








ORIGINAL RESEARCH

Points to consider for cost-effective use of biological and targeted synthetic DMARDs in inflammatory rheumatic diseases: results from an umbrella review and international Delphi study

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To cite: van der Togt CJT, Van den Bemt B, Aletaha D, *et al.* Points to consider for cost-effective use of biological and targeted synthetic DMARDs in inflammatory rheumatic diseases: results from an umbrella review and international Delphi study. *RMD Open* 2023;**9**:e002898. doi:10.1136/rmdopen-2022-002898

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/rmdopen-2022-002898>).

Received 1 December 2022
Accepted 8 February 2023



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ABSTRACT

Objectives To develop evidence-based points to consider for cost-effective use of biological and targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) in the treatment of inflammatory rheumatic diseases, specifically rheumatoid arthritis, psoriatic arthritis and axial spondyloarthritis.

Methods Following EULAR procedures, an international task force was formed, consisting of 13 experts in rheumatology, epidemiology and pharmacology from seven European countries. Twelve strategies for cost-effective use of b/tsDMARDs were identified through individual and group discussion. For each strategy, PubMed and Embase were systematically searched for relevant English-language systematic reviews and, for six strategies, additionally for randomised controlled trials (RCTs). Thirty systematic reviews and 21 RCTs were included. Based on the evidence, a set of overarching principles and points to consider was formulated by the task force using a Delphi procedure. Level of evidence (1a–5) and grade (A–D) were determined for each point to consider. Individual voting on the level of agreement (LoA; between 0 (completely disagree) and 10 (completely agree)) was performed anonymously.

Results The task force agreed on five overarching principles. For 10 of 12 strategies, the evidence was sufficient to formulate one or more points to consider, leading to 20 in total, regarding response prediction, drug formulary use, biosimilars, loading doses, low-dose initial therapy, concomitant conventional synthetic DMARD use, route of administration, medication adherence, disease activity-guided dose optimisation and non-medical drug switching. Ten points to consider (50%) were supported by level 1 or 2 evidence. The mean LoA (SD) varied between 7.9 (1.2) and 9.8 (0.4).

Conclusion These points to consider can be used in rheumatology practices and complement inflammatory rheumatic disease treatment guidelines to incorporate cost-effectiveness in b/tsDMARD treatment.

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- ⇒ Biological and targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) are effective drugs in the treatment of inflammatory rheumatic diseases but are also associated with side effects and high societal costs.
- ⇒ A systematic overview of the literature and practical points to consider in improving the cost-effective use of these drugs are missing.

WHAT DOES THIS STUDY ADD

- ⇒ In this Delphi study, 12 strategies for the cost-effective use of b/tsDMARDs have been identified. Furthermore, five overarching principles and 20 points to consider have been formulated.

HOW MIGHT THIS IMPACT CLINICAL PRACTICE?

- ⇒ These points to consider help rheumatology health-care providers to incorporate patient-centred and cost-effective use of b/tsDMARDs in their daily practice.

INTRODUCTION

In the last two decades, pharmacological treatment options for inflammatory rheumatic diseases (IRDs), including specifically rheumatoid arthritis (RA), psoriatic arthritis (PsA) and axial spondyloarthritis (axSpA), have vastly expanded. In particular, the biological and targeted synthetic disease-modifying antirheumatic drugs (bDMARDs and tsDMARDs, respectively) have taken an important place in IRD treatment, as they have been shown to reduce disease activity, slow down radiological progression and improve daily functioning.^{1–3}

Although b/tsDMARD therapy is effective, it has disadvantages, such as adverse events, the need for parenteral administration (for bDMARDs) and high costs. Concerning the costs, b/tsDMARDs are substantially more expensive per year than conventional synthetic DMARDs (csDMARDs),⁴ are used by an increasing number of patients and in principle require chronic use. With the arrival of biosimilars, some bDMARDs have become somewhat less expensive,⁵ but their impact on a pressured healthcare budget remains.

When following the current disease-specific recommendations, many patients can reach good disease control. Therefore, the current challenge for clinicians is not only controlling the disease but also achieving this in the most cost-effective way, to provide optimal rheumatology care from a societal perspective. This viewpoint has been adopted in the EULAR RA recommendations as follows: ‘RA incurs high individual, medical and societal costs, all of which should be considered in its management by the treating rheumatologist’.⁶ However, specific recommendations or points to consider on how to optimise cost-effectiveness have not been formulated.

Cost-effectiveness, expressed as the effect on health divided by the costs of an intervention, can be improved by either increasing effectiveness or reducing costs.⁷ So far, several strategies for improving cost-effectiveness of b/tsDMARDs have been investigated, with dose reduction and biosimilar use being the most systematically studied.^{8,9} Concerning the use of biosimilars, recommendations for clinical practice have been formulated by Kay *et al.*⁹ However, to facilitate that clinicians and rheumatology practices choose the optimal strategy in their specific situation, a systematic overview of all (possible and attempted) strategies to optimise cost-effectiveness with points to consider for all strategies, including less-known options, is needed.

Therefore, the aim of this project was to provide a systematic overview of evidence regarding strategies aimed at improving the cost-effective use and to develop international, consensus-based, interdisciplinary points to consider on cost-effective prescribing of b/tsDMARDs in IRD from a societal perspective.

