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Original article

Cost-effectiveness of adalimumab, etanercept, and tocilizumab as first-line treatments for moderate-to-severe rheumatoid arthritis

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Abstract

Objective:
The aim of this study was to assess the cost-utility and value of reducing the uncertainty associated with the decision to use first-line biologic treatment (bDMARD) after the failure of one or more traditional drugs (tDMARD) in moderate-to-severe rheumatoid arthritis (msRA) in Finland.

Research design and methods:
The treatment sequences were compared among 3000 hypothetical Finnish msRA patients using a probabilistic microsimulation model in a lifetime scenario. Adalimumab + methotrexate, etanercept + methotrexate, or tocilizumab + methotrexate were used as first biologics followed by rituximab + methotrexate and infliximab + methotrexate. Best supportive care (BSC), including tDMARDs, was assumed to be used after the exhaustion of the biologics. Methotrexate alone was added as a further comparator. Efficacy was based on ACR responses that were obtained from a mixed treatment comparison. The resources were valued with Finnish unit costs (year 2010) from the healthcare payer perspective. Additional analyses were carried out, including productivity losses. The Health Assessment Questionnaire (HAQ) values were mapped to the EQ-5D values using the tocilizumab trials; 3% annual discounting for costs and quality-adjusted life years (QALY) and extensive sensitivity analyses were completed.

Main outcome measures:
Incremental cost per QALY gained and multinomial expected value of perfect information (mEVPI).

Results:
bDMARDs significantly increase the QALYs gained when compared to methotrexate alone. Tocilizumab + methotrexate was more cost-effective than adalimumab + methotrexate or etanercept + methotrexate in comparison with methotrexate alone, and adalimumab + methotrexate was dominated by etanercept + methotraxate. A QALY gained with retail-priced (wholesale-priced) tocilizumab + methotrexate costs €18,957 (€17,057) compared to methotrexate alone. According to the cost-effectiveness efficiency frontier and cost-effectiveness acceptability frontier (CEAF), tocilizumab + methotrexate should be considered before rituximab + methotrexate, infliximab + methotrexate, and BSC. Based on the CEAF, tocilizumab + methotrexate had a 60–93% probability of being cost-effective with €20,000 per QALY gained (mEVPI €230–2182).

Conclusions:
Tocilizumab + methotrexate is a potentially cost-effective bDMARD treatment for msRA, indicating a low value of additional research information with the international threshold values.

Limitations:
Efficacy based on an indirect comparison (certolizumab pegol, golimumab excluded), fixed treatment sequence after the exhaustion of first bDMARD, Swedish resource use data according to HAQ scores, and inpatient costs assumed to include surgery.

Introduction

Rheumatoid arthritis (RA) is an autoimmune disease that causes a significant economic burden on society[1,2] and reduces the quality-of-life (QoL) of those affected[3–7]. Clinically significant RA has been diagnosed in 0.8% of the Finnish population[8] and the incidence is 44.5/100,000 in adults[9].

When ineffectively treated, RA can result in permanent disability[10]. The goal of RA treatment is to achieve remission or low disease activity, with normal functioning and QoL[11]. At the onset of RA, aggressive treatment with traditional disease modifying anti-rheumatic drugs (tDMARD) and low-dose corticosteroids[11,12] is recommended. Among tDMARDs, methotrexate (MTX) is the 'anchor drug'[12,13]. TNF inhibitors are usually started if the response to tDMARDs is not satisfactory[14]. TNF inhibitors are followed by rituximab (RTX), abatacept (ABAT), or tDMARDs (e.g., cyclosporine, leflunomide, or MTX).

This study assessed (1) the cost-effectiveness (CE) and (2) the value of additional research information in reducing the uncertainty related to the decision to use the first-line biologic disease modifying anti-rheumatic drug (bDMARD) + MTX or MTX alone in the treatment of moderate-to-severe RA (msRA) after one or more tDMARD failures. The first-line bDMARD comparators included two established and reimbursed TNF inhibitors – the most used (adalimumab, ADAL) and most affordable (etanercept, ETAN) – and a new option (tocilizumab, TOC). The compared sequences consisted of one first-line bDMARD comparator followed by (→) a fixed treatment sequence (RTX → infliximab [INFL] → best supportive care [BSC], including the sequence of leflunomide [LEFL] → cyclosporine [CSA] → MTX). The fixed treatment sequence was adapted based on the clinical expertise and the recent CE evaluation of second-line bDMARD treatments in Finland[15]. In line with clinical recommendations, the bDMARDs were given with MTX and an outcome assessment was conducted at 6-month intervals.

Patients and methods

The CE of different treatment sequences was assessed using an Excel-based probabilistic[16] individual sampling model. In the primary analysis, costs and outcomes were considered from the public healthcare payer perspective (named payer costs), whereas the societal perspective (including productivity losses) was adopted as the secondary perspective.

Patients and simulations

The CE was assessed in a hypothetical RA population consisting of 3000 patients with active msRA and an inadequate response to the first-line mono or combination therapy treatment with tDMARDs using a simulation model. The patient profiles were taken from the pooled TOC trial (OPTION, TOWARD and LITHE[17–19]) msRA population who had inadequate response (IR) to tDMARDs. The patients were 52.5 years old on average, had an HAQ score of 1.51 at the baseline and weighed 73 kg; 18% of the population were men. The characteristics of the patients in the TOC trials were comparable to the indirect comparison population[20], the Finnish RA population[21–23], and the average weight of Finns[24].

The model (Figure 1) used in the analysis was an individual sampling model with a structure that allows PSA (probabilistic sensitivity analysis, probability distributions for known uncertain parameters). The individual sampling means that the characteristics of the patients are tracked and the patients have individual histories that affect their outcomes. The analysis was performed by recording the outcomes of 3000 patients (seeding was used to force the inclusion of the same population) in 1000 PSA simulations.

