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The issue of comparators in economic evaluations of biologic response modifiers in rheumatoid arthritis

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Introduction: Over the last decade, a number of biologic response modifiers (BRMs) have emerged and transformed rheumatoid arthritis (RA) management. Due to their relatively high costs, economic evaluations have attempted to determine their place in the RA treatment armamentarium. This article reviews three key areas where changes to the treatment paradigm challenges findings of existing economic evaluations.

Methods: We performed a literature search of economic evaluations examining BRMs approved for use in North America for RA. Only economic evaluations that examined relevant direct costs and health outcomes were included. Data were extracted and summarised, then stratified by patient population and comparators. Reported incremental cost-effectiveness ratios (ICERs) were compared across studies.

Results: It appears that tumour necrosis factor (TNF) alpha inhibitors are less cost effective compared to disease-modifying anti-rheumatic drugs (DMARDs) for first-line treatment. In addition, it appears that treatment with a TNF alpha inhibitor in patients who were refractory to previous DMARD therapies is more cost effective, compared to switching to another DMARD. Finally, after an inadequate response to a TNF alpha inhibitor, it appears that therapy with rituximab is more cost effective than treatment with another TNF alpha inhibitor or abatacept.

Discussion: It is important to acknowledge that cost effectiveness depends on which comparators are included in the analyses and the evidence for the comparators. The most typical comparator in

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the studies was traditional DMARDs, mainly methotrexate. However, as more BRMs come into the market and new clinical evidences emerge on the comparative effectiveness of BRMs, new economic evaluations will need to incorporate this information such that reimbursement decisions can be fully informed regarding relative value.

Introduction

Rheumatoid arthritis (RA) is an inflammatory autoimmune disease affecting approximately 1% of the population; RA is characterised by joint damage, functional disability, reduced quality of life and premature mortality [1–5]. Due to the progressive nature of RA and associated long-term disability, there exists considerable economic burden to patients and society. Individuals with RA have been shown to incur disproportionately high resource use, and indirect costs including lost productivity, compared to other major chronic illnesses [6].

Earlier and more aggressive treatment with traditional disease-modifying anti-rheumatic drugs (tDMARDs) have become the mainstay of RA therapeutic management in North America and other areas of the world [7]. In North America, the most commonly prescribed tDMARDs include methotrexate (MTX), sulphasalazine (SSZ), hydroxychloroquine (HCQ) and leflunomide (LEF) [3]. Within the past 15 years, a number of biologic response modifiers (BRMs) have emerged. Currently approved BRMs for use in Canada include tumour necrosis factor (TNF) alpha inhibitors as a class, which consists of etanercept (ETA) (ENBREL; Immunex Corporation, Thousand Oaks, California, USA), infliximab (INF)

Abbreviations

ABA	abatacept
ADA	adalimumab
AKR	anakinra
BRM	biologic response modifier
CEA	cost-effectiveness analysis
CTZ	certolizumab
CUA	cost-utility analysis
DAS	disease activity score
DMARD	disease-modifying anti-rheumatic drug
ETA	etanercept
GOL	golimumab
HCQ	hydroxychloroquine
ICER	incremental cost-effectiveness ratio
INF	infliximab
JAK	Janus kinase
LDAS	low disease activity state
LEF	leflunomide
MTX	methotrexate
QALY	quality-adjusted life-year
RA	rheumatoid arthritis
RTX	rituximab
SSZ	sulfasalazine
TCZ	tocilizumab
TNF	tumour necrosis factor

(REMICADE®; Janssen Biotech Inc., Horsham, Pennsylvania, USA), adalimumab (ADA) (Abbott Laboratories Ltd.; North Chicago, Illinois, USA), golimumab (GOL) (Janssen Biotech Inc., Horsham, Pennsylvania, USA) and certolizumab pegol (CTZ) (CIMZIA®; UCB Inc., Brussels, Belgium); BRMs with mechanisms of action other than inhibiting TNF include abatacept (ABA) (ORENCIA®; Bristol-Myers Squibb, New York City, New York, USA) – a T-cell co-stimulatory inhibitor; rituximab (RTX) (RITUXAN®; Hoffman-La Roche Ltd., Basel, Switzerland) – a B-lymphocyte depleting agent; tocilizumab (TCZ) (ACTEMRA; Hoffman-La Roche Ltd., Basel, Switzerland) – an interleukin-6 antagonist; and anakinra (AKR) (Kineret®; Swedish Orphan Biovitrum AB, Stockholm, Sweden) – an interleukin-1 antagonist [2,8]. These BRMs have transformed the RA treatment paradigm with their superior ability to slow disease progression, reduce joint damage and functional disability when added to tDMARDs [8–10]. However, BRMs are considerably more expensive than tDMARDs, they may cost from $10,000–$20,000 or more annually compared to between $500 and $1000 annually for tDMARDs [2]. Beyond BRMs, the most recent development has been a novel class of small molecule DMARDs that can be administered orally, such as the Janus kinase (JAK) inhibitor, tofacitinib from Pfizer Inc., currently in phase III clinical trials for RA [11–13].

Due to the relatively high cost of BRMs, myriad economic evaluations have emerged in the past decade in attempts to inform policy makers on decisions regarding the allocation of resources to BRMs in the RA treatment armamentarium [14]. Economic evaluations such as cost-effectiveness analyses (CEAs) and cost-utility analyses (CUAs) compare the costs and consequences (outcomes) of two or more possible courses of action, to aid in the decision making of which course of action provides best value for money [14]. A ratio of costs and outcomes does not itself provide information about whether or not a treatment is cost effective, since a treatment strategy can only be judged to be cost effective in relation to status quo or other viable courses of action [14]. Guidelines specify that new treatments – here the BRMs – should therefore be compared to conventional care. Thus, the comparators chosen in the analysis become of paramount importance as results generated in the form of incremental cost-effectiveness ratios (ICERs) are relative to the costs and outcomes of the reference comparator. However, over the years that BRMs have been available, what constitutes conventional care has changed. Consequently, the relevance of previous CEAs are drawn into question.

This article reviews the key areas where changes to the RA treatment paradigm challenges findings of existing economic evaluations. The first key area is the first-line consideration of BRMs in individuals with RA who have not been treated with a tDMARD (DMARD naïve). The second key area is the consideration of BRMs for individuals with RA who have had an inadequate response to one or more previous traditional DMARDs (DMARD-IR). Lastly, since TNF alpha inhibitors have become the standard second-line therapy after tDMARDs in many jurisdictions, it is not clear which is the most cost-effective BRM to try after TNF alpha inhibitor failure.