METHODS

These consensus-based and evidence-based points to consider were developed for individual rheumatologists or groups of rheumatologists (eg, in a hospital). They were designed to be applicable across different healthcare systems. For the development of the points to consider, we used the EULAR standardised operating procedure for recommendations¹⁰ and the additional EULAR guidance on methodology.¹¹ Of note, where the word ‘rheumatologist’ is used, the task force means any rheumatology healthcare provider prescribing b/tsDMARDs, including among others rheumatology trainees, and in some countries also nurse specialists and physician assistants. For the definition of cost-effectiveness, we used an adapted

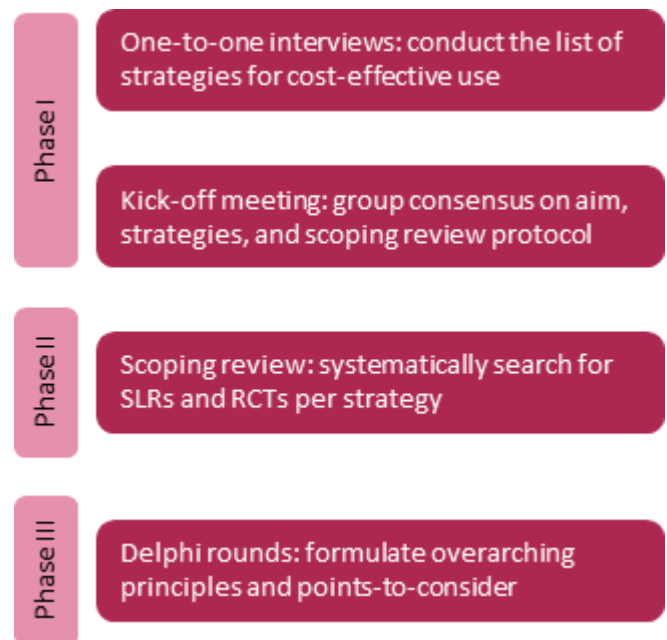


Figure 1 Study phases. RCT, randomised controlled trial; SLR, systematic literature review.

version of the NICE definition: ‘Guideline recommendations should be based on the estimated costs of the interventions or services in relation to their expected health benefits (that is, their “cost-effectiveness”), rather than on the total cost or resource impact of implementing them’.⁷

Task force

In September 2020, an international interdisciplinary task force of 13 experts from seven European countries was formed for this study, consisting of 7 rheumatologists (DA, RA, KC, JG, JI, DM and PV), 1 pharmacist (AGV), 1 epidemiologist-health technology assessment expert (PMJW), 1 research fellow (CJTvdT), 1 epidemiologist (LV), 1 pharmacist-clinical pharmacologist (BVdB) and 1 rheumatologist-epidemiologist (AAdB). The steering committee, consisting of CJTvdT, BVdB, LV and AAdB performed the scoping review and hosted the task force meetings. All task force members were involved in formulating the points to consider and voting for the level of agreement (LoA).

Phase I: scope and strategies

In October and November 2020, one-to-one open interviews with all members of the task force were performed by CJTvdT to identify all relevant strategies on the cost-effective use of b/tsDMARDs (figure 1). Thereafter, in November 2020, an online kick-off meeting took place to reach consensus on the included b/tsDMARDs (table 1), the definition of a strategy for cost-effective use, the included strategies with their definitions and the protocol of the scoping review. A study was considered eligible if it included: patients with RA, PsA or axSpA, (planning to be) treated with b/tsDMARDs (Population), comparison of treatment with and without a strategy [Intervention/

Table 1 Included drugs with abbreviation and their indications, authorised dose, interval and route of administration

Drug	Abbreviation	Indication for RA, PsA, axSpA? (EMA)	RoA	Authorised dosing scheme (EMA)		Different registration for FDA?
				Loading dose	Maintenance dose	
Abatacept	ABA	RA, PsA	IV	Weight-based infusion at weeks 0, 2, 4	Weight-based infusion every 4 weeks: <60 kg 500 mg, 60–100 kg 750 mg, >100 kg 1000 mg	No
			SC	Weight-based infusion	125 mg/week	No
Adalimumab	ADA	RA, PsA, axSpA	SC	None	40 mg/2 weeks	No
Apremilast	APR	PsA	Oral	None	30 mg once daily	No
Baricitinib	BARI	RA	Oral	None	4 mg once daily	Yes, 2 mg once daily
Certolizumab pegol	CER	RA, PsA, axSpA	SC	400 mg at weeks 0, 2, 4	200 mg/2 weeks or 400 mg/4 weeks	No
Etanercept	ETN	RA, PsA, axSpA	SC	None	50 mg/week	No
Filgotinib	FILG	RA	Oral	None	200 mg once daily	Not available in the USA
Golimumab	GOL	RA, PsA, axSpA	SC	None	50 mg/month. If weight is >100 kg and response is insufficient: increase to 100 mg/month	No
Infliximab	IFX	RA, PsA, axSpA	IV	Disease-based mg/kg infusion at weeks 0, 2, 6	3 mg/kg every 8 weeks for RA; 5 mg/kg every 8 weeks for PsA and axSpA	No
		RA, PsA, axSpA	SC		120 mg/2 weeks	Not available in the USA
Ixekizumab	IXE	PsA, axSpA	SC	160 mg at week 0	80 mg every 4 weeks	No
Rituximab	RTX	RA	IV	None	1000 mg/6 months	No
Sarilumab	SARI	RA	SC	None	200 mg/2 weeks	No
Secukinumab	SECU	PsA, axSpA	SC	150 mg at weeks 0, 1, 2, 3, 4	150 mg/month	No
Tocilizumab	TCZ	RA	IV	None	8 mg/kg every 4 weeks (max. 800 mg)	Yes, 4 mg/kg
			SC	None	162 mg/week	Yes, 162 mg/2 weeks if weight <100 kg
Tofacitinib	TOFA	RA, PsA, axSpA	Oral	None	5 mg twice daily or 11 mg XR once daily	No
Upadacitinib	UPA	RA, PsA, axSpA	Oral	None	15 mg once daily	No
Ustekinumab	UST	PsA	SC	45 mg at weeks 0, 4 90 mg if weight >100 kg	45 mg/12 weeks 90 mg if weight >100 kg	No

Abbreviation (as used in this publication and the online supplemental data)
EMA, European Medicines Agency; FDA, Food and Drug Administration; IV, intravenous; PsA, psoriatic arthritis; RA, rheumatoid arthritis; RoA, route of administration; SC, subcutaneous; SpA, spondyloarthritis; XR, extended release.