Efficacies

In the model, all patients were assumed to undertake the initiated treatment for at least one cycle (6 months). The response status of the patient was assessed after the first cycle to determine whether the treatment would continue or the patient would be switched to the next treatment line. The probability of transition to the next treatment was determined by the probability of response and a constant withdrawal rate (Table 1) from the initiated treatment. The ACR response rates[25–28] were used as the measure of efficacy. Response to treatment was defined as a response equal to or higher than ACR20. Due to a lack of head-to-head clinical data between bDMARDs, the results of a recent mixed treatment comparison (MTC[20]) were used to reflect the differences across treatments (Table 1, please see Bergman *et al.*[20] for further information regarding the indirect comparison methods used).

Response to treatment was assumed to have an impact on the disease severity reflected by the patients' HAQ scores. Data from the phase III TOC clinical trials[17–19] was analyzed to estimate the relationship between the ACR response and the individual HAQ score: the higher the observed response, the greater the drop in HAQ score (Table 1). For every response to a new treatment, the corresponding HAQ score reduction was applied in the first treatment cycle (negative HAQs were not permitted). The reduction was assumed to be the same regardless of treatment. The patients were at risk of withdrawal[29,30] while under treatment, and the HAQ score was assumed

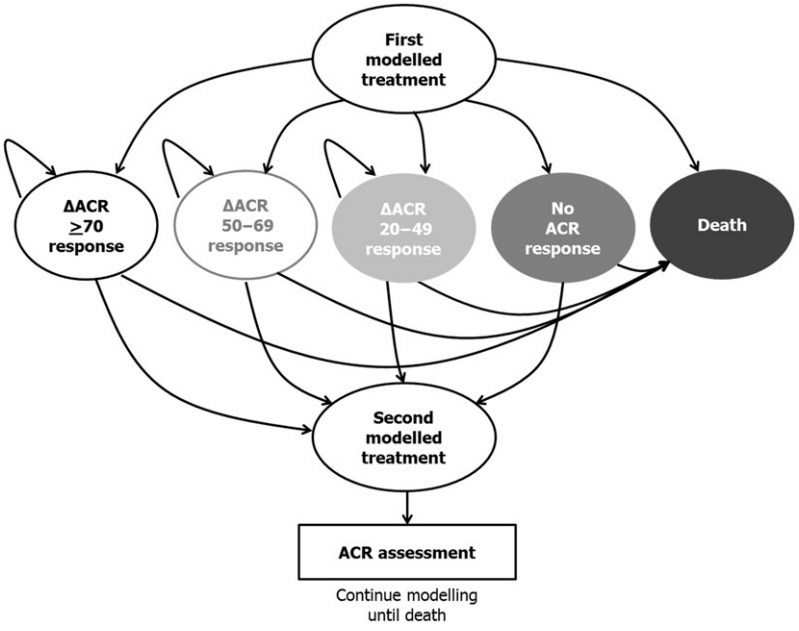

Figure 1. Simplified model structure.

Table 1. Adjusted ACR responses, constant withdrawal rates, HAQ drops, and HAQ progressions together with their probabilistic distributions.

Response	ACR20	ACR50	ACR70	Dirichlet D	Source[20]
ADAL, ETAN, INFL	0.63	0.39	0.16	One	First-line bDMARD
TOC	0.65	0.44	0.29	parameter	First-line bDMARD
RTX	0.60	0.35	0.18	Gamma	after bDMARD
ABAT	0.59	0.33	0.15	distribution	after bDMARD
tDMARDs	0.32	0.12	0.04		after tDMARD
Withdrawal	Rate (SE)	Probability (SE)		Beta D	
ETAN	0.080 (0.0135)	NA			[29]
INFL	0.120 (0.0207)	NA		NA	
bDMARDs	0.100 (0.0172)	0.095 (0.0156)		33.67, 320.15	[29] average
tDMARDs	NA	0.270 (0.0442)		26.97, 72.92	[30]
HAQ drop	Mean	SE		D	
No response	0.13572	0.01679		Normal	[17–19]
ACR 20	0.44266	0.01831			
ACR 50	0.66795	0.02610			
ACR 70	0.92257	0.03201			
HAQ progression	Mean	SE		D	
bDMARDs (not TOC)	0.00000	0.00162		Normal	[27]
TOC	−0.01622	0.00162			[31]
tDMARDs	0.02250	NA		Triangular, *R*:0.0150–0.0300	[NICE 2006: RTX appraisal data on file]
MTX (last resort)	0.03000	NA		Triangular, *R*:0.0225–0.0375	
Mortality	Multiplier	Lowest 2.5%		Highest 97.5%	
Per HAQ unit	1.330	1.099		1.610	[33]

D, distribution; MTX, methotrexate; ABAT, abatacept; ADAL, adalimumab; CSA, cyclosporine; LEFL, leflunomide; ETAN, etanercept; INFL, infliximab; RTX, rituximab; SE, standard error; TOC, tocilizumab; tDMARD, traditional drug; bDMARD, biologic drug; R, range.

to change according to the progression rates[27,31] shown in Table 1. The estimated rate of HAQ score change based on the ACR response was applied at the beginning of each treatment cycle (responders only) and assigned to each simulated individual regardless of the previous ACR response. Evidence related to the long-term sustained benefit of treatment after withdrawal is scarce. A rebound effect (increase in HAQ score) has been suggested to occur when therapy is withdrawn[32]. In our analysis, HAQ worsening equal to the initial HAQ improvement was assumed to occur immediately at the point of treatment withdrawal.

Mortality and transition limitations

The probability of death in the model was based on age- and gender-specific mortality in the year 2010 according to the official national statistics for Finland. The patients' HAQ scores modified the risk of death according to Wolfe *et al.*[33] (Table 1).