Methods

Literature search

We performed an electronic database search in MEDLINE (1946 to July week 3, 2012), EMBASE (1980 to July 2012), the National Health Services Economic Evaluation Database (third quarter 2012) and Centre for Reviews and Dissemination Health Technology Assessment database (2001 to present) for studies published in English between year '2000' and 'present'. A search strategy was employed with combinations of terms including, but not limited to, the following: 'rheumatoid arthritis'; 'TNF-alpha inhibitor or anti-TNF OR adalimumab or certolizumab or etanercept or golimumab or infliximab or rituximab or abatacept or anakinra or tocilizumab'; 'economic evaluation or cost-effectiveness or cost-utility or decision model or economic model or simulation model'. Reference lists of identified reviews were manually searched for additional studies to be included.

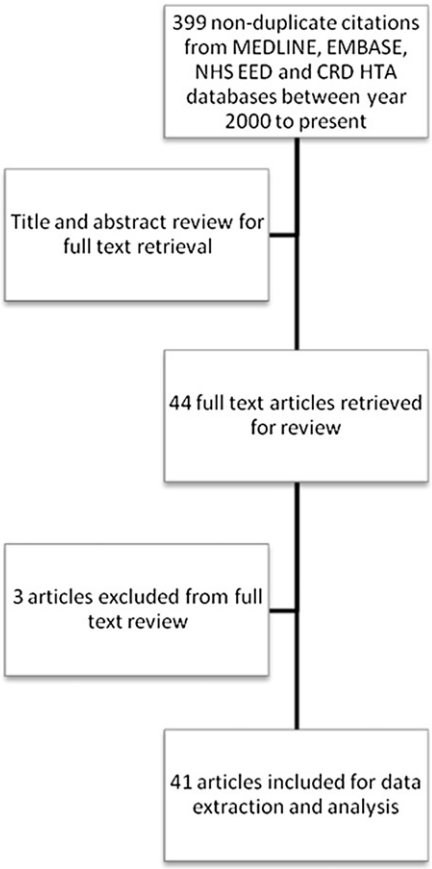
Study inclusion and exclusion

We included full text articles of economic evaluations comparing one or more BRMs approved for use in North America for RA (ETA, INF, ADA, AKR, ABA, RTX, GOL, TCZ and CTZ) to any comparator

consisting of one or more DMARDs, or one or more BRMs for the treatment of RA in adults. Only economic evaluations that were CEAs or CUAs were included; these consisted of analyses that examined relevant direct medical and non-medical costs with or without consideration of indirect costs, and health outcomes in the form of clinical end points achieved or quality-adjusted life-years (QALYs) [14]. Studies must have reported results in the form of ICERs as cost per clinical end point achieved (which we refer to as cost-effectiveness studies) or cost per QALY gained (which we refer to as cost-utility studies). Articles were excluded if not published in the English language. Studies evaluating the use of BRMs for other forms of arthritis, juvenile arthritis or other rheumatic diseases were excluded. Inclusion and exclusion of studies are shown in Fig. 1.

Analysis

Data on study characteristics were extracted and summarised, including patient population, comparators, study design, study country, perspective, time horizon, currency and year, discounting



NHS EED = National Health Services Economic Evaluation Database; CRD HTA = Centre for Reviews and Dissemination Health Technology Assessment database

Fig. 1. Schematic diagram of study identification, inclusion and exclusion.

rates, costs, QALYs and ICERs. To facilitate comparison of results across studies, all reported costs and ICERs were converted to Canadian dollars using the purchasing power parity conversion factor from Organisation for Economic Cooperation and Development [15] then adjusted to 2012 dollars using the health-care component of the Canadian consumer price index [16,17]. All costs were rounded to the nearest dollar.

Included studies were stratified by patient population and comparators into: (1) first-line BRM use (DMARD naïve) – where there has been no prior exposure to DMARDs, and BRMs are considered as first-line therapy; (2) second-line BRM use (DMARD-IR) – where there has been an inadequate response to one or more prior DMARDs, and BRMs are to be used as second-line therapy and comparators are other BRMs; (3) TNF alpha inadequate responders – where there has been an inadequate response to one or more prior TNF alpha inhibitors, and other BRMs are being considered as subsequent therapy.

Results

A total of 399 non-duplicate citations from all searched databases were screened for inclusion and exclusion by title and abstract screening (Fig. 1). Forty-four studies were retrieved for full-text screening and, of those, 41 studies were included for final data extraction (Fig. 1). There were nine included CEAs, one of which also reported results from its CUA and another 32 CUAs included (Tables 1–4). All costs have been converted to Canadian dollars, year 2012 for comparison purposes.

First-line BRM (DMARD naïve)

A total of seven CUAs [18–24] were found evaluating first-line use of BRMs between years 2006 and 2011, three of which conducted their analyses from the payer perspective [18,19,22], two conducted analyses from the societal perspective [20,24] and the remaining two considered both perspectives [21,23] (Table 2). None of the studies identified included newer BRMs such as ABA or RTX. All studies considered the use of TNF alpha inhibitors such as ADA, ETA and INF, and compared the cost effectiveness to tDMARDs (either monotherapy, in combination or sequential therapy) (Table 2). From the payer perspective, ICERs for ADA compared to tDMARDs ranged from $63,281 to $382,982/QALY; for INF ranged from $71,936 to $1464,344/QALY; and for ETA ranged from $110,389 to $175,721/QALY (Table 5). All of the upper bound values were reported from Chen et al., who found much higher ICERs than other included studies [18]. Chen et al. modelled TNF alpha inhibitors compared to sequential tDMARD therapy where there was a lack of efficacy data for treatment after failing upstream tDMARDs, and model inputs were largely based on assumptions. From the societal perspective, ICERs from the four studies [20,21,23,24] were generally lower and found to be below $50,000/QALY, with the exception of the study by van den Hout et al [20]. ICERs were reported to be $14,728/QALY for ETA and $141,827/QALY for INF, compared to tDMARDs (Table 5). The study by van den Hout et al. [20] reported the highest ICER out of the studies conducted from the societal perspective; however, it was also the only CUA that was done alongside a randomised controlled trial, which is one of the most robust approaches possible. Two other evaluations considered TNF alpha inhibitors as a class (Table 5), Finckh et al. found tDMARDs to be dominant over TNF alpha inhibitors in very early RA patients [21], while Schipper et al. reported ICERs around $138,000/QALY [23].

Second-line BRM (DMARD-IR)

There were four CEAs [2,25–27] published from 2000 to 2010, evaluating the first-line use of BRM therapies compared to tDMARDs in DMARD-IR patients (Table 1). Three of the four analyses [2,25,26] reported health outcomes using the American College of Rheumatology (ACR) 20/50/70 weighted response (WR) criteria [28]. One of these three studies also reported cost-utility results using QALYs as the outcome measure, and the results are summarised below [26]. The BRM therapies considered in these three studies were the TNF alpha inhibitors, ADA, ETA and INF. According

Table 1
Cost-effectiveness studies of BRM use in rheumatoid arthritis.