Comparison] and any of the following outcomes: cost-effectiveness, costs, efficacy, safety or patient-reported outcomes (PROMs) (Outcome). Of note, a formal cost-effectiveness assessment was considered the primary outcome of our review. However, when not available, a more informal approach for assessing costs and resource use in relation to effectiveness outcomes was performed. Only systematic literature reviews (SLRs) and randomised controlled trials (RCTs) were included, to search for available high-quality evidence and to conserve feasibility. Moreover, the panel agreed on two further limitations: (1) publications in English only, as this was the only

language understood by every participant in the project and (2) studies published in 2000 or thereafter since we did not expect any relevant publications beforehand.

Phase II: existing evidence

PubMed and Embase were systematically searched for each strategy using a two-step approach: an initial search for SLRs by filtering for systematic reviews in both PubMed and Embase, and a second search for RCTs for the remaining research gaps by adding the Cochrane high-sensitivity RCT search string in both PubMed and Embase.¹² In addition, reference lists of included articles

were screened for relevant studies. In general, the search string consisted of three parts: (IRDs) AND (drugs) AND (strategy). The first part (IRDs) was identical for all strategies, and the second part (drugs) for every strategy except for the route of administration, of which this part only focused on drugs with multiple administration routes available (abatacept, infliximab, tocilizumab). The outcomes were not included in the search string but checked for in the title/abstract screening. Further information on the search strategies and searches is included in the online supplemental file 1.

Title/abstract screening was performed by two steering committee members separately. Disagreements were discussed by the two reviewers until an agreement was reached, or, if persistent were resolved by the vote of another steering committee member. If more than five SLRs were accepted after title/abstract screening, full-texts of recent SLRs (published in 2019 or thereafter) were screened first. Full-texts of older reviews were only screened in case of research gaps. Full-text screening combined with risk of bias (RoB) assessment was performed by the same reviewers as title/abstract screening independently, using AMSTAR-2 for SLRs¹³ and the Cochrane RoB tool 2 for RCTs.¹⁴ The data extraction form was designed by LV and CJTvdt. CJTvdt performed the data extraction.

Phase III: consensus

The steering committee drafted a first version of the overarching principles and points to consider, the latter including level of evidence (LoE) and grade of recommendation (GR), based on the underlying evidence. Thereafter, a summary of the evidence and the proposed points-to-consider were communicated to all task force members prior to the meetings. In total, five online task force Delphi meetings took place between June and December 2021. In the first meeting, the overarching principles were discussed and accepted with ‘no objection’ during the meeting. In the following meetings, we discussed the content and phrasing of the definitive points to consider. Also, LoE and GR were determined in accordance with the EULAR additional guidance.¹¹ If consensus was reached on the formulation of the point to consider in the group meeting, task force members were asked afterwards by e-mail to vote on its LoA. LoA score ranged from 0 (completely disagree) to 10 (completely agree), based on the 2014 EULAR SOP.¹⁰

RESULTS

Phase I: scope and strategies

The task force formulated a definition for strategies of cost-effective b/tsDMARD use (see [box 1](#)). Of note, we assumed that the diagnosis of the patients should be sufficiently certain.

The task force identified four distinct ways for a strategy to increase cost-effectiveness (benefits): (1) a direct reduction of drug price per milligram, (2) a lower

Box 1 Definition for strategies of cost-effective b/tsDMARD use

Strategies on the level of an individual patient or a hospital, concerning cost-effective prescribing¹ or use of biological and targeted synthetic DMARDs in the treatment of rheumatoid arthritis, psoriatic arthritis or axial spondyloarthritis.

¹Includes the indication, selection, dose, interval, route of administration and monitoring of the drug, and any comedication interfering pharmacokinetically or pharmacodynamically. b/tsDMARD, biological and targeted synthetic disease-modifying antirheumatic drug.

drug quantity needed (dose/interval), (3) lower direct additional non-medication costs (eg, day care costs for infusion) and (4) improved efficacy or safety, or reduced patient burden. Furthermore, the task force identified 12 strategies: (1) response prediction, (2) drug formulary policy, (3) biosimilar/generic drug use, (4) avoid dose loading, (5) initial lower dose, (6) optimising pharmacokinetic exposure, (7) combination therapy, (8) route of administration, (9) drug wastage, (10) medication adherence, (11) disease activity-guided dose optimisation (DAGDO) and (12) non-medical drug switching. An overview of the strategies including their definition and potential benefits is displayed in [table 2](#).

Phase II: existing evidence

The SLR searches, performed on 24 February 2021 and 1 November 2021 (initial lower dose), identified 1104 publications. Of those, 57 were accepted after title-abstract screening. After full-text screening, 30 SLRs in total could be included. For five strategies, no systematic reviews could be included. Except for the strategy biosimilar/generic drug use, additional RCT searches were performed for the other 11 strategies between 22 March 2021 and 17 November 2021, identifying 4804 publications. Of those, 25 were accepted after title-abstract screening and eventually 21 full-text publications were included for six strategies. For the four strategies, no articles could be accepted, including drug formulary policy, optimising pharmacokinetic exposure, reducing drug wastage and non-medical drug switching (excluding biosimilar transitioning). The searches, output flowcharts per strategy and extracted data are included in the online supplemental file 1.

Phase III: consensus

In the Delphi meetings, the task force agreed on five overarching principles and 20 points to consider (see [table 3](#)), which are explained in the following paragraphs. The overall mean LoA was 8.9 (range 7.9–9.7). Of the 240 votes received, four times a 5 was voted (2%), five times a 6 (2%) and nine times a 7 (4%). All other votes were ≥ 8 . Except for the strategy ‘avoid dose loading’, all other strategies required only one Delphi meeting to agree with the completeness of the search and to reach consensus on the phrasing of the recommendation. Regarding the strategy ‘avoid dose loading’, the task force requested