Some transitions in the model were assumed to occur only once (patients cannot initiate the same treatment again and no transitions are allowed once an individual dies). Unlike the conventional Markov-type models, more than one transition could occur during a 6-month cycle (i.e., treatment response, withdrawal, and/or death may occur during a cycle) in the individualistic discrete event simulation model.

Quality-of-life values

The quality-of-life (QoL) effects of the treatments were estimated based on the generic EQ-5D. The EQ-5D values were assumed to change following the changes in the patients' HAQ scores. The association between HAQ scores and EQ-5D was estimated from the OPTION[17] and LITHE[19] data using a non-linear mixed model: $EQ5D = 0.82 - 0.11*HAQ - 0.07*(HAQ*HAQ)$ ($p < 0.0001$ for all HAQ coefficients)[34]. The model coefficients were in line with those reported by Boggs *et al.*[35]. In comparison to the linear model, the inclusion of the model term for the square of the HAQ score improved the model fit and produced a significant coefficient for the non-linear term.

Resource use and unit costs

All healthcare costs were presented in the most recent 2010 values (drug costs were from the Finnish Medicine Tariff 9/2011; the cheapest available generic prices were used and an assumption of no drug wastage was applied, Table 2). TOC costs were presented using two approaches: (1) the pharmacy retail price without value added tax (VAT 9%) – that is, the drug cost when the intravenous (IV) drug is given in private hospitals or homes – and (2) the wholesale price, which served as a proxy for the drug cost when the intravenous drug is given in publicly-funded hospitals. The national unit costs from the year 2006[36] were transformed into 2010 values using a multiplier of 1.12739 based on the official Finnish healthcare price index obtained from Statistics Finland. All unit cost parameters were handled as fixed tariffs.

Five different cost categories were considered for all treatments: drug, administration, monitoring, hospitalizations, and travelling. In Finland, the initiation of the first biologic treatment necessitates screening procedures (i.e., chest X-ray and laboratory tests) related to the evaluation of drug safety at the initiation and an application for reimbursement for bDMARD. In the model, all patients were assumed to follow a routine monitoring protocol: the patients visit a specialist physician and a general practitioner (GP) once every 6 months (Table 2), if not otherwise needed due to medication. The laboratory values of the patients during MTX (also in combination with bDMARD), CSA, and LEFL treatment were assumed to be monitored every 2 months on average, based on the Helsinki University Hospital practice [HUS care protocol 7/2009], with telephone contact after the laboratory results were ready.

All patients were assumed to be able to inject ETAN and ADAL. In the Finnish practice, TOC is given as an infusion once a month, and is assumed to take some 1.5 h of nursing time (a clinician visit takes place every three visits); please note that the TOC infusion typically takes 1 h. RTX is given as daily infusions every 9 months (a nurse gives the infusion and a clinician sees the patient every 6 months). INFL is given as infusions seven times per year, each taking some 2 h of nursing time (the clinician visit takes place every 6 months).

Due to scarce Finnish data, the method for estimating hospitalizations followed the Swedish study by Kobelt *et al.*[37] (Table 2). In the secondary scenario, productivity losses for the total societal costs were mapped based on Kobelt *et al.*[37] using the average Finnish annual productivity loss of €24,309[36] (in order to obtain conservative estimates productivity costs were not indexed to 2010 price level).

Outcomes

The primary outcome measure was the incremental cost per quality-adjusted life-year (QALY) gained, also illustrated as the CE efficiency frontier (CEEF). Overall survivals were reported as secondary outcomes. In addition, the CE acceptability frontier (CEAF) was drawn based on the PSA simulation results[16]. The microsimulation + PSA approach was used to depict the patient (heterogeneity) and parameter (variability) uncertainty associated with

Table 2. Resource use and costs (healthcare unit costs at 2010 values; drug costs at 9/2011 values).

Resource	Cost (€)	Specification	Resource use
ADAL per 40 mg	597.89	Finnish	40 mg/fortnight
ETAN per 50 mg	285.28	Medicine	50 mg/week
TOC per 20 mg	36.25[a]	Tariff	582.6 mg/month
(Retail without VAT)	(47.05)	9/2011	
RTX per 1 mg	3.05[a]		1000 mg twice every 9 months
Methylprednisolone per 1 mg	0.05[a]		100 mg twice every 9 months
ABAT per 250 mg	372.00[a]		750 mg days 1, 15, 29, every 4 weeks
INFL per 100 mg	622.20[a]		218.5 mg 7 times/year
CSA per 1 mg	0.05		236.7 mg daily
LEFL per 20 mg	1.26		20 mg daily
MTX per 1 mg	0.09		15 mg/week
TOC administration (1.5 h inf.)	131.30[c]	(incl. 2 clinician visits/cycle)	1/month
RTX administration (8 h inf.)	213.87[c]	(incl. 1 clinician visit/cycle)	every 9 months
ABAT administration (30 min inf.)	98.77[c]	(incl. 1 clinician visit/cycle)	days 1, 15, 29, then every 4 weeks
INFL administration (2 h inf.)	136.13[c]	(incl. 1 clinician visit/cycle)	7 times/year
Administration guidance	76.89[c]	ADAL, ETAN	Initiation
Outpatient visit (internal diseases)	196.39[c]	All treatments	1/cycle
General practitioner visit[b]	46.22[c]	All treatments	1/cycle
Inpatient day (internal diseases)	648.37[c]	0.0 <HAQ score <0.5	0.68/year[d]
		0.6 <HAQ score <1.0	2.77/year[d]
		1.1 <HAQ score <1.5	4.12/year[d]
		1.6 <HAQ score <2.0	8.86/year[d]
		2.1 <HAQ score <2.6	10.25/year[d]
		2.6 <HAQ score <3.0	4.56/year[d]
Phone consulting by patient[e]	19.28[c]	bDMARD, tDMARD	After tests
Chest X-ray, quantiferon, antibodies[g]	50.39[c]	First-line bDMARD	First bDMARD initiation
CBC, ALAT, creatine (twice year)[g]	13.75[c]	MTX[f]	3/cycle
CBC, ALAT, ALP, RR[g]	54.68[c]	LEFL	3/cycle
Creatine, RR[g]	54.45[c]	CSA	3/cycle
Travelling to primary health care	6.62[c]	Excl. VAT	*
Travelling to secondary health care	33.82[c]	Excl. VAT	*