Author, year	BRM(s)	Comparator(s)	Perspective, country	Currency price, year	Time horizon	Discount rates
First-line BRM use in rheumatoid arthritis						
Choi et al., 2000 [25]	1: ETA; 2: ETA + MTX; 3: HCQ + SSZ + MTX; 4: CSA + MTX	MTX	Societal, US	US dollar, 1999	6 months	N/A
Second-line BRM use in rheumatoid arthritis						
Choi et al., 2002 [66]	ETA	1: SSZ; 2: MTX; 3: LEF	Societal, US	US dollar, 1999	6 months	N/A
Coyle et al., 2006[a] [26]	ETA, INF + MTX (3rd, 4th positions in sequential DMARD therapy)	Sequential DMARD therapy (MTX > MTX + SSZ > MTX + SSZ + HCQ > Gold)	Payer, Canada	Canadian dollar, N/R[b]	5 years	Costs 5%, QALYs 5%
Russell et al., 2009[c] [27]	1: ABA > ETA > INF > DMARDs; 2: ETA > ABA > INF > DMARDs	ETA > INF > ADA > DMARDs	Payer, Canada	Canadian dollar, 2006	2 years	N/A
CADTH, 2010 [2]	1: ABA; 2: ADA; 3: ETA; 4: INF; 5: GOL	MTX	Payer, Canada	Canadian dollar, N/R[b]	5 years	N/R
BRM use in rheumatoid arthritis patients with inadequate response to TNF alpha inhibitors						
Russell et al., 2009 [27]	1: ABA > ETA > INF > DMARDs; 2: ETA > ABA > INF > DMARDs	ETA > INF > ADA > DMARDs	Payer, Canada	Canadian dollar, 2006	2 years	N/A
Saraux et al., 2010 [48]	1: ETA > ABA > ADA; 2: ETA > RTX > ADA; 3: ETA > ADA > ABA;	ETA > ADA > INF	Payer, France	Euro, 2008	2 years	N/A
Beresniak et al., 2011 [49]	1: ETA > ABA > ADA; 2: ETA > RTX > ADA; 3: ETA > ADA > ABA	ETA > ADA > INF	Payer, Spain	Euro, 2008	2 years	N/A
Cimmino et al., 2011 [50]	1: ETA > ABA > ADA; 2: ETA > RTX > ADA; 3: ETA > ADA > ABA	ETA > ADA > INF	Payer, Italy	Euro, 2008	2 years	N/A
Puolakka et al., 2012 [51]	1: ETA > ABA > ADA; 2: ETA > RTX > ADA; 3: ADA > ABA > ETA 4: ADA > RTX > ETA; 5: INF > ABA > ETA; 6: INF > RTX > ETA		Payer, Finland	Euro, 2009	2 years	N/A

BRM = biologic response modifier; ETA = etanercept; MTX = methotrexate; HCQ = hydroxychloroquine; SSZ = sulfasalazine; CSA = cyclosporin A; US = United States; N/A = not applied; LEF = leflunomide; INF = infliximab; DMARD = disease-modifying anti-rheumatic drug; N/R = not reported; QALYs = quality-adjusted life years; ABA = abatacept; ADA = adalimumab; GOL = golimumab; TNF = tumour necrosis factor; RTX = rituximab.

[a] Also conducted CUA (Table 3).

[b] For comparison purposes, assumed as one year prior to publication.

[c] Also examined second line use of BRMs.

Table 2
Cost-utility studies of first line BRM use in rheumatoid arthritis.

Author, year	BRM(s)	Comparator(s)	Perspective, country	Currency price, year	Time horizon	Discount rates
Chen et al., 2006[a] [18]	1: ADA; 2: ADA + MTX; 3: ETA; 4: ETA + MTX; 5: INF + MTX (1st, 3rd, and last positions in sequential DMARD therapy)	Sequential DMARD therapy (MTX > MTX + SSZ > MTX + SSZ + HCQ > LEF > gold > AZA > CSA > CSA + MTX > Pen)	Payer, US	British pound, 2004	Lifetime	Costs 6%, QALYs 1.5%
Spalding et al., 2006 [19]	1: ADA; 2: ADA + MTX; 3: ETA; 4: INF + MTX	MTX	Payer, US	US dollar, 2005	Lifetime	Costs 3%, QALYs 3%
van den Hout et al., 2009 [20]	1: Step up therapy (MTX > MTX + SSZ > MTX + SSZ + HCQ > MTX + SSZ + HCQ + pred > MTX + INF > MTX + CSA + pred + LEF > AZA + pred); 2: Initial combination therapy (MTX + SSZ + pred > MTX + CSA + pred > MTX + INF > LEF + Gold + mpred > AZA + pred); 3: Initial combination therapy with INF (MTX + INF > SSZ > LEF > MTX + CSA + pred > Gold + mpred > AZA + pred)	Sequential DMARD therapy (MTX > SSZ > LEF > MTX + INF > Gold + mpred > MTX + CSA + pred > AZA + pred)	Societal, The Netherlands	Euro, 2008	2 years	In second year: Costs 3%, QALYs 3%
Finckh et al., 2009 [21]	1: DMARDs (LEF, SSZ, HCQ or MTX) > TNF alpha inhibitors; 2: 3 sequential TNF alpha inhibitors (N/R) + MTX	1: NSAIDs + patient education + joint protection + exercise + pain management + low dose glucocorticoids PRN > DMARDs at 1 year	Payer, societal, US	US dollar, 2007	Lifetime	Costs 3%, QALYs 3%
Davies et al., 2009 [22]	1: ADA + MTX; 2: ETA; 3: INF + MTX; 4: ADA + MTX > ETA (1st position of sequential DMARD therapy)	Sequential DMARD therapy (MTX > MTX + HCQ > LEF > Gold > palliative)	Payer, US	US dollar, 2007	Lifetime	Costs 3%, QALYs 3%
Schipper et al., 2011 [23]	1: MTX + LEF > TNF alpha inhibitor + MTX > TNF alpha inhibitor > RTX; 2: TNF alpha inhibitor + MTX > TNF alpha inhibitor > RTX	MTX > MTX + LEF > TNF alpha inhibitor + MTX > TNF alpha inhibitor > RTX	Payer, societal, The Netherlands	Euro, N/R[b]	5 years	Costs 4%, QALYs 4%
Kobelt et al., 2011 [24]	ETA + MTX	MTX	Societal, Sweden	Euro, 2008	10 years	Costs 3%, QALYs 3%

BRM = biologic response modifier; ADA = adalimumab; MTX = methotrexate; ETA = etanercept; INF = infliximab; DMARD = disease-modifying anti-rheumatic drug; SSZ = sulfasalazine; HCQ = hydroxychloroquine; LEF = leflunomide; AZA = azathioprine; CSA = cyclosporin A; US = United States; QALYs = quality-adjusted life years; pred = prednisone; mpred = methylprednisolone; TNF = tumour necrosis factor; N/R = not reported; NSAIDs = non-steroidal anti-inflammatory drugs; PRN = as needed; RTX = rituximab.

[a] Also examined second line use of BRMs.

[b] For comparison purposes, assumed as one year prior to publication.