Table 2 Definition of strategies and how cost-effectiveness can be optimised

Strategy	Definition	Benefit(s)*
Response prediction	To use a predictor for optimising any drug use intervention, such as drug selection, drug dose reduction or drug discontinuation	4
Drug formulary policy	To prescribe b/tsDMARDs in a preferential order for the rheumatology practice, primarily based on effectiveness and safety but in case of equality also on cost-effectiveness	1
Biosimilar/generic drug use	To (allow the) start of or transition to the best value drug variant (biosimilar/generic or originator) of a b/tsDMARD	1
Avoid dose loading	To avoid the loading dose (initial higher dose than maintenance dose) that is part of an authorised dosing	2, 4
Initial lower dose	To use a lower dose than the authorised dose in the maintenance phase	2, 4
Optimising pharmacokinetic exposure	To improve exposure to the b/tsDMARD by influencing pharmacokinetic parameters	2, 4
Combination therapy	To choose for either combined treatment of a b/tsDMARD with a csDMARD or monotherapy of a specific b/tsDMARD	2, 3, 4
Route of administration	To start with or to transition to the most cost-effective route of administration for bDMARDs of which multiple routes are available	2, 3, 4
Drug wastage	To reduce wastage of the b/tsDMARD to reduce total amount of drug needed	2, 3
Medication adherence	To improve the extent to which a person's medication intake corresponds with agreed treatment decisions with the healthcare provider	3, 4
Disease activity-guided dose optimisation	To gradually reduce drug dosage or lengthen the interval of the b/tsDMARD to the minimal effective dose or discontinuation guided by the disease activity	2, 4
Non-medical drug switching	To switch patients to another more cost-effective b/tsDMARD (within or between classes), excluding biosimilars, to reduce drug costs	1

*1. A direct reduction of drug price per milligram. 2. A lower needed drug quantity (dose/interval). 3. Lower direct additional drug costs. 4. Improved efficacy or safety, or reduced patient burden.
b/tsDMARD, biological and targeted synthetic disease-modifying antirheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug.

for an additional search in the ‘summary of the product characteristics’ of the included drugs but no additional information was found.

Overarching principles

A. Treatment choices must be based on shared decision-making between the patient and the rheumatologist

RA, PsA and axSpA are diseases with a chronic course and require chronic treatment in the vast majority of patients. Shared decision-making can enhance medication adherence by adapting treatment to a patient's personal life/preferences, leading to increased satisfaction and control of treatment.

B. Treat-to-target (T2T) is the cornerstone of b/tsDMARD-based treatment in RA, PsA and axSpA

The T2T approach comprises tight monitoring of disease activity for the evaluation of treatment. This approach is recommended for RA, PsA and axSpA.^{15–17} T2T should be the standard background strategy for b/tsDMARD treatment.

C. Cost-effectiveness considerations are an important aspect of treatment, and rheumatologists should have a leading role regarding this

Currently, there are many drugs available for inflammatory arthritis. As most of these drugs are comparable in efficacy and safety, we believe that cost-effectiveness should be an additional selection criterium. Antirheumatic treatment has a significant impact on the rheumatology healthcare budget and as explained further in this paper, multiple strategies for more cost-effective use are available. Moreover, we believe that rheumatologists should have a leading role in this because of their knowledge, training, experience and direct involvement in b/tsDMARD prescription and the hospital's drug formulary.

D. Reimbursement policies should cover cost-effective use of pharmacological treatments, both on-label and off-label, when it is evidence based and supported by (inter)national guidelines

Some of these points to consider require off-label use of b/tsDMARDs, for example, a reduced dose, a prolonged interval or removal of a loading dose. We acknowledge

Table 3 Overarching principles and consensus-based points to consider

Overarching principles			
A. Treatment choices must be based on shared decision-making between the patient and the rheumatologist.			
B. Treat-to-target is the cornerstone of b/tsDMARD-based treatment in RA, PsA and axSpA.			
C. Cost-effectiveness considerations are an important aspect of treatment, and rheumatologists should have a leading role regarding this.			
D. Reimbursement policies should cover cost-effective use of pharmacological treatments, both on-label and off-label, when it is evidence based and supported by (inter)national guidelines.			
E. Bio-originators and biosimilars are considered similar, and thus all recommendations apply equally to bio-originators and biosimilars.			
Points to consider	LoE	GR	LoA
Response prediction			
1. Therapeutic drug monitoring* of b/tsDMARDs in patients with RA, PsA and axSpA is not advised because of the absence of evidence† on efficacy and safety.	5	D	8.3±1.4 (6–10)
2. Using other predictors for either choosing or tapering a particular b/tsDMARD is not advised because none have demonstrated superiority to standard care.	5	D	8.3±1.0 (7–10)
Drug formulary policy‡			
3. Rheumatologists might consider to adopt and use a drug formulary for their practice, primarily based on effectiveness and safety, and cost-effectiveness thereafter.	5	D	9.1±1.0 (7–10)
Biosimilar/generic drug use			
4. A biosimilar, if approved by a drug-regulating authority in a highly regulated area, should be preferred if it is the most cost-effective version of the drug.	1b	A	9.8±0.39 (9–10)
5. A single transition from a bio-originator to one of its biosimilars should be considered if it contributes to the cost-effectiveness of the treatment.	1b	A	9.4±0.51 (9–10)
Avoid dose loading			
6. When initiating abatacept or certolizumab in RA, or secukinumab in PsA or axSpA, rheumatologists might consider to initiate treatment using the maintenance dose, as dose loading has not shown superior efficacy.	1b	B	8.5±1.5 (5–10)
7. For the other b/tsDMARDs, there is no information on the effect of dose loading. Therefore, these drugs should be used as authorised.	5	D	9.4±1.0 (7–10)
Initial lower dose			
8. In RA, low-dose rituximab (1*1000mg or 2*500mg per cycle) has similar efficacy and less toxicity compared with authorised-dose rituximab (2*1000mg) and should thus be preferred over the authorised dose.	1a	A	9.3±1.3 (6–10)
9. In patients with RA, rheumatologists might start with the lower dose§ of baricitinib or tocilizumab because of a more favourable safety and/or cost-effectiveness profile.	4	D	7.9±1.2 (5–10)
Combination therapy			
10. In patients with RA, rheumatologists should combine the b/tsDMARD with methotrexate to maximise efficacy; in patients who cannot use methotrexate as comedication, IL-6 pathway inhibitors and JAK-inhibitors¶ might be preferred over other bDMARDs.	1a 2a¶	A	9.5±0.78 (8–10)
11. For patients with PsA or axSpA, combination therapy of a TNF inhibitor with methotrexate cannot be advised, because increased efficacy compared with TNF inhibitor monotherapy is not shown.	1a	A	8.4±1.3 (5–10)
12. For patients with PsA or axSpA, combination therapy of non-TNF inhibitors with methotrexate cannot be advised because of the absence of evidence on efficacy and safety.	5	D	8.7±1.2 (6–10)
Route of administration			
13. For patients with RA, non-inferiority of subcutaneous versus intravenous treatment of abatacept, infliximab and tocilizumab has been shown, and thus rheumatologists can choose the most cost-effective route of administration when initiating one of those drugs.	1b	A	9.5±0.52 (9–10)
14. For patients with RA, a single switch from subcutaneous to intravenous tocilizumab or vice versa did not affect efficacy or safety, and thus rheumatologists might consider this for cost-effectiveness reasons.	2b	C	8.9±1.0 (7–10)