MTX, methotrexate; ABAT, abatacept; ADAL, adalimumab; CSA, cyclosporine; LEFL, leflunomide; ETAN, etanercept; CBC, complete blood count; ALAT, alanine aminotransferase; ALP, alkaline phosphatise; INFL, infliximab; RR, blood pressure; RTX, rituximab; TOC, tocilizumab; VAT, value-added tax; tDMARD, traditional drug; bDMARD, biologic drug.
[a]Wholesale/hospital price used in publicly funded hospitals. [b] The unit cost of an outpatient visit in primary healthcare for rheumatic diseases. [c] Hujanen *et al.*[36]. [d]Kobelt *et al.*[37]. [e] The patient is informed of the laboratory results by phone. [f] Includes the tests for bDMARDs. [g] Includes the cost of test taking. * Number of visits varies according to treatment.

the CE results simultaneously. The multinomial expected value of perfect information (mEVPI) was estimated to assess the consequences of a wrong decision and the value of reducing uncertainty related to the model parameters.

Sensitivity analyses

Because there is uncertainty related to the choice of some model parameters, the impact of changing the assumptions was tested in multiple sensitivity analysis scenarios. The impact of response criteria was tested in two scenarios: a stricter scenario including only ACR50 and ACR70 responses, and the strictest scenario consisting of only ACR70 responses. The impact of treatment times on the studied drugs was tested using mean treatment times instead of the constant probabilities of withdrawal: ADAL/ETAN/INFL 2.5 years, ABAT/RTX/TOC 3.75 years, MTX alone 15 years and other tDMARD 2 years[15]. In one scenario we assumed no time-dependent HAQ improvement for the TOC responders.

In a sensitivity analysis scenario the patients were assumed to lose 50% of the benefit obtained from treatment at the point of discontinuation instead of the 100% rebounding. Because the risk of mortality may not be related to HAQ scores, we assumed no additional risk to die in one scenario. The impact of the chosen QoL assessment method was tested using EQ-5D and HAQ score relationships suggested by Bansback *et al.*[30], Hawthorne *et al.*[38], and Hurst *et al.*[39]. In addition, the requirement for positive QoL (i.e., QoL could not be worse than death in the base case) was relaxed. In further scenarios, a constant number of hospitalizations (4.11 days/year[40]), regardless of HAQ score, ABAT instead of RTX in the fixed sequence, baseline ages of 40 and 60 years, a 10-year modelling time, baseline HAQs of 1.3 and 1.7, as well as 6% and 0% discounting were applied.

Results

The detailed results of the base-case analyses are shown in Table 3. When the patients received MTX alone after

Table 3. Base-case simulation results.

Outcome	Life-years		Death	QALYs	Costs (discounted)	
Treatments	0%	3%	age	3%	Payer	Societal
MTX alone	25.575	17.205	78.061	5.833	96,753	111,927
Lower 2.5%	25.250	17.033	77.736	5.775	95,717	110,809
Higher 97.5%	25.900	17.377	78.386	5.892	97,789	113,044
ETAN + MTX[a]	27.022	17.864	79.508	9.515	173,159	190,184
Lower 2.5%	26.691	17.694	79.177	9.415	170,937	187,865
Higher 97.5%	27.353	18.035	79.838	9.615	175,381	192,503
ICUR of ETAN + MTX[a] vs MTX alone					20,754	21,257
ADAL + MTX[a]	27.022	17.864	79.508	9.515	175,348	192,373
Lower 2.5%	26.691	17.694	79.177	9.415	173,060	189,990
Higher 97.5%	27.353	18.035	79.838	9.615	177,636	194,757
ICUR of ADAL + MTX[a] vs MTX alone					21,349	21,852
TOC + MTX[a], wholesale	27.232	17.953	79.717	10.029	168,318	183,633
Lower 2.5%	26.899	17.782	79.385	9.916	166,275	181,541
Higher 97.5%	27.564	18.124	80.050	10.142	170,362	185,726
ICUR TOC (wholesale) + MTX[a] vs MTX alone					17,057	17,091
TOC + MTX[a], retail	27.232	17.953	79.717	10.029	176,289	191,604
Lower 2.5%	26.899	17.782	79.385	9.916	174,023	189,297
Higher 97.5%	27.564	18.124	80.050	10.142	178,556	193,911
ICUR TOC (retail sale) + MTX[a] vs MTX alone					18,957	18,991

QALY, quality-adjusted life-year; MTX, methotrexate; ADAL, adalimumab; ETAN, etanercept; TOC, tocilizumab; ICUR, incremental cost-utility ratio.
[a]→ RTX + MTX → INFL + MTX → BSC.