Table 3
Cost-utility studies of second line BRM use in rheumatoid arthritis.

Author, year	BRM(s)	Comparator(s)	Perspective, country	Currency price, year	Time horizon	Discount rates
Jobanputra et al., 2002 [31]	ETA, INF + MTX (3rd position in sequential DMARD therapy)	Sequential DMARD therapy (SSZ > MTX > gold > HCQ > AZA > Pen > HCQ > LEF > CSA > CSA + MTX)	Payer, UK	British pound, 2000	Lifetime	Costs 6%, QALYs 1.5%
Wong et al., 2002[a] [30]	INF + MTX	MTX	Payer, societal, US	US dollar, 1998	Lifetime	Costs 3%, QALYs 3%
Kobelt et al., 2003 [32]	INF + MTX	MTX	Payer, societal, Sweden, UK	Euro, British pound, SEK, N/R[b]	10 years	N/R
Brennan et al., 2004 [34]	ETA > sequential DMARD therapy	Sequential DMARD therapy (Gold > LEF > CSA + MTX)	Payer, UK	British pound, 2000	Lifetime	Costs 6%, QALYs 1.5%
Welsing et al., 2004 [35]	1: LEF > usual treatment; 2: ETA > usual care; 3: LEF > ETA > usual treatment; 4: ETA > LEF > usual treatment	Usual treatment (SSZ or MTX)	Payer, societal, The Netherlands	Euro, N/R[b]	5 years	Costs 4%, QALYs 4%
Barton et al., 2004 [33]	1: ETA; 2: INF + MTX (3rd, 4th, and 6th positions in sequential DMARD therapy)	Sequential DMARD therapy (1: SSZ > MTX > LEF > gold > AZA > CSA > CSA + MTX; 2: SSZ > MTX > HCQ > gold > LEF > AZA > CSA > CSA + MTX)	Payer, US	British pound, 2000	Lifetime	Costs 6%, QALYs 1.5%
Bansback et al., 2005 [38]	1: ETA; 2: ADA; 3; ADA + MTX; 4: INF + MTX (then sequential DMARD therapy)	Sequential DMARD therapy (3 DMARDs, N/R)	Payer, Sweden	Euro, 2001	Lifetime	Costs 3%, QALYs 3%
Barbieri et al., 2005 [36]	INF + MTX > DMARDs	MTX + placebo > DMARDs (N/R)	Payer, UK	British pound, 2000	Lifetime	Costs 6%, QALYs 1.5%
Kobelt et al., 2005 [37]	ETA + MTX	MTX	Societal, Sweden	Euro, 2004	5, 10 years	Costs 3%, QALYs 3%
Tanno et al., 2006 [39]	ETA > sequential DMARD therapy	Sequential DMARD therapy (MTX > SSZ > SSZ + MTX)	Societal, Japan	Japanese Yen, 2003	Lifetime	Costs 6%, QALYs 1.5%
Chen et al., 2006 [18]	1: ADA; 2: ADA + MTX; 3: ETA; 4: ETA + MTX; 5: INF + MTX (1st, 3rd, and last positions in sequential DMARD therapy)	Sequential DMARD therapy (MTX > MTX + SSZ > MTX + SSZ + HCQ > LEF > gold > AZA > CSA > CSA + MTX > Pen)	Payer, US	British pound, 2004	Lifetime	Costs 6%, QALYs 1.5%
Coyle et al., 2006[a] [26]	1: ETA; 2: INF + MTX (3rd, 4th positions in sequential DMARD therapy)	Sequential DMARD therapy (MTX > MTX + SSZ > MTX + SSZ + HCQ > gold)	Payer, Canada	Canadian dollar, N/R[b]	5 years	Costs 5%, QALYs 5%
Brennan et al., 2007 [40]	TNF alpha inhibitors	DMARDs (weighted average of registry patients on MTX, SSZ, LEF, HCQ, other)	Payer, UK	British pound, 2004	Lifetime	Costs 6%, QALYs 1.5%
Marra et al., 2007 [41]	1: INF; 2: INF + MTX	MTX	Societal, Canada	Canadian dollar, 2002	10 years	Costs 3%, QALYs 3%
Vera-Llonch et al., 2008 [67]	ABA + MTX	MTX	Payer, US	US dollar, 2006	10 years, lifetime	Costs 3%, QALYs 3%

Table 3 (*continued*)

Author, year	BRM(s)	Comparator(s)	Perspective, country	Currency price, year	Time horizon	Discount rates
Wailoo et al., 2008 [43]	1: ETA; 2: ADA; 3: AKR	INF	Payer, US	US dollars, 2005	Lifetime	Costs 3%, QALYs 3%
Lekander et al., 2010 [44]	INF + MTX	MTX	Payer, societal, Sweden	Euro, 2007	10 years	Costs 3%, QALYs 3%
Nguyen et al., 2012 [45]	1: ADA + MTX; 2: CTZ + MTX; 3: ETA + MTX; 4: GOL + MTX; 5: INF + MTX	MTX	Payer, US	US dollar, 2009	5 years	Costs 3%, QALYs 3%
Soini et al., 2012 [46]	1: ADA + MTX; 2: ETA + MTX; 3: TCZ + MTX	MTX	Payer, societal, Finland	Euro, 2010	Lifetime	N/R
Diamantopoulos et al., 2012 [47]	TCZ + MTX > ADA + MTX > RTX + MTX > ABA + MTX > palliative care	ETA + MTX > ADA + MTX > RTX + MTX > ABA + MTX > palliative care	Payer, Italy	Euro, 2009	Lifetime	Costs 3%, QALYs 3%

BRM = biologic response modifier; ETA = etanercept; INF = infliximab; MTX = methotrexate; DMARD = disease-modifying anti-rheumatic drug; SSZ = sulfasalazine; HCQ = hydroxychloroquine; AZA = azathioprine; Pen = penicillamine; LEF = leflunomide; CSA = cyclosporin A; UK = United Kingdom; QALYs = quality-adjusted life years; US = United States; SEK = Swedish Kronor; N/R = not reported; ADA = adalimumab; TNF = tumour necrosis factor; ABA = abatacept; AKR = anakinra; CTZ = certolizumab; GOL = golimumab; TCZ = tocilizumab; RTX = rituximab.

[a] Also conducted CEAs (See Table 1).

[b] For comparison purposes, assume as one year prior to publication.

Table 4
Cost-utility studies of BRM use in rheumatoid arthritis patients with inadequate response to TNF alpha inhibitors.