Continued

Table 3 Continued

Overarching principles			
Medication adherence			
15. Rheumatologists should take adherence into account in the management of their patients by using the current points to consider** to manage non-adherence of b/tsDMARDs.	5	D	9.5±0.52 (9–10)
Disease activity–guided dose optimisation			
16. For patients with RA in whom the treatment target is reached and sustained, rheumatologists should consider disease activity–guided dose optimisation of anti-TNF drugs.	1	A	9.6±0.90 (7–10)
17. For patients with RA in whom the treatment target is reached and sustained, rheumatologists might consider disease activity–guided dose optimisation of IL-6 inhibitors, rituximab, baricitinib or abatacept.	1b	B	8.8±0.87 (7–10)
18. For patients with axSpA†† and PsA†† in whom the treatment target is reached and sustained, rheumatologists might consider disease activity–guided dose optimisation of anti-TNF drugs.	1a†† 5††	B†† D††	8.2±1.1 (6–10)
19. Rheumatologists can use any disease activity–guided dose optimisation scheme, as none is preferential based on the evidence.	5	D	8.9±1.4 (5–10)
Non-medical drug switching‡			
20. Non-medical switching within or between b/tsDMARD classes is not advised because of the absence of evidence on efficacy and safety.	5	D	9.7±0.65 (8–10)

*Adjustments of dose and/or interval based on drug serum levels and/or antidrug antibodies.
†Except for (1) proactive TDM (drug doses and timing of doses are based on serum drug levels) of infliximab in RA, PsA and axSpA and (2) dose increase of infliximab based on baseline TNF-alpha for RA, this has not shown superiority (both LoE 1b, strength B).
‡No evidence (SLR or RCT) found for this strategy.
§2 mg once daily for baricitinib and 4 mg/kg (intravenously)* or 162 mg every 2 weeks (subcutaneously)* for tocilizumab, all three authorised doses in the USA. *Only for patients with a body weight <100 kg
¶Lower LoE for baricitinib
**Ritschl V, et al. *Ann Rheum Dis*. 2020.⁴⁷
††Different LoE and GR for PsA and axSpA.
axSpA, axial spondyloarthritis; b/tsDMARD, biological and targeted synthetic disease-modifying antirheumatic drug; GR, grade of point to consider; IL-6, interleukin 6; JAK, Janus kinase; LoA, level of agreement on a numeric rating scale from 0 (completely disagree) to 10 (completely agree), displayed as mean±SD (range); LoE, level of evidence; LoE, level of evidence; PsA, psoriatic arthritis; RA, rheumatoid arthritis; RCT, randomised controlled trial; SLR, systematic literature review; TDM, therapeutic drug monitoring; TNF, tumour necrosis factor.

that off-label use of medication is sometimes not included in reimbursement policies or not financially beneficial for the hospital while this could have multiple advantages regarding outcomes and/or costs at a societal level. We believe that every opportunity for healthcare cost reduction (without significant impact on the quality of care) should be taken advantage of for the preservation of affordable healthcare. We therefore advocate that reimbursement policies, either from governments or healthcare insurance companies, include off-label medication use in case of proven added value. We consider these points to consider a first step towards removing barriers for providing cost-effective care.

E. Bio-originators and approved biosimilars are considered similar, and thus all recommendations apply equally to bio-originators and biosimilars

As further explained in the online supplemental file 1 of the fourth point to consider (on biosimilar/generic drug use), we consider bio-originators and approved biosimilars clinically similar, in agreement with the American College of Rheumatology RA guideline.¹⁷ Therefore, all points to consider apply equally to biosimilars.

Consensus recommendations

Response prediction

1. *Therapeutic drug monitoring of b/tsDMARDs in patients with RA, PSA and axSpA is not advised because of the absence of evidence on efficacy and safety.*

Therapeutic drug monitoring (TDM) is a clinical practice in which adjustments of dose and/or interval are made based on drug serum levels and/or antidrug antibodies (ADAb).¹⁸ One can distinguish ‘proactive TDM’ in which drug levels and/or ADAb are measured with the aim to proactively adjust treatment, regardless of the clinical response, and ‘reactive TDM’ in which drug levels and/or ADAb are measured in case of loss of efficacy or side effects.¹⁸ A recent systematic review on the clinical effectiveness of TDM of anti-tumour necrosis factor (anti-TNF) in RA found one clinical study on this subject but could not draw conclusions because of the serious RoB of this study.¹⁹ We found another RCT (NORDRUM I), which compared proactive TDM of induction of infliximab treatment to standard care and did not find a difference in clinical remission at week 30.²⁰ Based on the available evidence, the task force concluded that TDM

can currently not be advised because of the absence of evidence on superiority.

2. *Using other predictors for either choosing or tapering a particular b/tsDMARD is not advised because none have demonstrated superiority to standard care.*

Other predictors could include either biomarkers, genetic markers or clinical markers. Disease activity was not included as a clinical marker because T2T is already incorporated in the overarching principles and disease activity-based tapering in the DAGDO section. Four systematic reviews found no clinical test-treatment trials with these markers.^{21–24} An RCT on circulating TNF-alpha levels as a predictor for increasing infliximab dosage in RA found no differences in sustained remission.²⁵ Therefore, using other predictors for selecting or tapering a b/tsDMARD is not advised.

