A report for
Universitätsklinikum Schleswig-Holstein/Campus Kiel
on shared decision making
for additional treatments for rheumatoid arthritis

Kleijnen Systematic Reviews Ltd

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LIST OF ABBREVIATIONS

ABA	abatacept
ACR	American College of Rheumatology
ADA	adalimumab
ANK	anakinra
BARI	baricitinib
bDMARDs	biological DMARDs
bsDMARDs	biosimilar DMARDs
CCT	controlled clinical trial
CI	confidence interval
CDAI	Clinical Disease Activity Index
CDSR	Cochrane Database of Systematic Reviews
CRD	Centre for Reviews and Dissemination
CrI	credible interval
CRP	C-reactive protein
csDMARDs	conventional synthetic DMARD
CVE	cardiovascular events
CTZ	certolizumab pegol
DA	decision aid
DARE	Database of Abstracts of Reviews of Effects
DAS28	Disease Activity Score 28
DMARD	disease-modifying antirheumatic drug
EMA	European Medicines Agency
ESR	erythrocyte sedimentation rate
ETN	etanercept
EULAR	the European League Against Rheumatism
FAQ	frequently asked question
FDA	Food and Drug Administration
FTN	filgotinib
GIN	Guidelines International Network
GOL	golimumab
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HAQ	Health Assessment Questionnaire
HAQ-DI	Health Assessment Questionnaire Disability Index
HCQ	hydroxychloroquine
HTA	Health Technology Assessment
ICU	intensive care unit
IFX	infliximab
InR	incidence rate
IR	insufficient response
JAK	janus kinase inhibitor

KSR	Kleijnen Systematic Reviews
MACE	major adverse cardiovascular events
mTSS	modified total Sharp/van der Heijde score
MTX	methotrexate
NA	not applicable
N	sample size
NHS	National Health Service (UK)
NICE	National Institute for Health and Care Excellence (UK)
NMSC	non-melanoma skin cancer
NR	not reported
NSAIDs	non-steroidal anti-inflammatory drugs
OR	odds ratio
PGA	patient global assessment
PICOS	participants, intervention, comparators, outcomes and study design
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QoL	quality of life
RA	rheumatoid arthritis
RCT	randomised controlled trial
RR	risk ratio
RTX	rituximab
SDAI	Simplified Disease Activity Score
SDM	shared decision making
SR	systematic review
SRL	sarilumab
SSZ	sulfasalazine
TNFi	tumour necrosis factor inhibitors
TOC	tocilizumab
TOF	tofacitinib
tsDMARDs	targeted synthetic DMARDs
UK	United Kingdom
UPA	upadacitinib
VAS	visual analogue scale
VTE	venous thromboembolism events

1. PROJECT OBJECTIVE

A key aim of the research project “Making SDM a reality” is to inform patients as part of shared decision making (SDM).

To support this, Kleijnen Systematic Reviews (KSR) Ltd has prepared an evidence report with a synthesis of the evidence of the relevant treatment options.

The objective of this evidence report is to present a summary of relevant clinical outcomes resulting from the use of additional treatments for patients with rheumatoid arthritis who were pre-treated with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs).

2. METHODS

2.1 INCLUSION CRITERIA

The research question underpinning the literature searches for this topic was developed in conjunction with clinical departments at Universitätsklinikum Schleswig-Holstein/Campus Kiel. The inclusion criteria were framed in terms of participants, intervention, comparators, outcomes, and study design (PICOS), see Table 1.

Table 1: Inclusion and exclusion criteria

	Included	Excluded
Population	Adult patients (≥18 years) with rheumatoid arthritis eligible for additional/targeted treatment options (including pregnant women). This limits the population to patients that have been previously treated with csDMARDs (methotrexate [MTX], leflunomide, sulfasalazine and hydroxychloroquine) (in combination with corticosteroids or not)	Children (i.e., <18 years old) Adults with other inflammatory diseases Treatment-naïve patients
Intervention	Biological DMARDs (bDMARDs; i.e., adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, sarilumab, tocilizumab, anakinra, abatacept, rituximab) or targeted synthetic DMARDs/JAK inhibitors (tsDMARDs; i.e., tofacitinib, baricitinib, upadacitinib, filgotinib); as a drug class, as monotherapy or combined with MTX or other csDMARDs	None
Comparator	Other treatments - MTX alone or other csDMARDs alone (or combined with corticosteroids); b/tsDMARDs (if comparative evidence available)	None
Outcomes	• Treatment duration • Impact on symptoms response (as measured by ACR50 criterion) and/or remission (DAS28, SDAI and/or CDAI) • Impact on join function and/or mobility • Quality of Life (QoL; any validated tool) • Impact on joint damage (radiographic assessment) • Impact on survival • Treatment-related risks and/or side effects (e.g. cardiovascular risk) • Impact on cancer risk	None
Study design	Systematic reviews, health technology assessments and guidelines; primary research including RCTs*, CCTs*, cohort studies*	Literature reviews; expert opinions; letters; case studies
Effect modification/ Subgroups**	Different age groups (if available)	Not applicable

* to be considered if evidence from SRs/CPGs is scarce
** to be considered if SRs or primary studies explicitly report on effect modifiers/subgroup analyses (no meta-regression etc. necessary)

	Included	Excluded
ACR50 = American College of Rheumatology 50; bDMARD = biological DMARD; CDAI = Clinical Disease Activity Score; csDMARD = conventional synthetic DMARD; DAS28 = Disease Activity Score 28; DMARD = disease-modifying antirheumatic drug; JAK = janus kinase; MTX = methotrexate; QoL = quality of life; SDAI = Simplified Disease Activity Score; tsDMARD = targeted synthetic DMARD		

2.2 FREQUENTLY ASKED QUESTIONS

The following research questions were identified as frequently asked questions (FAQs):

FAQ1: What does the treatment involve?
FAQ2: Will it help my symptoms (response)?
FAQ3: Will it help maintain remission of my disease?
FAQ4: How will treatment prevent damage to my joints? (i.e., mobility, functionality)
FAQ5: How will treatment impact my quality of life?
FAQ6: Will the treatment prolong my life expectancy?
FAQ7: What are the risks or side effects (i.e., cardiovascular risk)?
FAQ8: Does treatment increase my cancer risk in the long term?

2.3 LITERATURE SEARCHES

Literature searches were conducted to identify systematic reviews, health technology assessments (HTAs) and guidelines on treatments for patients who have previously received conventional therapies for rheumatoid arthritis.

The search strategies were developed specifically for each database and keywords adapted according to the configuration of each database. Searches were limited by date range to 2016-2021. Searches were not limited by language or publication status.

Search sources

The following systematic review specific databases were searched from 2016 to present:

- Cochrane Database of Systematic Reviews (CDSR) (Wiley): issue 3, March 2021
- Health Technology Assessment (HTA) database (CRD): 2016 to 31 March 2018
- KSR Evidence (www.ksrevidence.com): 2016 to 18 March 2021
- Epistemonikos (www.epistemonikos.org): 2016 to 18 March 2021
- International HTA database (INAHTA) (https://database.inahta.org): 2016 to 18 March 2021

The following guideline resources were searched from 2016 to present:

- Guidelines International Network (GIN) (guidelines.ebmportal.com): 2016 to 16 March 2021
- NHS Evidence (www.evidence.nhs.uk): 2016 to 18 March 2021
- NICE Guidance (www.nice.org.uk/guidance): 2016 to 18 March 2021
- ECRI Guidelines Trust (https://guidelines.ecri.org): 2016 to 16 March 2021

The following relevant organisation websites were scanned for guidelines from 2016 to present:

- British Society for Rheumatology (www.rheumatology.org.uk/practice-quality/guidelines/): 2016 to 12 March 2021
- America College of Rheumatology (www.rheumatology.org/Practice-Quality/Clinical-Practice-Guidelines/Rheumatoid-Arthritis): 2016 to 12 March 2021
- The Emerging European League Against Rheumatism (EULAR) Network (https://emeunet.eular.org/rheumatoid_arthritis.cfm): 2016 to 12 March 2021
- Canadian Rheumatology Association (http://rheum.ca/resources/publications/canadian-recommendations-for-management-of-ra/): 2016 to 12 March 2021

Targeted searches

To identify questions related to shared decision making and second-line therapies for rheumatoid interventions, targeted searches were undertaken in the following databases from 2016 to present:

- Embase (Ovid): 1974 to 17 March 2021
- MEDLINE and Epub Ahead of Print, In-Process, In-Data Review & Other Non-Indexed Citations, Daily and Versions (Ovid): 1946 to 17 March 2021

Full details of all search strategies are presented in Appendix 1.

Handling of citations

Identified references from all searches were downloaded into EndNote bibliographic management software for further assessment and handling.

2.4 Methods of study selection, quality assessment and data extraction

Study selection

A stepwise approach was used to identify the most recent and relevant evidence. Two reviewers independently screened the title and abstract of each record identified by the search and determined the potential relevance of each record. For potentially relevant records, the full paper was obtained, independently checked by two reviewers, and inclusion criteria applied. Any disagreements were resolved through discussion.

An evidence hierarchy was used to select the most appropriate study(ies) to populate the evidence tables. Where more than one study could provide evidence, the most relevant studies were selected using the following criteria: recency (most recent preferred), quality (highest quality preferred), representativeness (populations representative of the general target population preferred).

Data extraction

For studies which required data extraction, data were extracted by one reviewer and checked by another. Any disagreements were resolved by consensus.

Meta-analysis

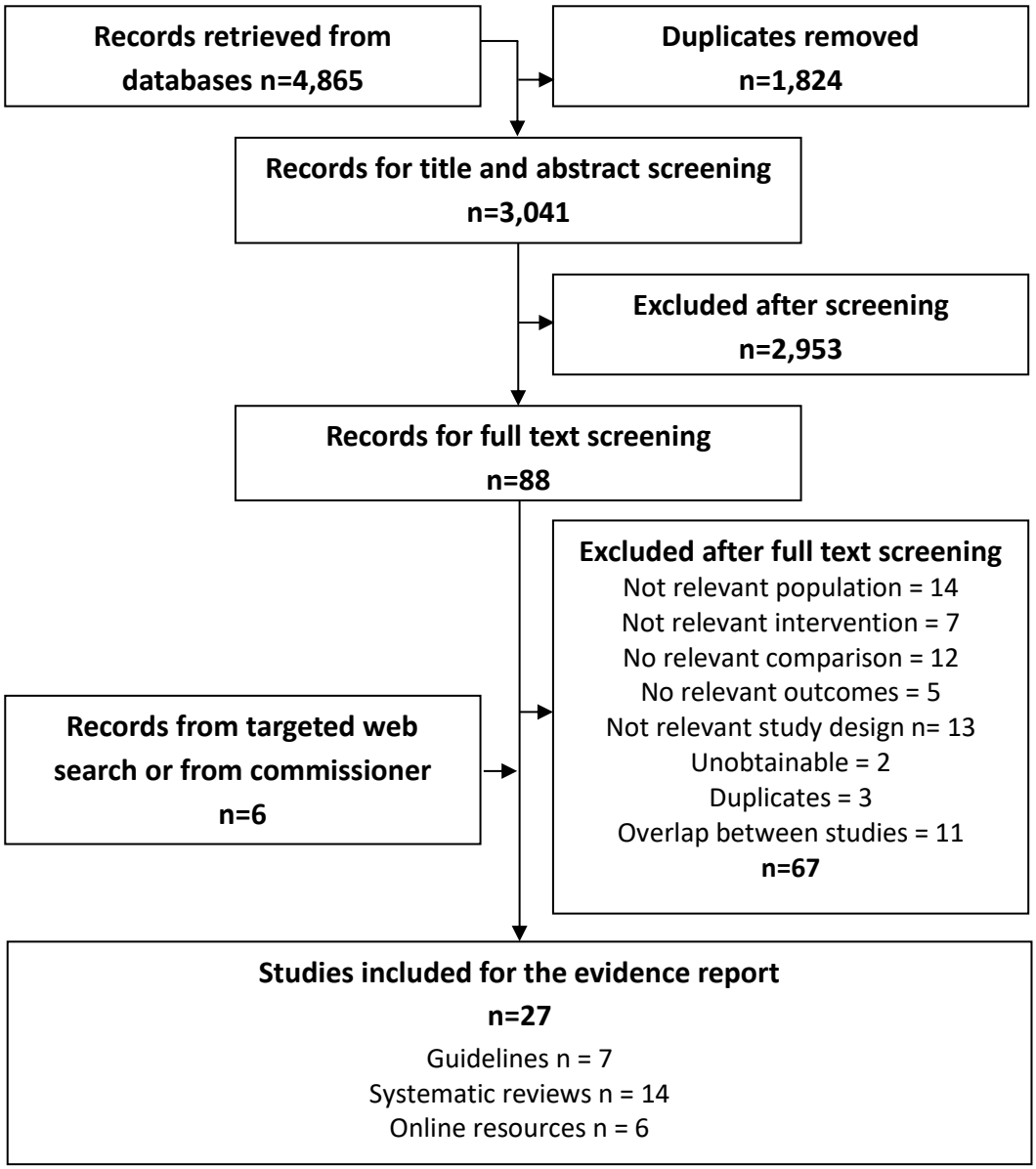
For systematic reviews that used methods of pooling the data judged as inappropriate or included the evidence for the drugs other than those of interest, one reviewer conducted random effects meta-analysis of the same data sets using RevMan 5.4.1. The pooled estimates are reported in the main body of the report and the individual study data for each meta-analysis are presented in Appendix 2.

3. RESULTS

3.1 LITERATURE SEARCH RESULTS AND INCLUSION ASSESSMENT

Searches were conducted in March 2021 to identify systematic reviews, health technology assessments or evidence-based guidelines. A total of 4,865 records were retrieved from the literature searches. After removal of duplicate records, 3,041 titles and abstracts were screened by two reviewers. After screening, 88 records were selected for further assessment from which 21 were selected as meeting the inclusion criteria. An additional six online resources were used to provide background information. A summary of the study selection process according to modified PRISMA reporting guidelines[1] is reported in Figure 1.

Figure 1: Study selection process



3.2 Overview of the evidence

Table 2 summarises the sources of evidence used to answer the eight FAQs in this report.