Author, year	BRM(s)	Comparator(s)	Perspective, country	Currency price, year	Time horizon	Discount rates
Kielhorn et al., 2008 [52]	1: RTX + MTX > sequential DMARD therapy; 2: RTX + MTX > sequential BRMs > sequential DMARD therapy	1: Sequential DMARD therapy (LEF > Gold > CSA > palliative care (MTX)); 2: sequential BRM therapy then sequential DMARD therapy (ADA + MTX > INF + MTX > sequential DMARD therapy)	Payer, UK	British pound, 2004	Lifetime	Costs 3.5%, QALYs 3.5%
Vera-Llonch et al., 2008 [42]	ABA + DMARD (N/R)	DMARD (N/R)	Payer, US	US dollar, 2006	10 years, lifetime	Costs 3%, QALYs 3%
Merkesdal et al., 2009 [53]	RTX + MTX > ADA + MTX > INF + MTX > Gold > CSA > MTX	ADA + MTX > INF + MTX > Gold > CSA > MTX	Payer, Germany	Euro, 2008	Lifetime	Costs 3.5%, QALYs 3.5%
Lindgren et al., 2009 [57]	RTX > 3 sequential TNF alpha inhibitor therapies	3 sequential TNF alpha inhibitor therapies	Societal, Sweden	Euro, 2008	Lifetime	Costs 3%, QALYs 3%
Hallinen et al., 2010 [54]	1: RTX + MTX; 2: ADA + MTX; 3: ETA + MTX; 4: INF + MTX; 5: ABA + MTX	Best supportive care (Gold > CSA + MTX)	Payer, Finland	Euro, 2008	Lifetime	Costs 3%, QALYs 3%
Yuan et al., 2010 [55]	1: RTX + MTX; 2: ABA + MTX	MTX	Payer, US	US dollar, 2007	Lifetime	Costs 3%, QALYs 3%
Malottki et al., 2011 [56]	1: ADA + MTX; 2: ETA + MTX; 3: INF + MTX; 4: RTX + MTX; 5: ABA + MTX (all followed by sequential DMARD therapy)	Sequential DMARD therapy (LEF > Gold > CSA > AZA > palliative care)	Payer, UK	British pound, 2008	Lifetime	Costs 3.5%, QALYs 3.5%

BRM = biologic response modifier; TNF = tumour necrosis factor; RTX = rituximab; MTX = methotrexate; DMARD = disease-modifying anti-rheumatic drug; CSA = cyclosporin A; ADA = adalimumab; INF = infliximab; UK = United Kingdom; QALYs = quality-adjusted life years; ABA = abatacept; N/R = not reported; US = United States; ETA = etanercept.

to the study by Choi et al., 2000 [25], from the societal perspective, ETA + MTX resulted in ICERs of $63,182 per patient with ACR 20 and $51,613 per ACR 70WR, when compared to tDMARDs, including a specific combination with MTX + SSZ + HCQ dubbed 'triple therapy'. A study by Coyle et al., 2006 [26], compared ETA or INF + MTX to sequential tDMARD therapy, also including triple therapy, and showed that ETA resulted in ICERs of $29,554 per year with ACR 20 response and $100,485 per year with ACR 70, while INF + MTX resulted in ICERs of $18,983 per year with ACR 20 and $102,077 per year with ACR 70 when considered from the payer's perspective. Though these two studies included triple therapy in their analyses, they are now fairly dated and new evidence has been published in the TEAR (treatment of early aggressive rheumatoid arthritis) trial by Moreland et al. [29], evidence from this trial has not yet been included in any published economic analyses that we could find. A more recent report from the Canadian Agency for Drugs and Technologies in Health [2] reported an ICER of $44,440 per year with ACR 50 for patients on ADA compared to MTX. Russell et al. [27], measured outcomes as proportion of patients achieving remission and low disease activity state (LDAS) – defined as Disease Activity Score (DAS28) < 2.6 and DAS28 ≤ 3.2, respectively. This was the only CEA that examined the use of ABA as second-line BRM agent in comparison to ETA in a sequence of BRM therapies, though the effectiveness data was not taken from head-to-head clinical trials of ABA and ETA. Russell et al. reported that ABA was the dominant strategy, that is, less costly and more likely to achieve remission or LDAS, from their analysis.

Table 5
Incremental cost-effectiveness of first line BRM use in rheumatoid arthritis.

BRMs	Comparators		ICERs ($/QALY)[a]	References
Payer perspective				
ADA	ADA	Sequential DMARDs	119,400	Chen et al., 2006 [18]
	ADA	MTX	87,927	Spalding et al., 2006 [19]
	ADA + MTX	Sequential DMARDs	382,982	Chen et al., 2006 [18]
	ADA + MTX	MTX	268,318	Spalding et al., 2006 [19]
	ADA + MTX	DMARD	63,281	Davies et al., 2009 [22]
ETA	ETA	Sequential DMARDs	110,389	Chen et al., 2006 [18]
	ETA	MTX	123,780	Spalding et al., 2006 [19]
	ETA + MTX	Sequential DMARDs	175,721	Chen et al., 2006 [18]
INF	INF + MTX	Sequential DMARDs	1,464,344	Chen et al., 2006 [18]
	INF + MTX	MTX	564,663	Spalding et al., 2006 [19]
	INF + MTX	DMARD	71,936	Davies et al., 2009 [22]
TNF alpha inhibitors (as a class)	3 sequential TNF alpha inhibitors (N/R) + MTX	DMARDs (LEF, SSZ, HCQ or MTX) > TNF alpha inhibitors	DMARDs dominant	Finckh et al., 2009 [21]
	TNF alpha inhibitor + MTX	MTX	139,744	Schipper et al., 2011 [23]
Societal perspective				
ETA	ETA + MTX	MTX	14,728	Kobelt et al., 2011 [24]
INF	INF + MTX	DMARD combination	141,827	van den Hout et al., 2009 [20]
TNF alpha inhibitors (as a class)	3 sequential TNF alpha inhibitors (N/R) + MTX	DMARDs (LEF, SSZ, HCQ or MTX) > TNF alpha inhibitors	DMARDs dominant	Finckh et al., 2009 [21]
	TNF alpha inhibitor + MTX	MTX	137,843	Schipper et al., 2011 [23]

BRM = biologic response modifier; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; ADA = adalimumab; DMARD = disease-modifying anti-rheumatic drug; MTX = methotrexate; ETA = etanercept; INF = infliximab; TNF = tumour necrosis factor; N/R = not reported; LEF = leflunomide; SSZ = sulfasalazine; HCQ = hydroxychloroquine.
[a] All costs reported in Canadian dollars, 2012.