Drug formulary policy

3. *Rheumatologists might consider to adopt and use a drug formulary for their practice, primarily based on effectiveness and safety, and cost-effectiveness thereafter.*

A drug formulary is a preferred order of b/tsDMARDs, established for a hospital, region or country. Formularies provide a structure for safe, rational and cost-effective drug use. As formularies uniformise and prioritise drug therapy strategies, they are also an important instrument for the cost-conscious procurement of medication. We found no supporting SLRs or RCTs on this topic. However, as these points to consider aim to inform rheumatologists on incorporating cost-effectiveness in their practice, and drug formulary policy was seen as an important strategy, the task force agreed on a point to consider based on expert opinion only.

Biosimilar/generic drug use

4. *A biosimilar, if approved by a drug regulating authority in a highly regulated area, should be preferred if it is the most cost-effective version of the drug.*

Biosimilars are available for an increasing number of bDMARDs, and from 2027 on, generic drug variants of tsDMARDs can also be expected. We found two systematic reviews supporting the use of biosimilars but both are of low quality.^{26,27} As mentioned in the introduction, the expert group of Kay *et al* has formulated consensus-based recommendations for biosimilar use in clinical care.⁹ The current point to consider is directly adapted from one of their overarching principles, which states that approved biosimilars in highly regulated areas are neither better nor worse in efficacy and non-inferior in safety to bio-originators. Our task force agreed on this principle and the addition that initiating therapy with a biosimilar can contribute to cost-effectiveness.

5. *A single transition from a bio-originator to one of its biosimilars should be considered if it contributes to the cost-effectiveness of the treatment.*

There is high-quality evidence available for the efficacy and safety of a single transition from bio-originator to biosimilar. Twelve RCTs regarding transitioning of

infliximab (6), adalimumab (5) and etanercept (1) were included in three systematic reviews, which demonstrated the efficacy and safety of a single switch.^{28–30} Furthermore, transitioning is also supported by the recommendations of Kay *et al*.⁹ Regarding multiple switching, there was no evidence available at the time of the systematic search. Therefore, only a single transition is included in the second point to consider.

Avoid dose loading

6. *When initiating abatacept or certolizumab in RA or secukinumab in PsA or axSpA, rheumatologists might consider to initiate treatment using the maintenance dose, as dose loading has not shown superior efficacy.*

7. *For the other b/tsDMARDs, there is no information on the effect of dose loading. Therefore, these drugs should be used as authorised.*

A loading dose is a higher initial dose given at the beginning of a treatment course with the aim to achieve steady-state concentrations of a drug earlier in time, especially when a drug has a long half-life. For six bDMARDs, a loading dose is advised (table 1). The task force advocates that a loading dose should not be used when superiority on effectiveness has not been demonstrated in a head-to-head study. A systematic review on this subject found comparative studies with/without loading doses for abatacept and certolizumab in RA and secukinumab in both PsA and axSpA.³¹ The authors concluded that there is insufficient evidence on the superiority of dose loading for these drugs. For the other drugs authorised with a loading dose, no comparative studies were found. Thus, the task force concluded that for the aforementioned drugs, a regimen without loading dose could optimise cost-effectiveness. However, these drugs were studied and authorised with loading dose, and therefore the decision should be made carefully and with a shared decision to the patient. For the other drugs, more research is required to evaluate the additional value of the loading dose.

Initial lower dose

8. *In RA, low-dose rituximab (1*1000 mg or 2*500 mg per cycle) has similar efficacy and less toxicity compared with authorised-dose rituximab (2*1000 mg) and should thus be preferred over the authorised dose.*

For some b/tsDMARDs, an initial dose lower than the authorised dose may be as efficacious. The authorised dose of rituximab is two infusions of 1000 mg (14 days apart) every 6 months (2*1000 mg). An updated systematic review of Bredemeier *et al* based on three RCTs concluded that there were no significant differences between 2*1000 mg and 1*1000 mg rituximab in the primary efficacy outcomes.³² Moreover, 1*1000 mg rituximab was associated with a lower incidence of first infusion reactions. Based on this systematic review, 1*1000 mg could be advised over 2*1000 mg for the treatment of RA.

9. In patients with RA, rheumatologists might start with the lower dose of baricitinib or tocilizumab because of a more favourable safety and/or cost-effectiveness profile

For both tocilizumab and baricitinib, the authorised doses in the European Union (EU) and the USA are different. Baricitinib is dosed as 2 mg daily for RA in the USA, in contrast to 4 mg daily in the EU, and tocilizumab as 162 mg every 2 weeks (subcutaneous) or 4 mg/kg (intravenous) in the USA, in contrast to 162 mg weekly (subcutaneous) or 8 mg/kg (intravenous) in the EU. Although no formal cost-benefit study has been performed between the two regimens, the task force suggests that, based on the evidence,^{33–36} these lower doses could also be used as initial doses in European clinical practice. The use of baricitinib 2 mg might not lead to lower drug costs due to the flat pricing of 2 and 4 mg tablets. As lower-dosed tocilizumab was associated with numerically lower infection rates, and fewer cases of hypercholesterolaemia and neutropaenia,³⁴ this regimen could especially be suitable for patients with safety concerns.

Combination therapy

Combining a b/tsDMARD with a csDMARD is known to increase the effectiveness of therapy and drug survival, and therefore cost-effectiveness. For this strategy, we specifically looked for evidence on starting a b/tsDMARD with or without concomitant csDMARD.

10. In patients with RA, rheumatologists should combine the b/tsDMARD with methotrexate (MTX) to maximise efficacy; in patients who cannot use MTX as comedication, interleukin 6 (IL-6) pathway inhibitors and Janus kinase (JAK) inhibitors might be preferred over other bDMARDs.