During the preparation of the report, evidence was available for various patient groups. This report includes evidence for those who were:

(1) pre-treated with at least one csDMARD (non-naïve)
(2) patients who had an insufficient response (IR) to the initial course(s) of csDMARD(s)
(3) patients with an IR to bDMARD(s)

The literature search identified six guidelines from various European countries: Germany[2], Spain[3, 4], France[5], UK[6] and recommendations published by the European League Against Rheumatism (EULAR).[6] One article provided recommendations on the use of biosimilars.[7] Five online resources were included to provide background information regarding the condition of interest, drugs and scores used in RA.[8-12]

For this report, 11 systematic reviews provided data for either bDMARDs or biosimilars (n=8[13-20]) or tsDMARDs only (n=3[21-23]) and three other articles included both bDMARDs and tsDMARDs.[24-26] One additional online resource included data for tsDMARDs which were not yet published.[27] Some data for all except one outcome (QoL) were reported.

Some systematic reviews failed to report the previous use of csDMARDs or any concomitant therapy. Whenever possible, the primary papers were checked for evidence of the use of csDMARDs before and during the study (see Table 2).

Seven resources (six systematic reviews and one online resource) included the data for patients which were, or were very likely, pre-treated with csDMARDs. [13-15, 21, 24, 25, 27] The articles provided the evidence for b/tsDMARDs ± csDMARDs regarding mortality (n=1[13]), risks or side effects of treatment (n=4[13, 15, 21, 27]) and cancer risk (n=5[13, 14, 24, 25, 27]). One systematic review focused on pregnant women compared to general population.[15] Other comparators included placebo ± csDMARDs[21, 24] or csDMARDs only.[13, 14, 24] One article reported the outcomes of patients with evidence of prior malignancy.[14] Two articles provided the evidence from either biologic registries[13] or long term extension studies (LTEs).[24]

The outcomes of RA patients with IR to csDMARDs were reported in two Cochrane reviews[17, 18] and four other systematic reviews.[16, 20, 22, 23] The evidence for b/tsDMARDs ± csDMARDs regarding symptom response and remission was covered by four reviews[16-18, 22], damage to joints by three[16-18] and joint function, risks and/or side effects or cancer risk by four articles.[16-18, 23] One review focused on symptom response, remission and risks and/or side effects of biosimilars in comparison with reference bDMARDs.[20] bDMARDs used as a monotherapy were investigated in one Cochrane review.[18] Most papers included csDMARDs[18, 22] or placebo ± csDMARDs[17, 23] as comparator whereas one systematic review compared treatment with bDMARDs to triple csDMARD therapy.[16]

RA patients with IR to bDMARDs were evaluated in one systematic review[26] as well as one Cochrane review.[19] The evidence for b/tsDMARDs ± csDMARDs regarding symptom response and risks and/or side effects of treatment was covered by two reviews[19, 26] whereas remission, damage to joints, joint function and cancer risk by one article.[19] The comparators where either csDMARDs alone[19] or placebo ± csDMARDs.[26]

Most of the systematic reviews provided the data of low or very low quality[13-16, 18, 20-26] with moderate or high quality evidence mostly from the Cochrane reviews.[17-20, 26]

Table 2: Evidence sources

Article	Population	Study ID	Intervention (±csDMARDs as concomitant therapy unless otherwise stated)	Comparator	FAQ1: background	FAQ 2: symptom response	FAQ 3: remission	FAQ 4: damage to joints	FAQ 5: joint function/ QoL	FAQ 6: survival	FAQ 7: risks or side effects	FAQ 8: cancer
b/tsDMARDs												
Guideline	all	AWMF 2018[2]	any	NA	✓							
		Daien 2019[5]			✓							
		NICE 2019[28]			✓							
		Smolen 2020[6]			✓							
		Spanish Society of Rheumatology 2019[3]			✓							
		Tornero-Molina 2020[4]	b/tsDMARDs		✓							
online	NA	Smolen 2014[8]	NA		✓							
		Singh 2011[12]			✓							
		Bruce 2005[11]			✓							
		WebMD 2020[9]			✓							
		Medicine Matters 2018[10]			✓							
	any	Pfizer 2021[27]	tsDMARD (TOF; (concomitant therapy unclear)	bDMARDs (TNFi)							✓	✓
SR	any*	de La Forest Divonne 2017[13]	bDMARDs (TNFi)	csDMARDs						✓	✓	✓
		Xie 2020a[14]	bDMARDs									✓
		Maneiro 2017[24]	bDMARD or tsDMARD (TOF)	csDMARDs ± placebo								✓
		Xie 2019[21]	tsDMARDs	placebo ± csDMARDs							✓	
		Xie 2020b[25]	csDMARDs, bDMARDs	NA								✓

Article	Population	Study ID	Intervention (±csDMARDs as concomitant therapy unless otherwise stated)	Comparator	FAQ1: background	FAQ 2: symptom response	FAQ 3: remission	FAQ 4: damage to joints	FAQ 5: joint function/ QoL	FAQ 6: survival	FAQ 7: risks or side effects	FAQ 8: cancer
			or tsDMARD (TOF)									
		Komaki 2017**[15]	bDMARDs (concomitant therapy unclear)	general population							✓	
	csDMARD-IR	Fleischmann 2017[16]	bDMARDs (TNFi)	triple csDMARD therapy (MTX, HCQ, SSZ)		✓	✓	✓	✓		✓	✓
		Pope 2020[22]	tsDMARDs (excl FTN; as monotherapy or combination with csDMARDs)	csDMARDs		✓	✓					
		Singh 2016b[18]	bDMARDs (monotherapy)			✓	✓	✓	✓		✓	✓
		Singh 2016a[17]	bDMARDs	placebo ± csDMARDs		✓	✓	✓	✓		✓	✓
		Wang 2020[23]	tsDMARD (excl FTN)						✓		✓	✓
	bDMARD-IR	Singh 2017[19]	bDMARDs	csDMARDs		✓	✓		✓		✓	✓
		Sung & Lee 2021[26]	bDMARDs (non-TNFi) or tsDMARDs	placebo ± csDMARDs		✓					✓	
bsDMARDs												

Article	Population	Study ID	Intervention (±csDMARDs as concomitant therapy unless otherwise stated)	Comparator	FAQ1: background	FAQ 2: symptom response	FAQ 3: remission	FAQ 4: damage to joints	FAQ 5: joint function/ QoL	FAQ 6: survival	FAQ 7: risks or side effects	FAQ 8: cancer
Guideline	all	Kay 2018[7]	bsDMARDs	NA	✓							
SR	csDMARD -IR	Tanaka 2021[20]	biosimilars of bDMARDs (concomitant therapy unclear)	bDMARDs		✓	✓				✓	

* patients who were pre-treated with csDMARDs, most commonly MTX; ** include pregnant women only

bsDMARD = biosimilar DMARD; csDMARD = conventional synthetic DMARD; DMARD = disease-modifying antirheumatic drug; excl = excluding; HCQ = Hydroxychloroquine; IR = inadequate response; MTX = Methotrexate; NA = not applicable; QoL = Quality of life; SR = systematic review; SSZ = Sulfasalazine; TNFi = tumour necrosis factor inhibitors; TOF = tofacitinib; tsDMARD = targeted synthetic DMARD

3.3 FAQ1: What does the treatment involve?

This section includes background information on the treatments of interest (i.e. csDMARDs, bDMARDs and tsDMARDs) and recommendations for practice for patients with RA at different stages of the treatment pathway. The current treatment pathway for patients in Germany is also presented.

The information on the treatments of interest is provided below (Table 3).

Table 3: Description of conditions and treatment options

<table>
<tr><th colspan="2">Rheumatoid arthritis (RA)</th></tr>
<tr><td colspan="2">RA is a systemic inflammatory condition characterised by inflammation of the synovial lining of the joints, tendons, and periarticular structures. Lack of treatment can lead to joint destruction, functional limitation, severe disability, and reduction in health-related QoL.

Treatment options include non-steroidal anti-inflammatory drugs (NSAIDs) and disease-modifying drugs (glucocorticoids, cs/b/tsDMARDs).[17]</td></tr>
<tr><th colspan="2">Disease-modifying antirheumatic drugs (DMARDs)</th></tr>
<tr><td colspan="2">DMARDs are medications that work by suppressing and/or reducing the activity of the immune system and are widely used in patients with RA. They aim to reduce the symptoms and slow down the progression of the disease.[9]

DMARDs can be administered orally, subcutaneously, or intravenously in various doses. They are often used in combinations and/or in conjugation with other medication such as NSAIDs or glucocorticoids to provide faster relief of ongoing symptoms.[9]

The most recent classification of DMARDs includes two major classes: synthetic (conventional and targeted) and biological DMARDs.[8]</td></tr>
<tr><th>Synthetic (or chemical)</th><th>Biological</th></tr>
<tr><th>csDMARDs</th><td rowspan="3">Biological original DMARDs are medications that are produced using molecular biology techniques which target a specific molecule on the cell surface to control the inflammation process. There are several types of drugs with various targets within the body:

• tumour necrosis factor inhibitors (TNFi) or anti-TNF:
○ adalimumab (ADA);
○ certolizumab pegol (CTZ);
○ etanercept (ETN);
○ golimumab (GOL);
○ infliximab (IFX);

• Interleukin 6 receptor inhibitors:
○ sarilumab (SRL);
○ tocilizumab (TOC);</td></tr>
<tr><td>Conventional synthetic DMARDs (developed conventionally with a molecular target identified subsequently) include:

• MTX
• Leflunomide
• Sulfasalazine (SSZ)
• Hydroxychloroquine (HCQ).[8, 9]</td></tr>
<tr><th>tsDMARDs</th></tr>
<tr><td>Targeted synthetic DMARDs (or janus kinase/JAK inhibitors) were developed by modelling methods to inhibit specific targets, i.e. the janus kinase family of enzymes, and include:

• tofacitinib (TOF);
• baricitinib (BARI);
• upadacitinib (UPA)</td></tr>
</table>

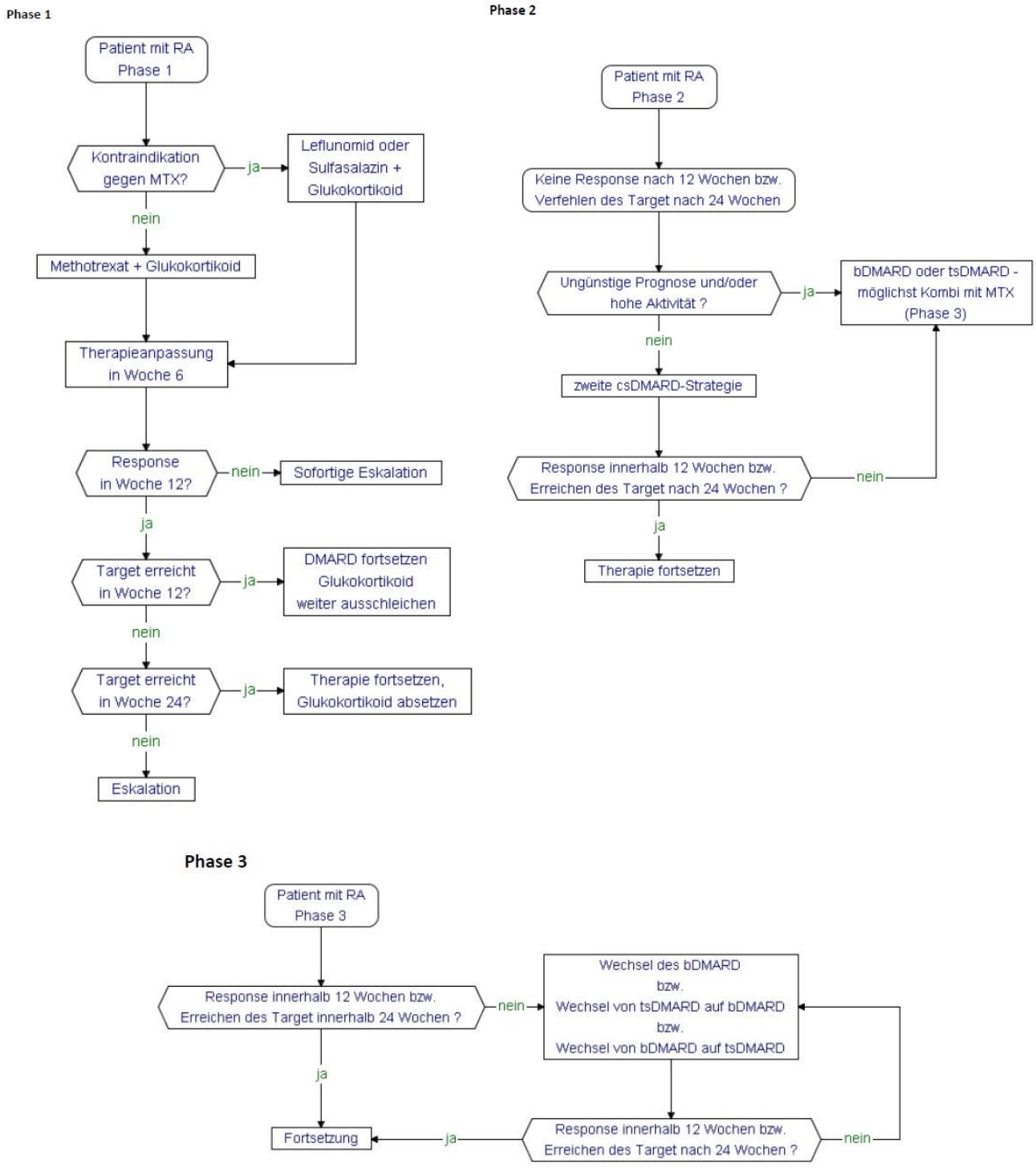
• filgotinib (FTN).[8, 9]	• Interleukin 1 receptor inhibitor: anakinra (ANK); • T cell inhibitor: abatacept (ABA) • B cell inhibitor: rituximab (RTX). SRL, TOC, ANK, ABA and RTX are referred as non-TNFi throughout the report. Some bDMARDs can be replaced by biosimilars (bsDMARDs) i.e. a very similar, but not exact copy of the biological drug that is already approved.[8, 9]

The recommendations from the guidelines can be summarised as follows:

- Therapy with DMARDs should start as soon as possible after RA diagnosis (preferably within 12 weeks after symptom onset) to achieve and maintain remission (and low disease activity)[2, 5, 6, 28]
- Frequent monitoring (every one to three months) is required; if no improvement is seen after three months of starting therapy or if after six months the goal is not achieved, therapy should be changed[2, 5, 6, 28]
- MTX (csDMARDs) should be part of the first line therapy; if MTX cannot be used (contraindication or early intolerance) leflunomide or SSZ should be considered.[2, 5, 6, 28] In addition, glucocorticoids can be administered alongside csDMARDs with quick tapering (after three or three to six months) or NSAIDs[2, 3, 5, 6, 28]
- If the treatment target is not achieved with the first csDMARD strategy, other csDMARDs should be considered in the absence of poor prognostic factors.[2, 3, 5, 6, 28] If two csDMARDs therapies failed, a b/tsDMARD therapy should be used.[2, 5, 6] If poor prognostic factors are present, a bDMARD or a tsDMARD should be added (including biosimilars) in combination with MTX.[2-6, 28]
- In case of b/tsDMARD failure (IR or intolerance), treatment with another bDMARD or tsDMARD should be considered[2, 3, 5, 6]

The treatment pathway for patients in Germany incorporating the above recommendations is presented in Figure 2.[2] The pathway is consistent with the updated recommendations published by the EULAR.[6]

Figure 2: The summary of treatment pathway for patients with RA



3.4 FAQ2: Will it help my symptoms (response)?

This section includes information on the symptom response (measured by ACR250 or EULAR criteria) for cs/bDMARDs-IR patients treated with b/tsDMARDs (in combination with csDMARDs or as monotherapy). Additional evidence for bsDMARDs is also presented.