There were 20 CUAs [18,26,30–47] found between year 2002 and 2012 evaluating the cost effectiveness of BRMs in DMARD-IR patients (Table 3). Most of these studies compared BRMs to switching to another tDMARD after inadequate response to previous tDMARDs, with the exception of six studies that looked at BRMs compared to each other in this patient population [31,33,43,45–47]. When compared to switching to another tDMARD or sequential use of tDMARDs from the payer perspective, ICERs were reported to be $29,654/QALY for TCZ; $58,376/QALY for ABA; and ranged from $32,465 to $154,057/QALY for ETA; $33,396 to $317,650/QALY for ADA; $37,225 to $313,144/QALY for INF; $53,802 to $291,531/QALY for TNF alpha inhibitors as a class and $58,376/QALY for ABA (Table 6) [18,26,30–36,38,40,42,44–46]. The reported ICERs were mostly below $100,000/QALY, however, one must consider that the analyses were done in a population of patients who have already failed to adequately respond to one or more previous tDMARDs. From the societal perspective, ICERs were generally lower or at least comparable, reported to range from a possible cost offset to $59,924/QALY for INF; between $25,727 and $76,089/QALY for ETA; $29,707/QALY for TCZ and $34,183/QALY for ADA (Table 6) [30,32,37,39,41,44,46]. From the six CUAs that evaluated BRMs compared to one another, some studies concluded that ADA dominates INF; ETA dominates INF and ADA; CTZ dominates ADA, INF and GOL; and TCZ dominates ADA and ETA (Table 6) [43,45–47]. Other studies found differing results, but in general of the TNF alpha inhibitors evaluated, CTZ and ETA appear to be more cost effective than other existing TNF alpha inhibitors and the new BRM, TCZ, appears to be most cost effective (Table 6). Only three of the six studies reported having used an indirect comparison or mixed treatment comparison approach to address the lack of head-to-head comparative effectiveness data [45–47].

TNF alpha inhibitor inadequate responders

Five CEAs were published between 2009 and 2011 [27,48–51], evaluating the cost effectiveness of sequential BRM therapies including TNF alpha inhibitors and BRMs such as RTX and ABA, after an

Table 6
Incremental cost-effectiveness of second line BRM use in rheumatoid arthritis.

BRMs	Comparators		ICERs ($/QALY)[a]	References
Compared to DMARDs				
Payer perspective				
ABA	ABA + MTX	MTX	58,376	Vera-Llonch et al., 2008 [67]
ADA	ADA + MTX	DMARD	58,778	Bansback et al., 2005 [38]
	ADA	DMARD	69,952	Bansback et al., 2005 [38]
	ADA	Sequential DMARDs	317,650	Chen et al., 2006 [18]
	ADA + MTX	Sequential DMARDs	145,083	Chen et al., 2006 [18]
	ADA + MTX	MTX	33,396	Soini et al., 2012 [46]
ETA	ETA	Sequential DMARDs	154,057	Jobanputra et al., 2002 [31]
	ETA	Sequential DMARDs	109,883	Barton et al., 2004 [33]
	ETA	Sequential DMARDs	38,775	Brennan et al., 2004 [34]
	ETA + MTX	DMARD	60,188	Bansback et al., 2005 [38]
	ETA	DMARD	62,152	Bansback et al., 2005 [38]
	ETA	Sequential DMARDs	164,482	Coyle et al., 2006 [26]
	ETA	Sequential DMARDs	106,784	Chen et al., 2006 [18]
	ETA + MTX	Sequential DMARDs	112,191	Chen et al., 2006 [18]
	ETA + MTX	MTX	32,465	Soini et al., 2012 [46]
	ETA + MTX	MTX	ETA dominates	Nguyen et al., 2012 [45]
INF	INF + MTX	MTX	46,028	Wong et al., 2002 [30]
	INF + MTX	Sequential DMARDs	213,637	Jobanputra et al., 2002 [31]
	INF + MTX	MTX	48,204	Kobelt et al., 2003 (Sweden) [32]
	INF + MTX	MTX	69,946	Kobelt et al., 2003 (UK) [32]
	INF + MTX	Sequential DMARDs	147,746	Barton et al., 2004 [33]
	INF + MTX	DMARD	81,350	Bansback et al., 2005 [38]
	INF + MTX	MTX	79,824	Barbieri et al., 2005 [36]
	INF + MTX	Sequential DMARDs	128,448	Coyle et al., 2006 [26]
	INF + MTX	Sequential DMARDs	313,144	Chen et al., 2006 [18]
	INF + MTX	MTX	37,225	Lekander et al., 2010 [44]
TCZ	TCZ + MTX	MTX	29,654	Soini et al., 2012 [46]
TNF alpha inhibitors (as a class)	TNF alpha inhibitors	Usual treatment (DMARDs)	291,531	Welsing et al., 2004 [35]
	TNF alpha inhibitors	DMARDs	53,802	Brennan et al., 2007 [40]
Societal perspective				
ADA	ADA + MTX	MTX	34,183	Soini et al., 2012 [46]
ETA	ETA + MTX	MTX	76,089	Kobelt et al., 2005 [37]
	ETA	Sequential DMARDs	25,727	Tanno et al., 2006 [39]
	ETA + MTX	MTX	33,252	Soini et al., 2012 [46]
INF	INF + MTX	MTX	13,733	Wong et al., 2002 [30]
	INF + MTX	MTX	5798	Kobelt et al., 2003 (Sweden) [32]
	INF + MTX	MTX	58,653	Kobelt et al., 2003 (UK) [32]
	INF + MTX	MTX	59,924[b]	Marra et al., 2007 [41]
	INF + MTX	MTX	Cost offset	Lekander et al., 2010 [44]
TCZ	TCZ + MTX	MTX	29,707	Soini et al., 2012 [46]
TNF alpha inhibitors (as a class)	TNF alpha inhibitors	Usual treatment (DMARDs)	269,331	Welsing et al., 2004 [35]
Compared to BRMs				
Payer perspective				
ADA	ADA	INF	ADA dominates	Wailoo et al., 2008 [43]
	ADA	AKR	196,957	Wailoo et al., 2008 [43]
CTZ	CTZ + MTX	ADA + MTX	CTZ dominates	Nguyen et al., 2012 [45]
	CTZ + MTX	INF + MTX	CTZ dominates	Nguyen et al., 2012 [45]
	CTZ + MTX	ETA + MTX	694,357	Nguyen et al., 2012 [45]
	CTZ + MTX	GOL + MTX	CTZ dominates	Nguyen et al., 2012 [45]
ETA	ETA	INF + MTX	83,650	Jobanputra et al., 2002 [31]
	ETA	INF + MTX	62,318	Barton et al., 2004 [33]
	ETA	INF	ETA dominates	Wailoo et al., 2008 [43]
	ETA + MTX	ADA + MTX	ETA dominates	Soini et al., 2012 [46]
	ETA	ADA	127,037	Wailoo et al., 2008 [43]

Table 6 (*continued*)

BRMs	Comparators		ICERs ($/QALY)[a]	References
TCZ	TCZ + MTX	ETA + MTX	9525	Soini et al., 2012 [46]
	TCZ + MTX	ETA + MTX	TCZ dominates	Diamantopoulos et al., 2012 [47]
	TCZ + MTX	ADA + MTX	TCZ dominates	Diamantopoulos et al., 2012 [47]
	TCZ + MTX	INF + MTX	4233	Diamantopoulos et al., 2012 [47]
Societal perspective				
TCZ	TCZ + MTX	ETA + MTX	4321	Soini et al., 2012 [46]

BRM = biologic response modifier; ICER = incremental cost-effectiveness ratio; QALYs = quality-adjusted life years; ABA = abatacept; MTX = methotrexate; ADA = adalimumab; DMARD = disease-modifying anti-rheumatic drug; ETA = etanercept; INF = infliximab; TCZ = tocilizumab; TNF = tumour necrosis factor; AKR = anakinra; CTZ = certolizumab pegol.