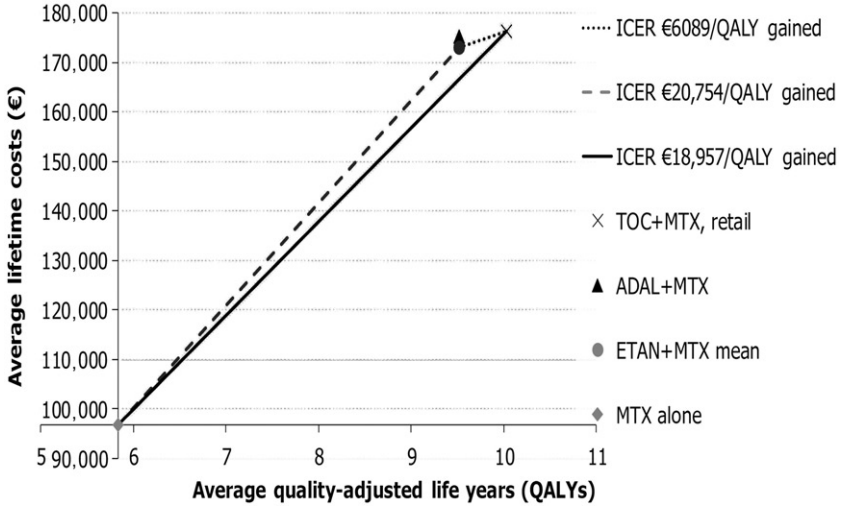

Figure 2. The cost-effectiveness efficiency frontier (CEEF) presents the cost-effective treatment options and their expected lifetime average costs and effectiveness.

tDMARD failure, the average expected payer (societal) lifetime costs were €96,753 (€111,927) and the remaining average lifetime's gain of QALYs was 5.83.

In comparison with MTX alone, the most cost-effective strategy from the payer (societal) viewpoint was to use TOC with the incremental cost-utility ratio (ICUR) of €17,057 (€17,091) and €18,957 (€18,991) per QALY gained based on the wholesale price and retail price of TOC, respectively. In comparison with ETAN, the ICURs of retail-priced TOC were €6089 (€2762), while the wholesale-priced TOC dominated ETAN. Treatment with ETAN was more cost-effective (dominating) than treatment with ADAL. The CEEF, average expected results, and ICURs are presented in Figure 2 from the payer perspective and using the retail price for TOC.

Probabilistic analysis

The results of PSA are depicted in Figure 3a and b, for which the four treatment sequences were considered. MTX alone was the optimal and potentially cost-effective treatment (highest expected net monetary benefit and

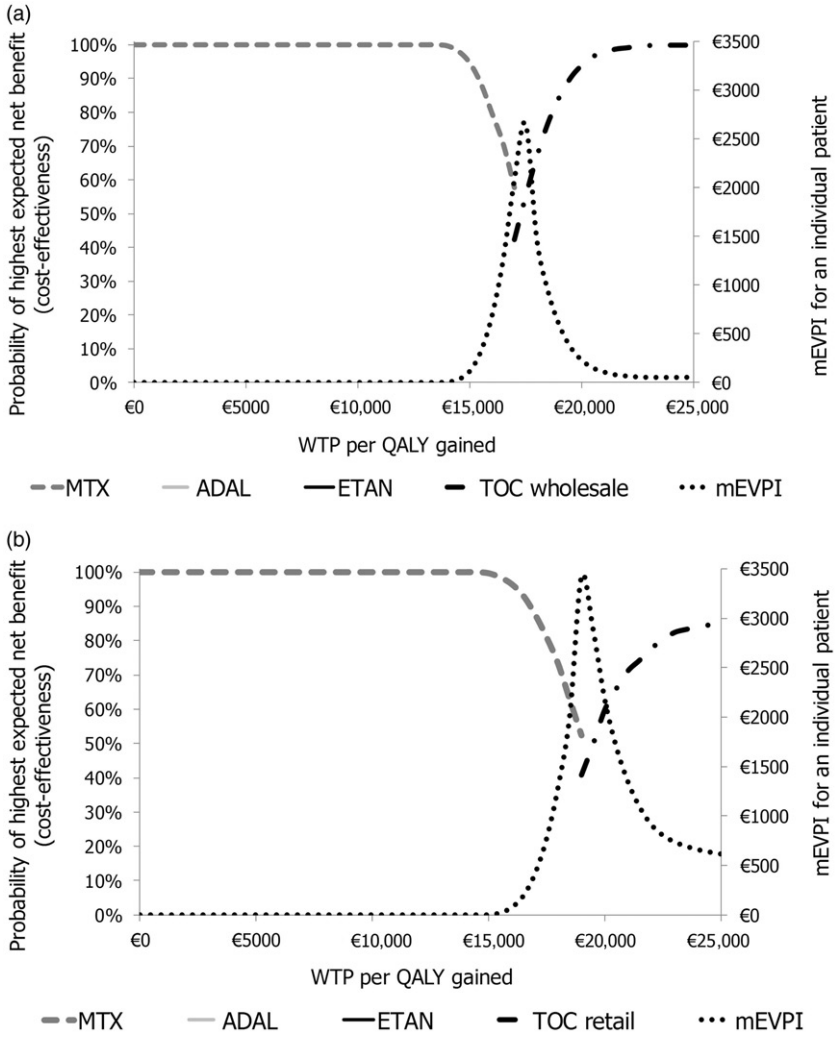

Figure 3. (a) Wholesale price for TOC, and (b) retail price for TOC. Probabilistic sensitivity analysis (PSA) results: cost-effectiveness acceptability frontier presenting the optimal treatments together with multinomial expected value of perfect information (mEVPI) for the comparison between ADAL, ETAN, and TOC before the fixed sequence of RTX followed by INFL followed by BSC, and MTX alone.

probability of CE > 50%) with the WTP below €17,276 per QALY gained when TOC had the wholesale price. The corresponding threshold was €19,107 when TOC had the retail price. With the WTP exceeding €17,323 (€19,516) per QALY gained, wholesale-priced (retail-priced) TOC was the optimal treatment.

With the WTP of €20,000 and €25,000 per QALY gained, the wholesale-price (retail-priced) TOC had a 93.4% (59.8%) and 98.7% (84.8%) CE probability (Figures 3a and b). With the WTP of €20,000 and €25,000 per QALY gained, the respective per-patient mEVPIs were €230 (€2182) and €53 (€616) (Figures 3a and b).