For RA, there is high-quality evidence supporting combination therapy. A meta-analysis investigated studies comparing b/tsDMARD treatment with and without MTX and found significantly better efficacy outcomes (ACR20/ACR50 response) for combination therapy for all bDMARDs.³⁷ For tsDMARDs, this effect was not significant. Two other reviews specifically investigated tocilizumab and found comparable ACR20 responses³⁸ and effectiveness measured with PROMs.³⁹ Regarding sarilumab, no specific evidence was found. In the 2019 EULAR recommendations, combination therapy is advised for all b/tsDMARDs, and therapy with an IL-6 inhibitor or a JAK-inhibitor alone, if combination therapy is not possible.⁶ We formulated the point to consider in line with the EULAR RA recommendation but with a specific focus on MTX instead of csDMARDs, based on the available evidence. In addition, a dose of 10 mg MTX weekly may be sufficient for the effect.⁴⁰

11. For patients with PsA or axSpA, combination therapy of a TNF-inhibitor (TNFi) with MTX cannot be advised, because increased efficacy compared with TNFi monotherapy is not shown.

For PsA and axSpA, two systematic reviews on combination therapy of TNFi^{41 42} found no additional effect of combination therapy on efficacy outcomes. However, the drug survival of TNFi, specifically infliximab, seemed

somewhat better when combined with MTX in PsA according to registry data.⁴¹ The current EULAR guideline on the management of PsA therefore advises to continue MTX but to reduce the dose in good responders. We advise, in the light of cost-effectiveness, to taper the csDMARD to full discontinuation when the bDMARD is efficacious, although stopping the csDMARD when starting the bDMARD is an alternative possibility.

12. For patients with PsA or axSpA, combination therapy of non-TNFis with MTX cannot be advised because of the absence of evidence on efficacy and safety.

We found no systematic reviews or RCTs on combination therapy for non-TNFi in PsA or axSpA. Therefore, an expert opinion point to consider was formed in which combination therapy for non-TNFi in these diseases was not advised.

Route of administration

13. For patients with RA, non-inferiority of subcutaneous versus intravenous treatment of abatacept, infliximab and tocilizumab has been shown, and thus rheumatologists can choose the most cost-effective route of administration when initiating one of those drugs.

For abatacept, infliximab and tocilizumab, both intravenous and subcutaneous formulations are available which may differ in yearly medication costs. However, intravenous administration of the medication comes with additional costs for day care treatment. Both routes of administration for those three drugs have shown to be non-inferior regarding efficacy and without differences in safety.^{43–45} Therefore, we advise that a rheumatologist chooses the most cost-effective route of administration, whenever possible.

14. For patients with RA, a single switch from subcutaneous to intravenous tocilizumab or vice versa did not affect efficacy or safety, and thus rheumatologists might consider this for cost-effectiveness reasons.

The extension of the SUMMACTA study investigated switching from intravenous to subcutaneous tocilizumab or vice versa in a subpopulation and found maintained efficacy and similar safety profiles.⁴⁶ For abatacept and infliximab, this has not yet been investigated. Therefore, the current point to consider is that a switch in the route of administration might be advised for tocilizumab to increase cost-effectiveness.

Medication adherence

15. Rheumatologists should take adherence into account in the management of their patients by using the current points to consider to manage non-adherence of b/tsDMARDs.

Even the most perfectly prescribed drug cannot have its desired effect in the case of non-adherence. Therefore, medication adherence should be included in points to consider for cost-effectiveness. We did not find any supporting systematic reviews or RCTs on this topic but refer to the current EULAR points to consider on non-adherence,⁴⁷ which can help rheumatologists to manage non-adherence.

Disease activity-guided dose optimisation

DAGDO (also known as tapering) is a strategy that includes a stepwise dose reduction (often by interval lengthening between injections) with or without complete discontinuation as final step. According to the task force, DAGDO should also fulfil the following criteria: (1) following the T2T principle with regular visits (every 1–3 months or up to every 6 months if there is sustained remission), (2) measurement of disease activity with a valid tool, (3) agreement on treatment target (remission or low disease activity) and (4) switching/intensifying treatment if treatment target is not reached. DAGDO should only be performed when the treatment target is sustained, defined as ≥ 3 months on target with two or more formal disease activity measurements.

16. For patients with RA in whom the treatment target is reached and sustained, rheumatologists should consider DAGDO of anti-TNF drugs.

17. For patients with RA in whom the treatment target is reached and sustained, rheumatologists might consider DAGDO of IL-6 inhibitors, rituximab, baricitinib or abatacept.

DAGDO of TNFis in RA is supported by two systematic reviews^{8 48} and should therefore be considered in patients in which the treatment target is reached and sustained. DAGDO of abatacept and tocilizumab is also supported by two reviews^{48 49} but with less evidence compared with TNFis. Dose reduction of rituximab (to 1*500 or 1*200mg every 6 months) was investigated in a double-blinded RCT and advised by the authors, although formal non-inferiority criteria were not met.⁵⁰ A study investigating the dose reduction of baricitinib to 2mg found that many patients could maintain control of disease activity, and if not, disease control could be recaptured with return to 4mg.⁵¹

18. For patients with axSpA and PsA in whom the treatment target is reached and sustained, rheumatologists might consider DAGDO of anti-TNF drugs.

Evidence on DAGDO of TNFi in axSpA has been included in two low-quality reviews, supporting stepwise tapering of these drugs.^{49 52} One review also looked into DAGDO of PsA but was not able to draw conclusions because of the absence of evidence.⁴⁹ Therefore, the point to consider for PsA is expert opinion level only.

19. Rheumatologists can use any DAGDO scheme, as none is preferential based on the evidence.

An expert opinion point to consider was formulated on the dose reduction scheme. Although no scheme is preferential, the task force advises dose reduction by interval lengthening in 1–4 steps with or without complete discontinuation, for example, 100%–50%–0% or 100%–66%–50%–33%–0%. Whenever a flare or loss of disease control occurs, it is advised to return to last effective dose.

Non-medical drug switching

20. Non-medical switching within or between b/tsDMARD classes is not advised because of the absence of evidence on efficacy and safety.