Background information and definitions

For symptom response, studies often used ACR20/50/70 response criteria which are defined as "*at least a 20%, 50%, or 70% improvement in the number of tender and swollen joints, and at least a 20%, 50%, or 70% improvement in three of the following five criteria: patient global or pain visual analogue scale (VAS), physician global VAS, HAQ score and acute-phase reactant value (erythrocyte sedimentation rate [ESR] or C-reactive protein [CRP] levels)*".[10] The studies used EULAR response criteria which are based on the Disease Activity Score 28 (DAS28) index.[10]

Results

No evidence for symptom response was reported in patients pre-treated with csDMARDs.

Tables 4 and 5 report the results for symptom response measured by ACR50 in patients with IR to csDMARDs or bDMARDs, respectively. Note that additional results for e.g., ACR20 or ACR70 are present in some of the articles.

Patients with csDMARD-IR

csDMARD-IR patients reported significantly better symptom response (as measured by ACR50) following the treatment with bDMARDs (± csDMARDs or as monotherapy) in comparison to placebo ± csDMARDs or csDMARDs only (combination therapy: risk ratio [RR] 2.71, 95% Confidence Interval [CI] 2.36 to 3.10; monotherapy: RR 1.54, 95%CI 1.14 to 2.08; Table 4).[17, 18] Similarly, significantly better symptom response was reported following the treatment with tsDMARDs (± csDMARDs) in comparison to csDMARDs only (Table 4).[22] The improvements are clinically meaningful.[17, 18]

No difference was reported for ACR50 or EULAR good/moderate response for the comparison between bDMARDs (TNFi only; ± csDMARDs) and triple csDMARDs therapy in patients with IR to csDMARDs (Table 4).[16] No difference in ACR50 between bsDMARDs and reference bDMARDs was reported at 2.76 and 5.5 months for patients with IR to csDMARD, however, a marginal difference in favour of biosimilars was reported for ACR50 at one year (RR 1.10, 95%CI 1.02 to 1.09; Table 4).[20] It is unclear from the article if the improvement is clinically meaningful.[20]

Patients with bDMARD-IR

Patients with IR to bDMARDs achieved significantly better symptom response, in comparison to patients receiving csDMARDs only, following the treatment with bDMARDs (± csDMARDs; RR 4.07, 95%CI 2.76 to 5.99; Table 5).[19] Similarly, the same patient population achieved significantly better symptom response, in comparison to patients receiving placebo ± csDMARDs, following the treatment with b/tsDMARDs (± csDMARDs; bDMARDs

[non-TNFi]: odds ratio [OR] 4.08, 95%CI 2.86 to 6.22; tsDMARDs: OR 4.31, 95%CI 2.85 to 6.54; Table 5).[26] No difference was reported for the comparison between tsDMARDs and bDMARDs (non-TNFi) in regards to symptom response.[26]

The improvement is clinically meaningful for bDMARDs ± csDMARDs[19] and unclear from the article for tsDMARDs ± csDMARDs.[26]

Table 4: FAQ 2 – symptom response (patients with IR to csDMARD)

Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimate with 95% CIs , e.g. mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event n/N (nr of patients per 100)				
ACR50*							
Singh 2016a[17]	50 RCTs	Unclear (range 3 to 24 months)	bDMARDs ± csDMARDs: 4445/12212 (36.4 per 100)	placebo ± csDMARDs: 904/6416 (14.1 per 100)	RR = 2.71 (95%CI 2.36 to 3.10)	Moderate (inconsistency)	Difference in favour of intervention but data of moderate quality ⇗
Singh 2016b[18]	10 RCTs	Unclear (range 1 to 24 months)	bDMARDs (mono): 883/2150 (41.1 per 100)	csDMARDs: 421/1454 (29 per 100)	RR = 1.54 (95%CI 1.14 to 2.08)		
Pope 2020[22]	11 RCTs	2.76 months^	tsDMARDs ± csDMARDs: NR	csDMARDs: NR	OR = 3.6 to 4.8^^	Low (unclear risk of bias)	Difference in favour of intervention but data of low quality ⇗
			tsDMARDs (mono): NR		OR = 2.7 to 3.9^^		
		5.5 months^	tsDMARDs ± csDMARDs: NR		OR = 3.0 to 4.5^^		
Fleischmann 2017[16]	23 RCTs	3 months	bDMARDs (TNFi) ± csDMARDs: NR	Triple csDMARDs: NR	OR = 0.55 (95%CrI 0.18 to 1.61)	Low (mostly unclear risk of bias)	No difference shown ⇔
	21 RCTs	6 months			OR = 0.6 (95%CrI 0.13 to 2.83)		
	8 RCTs	1 year			OR = 0.5 (95%CrI 0.07 to 3.61)		
	3 RCTs	2 years			OR = 0.65 (95%CrI 0 to347.7)		

Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimate with 95% CIs , e.g. mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event n/N (nr of patients per 100)				
Tanaka 2021[20]	7 RCTs	2.76 months^	bsDMARDs: 450/1144 (39.3 per 100)	bDMARDs: 438/1136 (38.6 per 100)	RR = 1.03 (95%CI 0.93 to 1.13)	Moderate (moderate risk of bias and imprecision)	
	12 RCTs	5.5 months^	bsDMARDs: 1139/2368 (48.1 per 100)	bDMARDs: 1095/2362 (46.4 per 100)	RR = 1.04 (95%CI 0.98 to 1.10)		
	6 RCTs	1 year^	bsDMARDs: 633/1235 (51.3 per 100)	bDMARDs: 567/1208 (46.9 per 100)	RR = 1.10 (95%CI 1.02 to 1.19)		Difference in favour of intervention but data of low quality ⇗
EULAR good/moderate**							
Fleischmann 2017[16]	7 RCTs	3 months	bDMARDs (TNFi) ± csDMARDs: NR	Triple csDMARDs: NR	OR = 0.94 (95%CrI 0.07 to 13.54)	Low (mostly unclear risk of bias and incoherence)	No difference shown ⇔
	7 RCTs	6 months			OR = 0.62 (95%CrI 0.03 to 14.41)		

*only the data for ACR50 is reported in the table, however, some studies report the results for ACR20 and/or ACR70
**only the data for EULAR good/moderate response is reported in the table, however, the study reports the results for EULAR good response separately
^recalculated by the reviewer for consistency
^^the range of results is provided (i.e. OR without 95%CrI) due to lack of pooling of the results by the study authors; data per drug and dose is available in the article
ACR = American College of Rheumatology; bDMARDs = biological DMARD; bsDMARDs = biosimilar DMARDs; csDMARDs = conventional synthetic DMARDs; CrI = credible intervals; DMARD = disease-modifying antirheumatic drug; MD = mean difference; NR = not reported; OR = odds ratio; RCT = randomised controlled trial; RR = relative risk/risk ratio; TNFi = tumour necrosis factor inhibitors; TOF = tofacitinib; tsDMARDs = targeted synthetic DMARDs

Table 5: FAQ 2 – symptom response (patients with IR to bDMARD)

Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimate with 95% CIs , e.g. mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			P Proportion with event n/N (nr of patients per 100)				
ACR50*							
Singh 2017[19]	3 RCTs	Unclear (range 3 to 24 months)	bDMARDs ± csDMARDs: 200/955 (20.9 per 100)	csDMARDs: 27/524 (5.2 per 100)	RR = 4.07 (95%CI 2.76 to 5.99)	High (low risk of bias)	Difference in favour of intervention ⇧
Sung 2021[26]	RCTs (n = NR)	2.76 months^	bDMARDs (non-TNFi) ± csDMARDs: NR	placebo ± csDMARDs: NR	OR = 4.08 (95%CrI 2.86 to 6.22)	Moderate (moderate risk of bias)	Difference in favour of intervention but data of moderate quality ⇗
	RCTs (n = NR)		tsDMARDs ± csDMARDs: NR		OR = 4.31 (95%CrI 2.85 to 6.54)		
	RCTs (n = NR)		tsDMARDs ± csDMARDs: NR	bDMARDs (non-TNFi) ± csDMARDs: NR	OR = 1.06 (95%CrI 0.58 to 1.81)		No difference shown ⇔

*only the data for ACR50 is reported in the table, however, some studies report the results for ACR20 and/or ACR70
^recalculated by the reviewer for consistency
^^the range of results is provided (i.e. OR without 95%CI) due to lack of pooling of the results by the study authors
ACR = American College of Rheumatology; bDMARDs = biological DMARD; bsDMARDs = biosimilar DMARDs; CrI = credible interval; csDMARDs = conventional synthetic DMARDs; DMARD = disease-modifying antirheumatic drug; NR = not reported; OR = odds ratio; RCT = randomised controlled trial; TNFi = tumour necrosis factor inhibitors; tsDMARDs = targeted synthetic DMARDs

3.5 FAQ3: Will it help maintain remission of my disease?

The section summarises the evidence related to remission of RA (measured by DAS28 or Boolean remission) for cs/bDMARD-IR patients treated with b/tsDMARDs ± csDMARDs. Additional evidence for bsDMARDs is also presented.

Background information and definitions

For remission, studies most often reported DAS and/or DAS28, i.e., combined index providing a measure of disease activity including the number of swollen and tender joints of possible 28 and either ESR or CRP levels (i.e., DAS28-ESR/CRP). DAS28 (range score 0 to 9.4) >5.1 implies active disease, ≤3.2 low disease activity and <2.6 remission (<1.6 for DAS). The Boolean-based definition of remission requires that the patient satisfies all of the following: swollen and tender joint count ≤1, CRP ≤1 mg/dl and patient global assessment (PGA) ≤1 (on 0-10 scale).[10]

Results

No evidence for remission was reported in patients pre-treated with csDMARDs.

Tables 6 and 7 report the results for remission measured by different version of DAS28 or Boolean remission in patients with IR to csDMARDs or bDMARDs, respectively. Note that additional results e.g. DAS28-ESR are present in one article.[16]

Patients with csDMARD-IR

Significantly more patients with IR to csDMARDs reported remission (measured by DAS <1.6, DAS28 <2.6) following treatment with bDMARDs (± csDMARDs) in comparison to placebo ± csDMARDs (RR 2.81, 95%CI 2.23 to 3.53; Table 6).[17] For the same population, patients treated with tsDMARDs (± csDMARDs) reported significantly better symptom response (measured by DAS28-CRP) when compared to csDMARDs only (OR 3.8 to 6.4; Table 6).[22] No difference was reported for remission between bDMARDs used as a monotherapy and csDMARDs (difference at borderline of significance; Table 6).[18]

The improvement is clinically meaningful for bDMARDs ± csDMARDs[17], but unclear from the article for tsDMARDs ± csDMARDs.[22]

For csDMARD-IR patients, no difference was shown for DAS28-ESR/CRP remission for the comparison between bDMARDs (TNFi only; ± csDMARDs) and triple csDMARDs therapy[16] or Boolean remission for the comparison between bsDMARDs and reference bDMARDs (Table 6).[20]

Patients with bDMARD-IR

Significantly more RA patients with IR to bDMARDs reported remission (measured by DAS <1.6 or DAS28 <2.6) following treatment with bDMARDs (± csDMARDs) in comparison to csDMARDs only (imprecise data; RR 20.73, 95%CI 4.13 to 104.16; Table 7).[19] No results were available for tsDMARDs for the same population. The improvement is clinically meaningful.[19]

Table 6: FAQ 3 – remission (patients with IR to csDMARD)

Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimate with 95% CIs , e.g. mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event n/N (nr of patients per 100)				
DAS <1.6 or DAS28 <2.6							
Singh 2016a[17]	21 RCTs	Unclear (range 3 to 24 months)	bDMARDs ± csDMARDs: 1369/5692 (24.1 per 100)	placebo ± csDMARDs: 307/2999 (10.2 per 100)	RR = 2.81 (95%CI 2.23 to 3.53)	Moderate (inconsistency)	Difference in favour of intervention but data of moderate quality ⇗
Singh 2016b[18]	4 RCTs	Unclear (range 1 to 24 months)	bDMARDs (mono): 128/665 (19.2 per 100)	csDMARDs: 83/539 (15.4 per 100)	RR = 1.55 (95%CI 0.94 to 2.53)	Low (imprecision and inconsistency)	No difference shown ⇔
DAS28-CRP							
Pope 2020[22]	11 RCTs	2.76 months^	tsDMARDs ± csDMARDs: NR	csDMARDs: NR	OR = 3.8 to 6.4^^	Low (unclear risk of bias)	Difference in favour of intervention but data of low quality ⇗
		5.5 months^	tsDMARDs ± csDMARDs: NR		OR = 1.8 to 6.5^^		
DAS28-ESR/CRP*							
Fleischmann 2017[16]	13 RCTs	6 months	bDMARDs (TNFi) ± csDMARDs: NR	Triple csDMARDs: NR	OR = 0.52 (95%CrI 0.11 to 2.56)	Low (mostly unclear risk of bias and imprecision)	No difference shown ⇔
	12 RCTs		Triple csDMARDs: NR	bDMARDs (TNFi) ± csDMARDs: NR	MD = 0.27 (95%CrI -1.10 to 1.65)		

Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimate with 95% CIs , e.g. mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event n/N (nr of patients per 100)				
Boolean remission							
Tanaka 2021[20]	2 RCTs	2.76 months^	bsDMARDs: 17/623 (2.7 per 100)	bDMARDs: 15/622 (2.4 per 100)	RR = 1.71 (95%CI 0.24 to 12.04)	Very low (high risk of bias and imprecision)	No difference shown ⇔
	3 RCTs	5.5 months^	bsDMARDs: 35/738 (4.7 per 100)	bDMARDs: 34/740 (4.6 per 100)	RR = 1.03 (95%CI 0.66 to 1.62)		
	2 RCTs	1 year^	bsDMARDs: 55/562 (9.8 per 100)	bDMARDs: 51/549 (9.3 per 100)	RR = 1.04 (95%CI 0.73 to 1.50)		

*only the data for DAS28-ESR/CRP is reported in the table, however, the study report the results for DAS28-ESR separately
^recalculated by the reviewer for consistency
^^the range of results is provided (i.e. OR without 95%CrI) due to lack of pooling of the results by the study authors; data per drug and dose is available in the article
bDMARDs = biological DMARD; CRP = C-reactive protein; CrI = credible interval; csDMARDs = conventional synthetic DMARDs; DAS = Disease Activity Score; DMARD = disease-modifying antirheumatic drug; ESR = erythrocyte sedimentation rate; MD = mean difference; NR = not reported; OR = odds ratio; RCT = randomised controlled trial; RR = risk ratio; TNFi = tumour necrosis factor inhibitors; TOF = tofacitinib; tsDMARDs = targeted synthetic DMARDs

Table 7: FAQ 3 – remission (patients with IR to bDMARD)

Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimate with 95% CIs , e.g. mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event n/N (nr of patients per 100)				
DAS <1.6 or DAS28 <2.6							
Singh 2017[19]	2 RCTs	Unclear (range 3 to 24 months)	bDMARDs ± csDMARDs: 67/644 (10.4 per 100)	csDMARDs: 1/315 (0.7 per 100)	RR = 20.73 (95%CI 4.13 to 104.16)	Moderate (low risk of bias, but imprecise)	Difference in favour of intervention but imprecise data ⇗
*only the data for DAS28-ESR/CRP is reported in the table, however, the study reports the results for DAS28-ESR separately bDMARDs = biological DMARD; csDMARDs = conventional synthetic DMARDs; DAS = Disease Activity Score; DMARD = disease-modifying antirheumatic drug; OR = odds ratio; RCT = randomised controlled trial;							

3.6 FAQ4: How will treatment prevent damage to my joints? (i.e., mobility, functionality)

The section summarises the evidence related to joint damage in patients with RA (measured by the change in joint erosion and space narrowing, mTSS) for csDMARD-IR patients treated with bDMARDs (TNFi only) ± csDMARDs.

Background information and definitions

Damage to the joints was reported as a change in joint erosion and space narrowing (radiographic measurements). Modified total Sharp/van der Heijde score (mTSS) score is a standard scoring method for analysing radiographs to assess disease progression with a range of 0 (no damage) to 448 (severe damage).[10] It is likely that the smallest detectable difference of 5 points can be interpreted as the minimal clinically important difference.[29] No information is available on the clinically important difference for the change in space narrowing and joint erosion.

Results

No evidence for symptom response was reported in patients pre-treated with csDMARDs or with IR to bDMARDs.

Table 8 reports the results for joint damage measured by the change in mTSS, joint erosion or joint space narrowing in patients with IR to csDMARDs.

Patients with csDMARD-IR

For patients with IR to csDMARDs, a significant decrease in the change of mTSS was reported in favour of bDMARDs (TNFi only; ± csDMARDs or as monotherapy) in comparison to placebo ± csDMARDs (combination therapy: mean difference [MD] -2.61, 95%CI -4.08 to -1.14; monotherapy: MD -4.34, 95%CI -7.56 to -1.12; Table 8).[17, 18] No results were available for tsDMARDs for the same population. It is unlikely that the differences are clinically meaningful.[17, 18]

No difference in joint damage (change in mTSS, joint erosion or space narrowing) was reported for the comparison of bDMARDs (TNFi; ± csDMARDs) and triple csDMARD therapy in patients with IR to csDMARD (Table 8).[16]

Table 8: FAQ4 – damage to joints (patients with IR to csDMARD)

Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimate with 95% CIs , e.g. mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event n/N (nr of patients per 100)				
ΔmTSS (radiographic progression)							
Singh 2016a[17]	7 RCTs	Unclear (range 3 to 24 months)	bDMARDs (TNFi) ± csDMARDs: NA/1532	placebo ± csDMARDs: NA/866	MD = -2.61 (95%CI -4.08 to -1.14)	Moderate (inconsistency)	Difference in favour of intervention but inconsistent data ⇗
Singh 2016b[18]	1 RCT	Unclear (range 1 to 24 months)	bDMARDs (TNFi; mono): NA/223	csDMARDs: NA/228	MD = -4.34 (95%CI -7.56 to -1.12)	Moderate (imprecision)	
Fleischmann 2017[16]	8 RCTs	6 months	Triple csDMARDs: NR	bDMARDs (TNFi) ± csDMARDs: NR	MD = 0.42 (95%CrI -1.37 to 2.18)	Low (mostly unclear risk of bias and high heterogeneity)	No difference shown ⇔
	6 RCTs	1 year			MD = 2.08 (95%CrI -4.79 to 8.9)		
	3 RCTs	2 years			MD = 3.22 (95%CrI -3.5 to 10)		
Δjoint erosion							
Fleischmann 2017[16]	8 RCTs	6 months	Triple csDMARDs: NR	bDMARDs (TNFi) ± csDMARDs: NR	MD = 0.26 (95%CrI -1.60 to 2.17)	Low (mostly unclear risk of bias and high heterogeneity)	No difference shown ⇔
	5 RCTs	1 year			MD = 0.92 (95%CrI -5.5 to 7.33)		
	unclear	2 years			MD = 1.54 (95%CrI -4.9 to 7.96)		

Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimate with 95% CIs , e.g. mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event n/N (nr of patients per 100)				
Δjoint space narrowing							
Fleischmann 2017[16]	8 RCTs	6 months	Triple csDMARDs: NR	bDMARDs (TNFi) ± csDMARDs: NR	MD = 0.16 (95%CrI -0.48 to 0.81)	Low (mostly unclear risk of bias and high heterogeneity)	No difference shown ⇔
	5 RCTs	1 year			MD = 1.25 (95%CrI -4.35 to 6.86)		
	3 RCTs	2 years			MD = 1.66 (95%CrI -4.82 to 8.10)		

bDMARDs = biological DMARD; CrI = credible interval; csDMARDs = conventional synthetic DMARDs; DMARD = disease-modifying antirheumatic drug; MD = mean difference; NR = not reported; RCT = randomised controlled trial; TNFi = tumour necrosis factor inhibitors; Δ = change in score

3.7 FAQ5: How will treatment impact my joint function and/or quality of life?

The section summarises the evidence related to joint function and/or pain in patients with RA (measured by HAQ or HAQ-DI, PGA, and VAS) for cs/bDMARD-IR patients treated with b/tsDMARDs ± csDMARDs. Results for QoL in any population were not available.

Background information and definitions

Joint function was measured with Health Assessment Questionnaire (HAQ; range 0 to 3 with higher = worse) which "*assesses all five dimensions of health outcome which includes drug side effects and medical costs, as well as supplemental sections on demographics, lifestyle and health behaviours*".[11] HAQ-Disability Index (HAQ-DI), i.e. the physical function scale of HAQ, includes 20 items in eight categories representing activities including dressing, eating, walking, grip, and reach.[10] An improvement of 0.22 points or more is defined as the minimal clinically important difference.[23] Pain and PGA was measured using VAS.

Results

No evidence for the joint function was reported in patients pre-treated with csDMARDs. No evidence on the patient's QoL was reported for any population (pre-treated or cs/bDMARD-IR).

Tables 9 and 10 report the results for joint function measured by the change in HAQ, HAQ-DI, PGA or pain in patients with IR to csDMARDs or bDMARDs, respectively.

Patients with csDMARD-IR

For patients with IR to csDMARDs, a significant decrease in change of HAQ or HAQ-DI was reported in favour of bDMARDs (± csDMARDs or as monotherapy)[17, 18] and tsDMARDs (± csDMARDs)[23] in comparison to placebo ± csDMARDs or csDMARDs only (bDMARDs combination therapy: MD -0.25, 95%CI -0.28 to -0.22; bDMARDs monotherapy: MD -0.27, 95%CI -0.4 to -0.14; tsDMARDs: MD -0.31, 95%CI -0.34 to -0.28; Table 9). All differences were clinically meaningful.[17, 18, 23]

No difference was reported for the change in HAQ-DI, PGA and pain for the comparison of bDMARDs (TNFi; ± csDMARDs) and triple csDMARD therapy in patients with IR to csDMARD (Table 9).[16]

Patients with bDMARD-IR

For patients with IR to bDMARDs, a significant decrease in change of HAQ was reported in favour of bDMARDs (± csDMARDs) in comparison to csDMARDs only (MD -0.29, 95%CI -0.36 to -0.21; Table 10).[19] No results were available for tsDMARDs for the same population. The difference was clinically meaningful.[19]

Table 9: FAQ5 – joint function (patients with IR to csDMARDs)

Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimate with 95% CIs , e.g. mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event n/N (nr of patients per 100)				
ΔHAQ score (function)							
Singh 2016a[17]	29 RCTs	Unclear (range 3 to 24 months)	bDMARDs ± csDMARDs: NA/7069	placebo ± csDMARDs: NA/3334	MD = -0.25 (95%CI -0.28 to -0.22)	Moderate (inconsistency)	Difference in favour of intervention but data of moderate quality ⇗
Singh 2016b[18]	6 RCTs	Unclear (range 1 to 24 months)	bDMARDs (mono): NA/918	csDMARDs: NA/913	MD = -0.27 (95%CI -0.40 to -0.14)		
ΔHAQ-DI							
Wang 2020[23]	12 RCTs	Range 0.92 to 5.52 months^	tsDMARDs ± csDMARDs: NR	placebo ± csDMARDs: NR	MD = -0.31 (95%CI -0.34 to -0.28)	Very low (high risk of bias and imprecision)	Difference in favour of intervention but data of very low quality ⇗
Fleischmann 2017[16]	RCTs (n = NR)	6 months	Triple csDMARDs: NR	bDMARDs (TNFi) ± csDMARDs: NR	MD = 0.07 (95%CI -0.17 to 0.31)	Low (mostly unclear risk of bias and heterogeneity)	No difference shown ⇔
ΔPGA							
Fleischmann 2017[16]	RCTs (n = NR)	6 months	Triple csDMARDs: NR	bDMARDs (TNFi) ± csDMARDs: NR	MD = 5.29 (95%CI -3.66 to 14.21)	Low (mostly unclear risk of bias and imprecision)	No difference shown ⇔
Δpain							
Fleischmann 2017[16]	RCTs (n = NR)	6 months	Triple csDMARDs: NR	bDMARDs (TNFi) ± csDMARDs: NR	MD = 3.15 (95%CI -3.49 to 9.78)	Low (mostly unclear risk of bias and	No difference shown

Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimate with 95% CIs , e.g. mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event n/N (nr of patients per 100)				
						imprecision)	⇔
bDMARDs = biological DMARD; csDMARDs = conventional synthetic DMARDs; DMARD = disease-modifying antirheumatic drug; HAQ = Health Assessment Questionnaire; MD = mean difference; NA = not available; NR = not reported; OR = odds ratio; PGA = patient global assessment; RCT = randomised controlled trial; TNFi = tumour necrosis factor inhibitors; TOF = tofacitinib							

Table 10: FAQ5 – joint function (patients with IR to bDMARDs)

Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimate with 95% CIs , e.g. mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event n/N (nr of patients per 100)				
ΔHAQ							
Singh 2017[19]	2 RCTs	Unclear (range 6 to 24 months)	bDMARDs ± csDMARDs: NA/617	csDMARDs: NA/364	MD = -0.29 (95%CI -0.36 to -0.21)	High (low risk of bias and imprecision)	Difference in favour of intervention ⇗
bDMARDs = biological DMARD; csDMARDs = conventional synthetic DMARDs; DMARD = disease-modifying antirheumatic drug; HAQ = Health Assessment Questionnaire; NA = not available; MD = mean difference; RCT = randomised controlled trial; Δ = change in score							

3.8 FAQ6: WILL THE TREATMENT PROLONG MY LIFE EXPECTANCY?

This section summarises the evidence related to mortality of csDMARD pre-treated RA patients treated with bDMARDs (TNFi) in combination with csDMARDs. No results for life expectancy of patients were available for any population.

Results

No evidence for mortality was reported in patients with IR to cs/bDMARDs.