[a] All costs reported in Canadian dollars, 2012.

[b] Took an average ICER from reported ICERs using different utility instruments in this study.

inadequate response to a TNF alpha inhibitor (Table 1). Four of the five studies [48–51] evaluated the same comparators, from the payer perspective in the setting of four different countries. The comparators were sequential BRM therapies with ABA or RTX among a sequence of TNF alpha inhibitors. All three studies found that using ABA was more cost effective than RTX after inadequate response to a TNF alpha inhibitor as well as more cost effective than INF after inadequate response to two sequential TNF alpha inhibitors (ETA then ADA) [48–51]. Outcomes were measured as days in remission and LDAS – defined as DAS28 < 2.6 and DAS28 ≤ 3.2, respectively. From the four studies, it was found that cost per day in LDAS when using ABA after inadequate response to a TNF alpha inhibitor ranged from $463 to $712, compared to $505–$847 for RTX [48–51]. Costs per day in remission were generally higher, at the range of $877–$1410 for ABA; and $1237–$2169 for RTX after inadequate response to a TNF alpha inhibitor [48–51]. For the use of ABA after inadequate response to two sequential TNF alpha inhibitors, costs per day ranged from $788 to $1215 and $2535 to $4149 in LDAS and remission, respectively [48–50]. This was compared to the use of INF, which resulted in costs per day ranging from $1361 to $2253 and $4462 to $7614 in LDAS and remission, respectively [48–50]. Costs tended to be lower in the CEA conducted in France, then Italy, and Spain having the highest costs [48–50]. Since there are no head-to-head randomised controlled trials comparing ABA to RTX, these CEAs were based on the assumption that the baseline patient characteristics in the clinical trials for ABA and RTX were comparable. One Canadian CEA by Russell et al. [27], also examined the cost effectiveness of ABA after inadequate response to ETA compared to INF; it was found that the ICERs were $22,878 and $29,647 per additional case of LDAS and remission, respectively.

Seven CUAs [42,52–56] were found published between year 2008 and 2011 evaluating the cost effectiveness of BRMs after an inadequate response to a TNF alpha inhibitor (Table 4). All CUAs were conducted from the payer perspective, except one by Lindgren et al., 2009 [57], which was conducted from the societal perspective. Lindgren et al. found that treatment with RTX after inadequate response to prior TNF alpha inhibitor was more effective and less costly than treatment with subsequent series of TNF alpha inhibitors [57]. Results from the six other studies (Table 7) demonstrated that when compared to subsequent therapy with traditional DMARDs, ICERs ranged from: $33,067 to $73,659/QALY for treatment with RTX; $51,623 to $111,690/QALY for ABA; $60,211 to $74,782/QALY for INF; $71,053 to $84,916/QALY for ADA and $80,582 to $83,967/QALY for ETA [42,52–56]. Four of the total seven studies [52,53,56,57] analysed the cost effectiveness of BRMs compared to one another and found that RTX either dominated over TNF alpha inhibitors or resulted in ICERs ranging from $26,314 to $40,868/QALY (Table 7). It was also reported that ABA was more effective but more costly than the TNF alpha inhibitors, with ICERs ranging from $78,303 to $96,118/QALY (Table 7) [56]. Malottki et al. found that ABA was not cost effective when compared to RTX with an ICER of $270,539/QALY [56]. These results are directly contradictory to results reported from the CEAs mentioned above, this could be due to the short time horizon employed for CEAs (2-year time horizon vs. lifetime horizon by Malottki et al.), as RTX has potential to be more cost effective as time goes on due to its infrequent administration.

Table 7
Incremental cost-effectiveness of BRM use in rheumatoid arthritis patients with inadequate response to TNF alpha inhibitors.

BRMs	Comparators		ICERs ($/QALY)[a]	References
Compared to DMARDs				
ABA	ABA + MTX	MTX	63,326	Yuan et al., 2010 [55]
	ABA + DMARD (N/R)	DMARD (N/R)	51,623	Vera-Llonch et al., 2008 [42]
	ABA + MTX	BSC	111,690	Hallinen et al., 2010 [54]
	ABA + MTX	DMARDs	79,546	Malottki et al., 2011 [56]
ADA	ADA + MTX	BSC	84,916	Hallinen et al., 2010 [54]
	ADA + MTX	DMARDs	71,053	Malottki et al., 2011 [56]
ETA	ETA + MTX	BSC	83,967	Hallinen et al., 2010 [54]
	ETA + MTX	DMARDs	80,582	Malottki et al., 2011 [56]
INF	INF + MTX	BSC	60,211	Hallinen et al., 2010 [54]
	INF + MTX	DMARDs	74,782	Malottki et al., 2011 [56]
RTX	RTX + MTX	MTX	73,659	Yuan et al., 2010 [55]
	RTX + MTX	BSC	50,422	Hallinen et al., 2010 [54]
	RTX + MTX	Sequential DMARDs	33,067	Kielhorn et al., 2008 [52]
	RTX + MTX	DMARDs	43,709	Malottki et al., 2011 [56]
Compared to BRMs				
ABA	ABA + MTX	RTX + MTX	270,539	Malottki et al., 2011 [56]
	ABA + MTX	ADA + MTX	96,118	Malottki et al., 2011 [56]
	ABA + MTX	ETA + MTX	78,303	Malottki et al., 2011 [56]
	ABA + MTX	INF + MTX	86,382	Malottki et al., 2011 [56]
ADA	ADA + MTX	ETA + MTX	ADA dominates	Malottki et al., 2011 [56]
	ADA + MTX	INF + MTX	42,466	Malottki et al., 2011 [56]
ETA	ETA + MTX	INF + MTX	946,059	Malottki et al., 2011 [56]
RTX	RTX	3 sequential TNF alpha inhibitor therapies	RTX dominates[b]	Lindgren et al., 2009 [57]
	RTX + MTX	ADA + MTX > INF + MTX > sequential DMARD therapy	26,314	Kielhorn et al., 2008 [52]
	RTX + MTX	ADA + MTX	40,868	Merkesdal et al., 2009 [53]
	RTX + MTX	ADA + MTX	RTX dominates	Malottki et al., 2011 [56]
	RTX + MTX	ETA + MTX	RTX dominates	Malottki et al., 2011 [56]
	RTX + MTX	INF + MTX	RTX dominates	Malottki et al., 2011 [56]

BRM = biologic response modifier; ICER = incremental cost-effectiveness ratio; QALYs = quality-adjusted life years; ABA = abatacept; MTX = methotrexate; ADA = adalimumab; DMARD = disease-modifying anti-rheumatic drug; N/R = not reported; BSC = best supportive care; ETA = etanercept; INF = infliximab; RTX = rituximab; TNF = tumour necrosis factor.
[a] All costs reported in Canadian dollars, 2012.
[b] Societal perspective.