Non-medical drug switching is drug switching for other reasons than (loss of) efficacy, side effects or adherence, for example, to reduce drug costs.⁵³ For these recommendations, this includes switching within or between a drug class but excludes non-medical biosimilar transitioning (which is addressed as a separate strategy). We found no supporting evidence on this topic. Therefore, non-medical drug switching is not advised and should be further investigated. Of note, when a drug is not available temporarily or definitively, which was the case, for example for tocilizumab, sarilumab and abatacept in COVID times, non-medical switching cannot be avoided and should be offered of course.

DISCUSSION

In this study, we were able to identify 12 strategies for cost-effective use of b/tsDMARDs in IRD: response prediction, drug formulary policy, biosimilar/generic drug use, avoid dose loading, initial lower dose, optimising pharmacokinetic exposure, combination therapy, route of administration, drug wastage, medication adherence, DAGDO and non-medical drug switching. Moreover, we formulated high-quality clinical points to consider for the majority of those strategies, based on an extensive literature review and stakeholder engagement. These points to consider can be used in addition to the recommendations for the management of RA, PsA or axSpA and are broadly applicable across many healthcare environments.

Our points to consider have some limitations. First, we did not include patient representatives to our task force, but we would fully recommend this for an updated version. Second, because of feasibility, we only included systematic reviews and RCTs as a consequence of which we could have missed some important non-randomised clinical studies. For the strategy of initial lower dose specifically, we planned to look in the registration data of all b/tsDMARDs to check for lower effective doses tested in phase 1 and 2 trials, but this was deemed not feasible. Third, most included systematic reviews were of low or critically low AMSTAR-2 quality. Nevertheless, we were able to combine multiple reviews with high-quality RCTs to form high-quality points to consider. Four, we mainly focused on drug costs as the main cost component of cost-effectiveness and might have missed other important costs which can influence cost-effectiveness of therapy. Also, net drug costs fluctuate over time which may affect the points to consider. Last, because of contextual differences in healthcare systems and reimbursement policies across countries, the generalisability of these points-to-consider may be limited in certain contexts.

Although we could form points to consider for most strategies, some research gaps have been identified through the scoping review. An important one is less overall evidence for PsA and axSpA compared with RA at the time of our search, for example, for DAGDO and combination therapy. Moreover, for the four strategies, there was no SLR or RCT evidence available. A research

agenda is included in the supplementary online supplemental box 1. Of note, important studies have been published after our search which could not be included when formulating the points to consider, such as the NOR-DRUM B study and a DAGDO RCT in PsA and axSpA.^{54 55}

Changes in b/tsDMARD prices require these points to consider to be kept under review and, if necessary, updated. As an increasing number of b/tsDMARDs will lose their patent and thus the possibility for biosimilar or generic drug variants becomes available, this might lead to increased competition and lower drug prices. However, the drug losing patent protection does not equate to direct availability of a biosimilar, for example, rituximab (4 years after patent expiry), and tocilizumab and abatacept (no biosimilars available yet). Also, new b/tsDMARDs are still entering the market, leading to an increased number to choose from and more price competition. Finally, some points to consider are of value to the patient also when leaving costs out of the equation, for example, lower-dosed rituximab for the same effect but with less infusion time and side effects. Therefore, we think that these points to consider on cost-effectiveness will remain of value and require an update in the future.

In conclusion, healthcare costs are spiralling up, and yet we have a finite financial envelope. For clinicians to provide the best care to the greatest number, it is our responsibility to be cognisant of costs and use high-cost medications wisely. This framework of strategies and corresponding points to consider for cost-effective use of b/tsDMARDs in IRD can be a starting point to incorporate cost-effectiveness into clinical care.

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Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests BVdB: speakers bureau for UCB, Pfizer, Sanofi-Aventis, Galapagos, Amgen and Eli Lilly. DA: speakers bureau for Abbvie, Amgen, Lilly, Janssen, Merck, Novartis, Pfizer, Roche and Sandoz; consultant of Abbvie, Amgen,

Lilly, Janssen, Merck, Novartis, Pfizer, Roche and Sandoz; research support from: Abbvie, Amgen, Lilly, Novartis, Roche, SoBi and Sanofi. RA: speakers bureau for Abbvie, BMS, Celltrion, Galapagos, Gilead, Janssen, Lilly, Novartis, Pfizer and Roche; paid instructor for Abbvie, BMS, Celltrion, Galapagos, Gilead, Janssen, Lilly, Novartis, Pfizer and Roche; consultant of Abbvie, BMS, Celltrion, Galapagos, Gilead, Janssen, Lilly, Novartis, Pfizer and Roche; research support from Abbvie, BMS, Celltrion, Galapagos, Gilead, Janssen, Lilly, Novartis, Pfizer and Roche. KC: consultant of Eli Lilly, AbbVie and Pfizer. JI: speakers bureau for AbbVie, Gilead, Roche and UCB; research support from GSK, Janssen and Pfizer. DM: invitation to attend congress: Celltrion Healthcare and GSK. PV: speakers bureau for Eli Lilly, MSD, Galapagos and Roularta; consultant of Galapagos, Gilead, Pfizer, Sidekick Health, Eli Lilly, Nordic Pharma, Abbvie, Celltrion, BMS and UCB; research support from Pfizer. AGV: speakers bureau for Amgen, Biogen Idec, Bristol Meyers Squibb, Effik Benelux, F. Hoffmann-La Roche, Eli Lilly, Febelgen/Medaxes, Medicines for Europe AISBL, Mundipharma, Pfizer/Hospira and Hexal/Sandoz; paid instructor for Effik Benelux, Fresenius/Kabi, Amgen and Sandoz/Novartis; consultant of Biogen Idec, Effik Benelux, Fresenius/Kabi, Pfizer/Hospira, Sandoz/Novartis and Samsung Bioepis. AAdB: research support from Abbvie, Galapagos, Pfizer, Novartis, Lilly, Sanofi and Gilead. CJTvdt, JG, PMJW and LV have no competing interests to declare.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

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