Patients pre-treated with csDMARDs

The only systematic review reporting on mortality of csDMARD pre-treated RA patients managed with bDMARDs (TNFi only; ± csDMARDs) utilised the observational data from the registries (Table 11).[13] The pooled results showed a decrease in mortality of RA patients receiving bDMARDs (TNFi; ± csDMARDs) in comparison to csDMARDs, however, the data are of very low quality (RR 0.6, 95%CI 0.38 to 0.94). No results were available for tsDMARDs for the same population. It is unclear from the article if the improvement is clinically meaningful.[13]

Table 11: FAQ 6 – mortality (csDMARD pre-treated population only)

Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimate with 95% CIs , e.g. mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event n/N (nr of patients per 100)				
Mortality							
de La Forest Divonne 2017[13]	5 observational studies (registries)	NR	bDMARDs (TNFi) ± csDMARDs: 1266/26000 (4.7 per 100)	csDMARDs: 736/15579 (4.7 per 100)	RR = 0.60 (95%CI 0.38 to 0.94)	Very low (high risk of bias and high heterogeneity)	Difference in favour of intervention but data of very low quality ⇗

bDMARDs = biological DMARD; csDMARDs = conventional synthetic DMARDs; DMARD = disease-modifying antirheumatic drug; NR = not reported; RCT = randomised controlled trial; RR = risk ratio; TNFi = tumour necrosis factor inhibitors

3.9 FAQ7: What are the risks or side effects (i.e., cardiovascular risk)?

The section summarises the evidence related to risks and side effects of treatment with b/tsDMARDs in patients with RA (all populations). Additional evidence for bsDMARDs is also presented.

Results

Tables 12, 14 and 15 report the results for risks and/or side effects of treatments of interest in patients pre-treated with csDMARDs, with IR to csDMARDs or bDMARDs, respectively. Table 13 reports the results for the same outcome in pregnant women assumed to be pre-treated with csDMARDs.

Patients pre-treated with csDMARDs

Patients pre-treated with csDMARDs reported a significant decrease in cardiovascular events (CVEs) in favour of bDMARDs (TNFi; ± csDMARDs) when compared to patients receiving csDMARDs only (RR 0.62, 95%CI 0.44 to 0.88; Table 12).[13] No other outcomes were reported for this population of patients receiving bDMARDs (± csDMARDs).

No difference was reported for CVEs, major adverse cardiovascular events (MACEs) and venous thromboembolism events (VTEs) for comparison between tsDMARDs (± csDMARDs) and placebo ± csDMARDs for patients pre-treated with csDMARDs (Table 12).[21] However, the latest post-marketing surveillance study reported that patients using TOF (tsDMARD) had a higher incidence of MACEs when compared to patients receiving bDMARDs (TNFi; hazard ratio [HR] 1.33, 95%CI 0.91 to 1.94; Table 12).[27]

For pregnant women, no difference was found for the following outcomes: live or preterm birth, spontaneous abortion and anomalies (any or major). In comparison to the general population, bDMARD users (non-TNFi) had significantly higher odds of preterm birth (OR 4.10, 95%CI 1.44 to 11.69). However, the results are based only on a single observation study (Table 13).[15]

It is unclear from the articles if the differences are clinically meaningful.[13, 15]

Patients with csDMARD-IR

For patients with IR to csDMARDs, no difference was reported for the discontinuation due to adverse events (AEs) or overall serious AEs for patients receiving bDMARDs (± csDMARDs or monotherapy) when compared to placebo ± csDMARDs or csDMARDs only (Table 14).[17, 18] However, some results were at borderline of statistical significance.[17, 18]

For the same population, patients receiving tsDMARDs (± csDMARDs) were at higher risk of overall AEs (RR 1.09, 95%CI 1.05 to 1.13), overall infection (RR 1.34, 95%CI 1.17 to 1.52), herpes zoster infection (RR 2.57, 95%CI 1.43 to 4.62) and upper respiratory tract infection (RR 1.32, 95%CI 1.07 to 1.63) when compared to patients receiving placebo ± csDMARDs (Table 14).[23] No difference was shown for the comparison of tsDMARDs (± csDMARDs) and placebo ± csDMARDS for overall serious AEs and serious infections or VTEs in the same population (Table 14).[23]

No difference was reported for discontinuation due to AEs, overall AEs and overall serious AEs for the comparison of bDMARDs (TNFi; ± csDMARDs) and triple csDMARD therapy in patients with IR to csDMARD. However, patients receiving triple csDMARD therapy reported significantly lower odds of overall infection at six months when compared to bDMARDs (TNFi; ± csDMARDs; OR 0.08, 95%CI 0.00 to 0.57; Table 14).[16]

No difference in discontinuation due to any reason, overall serious AEs and overall serious infections was reported for csDMARD-IR patients receiving bsDMARDs or reference bDMARDs (Table 14).[20]

It is unclear from the articles if the differences are clinically meaningful.[16, 23]

Patients with bDMARD-IR

For patients with IR to bDMARDs, no difference was shown for discontinuation due to AEs, overall AEs and overall serious AEs for b/tsDMARDs (± csDMARDs) in comparison to placebo ± csDMARDs or csDMARDs only.[19, 26] No differences were reported for the same outcomes for head to head comparison between bDMARDs (non-TNFi) and tsDMARDs used in combination with csDMARDs (Table 15).[26] It is important to note that no evidence relating to infection rates were reported for tsDMARDs in this population.

Notes

All tsDMARDs (TOF, BARI, UPA and FLN) and some newer csDMARDs (ADA, ETN, IFX, SRL and RTX) are currently on the European Medicines Agency's (EMA) list of medicines under additional monitoring and listed as new active substances and/or new biologicals.[30]

Based on the results of the post-marketing surveillance study[27] (Table 12), TOF received a warning for use in practice in Germany.[27]

FLN is authorised for use in Europe[30], however, the drug was rejected by FDA mid-2020 for use in patients with RA due to concerns of testicular toxicity associated with high doses of FLN.[31] The safety trial is currently underway with the primary results expected by mid-2021.[32]

Table 12: FAQ 7 – risks and/or side effects (csDMARD pre-treated population only)

Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimate with 95% CIs , e.g. mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event n/N (nr of patients per 100)				
CVEs^							
de La Forest Divonne 2017[13]	7 observational studies (registries)	NR	bDMARDs (TNFi) ± csDMARDs: 402/29054 (1.4 per 100)	csDMARDs: 551/19949 (2.8 per 100)	RR = 0.62 (95%CI 0.44 to 0.88)	Very low (high risk of bias and high heterogeneity)	Difference in favour of intervention but data of very low quality ⇗
Xie 2019[21]	17 RCTs	≥2.76 months^	tsDMARDs ± csDMARDs: 35 events per 1836 patient-years	placebo ± csDMARDs: 10 events per 898 patient-years	OR = 1.14 (95%CI 0.59 to 2.21) [$]	Low (high risk of bias and imprecision)	No difference shown ⇔
MACE^^							
Xie 2019[21]	10 RCTs	≥2.76 months^	tsDMARDs ± csDMARDs: 8 events per 1836 patient-years	placebo ± csDMARDs: 3 events per 898 patient-years	OR = 0.84 (95%CI 0.31 to 2.33)[$]	Low (high risk of bias and imprecision)	No difference shown ⇔
Pfizer 2021[27]	1 RCT	NR	tsDMARD (TOF): 98/2911* (3.4 per 100)	bDMARDs (TNFi): 37/1451* (2.5 per 100)	HR = 1.33 (95%CI 0.91 to 1.94)**	Low (unclear risk of bias and imprecision)	Difference in favour of control but data of low quality ⇗
VTEs							

Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimate with 95% CIs , e.g. mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event n/N (nr of patients per 100)				
Xie 2019[21]	8 RCTs	≥2.76 months^	tsDMARDs ± csDMARDs: 12 events per 1836 patient-years	placebo ± csDMARDs: 3 events per 898 patient-years	OR = 1.08 (95%CI 0.35 to 3.32)[$]	Low (high risk of bias and imprecision)	No difference shown ⇔

*Number of subjects with first event within the risk period defined as from start of therapy up to 60 days past last dose.
**The non-inferiority criterion was not met for the primary comparison of the combined tofacitinib doses to TNFi since the upper limit of the 95% CI exceeded the pre-specified non-inferiority criterion of 1.8, i.e., 1.94 >1.8.
^ de La Forest Divonne 2017[13]: cardiovascular events were defined as all events reported as acute myocardial infarction, cardiac failure, and stroke); Xie 2019[21]: definition not reported
^^definitions not reported
[$]own re-calculation with RevMan 5.4.1 (please refer to Appendix 2)
bDMARDs = biological DMARD; csDMARDs = conventional synthetic DMARDs; CVE = cardiovascular events; DMARD = disease-modifying antirheumatic drug; HR = hazard ratio; MACE = major adverse cardiovascular events; NR = not reported; RCT = randomised controlled trial; RR = risk ratio; TNFi = tumour necrosis factor inhibitors; TOF = tofacitinib; tsDMARD = targeted synthetic DMARD; VTE = venous thromboembolism events

Table 13: FAQ 7 – risks and/or side effects (csDMARD pre-treated pregnant women only)

Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimate with 95% CIs , e.g. mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event n/N (nr of patients per 100)				
Live birth							
Komaki 2017 [15]	2 observational studies	NR	bDMARDs (TNFi) ± csDMARDs: 86/93 (92.5 per 100)	general population: 169/184 (91.8 per 100)	OR = 1.10 (95%CI 0.15 to 8.02)	Very low (high risk of bias and imprecision)	No difference shown ⇔
			bDMARDs (non-TNFi) ± csDMARDs: 137/145 (94.5 per 100)		OR = 1.13 (95%CI 0.45 to 2.85)		
Preterm birth							
Komaki 2017 [15]	1 observational study	NR	bDMARDs (TNFi) ± csDMARDs: 7/53 (13.2 per 100)	general population: 6/120 (5 per 100)	OR = 2.89 (95%CI 0.91 to 9.16)	Very low (high risk of bias and imprecision)	No difference shown ⇔
			bDMARDs (non-TNFi) ± csDMARDs: 3/62 (4.8 per 100)		OR = 4.10 (95%CI 1.44 to 11.69)		Difference in favour of control but data of very low quality ⇗
Spontaneous abortion							
Komaki 2017 [15]	1 observational study	NR	bDMARDs (TNFi) ± csDMARDs: 6/60 (10 per 100)	general population: 2/134 (1.5 per 100)	OR = 7.33 (95%CI 0.76 to 70.56)	Very low (high risk of bias and imprecision)	No difference shown ⇔
			bDMARDs (non-TNFi) ± csDMARDs: 3/68 (4.4 per 100)		OR = 3.05 (95%CI 0.5 to 18.68)		

Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimate with 95% CIs , e.g. mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event n/N (nr of patients per 100)				
Anomalies (any)							
Komaki 2017 [15]	1 observational study	NR	bDMARDs (TNFi) ± csDMARDs: 1/33 (3 per 100)	general population: 2/50 (4 per 100)	OR = 0.75 (95%CI 0.07 to 8.62)	Very low (high risk of bias and imprecision)	No difference shown ⇔
			bDMARDs (non-TNFi) ± csDMARDs: 3/77 (3.9 per 100)		OR = 0.97 (95%CI 0.16 to 6.04)		
Anomalies (major)							
Komaki 2017 [15]	1 observational study	NR	bDMARDs (TNFi) ± csDMARDs: 2/59 (3.4 per 100)	general population: 5/123 (4.1 per 100)	OR = 0.83 (95%CI 0.16 to 4.40)	Very low (high risk of bias and imprecision)	No difference shown ⇔
			bDMARDs (non-TNFi) ± csDMARDs: 3/65 (4.6 per 100)		OR = 1.14 (95%CI 0.26 to 4.94)		

bDMARDs = biological DMARD; DMARD = disease-modifying antirheumatic drug; NR = not reported; OR = odds ratio; TNFi = tumour necrosis factor inhibitors; TOF = tofacitinib; tsDMARD = targeted synthetic DMARD

Table 14: FAQ7 - risks and/or side effects (patients with IR to csDMARDs)

Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimate with 95% CIs , e.g. mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event n/N (nr of patients per 100)				
Discontinuation (any reason)							
Tanaka 2021[20]	7 RCTs	5.5 months^	bsDMARDs: 71/1564 (4.5 per 100)	bDMARDs: 80/1558 (5.1 per 100)	RR = 0.88 (95%CI 0.64 to 1.20)	Moderate (moderate risk of bias and imprecision)	No difference shown ⇔
	3 RCTs	1 year^	bsDMARDs: 59/748 (7.9 per 100)	bDMARDs: 78/747 (10.4 per 100)	RR = 0.76 (95%CI 0.55 to 1.04)		
Discontinuation due to AEs							
Singh 2016a[17]	42 RCTs	Unclear (range 3 to 24 months)	bDMARDs ± csDMARDs: 523/10952 (4.8 per 100)	placebo ± csDMARDs: 258/5804 (4.4 per 100)	RR = 1.11 (95%CI 0.96 to 1.30)	Moderate (imprecision)	No difference shown ⇔
Singh 2016b[18]	9 RCTs	Unclear (range 1 to 24 months)	bDMARDs (mono): 162/1893 (8.6 per 100)	csDMARDs: 117/1325 (8.8 per 100)	RR = 1.08 (95%CrI 0.69 to 1.69)	Low (imprecision and inconsistency)	
Fleischmann 2017[16]	RCT (n = NR)	6 months	Triple csDMARDs: NR	bDMARDs (TNFi) ± csDMARDs: NR	OR = 1.17 (95%CrI 0.47 to 2.98)	Very low (mostly unclear risk of bias and high imprecision)	
Overall AEs*							

Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimate with 95% CIs , e.g. mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event n/N (nr of patients per 100)				
Wang 2020[23]	17 RCTs	0.92 to 5.52 months^	tsDMARDs ± csDMARDs: 3514/5777 (60.8 per 100)	placebo ± csDMARDs: 2599/4638 (56 per 100)	RR = 1.09 (95%CI 1.05 to 1.13)	Low (high risk of bias)	Difference in favour of control but data of low quality ⇗
Fleischmann 2017[16]	RCT (n = NR)	6 months	Triple csDMARDs: NR	bDMARDs (TNFi) ± csDMARDs: NR	OR = 1.30 (95%CrI 0.63 to 2.65)	Very low (mostly unclear risk of bias and high imprecision)	No difference shown ⇔
Overall serious AEs*							
Singh 2016a[17]	42 RCTs	Unclear (range 3 to 24 months)	bDMARDs ± csDMARDs: 892/11564 (7.7 per 100)	placebo ± csDMARDs: 404/5935 (6.8 per 100)	RR = 1.12 (95%CI 0.99 to 1.27)	High	No difference shown ⇔
Singh 2016b[18]	7 RCTs	Unclear (range 1 to 24 months)	bDMARDs (mono): 102/1353 (7.5 per 100)	csDMARDs: 47/960 (4.9 per 100)	RR = 1.45 (95%CI 0.94 to 2.22)	Low (imprecision and inconsistency)	
Wang 2020[23]	18 RCTs	range 0.92 to 5.52 months^	tsDMARDs ± csDMARDs: 238/5821 (4.1 per 100)	placebo ± csDMARDs: 163/4727 (3.4 per 100)	RR = 1.11 (95%CI 0.86 to 1.42)	Low (high risk of bias)	
Fleischmann 2017[16]	RCT (n = NR)	6 months	Triple csDMARDs: NR	bDMARDs (TNFi) ± csDMARDs: NR	OR = 0.38 (95%CrI 0.01 to 6.26)	Very low (mostly unclear risk of bias and high imprecision)	

Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimate with 95% CIs , e.g. mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event n/N (nr of patients per 100)				
Tanaka 2021[20]	1 RCT	2.76 months^	bsDMARDs: 2/60 (3.3 per 100)	bDMARDs: 1/59 (1.7 per 100)	RR = 1.97 (95%CI 0.18 to 21.11)	Moderate (moderate risk of bias and imprecision)	
	7 RCTs	5.5 months^	bsDMARDs: 64/1764 (3.6 per 100)	bDMARDs: 77/1763 (4.4 per 100)	RR = 0.84 (95%CI 0.61 to 1.18)		
	5 RCTs	1 year^	bsDMARDs: 133/1225 (10.9 per 100)	bDMARDs: 111/1227 (9 per 100)	RR = 1.20 (95%CI 0.94 to 1.52)		
Overall infection*							
Wang 2020[23]	11 RCTs	range 0.92 to 5.52 months^	tsDMARDs ± csDMARDs: 1069/3130 (34.2 per 100)	placebo ± csDMARDs: 821/3203 (25.6 per 100)	RR = 1.34 (95%CI 1.17 to 1.52)	Low (high risk of bias)	Difference in favour of control but data of low quality ⇗
Fleischmann 2017[16]	RCT (n = NR)	6 months	Triple csDMARDs: NR	bDMARDs (TNFi) ± csDMARDs: NR	OR = 0.08 (95%CrI 0.00 to 0.57)	Very low (mostly unclear risk of bias and high imprecision)	Difference in favour of intervention but data of very low quality ⇗
Overall serious infection*							
Wang 2020[23]	14 RCTs	range 0.92 to 5.52 months^	tsDMARDs ± csDMARDs: 60/4971 (1.2 per 100)	placebo ± csDMARDs: 145/4325 (3.4 per 100)	RR = 1.42 (95%CI 0.93 to 2.17)	Low (high risk of bias)	No difference shown ⇔

Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimate with 95% CIs , e.g. mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event n/N (nr of patients per 100)				
Tanaka 2021[20]	2 RCTs	5.5 months^	bsDMARDs: 10/558 (1.8 per 100)	bDMARDs: 8/566 (1.4 per 100)	RR = 1.28 (95%CI 0.5 to 3.28)	Moderate (moderate risk of bias and imprecision)	
	1 RCTs	1 year^	bsDMARDs: 9/290 (3.1 per 100)	bDMARDs: 7/293 (2.4 per 100)	RR = 1.30 (95%CI 0.49 to 13.44)		
Herpes zoster infection**							
Wang 2020[23]	10 RCTs	range 0.92 to 5.52 months^	tsDMARDs ± csDMARDs: 47/3334 (1.4 per 100)	placebo ± csDMARDs: 64/3211 (2 per 100)	RR = 2.57 (95%CI 1.43 to 4.62)	Low (high risk of bias)	Difference in favour of control but data of low quality ⇗
Upper respiratory tract infection							
Wang 2020[23]	12 RCTs	range 0.92 to 5.52 months^	tsDMARDs ± csDMARDs: 318/4541 (7 per 100)	placebo ± csDMARDs: 168/3258 (5.2 per 100)	RR = 1.32 (95%CI 1.07 to 1.63)	Low (high risk of bias)	Difference in favour of control but data of low quality ⇗
VTEs							
Wang 2020[23]	3 RCTs	range 0.92 to 5.52 months^	tsDMARDs ± csDMARDs: 3/1420 (0.2 per 100)	placebo ± csDMARDs: 1/1432 (0.07 per 100)	RR = 2.34 (95%CI 0.34 to 15.92)	Very low (high risk of bias and imprecision)	No difference shown ⇔

* definition not provided; ** independent of infection or serious infection occurrence; ^ recalculated by the reviewer for consistency

AE = adverse event; bDMARDs = biological DMARD; bsDMARDs = biosimilar DMARDs; CrI = credible interval; csDMARDs = conventional synthetic DMARDs; DMARD = disease-modifying antirheumatic drug; NR = not reported; OR = odds ratio; RCT = randomised controlled trial; RR = risk ratio; TNFi = tumour necrosis factor inhibitors; VTEs = venous thromboembolic events

Table 15: FAQ7 - risks and/or side effects (patients with IR to bDMARDs)

Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimate with 95% CIs , e.g. mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event n/N (nr of patients per 100)				
Discontinuation due to AEs							
Singh 2017[19]	2 RCTs	Unclear (range 3 to 24 months)	bDMARDs ± csDMARDs: 14/371 (3.8 per 100)	csDMARDs: 2/240 (0.8 per 100)	RR = 3.32 (95%CI 0.86 to 12.85)	Low (serious imprecision)	No difference shown ⇔
Sung 2021[26]	RCTs (n = NR)	2.76 months^	placebo ± csDMARDs: NR	bDMARDs (non-TNFi) ± csDMARDs: NR	OR = 0.57 (95%CrI 0.29 to 1.09)	Low (high risk of bias)	
	RCTs (n = NR)			tsDMARDs ± csDMARDs: NR	OR = 0.88 (95%CrI 0.38 to 1.91)		
	RCTs (n = NR)		tsDMARDs ± csDMARDs: NR	bDMARDs (non-TNFi) ± csDMARDs: NR	OR = 0.64 (95%CrI 0.23 to 1.87)		
Overall AEs*							
Sung 2021[26]	RCTs (n = NR)	2.76 months^	placebo ± csDMARDs: NR	bDMARDs (non-TNFi) ± csDMARDs: NR	OR = 0.77 (95%CrI 0.55 to 1.08)	Moderate (moderate risk of bias)	No difference shown ⇔
	RCTs (n = NR)			tsDMARDs ± csDMARDs: NR	OR = 0.88 (95%CrI 0.61 to 1.30)		
	RCTs (n = NR)		tsDMARDs ± csDMARDs: NR	bDMARDs (non-TNFi) ± csDMARDs: NR	OR = 0.86 (95%CrI 0.52 to 1.43)		

Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimate with 95% CIs , e.g. mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event n/N (nr of patients per 100)				
Overall serious AEs*							
Singh 2017[19]	3 RCTs	Unclear (range 3 to 24 months)	bDMARDs ± csDMARDs: 38/677 (5.6 per 100)	csDMARDs: 33/395 (8.4 per 100)	RR = 0.69 (95%CI 0.44 to 1.09)	Moderate (imprecision)	No difference shown ⇔
Sung 2021[26]	RCTs (n = NR)	2.76 months^	placebo ± csDMARDs: NR	bDMARDs (non-TNFi) ± csDMARDs: NR	OR = 0.97 (95%CrI 0.45 to 2)	Moderate (moderate risk of bias)	
	RCTs (n = NR)			tsDMARDs ± csDMARDs: NR	OR = 0.68 (95%CrI 0.25 to 1.85)		
	RCTs (n = NR)		bDMARDs (non-TNFi) ± csDMARDs: NR	tsDMARDs ± csDMARDs: NR	OR = 0.71 (95%CrI 0.2 to 2.55)		

*definition not provided; ** independent of infection or serious infection occurrence; ^recalculated by the reviewer for consistency
AE = adverse event; bDMARDs = biological DMARD; bsDMARDs = biosimilar DMARDs; CrI = credible interval; csDMARDs = conventional synthetic DMARDs; DMARD = disease-modifying antirheumatic drug; OR = odds ratio; RCT = randomised controlled trial; TNFi = tumour necrosis factor inhibitors;

3.10 FAQ8: DOES TREATMENT INCREASE MY CANCER RISK IN THE LONG TERM?

This section summarises the evidence related to the risk of developing cancer following treatment with b/tsDMARDs in patients with RA (all populations).

Results

Tables 16, 17 and 18 reports the results for cancer risk in patients pre-treated with csDMARDs, with IR to csDMARDs to bDMARDs, respectively.

Patients pre-treated with csDMARDs

For patients pre-treated with csDMARDs, systematic reviews reported similar risk or incidence rates of developing solid cancer, haematological cancer, lymphoma, skin cancers (melanoma and non-melanoma skin cancer [NMSC]) or breast cancer following treatment with bDMARDs or tsDMARDs (TOF only) in combination with csDMARDs when compared to csDMARDs alone or csDMARDs ± placebo (Table 16).[13, 14, 24, 25] All results for skin and breast cancer and some results for solid cancer include patients with previous malignancy.[13, 14] Results for breast cancer and lymphoma were only available for bDMARDs (TNFi).[14]

The latest post-marketing surveillance study reported that patients using TOF (tsDMARD) had a higher incidence of malignancies (excluding NMSC) when compared to patients receiving bDMARDs (TNFi; HR 1.48, 95%CI 1.04 to 2.09; Table 16).[27]

Patients with csDMARD-IR

Treatment with bDMARDs (± csDMARDs or as monotherapy)[17, 18] or tsDMARDs (± csDMARDs)[23], compared to placebo ± csDMARDs or csDMARDs alone, is not shown to increase the risk of malignancies or cancer in patients with IR to csDMARDs (Table 17). Similarly, for the same population, the risk of developing malignancy was similar between bDMARDs (TNFi; ± csDMARDs) and triple csDMARDs treatment arms (Table 17).[16]

Patients with bDMARD-IR

Patients with IR to bDMARDs have a similar risk of developing cancer following treatment with bDMARDs (± csDMARDs) or csDMARDs only (Table 18).[19] No results were available for the same population treated with tsDMARDs.

Notes

Based on the results of the post-marketing surveillance study[27] (Table 12), TOF received a warning for use in practice in Germany.[27]

Table 16: FAQ 8 – cancer risk (csDMARD pre-treated population only)

Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimate with 95% CIs , e.g. mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event n/N (nr of patients per 100)				
Solid cancer							
de La Forest Divonne 2017[13]	3 observational studies (registries) Patients with previous malignancy	NR	bDMARDs (TNFi) ± csDMARDs: 22/439 (5 per 100)	csDMARDs: 16/208 (7.7 per 100)	RR = 0.77 (95%CI 0.29 to 2.03)	Very low (high risk of bias and heterogeneity)	No difference shown ⇔
	9 observational studies (registries) Patients without previous malignancy		bDMARDs (TNFi) ± csDMARDs: 1407/50734 (2.8 per 100)	csDMARDs: 5126/87018 (5.9 per 100)	RR = 0.84 (95%CI 0.6 to 1.18)	Very low (high risk of bias and high heterogeneity)	No difference shown ⇔
Maneiro 2017[24]	28 RCTs	NR (minimum 12 weeks)	bDMARDs (TNFi): NR	csDMARDs ± placebo: NR	OR = 0.83 (95%CI 0.53 to 1.3)	Very low (high risk of bias and heterogeneity)	No difference shown ⇔
	7 RCTs		bDMARDs (non-TNFi): NR		OR = 0.08 to 2.54***		
	4 RCTs		tsDMARD (TOF): NR		OR = 1.76 (95%CI 0.34 to 8.97)		
	26 LTEs		bDMARDs (TNFi): 173 events per 24559.1 patient-years	NA	InR = 0.72* (95%CI 0.62 to 0.83)	Very low (high risk of bias)	NA
	7 LTEs		bDMARDs (non-TNFi): NR		InR = 0.65 to 0.8*	Very low (high risk of bias and heterogeneity)	

Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimate with 95% CIs , e.g. mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event n/N (nr of patients per 100)				
	17 LTEs		tsDMARD (TOF): 121 events per 16832.7 patient-years		lnR = 0.74* (95%CI 0.57 to 0.93)	Very low (high risk of bias)	
Xie 2020b[25]	Observational studies (n=NR)	NR	csDMARDs: NR	NA	lnR = 3.84 to 11.75**	Very high (high risk of bias)	NA
			bDMARDs (TNFi): NR		lnR = 1.94 to 10.19**		
			bDMARDs (non-TNFi): NR		lnR = 4.05 to 10.48**		
			tsDMARD (TOF): NR		lnR = 11.38**		
Xie 2020a[14]	8 observational studies	≥1 year	bDMARDs (TNFi) ± csDMARDs: 228 events per 6454 patient years	csDMARDs: 620 events per 19862 patient years	RR = 1.00 (95%CI 0.86 to 1.17)[&]	Very low (high risk of bias and imprecision)	No difference shown ⇔
Haematological malignancies							
Maneiro 2017[24]	14 RCTs	NR (minimum 12 weeks)	bDMARDs (TNFi): NR	csDMARDs ± placebo: NR	OR = 2.49 (95%CI 0.82 to 7.54)	Very low (high risk of bias and imprecision)	No difference shown ⇔
	2 RCTs		bDMARDs (non-TNFi): NR		OR = 4.51 (95%CI 0.07 to 285.8); 0.05 (95%CI 0 to 3.19)		
	1 RCT		tsDMARD (TOF): NR		OR = 1.76* (95%CI 0.34 to 8.97)		
	27 LTEs		bDMARDs (TNFi): 51 events per 33814.3 patient-years	NA	lnR = 0.16* (95%CI 0.12 to 0.21)	Very low (high risk of bias and heterogeneity)	NA
	9 LTEs		bDMARDs (non-TNFi): NR		lnR = 0.08 to 0.1*		

Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimate with 95% CIs , e.g. mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event n/N (nr of patients per 100)				
	17 LTEs		tsDMARD (TOF): 19 events per 16832.7 patient-years		lnR = 0.13* (95%CI 0.08 to 0.19)		
Xie 2020b[25]	Observational studies (n=NR)	NR	csDMARDs: NR	NA	lnR = 0.69 to 11.78**	Very high (high risk of bias)	NA
			bDMARDs (TNFi): NR		lnR = 0.19 to 10.71**		
			bDMARDs (non-TNFi): NR		lnR = 0.0 to 2.4**		
			tsDMARD (TOF): NR		lnR = 0**		
Lymphoma							
de La Forest Divonne 2017[13]	6 observational studies (registries)	NR	bDMARDs (TNFi) ± csDMARDs: 68/27160 (0.3 per 100)	csDMARDs: 378/87756 (0.4 per 100)	RR = 0.9 (95%CI 0.62 to 1.31)	Very low (high risk of bias and heterogeneity)	No difference shown ⇔
Skin cancer[$]							
Xie 2020a[14]	4 observational studies	≥1 year	bDMARDs (TNFi) ± csDMARDs: 144 events per 2393 patient years	csDMARDs: 368 events per 6305 patient years	RR = 0.92 (95%CI 0.55 to 1.55)[&]	Very low (high risk of bias and imprecision)	No difference shown ⇔
NMSC							
Maneiro 2017[24]	14 RCTs	NR (minimum 12 weeks)	bDMARDs (TNFi): NR	csDMARDs ± placebo: NR	OR = 1.35 (95%CI 0.67 to 2.73)	Very low (high risk of bias)	No difference shown ⇔
	4 RCTs		bDMARDs (non-TNFi): NR		OR = 0.97 to 1***		
	26 LTEs		bDMARDs (TNFi): 132 events per 29604.3 patient-years	NA	lnR = 0.42* (95%CI 0.29 to 0.56)	Very low (high risk of bias and high	NA

Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimate with 95% CIs , e.g. mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event n/N (nr of patients per 100)				
	8 LTEs		bDMARDs (non-TNFi): NR		lnR = 0.14 to 0.55*	heterogeneity)	
	17 LTEs		tsDMARD (TOF): 151 events per 16832.7 patient-years		lnR = 0.72* (95%CI 0.49 to 1.01)		
Xie 2020b[25]	Observational studies (n=NR)	NR	csDMARDs: NR	NA	lnR = 1.71 to 7.10**	Very high (high risk of bias)	NA
			bDMARDs (TNFi): NR		lnR = 1.04 to 14.6**		
			bDMARDs (non-TNFi): NR		lnR = 0.0 to 21.2**		
			tsDMARD (TOF): NR		lnR = 10.93**		
Melanoma							
de La Forest Divonne 2017[13]	3 observational studies (registries)	NR	bDMARDs (TNFi) ± csDMARDs: 57/17986 (0.3 per 100)	csDMARDs: 173/48480 (0.4 per 100)	RR = 1.17 (95%CI 0.86 to 1.59)	Very low (high risk of bias)	No difference shown ⇔
Maneiro 2017[24]	6 RCTs	NR (minimum 12 weeks)	bDMARDs (TNFi): NR	csDMARDs ± placebo: NR	OR = 1.13 (95%CI 0.23 to 5.58)	Very low (high risk of bias)	
	1 RCT		bDMARDs (non-TNFi): NR		OR = 0.06 (95%CI 0 to 3.52)		
	24 LTEs		bDMARDs (TNFi): 7 events per 20575.2 patient-years	NA	lnR = 0.04* (95%CI 0.02 to 0.06)	Very low (high risk of bias)	NA
	8 LTEs		bDMARDs (non-TNFi): NR		lnR = 0.03 to 0.14*		
	17 LTEs		tsDMARD (TOF): 9 events per 16832.7		lnR = 0.08* (95%CI 0.09 to 0.13)		

Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimate with 95% CIs , e.g. mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event n/N (nr of patients per 100)				
			patient-years				
Xie 2020b[25]	Observational studies (n=NR)	NR	csDMARDs: NR	NA	lnR = 0 to 0.86**	Very high (high risk of bias)	NA
			bDMARDs (TNFi): NR		lnR = 0.19 to 1.36**		
			bDMARDs (non-TNFi): NR		lnR = 0.0 to 1.10**		
Breast cancer							
Xie 2020a[14]	2 observational studies	≥1 year	bDMARDs (TNFi) ± csDMARDs: 137 events per 1356 patient years	csDMARDs: 168 events per 3016 patient years	RR = 0.96 (95%CI 0.78 to 1.18) [&]	Very low (high risk of bias and imprecision)	No difference shown ⇔
Malignancies[$]							
Pfizer 2021[27]	1 RCT	NR	tsDMARD (TOF): 122/2911^ (4.2 per 100)	bDMARDs (TNFi): 42/1451^ (2.9 per 100)	HR = 1.48 (95%CI 1.04 to 2.09)^^	Low (unclear risk of bias and imprecision)	Difference in favour of control but data of low quality ⇗

*per 100 patient-years; for non-TNFi, the range of results is provided (i.e. lnR without 95%CI) due to lack of pooling of the results by the study authors
**per 1000 patient-years; for non-TNFi, the range of results is provided (i.e. lnR without 95%CI) due to lack of pooling of the results by the study authors
***the article provides only the data per drug, hence, the range of OR is reported
^Number of subjects with first event within the risk period that included all available follow-up regardless of treatment exposure. Excluding NMSC.
^^The non-inferiority criterion was not met for the primary comparison of the combined tofacitinib doses to TNFi since the upper limit of the 95% CI exceeded the pre-specified non-inferiority criterion of 1.8, i.e., 1.94 >1.8.
[$]definition not reported
[&]own re-calculation with RevMan 5.4.1 (please refer to Appendix 2)
bDMARDs = biological DMARD; csDMARDs = conventional synthetic DMARDs; DMARD = disease-modifying antirheumatic drug; HR = hazard ratio; InR = incidence rate; LTE = long extension studies; NMSC = non-melanoma skin cancer; NA = not available; NR = not reported; OR = odds ratio; RCT = randomised controlled trial; RR = risk ratio; TNFi =

Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimate with 95% CIs , e.g. mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event n/N (nr of patients per 100)				
tumour necrosis factor inhibitors; TOF = tofacitinib; tsDMARD = targeted synthetic DMARD							

Table 17: FAQ 8 – cancer risk (patients with IR to csDMARDs)

Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimate with 95% CIs , e.g. mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event n/N (nr of patients per 100)				
Malignancies/cancer*							
Singh 2016a[17]	15 RCTs	Unclear (range 3 to 24 months)	bDMARDs ± csDMARDs: 56/3539 (1.6 per 100)	placebo ± csDMARDs: 29/2122 (1.4 per 100)	RR = 1.07 (95%CI 0.68 to 1.68)	Low (serious imprecision)	No difference shown ⇔
Singh 2016b[18]	6 RCTs	Unclear (range 1 to 24 months)	bDMARDs (mono): 20/1561 (1.3 per 100)	csDMARDs: 10/1103 (0.9 per 100)	OR = 1.40 (95%CI 0.67 to 2.93)		
Wang 2020[23]	7 RCTs	range 0.92 to 5.52 months^	tsDMARDs ± csDMARDs: 8/3034 (0.3 per 100)	placebo ± csDMARDs: 3/2888 (0.1 per 100)	RR = 1.68 (95%CI 0.57 to 4.95)	Low (high risk of bias)	
Fleischmann 2017[16]	RCT (n = NR)	6 months	Triple csDMARDs: NR	bDMARDs (TNFi) ± csDMARDs: NR	OR = 0.97 (95%CrI 0.0 to 603.4)	Very low (mostly unclear risk of bias and high	

						imprecision)	
*definition not provided bDMARDs = biological DMARD; csDMARDs = conventional synthetic DMARDs; DMARD = disease-modifying antirheumatic drug; NR = not reported; OR = odds ratio; RCT = randomised controlled trial; TNFi = tumour necrosis factor inhibitors; TOF = tofacitinib							

Table 18: FAQ 8 – cancer risk (patients with IR to bDMARDs)

Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimate with 95% CIs , e.g. mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event n/N (nr of patients per 100)				
Cancer*							
Singh 2017[19]	2 RCTs	Unclear (range 3 to 24 months)	bDMARDs ± csDMARDs: NR	csDMARDs: NR	RR = 4.54 (95%CI 0.24 to 85.36)	Low (serious imprecision)	No difference shown ⇔

* definition not provided
bDMARDs = biological DMARD; CrI = credible interval; csDMARDs = conventional synthetic DMARDs; DMARD = disease-modifying antirheumatic drug; NR = not reported; OR = odds ratio; RCT = randomised controlled trial

4. DISCUSSION

4.1 SUMMARY OF FINDINGS

This report is based on the results of the systematic literature search of any available evidence published between 2016-2021. After screening 3,041 references, the content is based on 27 eligible resources including seven guidelines with recommendations for practice from Germany, Spain, France and UK, and additional recommendations on biosimilars from experts based in the USA, as well as 14 systematic reviews covering various outcomes for b/tsDMARDs for patients pre-treated with csDMARDs or IR to cs/bDMARDs. Additional information from online resources (n=6) is included.

Based on personal communication, 2021 Rheumatoid Arthritis Guideline published by the ACR is estimated to be available online mid-June 2021.[33]

Most of the outcomes were reported for patients with IR to either csDMARDs or bDMARDs. Insufficient reporting of outcomes for patients pre-treated with MTX only is consistent with the patient pathway in which patients receive b/tsDMARDs following IR to csDMARDs.[2-6, 28] Despite lack of recommendations to use bDMARDs over tsDMARDs as the first-line therapy for csDMARD-IR patients,[2, 6] bDMARDs are often used as the preferred option instead of tsDMARDs.[2] This is reflected in the evidence included in this report which is summarised below.

FAQ1 (What does the treatment involve?)

This section presents the background information on the drugs of interest and recommendations for practice. The patient pathway for Germany, based on the most current German guideline[2], is also presented. The volume of the evidence for the other outcomes for each of the FAQs can be summarised as follows:

FAQ2: Will it help my symptoms (response)?

- Pre-treated with csDMARDs: lack of evidence
- csDMARD-IR:
    - improved symptom response following the use of bDMARDs (± csDMARDs or as monotherapy) and tsDMARDs (± csDMARDs) when compared to placebo ± csDMARDs or csDMARDs only
    - similar symptom response for bDMARDs (TNFi; ± csDMARDs) compared to triple csDMARD therapy
    - improved symptom response following the use of bsDMARDs when compared to reference bDMARDs at one year (at borderline of significance), but not at 2.76 and 5.5 months
- bDMARD-IR:
    - improved symptom response following the use of b/tsDMARDs (± csDMARDs) when compared to placebo ± csDMARDs or csDMARDs only
    - similar symptom response for comparison bDMARDs (TNFi) and tsDMARDs

FAQ3: Will it help maintain remission of my disease?

- Pre-treated with csDMARDs: lack of evidence
- csDMARD-IR:
    - significantly more patients achieved remission following the use of b/tsDMARDs (± csDMARDs) when compared to placebo ± csDMARDs or csDMARDs only
    - a similar impact on remission in patients treated with bDMARDs as monotherapy when compared to those treated with csDMARDs only (borderline of significance)
    - a similar impact on remission for bDMARDs (TNFi; ± csDMARDs) and triple csDMARD therapy or bsDMARDs and reference csDMARDs
- bDMARD-IR:
    - significantly more patients achieved remission following the use of bDMARDs (± csDMARDs) when compared to csDMARDs only
    - lack of evidence for tsDMARDs

FAQ4: How will treatment prevent damage to my joints? (i.e., mobility, functionality)

- Pre-treated with csDMARDs: lack of evidence
- csDMARD-IR:
    - significant decrease in disease progression following the use of bDMARDs (± csDMARDs or as monotherapy) when compared to placebo ± csDMARDs
    - no difference in joint damage for bDMARDs (TNFi; ± csDMARDs) and triple csDMARD therapy
    - lack of evidence for tsDMARDs
- bDMARD-IR: lack of evidence

FAQ5: How will treatment impact my joint function and/or quality of life?

- Lack of evidence for QoL for any population
- Pre-treated with csDMARDs: lack of evidence
- csDMARD-IR:
    - significantly improved joint function following the use of bDMARDs (± csDMARDs or as monotherapy) and tsDMARDs (± csDMARDs) when compared to placebo ± csDMARDs or csDMARDs only
    - a similar impact on joint function in patients using bDMARDs (TNFi; ± csDMARDs) and triple csDMARD therapy
- bDMARD-IR:
    - significantly improved joint function following the use of bDMARDs (± csDMARDs) when compared to csDMARDs only
    - lack of evidence for tsDMARDs

FAQ6: Will the treatment prolong my life expectancy?

- Life expectancy was not reported in any study and mortality of patients, from only one study, was reported
- Pre-treated with csDMARDs:
    - Significant decrease in mortality following the use of bDMARDs (TNFi; ± csDMARDs) in comparison to csDMARDs only
    - Lack of evidence for tsDMARDs
- csDMARD-IR: lack of evidence
- bDMARD-IR: lack of evidence

FAQ7: What are the risks or side effects (i.e., cardiovascular risk)?