Sensitivity analyses

The results of the one-way sensitivity analysis scenarios are shown for the most cost-effective options (ADAL + MTX excluded) in Table 4. The modelling assumptions only had a small impact on the relative results. Exclusion of the ACR20 responses reduced the ICURs by €2822–4456, whereas exclusion of both ACR20 and ACR50 responses (i.e., use of ACR70 responses only) reduced the ICURs by €4483–8755. The use of fixed mean treatment times instead of constant risk of withdrawal increased the ICURs by €4608–6283. When no HAQ improvement for TOC responders over time was assumed, the ICUR for TOC increased by €2937–3631.

The assumed rebound rate had the most significant effect in the lifetime scenario: when a 50% rebound effect was assumed instead of 100%, the ICURs decreased by €9684–12,646. The exclusion of excess HAQ scores associated with the mortality risk reduced the ICURs by €1178–1381.

The chosen method for mapping the QoL and HAQ scores had a significant impact on the absolute results.

Table 4. Deterministic sensitivity analyses.

Sensitivity analysis scenario	Lifetime outcomes		Treatments*				ICUR (€/QALY gained) vs MTX			ICUR (€/QALY gained) change		
			TOC + MTX (wholesale)	*TOC + MTX* (retail sale)	*ETAN + MTX*	*MTX* alone	*TOC + MTX* (wholesale)	*TOC + MTX* (retail sale)	*ETAN + MTX*	*TOC + MTX* (wholesale)	*TOC + MTX* (retail sale)	*ETAN + MTX*
Base case[a]	Costs	Payer	168,318	176,289	173,159	96,753	17,057	18,957	20,754			
		Societal	183,633	191,604	190,184	111,927	17,091	18,991	21,257			
	QALYs		10.029	10.029	10.029	9.515	5.833					
ACR50 and ACR70 responses	Costs	Payer	143,630	149,200	144,804	98,331	14,235	15,985	16,963	−2822	−2972	−3791
		Societal	157,640	163,211	160,468	114,439	13,576	15,326	16,801	−3515	−3664	−4456
	QALYs		8.640	8.640	8.640	8.197	5.458					
ACR70 responses only	Costs	Payer	127,917	131,799	123,962	99,466	12,574	14,290	13,589	−4483	−4667	−7165
		Societal	140,934	144,816	138,402	115,865	11,080	12,796	12,503	−6011	−6195	−8755
	QALYs		7.495	7.495	7.495	7.036	5.233					
Fixed treatment times[15]	Costs	Payer	153,834	159,836	148,079	96,753	21,665	23,943	26,887	4608	4986	6133
		Societal	169,008	175,010	164,499	111,927	21,665	23,943	27,540	4574	4952	6283
	QALYs		8.468	8.468	8.468	7.742	5.833					
No HAQ improvement for TOC	Costs	Payer	171,874	179,844	173,159	96,753	19,994	22,115	20,754	2937	3158	0
		Societal	188,949	196,919	190,184	111,927	20,500	22,621	21,257	3409	3631	0
	QALYs		9.591	9.591	9.591	9.515	0.833					
50% rebound, one cycle	Costs	Payer	147,755	155,726	152,866	96,753	7373	8525	8643	−9684	−10,432	−12,112
		Societal	160,082	168,053	167,837	111,927	6961	8114	8611	−10,129	−10,877	−12,646
	QALYs		12.751	12.751	12.751	12.326	5.833					
No excess mortality	Costs	Payer	177,635	185,609	183,084	108,043	15,879	17,698	19,430	−1178	−1259	−1325
		Societal	193,083	201,057	200,253	123,488	15,880	17,699	19,876	−1,211	−1291	−1381
	QALYs		10.375	10.375	10.375	9.855	5.993					
Bansback *et al.*[30] QoL	Costs	Payer	168,318	176,289	173,159	96,753	19,293	21,442	24,189	2236	2485	3435
		Societal	183,633	191,604	190,184	111,927	19,331	21,480	24,775	2240	2489	3518
	QALYs		8.233	8.233	8.233	7.683	4.524					
Hawthorne *et al.*[38] QoL	Costs	Payer	168,318	176,289	173,159	96,753	24,769	27,528	30,934	7712	8571	10,179
		Societal	183,633	191,604	190,184	111,927	24,818	27,576	31,683	7727	8586	10,426
	QALYs		11.045	11.045	11.045	10.626	8.156					
Hurst *et al.*[39] QoL	Costs	Payer	168,318	176,289	173,159	96,753	17,160	19,071	21,604	103	114	850
		Societal	183,633	191,604	190,184	111,927	17,194	19,105	22,127	103	115	870
	QALYs		8.314	8.314	8.314	7.680	4.143					
QoL can be worse than death	Costs	Payer	16,8318	176,289	173,159	96,753	16,500	18,337	20,000	−558	−620	−754
		Societal	18,3633	191,604	190,184	111,927	16,532	18,370	20,485	−559	−621	−772
	QALYs		10.009	10.009	10.009	9.492	5.672					
Constant hospitali- zations[40]	Costs	Payer	164,234	172,205	164,951	62,940	24,143	26,042	27,709	7085	7085	6955
		Societal	179,548	187,519	181,976	78,114	24,176	26,076	28,212	7085	7085	6955
	QALYs		10.029	10.029	10.029	9.515	5.833					
ABAT instead of RTX	Costs	Payer	186,584	194,555	191,308	96,753	21,733	23,662	26,152	4676	4705	5398
		Societal	202,053	210,024	208,315	111,927	21,805	23,733	26,659	4714	4743	5402
	QALYs		9.967	9.967	9.967	9.449	5.833					
Baseline age 40 years	Costs	Payer	190,740	198,730	196,006	116,083	15,418	17,069	18,914	−1639	−1888	−1841
		Societal	216,340	224,331	224,243	142,025	15,348	16,998	19,456	−1743	−1993	−1801
	QALYs		10.947	10.947	10.330	6.105						
Baseline age 60 years	Costs	Payer	149,364	157,290	153,441	80,516	19,604	21,861	23,650	2547	2904	2896
		Societal	156,785	164,711	161,399	85,465	20,308	22,565	24,626	3218	3575	3369
	QALYs		8.963	8.963	8.535	5.451						

