systems differing considerably from Finland. Perhaps the biggest issue in this respect is created by the Finnish two-tiered health care financing system, where the pharmaceuticals given in hospital are funded by municipalities and outpatient pharmaceuticals are funded by the Social Insurance Institution. The Finnish system essentially leads to discrepancy in the cost structure of outpatient and inpatient pharmaceuticals, because a regulatory sales margin is added only to the outpatient pharmaceuticals (this margin is relatively high in Finland). The impact of this system-associated ‘distortion’ was assessed in a sensitivity analysis, where the wholesale prices were used for all products (the wholesale prices of pharmaceuticals in Finland are relatively low). In this sensitivity scenario, RTX + MTX still dominated ADAL + MTX and ETAN + MTX, although the ICERs of ADAL + MTX and ETAN + MTX compared with BSC dropped some 7700 euros. In countries such as Sweden where the pharmacy premium (i.e. difference between retail and wholesale price) is high and wholesale prices are very low, these results can be readily appealing. Also, the use of the same standard monitoring protocol for all treatments in our evaluation and the use of HAQ-based resource use is likely to improve the generalization of the study results, as long as the monitoring protocols, (relative) prices between different biologic treatments and baseline HAQ scores do not differ in other countries.

Last, it must be noted that the model simplifies the actual treatment process in RA. In reality, patients can receive the same pharmaceutical treatment again after discontinuing it the first time. In our model, this is not possible. However, the efficacy related to the reuse of the same pharmaceutical may be less than in a naïve patient and would have been very hard to capture in a model. Patients initiating biological treatments also do not necessarily discontinue their previous medications. In our study, we assumed that the use of ‘golden standard’ MTX continues. The impact of continuing tDMARD(s) is, however, likely to be minimal as tDMARDs are relatively cheap. In addition, the BSC option in the model is constrained. In reality, the BSC option is not fixed to include intramuscular gold, CSA and MTX, but is instead tailored for each patient. However, when modelling treatment processes, some simplifying assumptions have to be made to prevent the models from becoming extremely complex. If we assume that the patients are identical with regard to their other medications and the type of BSC suitable for them, changing these aspects in the model would not have changed the relative results (i.e. they would equally affect all compared alternatives).
Conclusion

Based on current evidence, treatment with RTX followed by BSC, and treatment with RTX followed by INF-L and BSC are the most cost-effective treatment alternatives for Finnish patients with RA who have failed TNF-inhibitor treatment. The efficacy estimates of TNF-inhibitors in this study were derived from trials with TNF-inhibitor naive patients, and therefore the results may well overestimate the cost-effectiveness of these products in the study patient population compared with RTX and ABAT. Because of this, no definite conclusions can be drawn about the cost-effectiveness of ABAT compared with the TNF-inhibitors.

Rheumatology key message

- RTX is a cost-effective treatment strategy in RA after failure of TNF-inhibitor in the Finnish setting.

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Supplementary data

Supplementary data are available at Rheumatology Online.

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