Discussion

The principle findings of our review are that the determination of whether BRMs are a cost-effective use of health-care resources depends on the place the patient is on the treatment course, and what the analysis compares the BRM to.

Based on our review of the literature on RA patients who are DMARD naive, it appears that TNF alpha inhibitors are less cost-effective options for first-line treatment compared to tDMARDs, at least from the payer's perspective using currently acceptable ICER thresholds of $50,000–$100,000/QALY gained. The inclusion of indirect costs drastically reduces ICERs to a more acceptable range; however, there are no established standards on methods of valuing work productivity losses making this a barrier against valid comparisons between studies (see Anis et al. in this issue). In addition, many jurisdictions do not accept productivity gains in the value for money proposition for funding decisions. These data therefore support the requirement of most payers in that they require a trial of tDMARDs including MTX before they will pay for a BRM. In addition, it appears that treatment with a TNF alpha inhibitor in patients who were refractory to previous tDMARD therapies is more cost effective, compared to switching to another tDMARD [2]. Most of the studies have reported ICERs between $50,000 per QALY and $100,000 per QALY in this patient population [32,34,38,40,46]. These data support the coverage of TNF alpha inhibitors in DMARD-IR patients. Finally, in analyses that examined the value for money of BRMs after an inadequate response to a TNF alpha inhibitor, it appears that therapy with RTX + MTX is more cost effective than

treatment with another TNF alpha inhibitor (+MTX) or ABA (+MTX) [52,53,56,57], whereas treatment with ABA + MTX, compared to with a second TNF alpha inhibitor (+MTX) in this patient population had ICERs in the $50,000–$100,000 per QALY range [56].

It is important to note that the recommended MTX dosing has increased over the past 15 years; previously oral MTX 15 mg weekly was the upper limit, now many countries use MTX up to 20 mg once weekly or subcutaneously up to 25 mg per week. Most clinical trials within the last decade have used MTX protocols with an average of 15 mg or more per week oral dosing and represent the clinical evidence from which these economic analyses are drawn [2]. However, these current studies have not considered differences between higher doses of MTX and/or subcutaneous administration, which have potential to alter the costs and outcomes of the tDMARD treatment group [58,59]. In addition, definitions have changed over the years. Earlier, economic evaluations defined early treatment quite differently than the current definition which could also change the cost effectiveness of various treatment strategies. As such, it is important to consider these factors when comparing the economic evaluations conducted over the years.

A point of interest from the reviewed studies (and of economic evaluations in general) is that cost effectiveness depends on which comparators are included in the analyses and the evidence for the comparators. For example, the current CEAs that compare the effect of triple therapy with tDMARDs have not used the most up-to-date evidence from recent clinical trials and thus need to be updated. For example, the recent publication by Moreland et al. (the TEAR trial) showed that in early RA, there were no differences in the mean DAS-28-erythrocyte sedimentation rate (ESR) between participants randomised to MTX plus ETA or triple therapy and both were better than initial therapy with MTX monotherapy (oral dosing to a maximum of 20 mg per week) [29]. However, the combination of ETA plus MTX resulted in a statistically significant radiographic benefit over oral triple therapy. Similar trials are currently being analysed in established RA. For both scenarios (early and established RA), it is not clear how these results will translate into long-term cost effectiveness and which strategy will emerge as acceptable value for money. These economic evaluations are currently being completed and the results are highly anticipated.

The most typical comparator in those analyses that examined the economic outcomes in DMARD-IR patients was MTX. As such, many of the results that claim cost effectiveness of the BRMs (specifically, in this case, almost exclusively TNF alpha inhibitors) do so only in the context of comparing to a drug that most of the patients in the clinical trials (where the results for the economic evaluations were taken from) had already failed on. As a result, TNF alpha inhibitors have become standard therapy in many jurisdictions after MTX or other tDMARD failure. As new comparative effectiveness data becomes available (e.g., the recent results of the ADACTA trial reveal that TCZ appears to be more effective than ADA for DAS28 remission, 39.9% vs. 10.5%, $p < 0.001$), the issue of which BRM offers the best value for money after tDMARD failure becomes critical [60]. New economic evaluations will need to address this issue such that reimbursement decisions can be fully informed regarding relative value.

Another point of interest is the use of different methodologies to determine incremental cost effectiveness of the BRMs. The bulk of the studies reviewed used modelling approaches (either Markov, or individual patient sampling methods) [61]. In economic evaluations, two general approaches can be used – the construction of models where various sources of evidence are pieced together or where the economic evaluation is 'piggybacked' onto a clinical trial and the measurement of resource use and health state utility values to determine QALYs is done prospectively [62]. The only analysis that was directly 'piggy-backed' onto a clinical trial (and not a modelling study) was that by van den Hout et al. [20], which was a prospective economic analysis of the BeST trial [63]. The strengths of this approach and this specific study were the methodological rigour and the application of the current evidence into directly informing the economic evaluation. The limitations were the same as those experienced with most clinical trials – the time horizon was quite short and may not have captured all the relevant outcomes to inform the funding decision.

Finally, as the incremental cost effectiveness of BRMs at various points of RA (early, established or post BRM failure) becomes sorted out, additional issues will need to be resolved. For example, the denominator currently used by most economic evaluations is the QALY. This metric captures both the quality of health states and the time spent in the health states. However, the quality is usually a societal valuation of a health state based on certain domains of health (e.g., the EQ-5D is based on health states defined on mobility, self-care, usual activity, pain and anxiety/depression). As such, certain elements

such as route of administration, dosing frequency and fear of adverse events (unless captured in anxiety/depression) are not accounted for by using the QALY. As new BRMs or other RA therapies become available with innovative properties (such as oral route of administration), other methods to account for patient preferences should be considered (such as discrete choice experiments or other preference-based assessments) when making funding decisions.

Our review has many limitations. First of all, because it was beyond the scope of our review, we did not use an instrument to evaluate the quality of the economic evaluations that we included in our review. Recent reviews such as that by van der Velde et al. used such an instrument and, as such, we did not want to duplicate their efforts [64]. In addition, we did not consider the differences between the various tDMARDs, combination DMARDs, sequential DMARDs and sequential BRMs. The sequential use of tDMARDs and BRMs has been a focus for recent reviews such as that by Fautrel et al. [65]. We did not address many of the relevant issues that currently exist within the rheumatology economic literature. Specifically, some of these issues include the methods for the inclusion of work productivity/indirect costs (see Anis et al. in this issue); lack of standardised method of deriving health state utility values for CUAs; issues with methodology and transparency of mixed treatment comparisons; and, the long-term relative economic impact of BRMs.

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