(continued)

Table 4. Continued

Sensitivity analysis scenario	Lifetime outcomes	Treatments*				ICUR (€/QALY gained) vs MTX			ICUR (€/QALY gained) change		
		TOC + MTX (wholesale)	*TOC + MTX* (retail sale)	*ETAN + MTX*	*MTX* alone	*TOC + MTX* (wholesale)	*TOC + MTX* (retail sale)	*ETAN + MTX*	*TOC + MTX* (wholesale)	*TOC + MTX* (retail sale)	*ETAN + MTX*
Baseline HAQ 1.3	Costs	161,215	169,187	166,195	90,460	17,475	19,443	21,172	417	486	417
	Societal	173,312	181,283	179,809	103,161	17,325	19,294	21,427	235	303	170
	QALYs	11.081	11.081	10.609	7.032						
Baseline HAQ 1.7	Costs	175,758	183,728	179,725	102,012	17,354	19,229	21,020	296	272	266
	Societal	190,196	198,166	193,704	118,600	16,848	18,723	20,314	−243	−267	−943
	QALYs	9.001	9.001	8.448	4.751						
10-year analysis	Costs	99,178	106,331	101,701	40,512	42,578	47,770	50,048	25,521	28,813	29,294
	Societal	112,113	119,266	116,034	52,419	43,324	48,516	52,032	26,234	29,525	30,775
	QALYs	5.493	5.493	5.338	4.115						
0% discounting	Costs	237,876	247,108	244,642	145,623	13,531	14,885	16,684	−3527	−4072	−4070
	Societal	256,145	265,377	265,034	164,348	13,464	14,818	16,965	−3627	−4173	−4292
	QALYs	14.256	14.256	14.256	13.373	7.438					
6% discounting	Costs	128,104	135,139	131,738	68,468	21,386	23,908	25,727	4329	4951	4973
	Societal	141,149	148,184	146,178	80,962	21,583	24,106	26,518	4492	5115	5261
	QALYs	7.524	7.524	7.524	7.195	4.735					

*→ RTX + MTX → INFL + MTX → BSC. Baseline: HAQ 1.51 and age 52.49 years. Please note that only the most cost-effective treatments are presented here (i.e., ADAL + MTX is excluded).

The formulae by Bansback *et al.*[31], Hawthorne *et al.*[38] and Hurst *et al.*[39] resulted in €2236–3518, €7712–10,426 and €103–870 higher ICURs, respectively. The acceptance of negative QoL reduced the ICURs by €558–772.

The highly unlikely constant rate of hospitalizations (i.e., 4.11 hospital days/year were assumed to be independent of the patient's status) based on a Finnish source[40] resulted in €6955–7085 higher ICURs. When RTX was replaced with ABAT, the ICURs increased by €4676–5402.

Patients with the average baseline age of 40 years resulted in €1639–1993 lower ICURs and the average baseline age of 60 years resulted in €2547–3575 higher ICURs in comparison with the base-case results with the average age of 52.5 years. Truncating the modelling to the 10-year timeframe increased the ICURs by €25,521–30,775. Varying the baseline HAQ from 1.3 to 1.7 only had a minor effect on the ICURs. Undiscounted ICURs were €3527–4292 lower and 6% discounted ICURs were €4329–5261 higher compared to the base-case results with the 3% annual discounting.

Discussion

According to this study, both retail and wholesale-priced TOC was more cost-effective than ETAN and ADAL in comparison with MTX alone, and both ETAN and wholesale-priced TOC dominated ADAL. When using wholesale prices and the payer perspective, additional QALY was gained with TOC costs of €17,057 compared to MTX alone. Additional QALY was gained with retail-priced TOC costs of €18,957 compared to MTX alone, and €6089 compared to ETAN from the payer perspective. TOC was cost-effective due to its ACR responses and due to HAQ improvement over time when using TOC (and resulting changes in costs, QoL, and mortality): the sensitivity analyses on these, however, indicated only a minor effect on the CE results. Generally, the pricing of ADAL, ETAN, and retail-priced TOC seems to be relatively similar in Finland and, thus, efficacy made the biggest difference.

The maximum per patient mEVPIs were €3421 (TOC retail pricing) and €2657 (TOC wholesale pricing) with the ICUR values. The estimates were rather low, suggesting that both the value of the additional research information and the consequences of a wrong decision were likely to be low in this setting. With the WTP of €20,000 per QALY gained, TOC + MTX had a 60–93% CE probability, depending on the place of use. With WTP of €0–30,000 per QALY gained, only treatments with MTX alone and TOC + MTX were potentially cost-effective.

When comparing the results of this analysis with a recent Finnish analysis[15] for second-line treatments, we

see that the results of this analysis are less uncertain (i.e., the CE probabilities are higher). We used averages (strictly speaking, average is the expected value of distribution; thus averages should be used in economic evaluations) instead of the medians reported in another recent Finnish study of INFL[41]. In addition, their[41] setting was not decision analytical and did not include an active comparator drug, even though they reported ICERs[42]. Thus, our results are not comparable with that study.

Consequently, direct comparisons between the current and previous CE studies in RA must be done with caution due to the differing study designs, comparators, costs, timelines, treatment lines, response definitions, outcome definitions, and patient populations. High variations in the reported ICERs were found in the review by Chen *et al.*[43], but, on average, the ICERs were some £30,000 per QALY. Our results also seem to be in line with more recent studies (not included in the review[43]) assessing the life-time CE of first-line biologic treatment for RA[44–47]. These studies, however, did not include TOC as a comparator and, in comparison with the most previous RA models, our analysis was based on a microsimulation + PSA model with, for example, patient tracks and multiple event risks (not the more common Markov model without patient tracks, mutually exhaustive events and/or PSA), MTC results based on the iteration process (not on the more common simple meta-analysis or mathematically adjusted indirect comparison), and non-linear QoL values from relevant studies (TOC trials, not from independent sources). In addition, we reported mEVPI. A review of existing RA models based on the publications would be an interesting study.

There were some limitations in our analyses that may influence the usability of our results. Because there were no randomized, controlled clinical trials comparing the efficacy of all biologics after tDMARD failure, the results from MTC[20] were used. Because certolizumab pegol and golimumab were not included in the MTC, their CE was not assessed. Adherence and persistence were not modelled due to data limitations, comparability of available data (i.e., the assessment of adherence/persistence in patients obtaining infusions is likely to be easier than in patients using subcutaneous injections or tablets) and the 'cost-efficacy' type of analysis (i.e., can the treatments be efficient?). Moreover, ADAL and ETAN have had around a 75% market share among all TNFs in Finland; ADAL having the highest share.

To simplify the relatively complex analysis we fixed the treatment sequence after the initial bDMARDs to consist of RTX, INFL, and BSC, as this was observed to be a cost-effective second-line treatment sequence in Hallinen *et al.*[15]. The BSC sequence was assumed to include CSA, LEFL, and MTX in that order. In reality, the treatment sequence after the failure of the first bDMARD varies and is individually tailored. However, the choice of a fixed treatment sequence did not have a significant impact on the results because the same sequences were applied in all comparisons (except MTX alone). The choice of RTX as the first biologic treatment after the first bDMARDs was supported by a sensitivity analysis replacing RTX with ABAT (the sequence with RTX is more cost-effective).

In our model we made assumptions regarding the changes in the patients' condition (HAQ scores) while under treatment. For bDMARDs other than TOC, the condition was assumed to remain at the level of the initial response to treatment as long as they were receiving treatment[28]. As long-term TOC studies have demonstrated improvements in HAQ over time, a slight reduction in the HAQ score (−0.01622) was assumed to occur in each cycle while under treatment[31]. In a sensitivity analysis we assumed no HAQ improvement for TOC; the resulting ICURs for TOC were comparable with the ICUR for ETAN in comparison with MTX alone. The base case HAQ of 1.3–1.7 only had a minor effect on the ICURs. The probability of discontinuing the treatment after the initial response (withdrawal rate) was assumed to be the same for all bDMARDs. Because the estimate was an average estimate reported in one study[29], we tested the impact of this assumption in a sensitivity analysis with fixed treatment times[15]. The method of handling time under treatment had an impact on the absolute but not the relative results.

In the absence of Finnish resource use data in RA according to patients' HAQ scores, we estimated hospitalizations and productivity losses based on a Swedish study[37]. The assumption seems reasonable because the mean HAQ and annual days in hospital were comparable in Sweden and Finland[37,40]. In a sensitivity scenario we assessed the impact of hospital days by using constant hospital days irrespective of the patients' HAQ scores. The change in this assumption did not change the relative results. For simplicity, the average inpatient costs were assumed to include the costs of any possible surgery, and the drug administration/monitoring was assumed to include all outpatient costs.

The method used for linking the EQ-5D measured quality-of-life and HAQ scores had a relatively large impact on the obtained absolute ICURs (€103–10,426 higher ICURs). Although the ICURs in the primary analysis are lower, we believe them to be reasonable as the TOC trial data indicated a superior fit for the non-linear relationship between HAQ and EQ-5D compared to the linear relationship[34] that was used in Hawthorne *et al.*[38] and Bansback *et al.*[30]. Also, the results based on Hurst *et al.*[39] were close to those used in this study.

The modelled msRA patients died just before their 80th birthday. In comparison with the gender-weighted expected lifetime of 50-year-old Finns (79 years) based on the official Finnish statistics, the survival of the modelled patients seemed to be credible.

Finally, intensive anti-rheumatic drug therapy can make a difference in a variety of outcomes[9,48,49]. However, new options are needed: in real life, ~25% of the patients get hardly any response from the currently used bDMARDs[14]. TOC is one of the newest RA drugs and the CE of TOC may encourage its use in clinical care.

Conclusion

Tocilizumab + methotrexate is a cost-effective initial biologic treatment for patients with moderate-to-severe rheumatoid arthritis after failure with one or more tDMARDs. The results are relatively robust and indicate a relatively low value for additional research information for the adaptation decision with the corresponding population and parameter definitions.

Transparency

Declaration of funding and author contributions
This work was supported by Roche Oy, Espoo, Finland. EJS contributed to the concept, design, and modelling, acquired data, analysed and interpreted data, and drafted and revised the manuscript. TAH contributed to the design and interpretation of data, and helped to draft and revise the manuscript. VV acquired data, and helped to draft the manuscript. MJK and KP contributed to the concept and interpretation of data, and revised the manuscript. All authors read and approved the final manuscript.

Declaration of financial and other relevant relationships
EJS and TAH have disclosed that they are consultants and shareholders in ESiOR Oy, a company that was commissioned by Roche Oy to perform this study. VV has disclosed that he is an employee of Roche. KP and MJK have disclosed that they received consulting fees from Roche and other companies such as Abbott, Bristol Myers-Squibb, MSD, Pfizer, and UCB. The final manuscript has been read and approved by all the authors, and all authorship decisions were made on the basis of scientific consideration.

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