- Pre-treated with csDMARDs:
    - Significant decrease in CVEs following the use of bDMARDs (TNFi; ± csDMARDs) when compared to csDMARDs only. No other outcomes were reported
    - A similar safety profile between tsDMARDs (± csDMARDs) and placebo ± csDMARDs (outcomes: CVEs, MACEs, and VTEs)
    - Increase in the incidence of MACEs following the use of TOF (tsDMARD) when compared to bDMARDs (TNFi)
    - Similar safety profile for a population of pregnant women (except preterm birth) between bDMARDs (non-TNFi) and the general population, however, only very low-quality data available
- csDMARD-IR:
    - Similar safety profile between bDMARDs (± csDMARDs) and placebo ± csDMARDs or csDMARDs only (outcomes: discontinuation due to AEs, overall serious AEs)
    - Increased risk of overall AEs, overall infection, herpes zoster infection and upper respiratory tract infection following the use of tsDMARDs (± csDMARDs) when compared to placebo ± csDMARDs. A similar safety profile for the same comparison for the following outcomes: overall serious AEs, serious infection and VTEs
    - Similar safety profile between bDMARDs (TNFi; ± csDMARDs) and triple csDMARD therapy (outcomes: discontinuation due to AEs, overall AEs, and overall serious AEs) with exception of lower odds of infection in favour of triple csDMARD therapy
    - Similar safety profile between bsDMARDs and reference bDMARDs (outcomes: discontinuation due to any reason, overall serious AEs and overall serious infections)
- bDMARD-IR:
    - Similar safety profile between b/tsDMARDs (± csDMARDs) and placebo ± csDMARDs or csDMARDs only

- No information regarding the risk of infection was reported for tsDMARDs in this population
- Similar safety profile between bDMARDs (non-TNFi; ± csDMARDs) and tsDMARDs (± csDMARDs)

FAQ8: Does treatment increase my cancer risk in the long term?

- Pre-treated with csDMARDs:
  - Similar risk of developing cancer (solid cancer, haematological cancer, lymphoma, skin cancers [melanoma and NMSC] or breast cancer) following the use of b/tsDMARDs (± csDMARDs) and csDMARDs alone or csDMARDs ± placebo
  - Increase in the incidence of malignancies (except NMSC) following the use of TOF (tsDMARD) when compared to bDMARDs (TNFi)
- csDMARD-IR:
  - Similar risk of developing malignancies/cancer following the use of bDMARDs (± csDMARDs or as monotherapy) or tsDMARDs (± csDMARDs) and placebo ± csDMARDs or csDMARDs only
  - Similar risk of developing cancer following the use of bDMARDs (TNFi) ± csDMARDs and triple csDMARD therapy
- bDMARD-IR:
  - Similar risk of developing cancer following the use of bDMARDs (± csDMARDs) and csDMARDs
  - Lack of evidence for tsDMARDs

Note on safety of treatments

Following the latest results of the ORAL Surveillance study presented in Tables 12 and 16, TOF (tsDMARD) received a warning for use due to increased MACE and malignant disorders (excluding NMSC).[27] Moreover, all tsDMARDs (TOF, BARI, UPA and FLN) and some newer csDMARDs (ADA, ETN, IFX, SRL and RTX) are currently on the list of medicines under additional monitoring published by the EMA due to being a new active substance and/or new biological.[30]

Currently, FLN is authorised for use in Europe[30], however, the drug was rejected by FDA mid-2020 for use in patients with RA due to concerns of testicular toxicity associated with high doses of FLN.[31] The safety trial is currently underway with the primary results expected by mid-2021.[32]

4.2 Strengths, limitations and uncertainties

This report was developed using evidence from systematic reviews and supplemented by online resources. Its strengths include comprehensive literature searches without language restriction, the inclusion of the highest certainty evidence screened by two reviewers as well as coverage of a wide range of FAQs. However, some limitations or/and uncertainties should be taken into consideration.

The German guideline summarised in this report included evidence up to 2016, thus, our literature searches focused on the evidence published since 2016 (for details see 2.4 methods section).

The systematic reviews included mostly drugs that were approved for use in practice at the time of preparation of the article by the authors. Thus, older systematic reviews might not include all drugs of interest as specified in the PICO (Table 1). Moreover, due to ongoing research on some of the newer substances, such as FLN, some evidence might not yet be available and included in the systematic reviews. Wherever possible, we included the evidence for patients pre-treated with csDMARDs, however, systematic reviews often failed to appropriately report on the concomitant therapy, used alongside the treatments of interest. Thus, it is very likely that some systematic reviews may include patients who were csDMARDs-naïve.

The report is focused mostly on the combined effects of the drugs at the class level (where possible) rather than focusing on each drug in each class specifically. Thus, the actual effects of individual medications used by patients in practice may differ. In most articles, the effects of all drug doses available at the time of preparation of systematic reviews were combined in a single estimate. For non-TNFis, the reviewer had to provide the range of the results as most often the data was reported per drug and/or dosage. Some estimates are based on the underpowered analysis (with wide 95%CI) and it is unclear if those differences are clinically meaningful (e.g. VTEs reported in Wang 2020[23]; Table 14).

Due to the time constraints, the current evidence report does not include any evidence related to down-titration or discontinuation of the drugs of interest and their effect on patients with RA. The evidence for pregnant women who are treated with the drugs of interest was included if available. Additional searches for this patient population were not performed.

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APPENDIX 1: SEARCH STRATEGIES

Database	Dates	Results
CDSR	2016 – Iss 3, Mar 2021	31
HTA	2016 – 18 Mar 2021	24
KSR Evidence	2016 – 18 Mar 2021	1053
Epistemonikos	2016 – 18 Mar 2021	1747
INAHTA	2016 – 18 Mar 2021	25
GIN	2016 – 16 Mar 2021	6
NHS Evidence	2016 – 18 Mar 2021	764
NICE	2016 – 18 Mar 2021	10
ECRI	2016 – 16 Mar 2021	17
BSR	2016 – 12 Mar 2021	2
ACR	2016 – 12 Mar 2021	1
The Emerging EULAR Network	2016 – 12 Mar 2021	2
CRA	2016 – 12 Mar 2021	0
Embase	2016 – 17 Mar 2021	816
MEDLINE	2016 – 17 Mar 2021	367
Total		**4865**
Total after deduplication		**3041**

CDSR (Wiley): up to Issue 3, March 2021
Searched: 18.3.21

#1 MeSH descriptor: [Arthritis, Rheumatoid] explode all trees 6170
#2 ((Arthrit* or artrit* or disease* or condition* or nodule*) near/2 (deformans or rheumat* or reumat* or revmatoid or revmatic or revmarthrit*)):ti,ab,kw 18896
#3 (rheumarthritis or (beauvais near/2 disease*)):ti,ab,kw 0
#4 ((Chronic or rheumatic) near/2 (polyarthritis or "poly arthritis" or rheumatism)):ti,ab,kw 185
#5 MeSH descriptor: [Felty Syndrome] explode all trees 0
#6 MeSH descriptor: [Pneumoconiosis] explode all trees 97
#7 (((felty* or caplan*) near/2 (syndrome* or disease*)) or lung coniosis or pneumoconiosis or pneumoconiotic lesion* or pneumokoniosis or pneumonoconiosis or pneumonokoniosis or silicoarthritis):ti,ab,kw 79
#8 #1 or #2 or #3 or #4 or #5 or #6 or #7 with Cochrane Library publication date Between Jan 2016 and Apr 2021 11467

CDSR = 31
Cochrane Protocols = 4
CENTRAL = 11425
Clinical Answers = 7

Health Technology Assessment database (HTA) (www.crd.york.ac.uk/): up to 31 March 2018
Searched: 18.3.21

☐	1	MeSH DESCRIPTOR Arthritis, Rheumatoid EXPLODE ALL TREES	537
☐	2	(Arthrit* or artrit* or disease* or condition* or nodule*) AND (deformans or rheumat* or reumat* or revmatoid or revmatic or revmarthrit*)	1261
☐	3	(rheumarthritis) OR ("beauvais disease*")	0
☐	4	(Chronic or rheumatic) AND (polyarthritis or "poly arthritis" or rheumatism)	57
☐	5	MeSH DESCRIPTOR Felty Syndrome EXPLODE ALL TREES	0
☐	6	MeSH DESCRIPTOR Pneumoconiosis EXPLODE ALL TREES	8
☐	7	(felty* or caplan*) AND (syndrome* or disease*)	3
☐	8	("lung coniosis" or pneumoconiosis or pneumoconiotic lesion* or pneumokoniosis or pneumonoconiosis or pneumonokoniosis or silicoarthritis)	2
☐	9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8	1275
☐	10	(9) IN HTA FROM 2016 TO 2021	24

KSR Evidence (www.ksrevidence.com): up to 18 March 2018
Searched: 18.3.21

1 ((Arthrit* or artrit* or disease* or condition* or nodule*) near/2 (deformans or rheumat* or reumat* or revmatoid or revmatic or revmarthrit*)) in Title or Abstract 1251 results
2 rheumarthritis in Title or Abstract 0 results
3 beauvais near/2 disease* in Title or Abstract 0 results
4 ((Chronic or rheumatic) near/2 (polyarthritis or "poly arthritis" or rheumatism)) in Title or Abstract 2 results
5 (((felty* or caplan*) near/2 (syndrome* or disease*)) or lung coniosis or pneumoconiosis or pneumoconiotic lesion* or pneumokoniosis or pneumonoconiosis or pneumonokoniosis or silicoarthritis) in Title or Abstract 11 results
6 #1 or #2 or #3 or #4 or #5 in All text Date published: 2016 - 2021 1053 results
Sorted by risk of bias
Search run Thu Mar 18 2021

Epistemonikos (epistemonikos.org): up to 18 March 2021
Searched: 18.3.21

(title:((title:((Arthrit* OR artrit* OR disease* OR condition* OR nodule*) AND (deformans OR rheumat* OR reumat* OR revmatoid OR revmatic OR revmarthrit*)) OR abstract:((Arthrit* OR artrit* OR disease* OR condition* OR nodule*) AND (deformans OR rheumat* OR reumat* OR revmatoid OR revmatic OR revmarthrit*))) OR (title:(rheumarthritis) OR abstract:(rheumarthritis)) OR (title:("beauvais disease*") OR abstract:("beauvais disease*")) OR (title:((Chronic OR rheumatic) AND (polyarthritis OR "poly arthritis" OR rheumatism)) OR abstract:((Chronic OR rheumatic) AND (polyarthritis OR "poly arthritis" OR rheumatism))) OR (title:((felty* OR caplan*) AND (syndrome* OR

disease*)) OR abstract:((felty* OR caplan*) AND (syndrome* OR disease*))) OR (title:("lung coniosis" OR pneumoconiosis OR "pneumoconiotic lesion*" OR pneumokoniosis OR pneumonoconiosis OR pneumonokoniosis OR silicoarthritis) OR abstract:("lung coniosis" OR pneumoconiosis OR "pneumoconiotic lesion*" OR pneumokoniosis OR pneumonoconiosis OR pneumonokoniosis OR silicoarthritis))) OR abstract:((title:((Arthrit* OR artrit* OR disease* OR condition* OR nodule*) AND (deformans OR rheumat* OR reumat* OR revmatoid OR revmatic OR revmarthrit*)) OR abstract:((Arthrit* OR artrit* OR disease* OR condition* OR nodule*) AND (deformans OR rheumat* OR reumat* OR revmatoid OR revmatic OR revmarthrit*))) OR (title:(rheumarthritis) OR abstract:(rheumarthritis)) OR (title:("beauvais disease*") OR abstract:("beauvais disease*")) OR (title:((Chronic OR rheumatic) AND (polyarthritis OR "poly arthritis" OR rheumatism)) OR abstract:((Chronic OR rheumatic) AND (polyarthritis OR "poly arthritis" OR rheumatism))) OR (title:((felty* OR caplan*) AND (syndrome* OR disease*)) OR abstract:((felty* OR caplan*) AND (syndrome* OR disease*))) OR (title:("lung coniosis" OR pneumoconiosis OR "pneumoconiotic lesion*" OR pneumokoniosis OR pneumonoconiosis OR pneumonokoniosis OR silicoarthritis) OR abstract:("lung coniosis" OR pneumoconiosis OR "pneumoconiotic lesion*" OR pneumokoniosis OR pneumonoconiosis OR pneumonokoniosis OR silicoarthritis))))

Restricted to Systematic reviews, 2016-2021

1747 results

International HTA Database (database.inahta.org/): up to 18 March 2021
Searched: 18.3.21

(("lung coniosis" OR pneumoconiosis OR "pneumoconiotic lesion*" OR pneumokoniosis OR pneumonoconiosis OR pneumonokoniosis OR silicoarthritis)) OR ((felty* OR caplan*) AND (syndrome* OR disease*)) OR ("Pneumoconiosis"[mh]) OR ("Felty Syndrome"[mh]) OR ((Chronic OR rheumatic) AND (polyarthritis OR "poly arthritis" OR rheumatism)) OR ((rheumarthritis) OR ("beauvais disease*")) OR ((Arthrit* OR artrit* OR disease* OR condition* OR nodule*) AND (deformans OR rheumat* OR reumat* OR revmatoid OR revmatic OR revmarthrit*)) OR ("Arthritis, Rheumatoid"[mh])

220 results

Filtered by date 2016-2021 **25 results**

Guidelines International Network (guidelines.ebmportal.com)

Searched: 16.3.21

Search term – restricted to 2016-2021 and completed guidelines	**Hits**
"rheumatoid arthritis"	6

NHS Evidence (evidence.nhs.uk): up to 18 March 2021
Searched: 18.3.21

Search terms – limited to Guidance / Systematic reviews 2016-2021	Hits
"rheumatoid arthritis"	764
"arthritis, rheumatoid"	0
"chronic rheumatism"	0
"rheumatic polyarthritis"	0
"rheumatic poly arthritis"	0
Total	**764**

National Institute for Health and Care Excellence (nice.org.uk)
Searched: 18.3.21

Search terms – restricted 2016-2021	Hits
rheumatoid arthritis	10
chronic rheumatism	0
rheumatic polyarthritis	0
rheumatic poly arthritis	0
Total	**10**

ECRI https://guidelines.ecri.org/
Searched: 16.3.21

Search terms	Hits
Rheumatoid or rheumatic near/2 arthritis	17

British Society for Rheumatology (https://www.rheumatology.org.uk/)
Searched: 12.3.21

Home page / Guidelines / Current guidelines – scanned for relevancy

2 results

American College of Rheumatology (https://www.rheumatology.org/)
Searched: 12.3.21

Home page / Guidelines / Rheumatoid Arthritis

1 result

The Emerging EULAR Network (https://emeunet.eular.org/index.cfm)
Searched: 12.3.21

Home page / Rheumatoid Arthritis / Recommendations and Guidelines – restricted to 2016-2021 and scanned for relevancy

2 results

Canadian Rheumatology Association (https://rheum.ca/)
Searched: 12.3.21

Home page/ Clinical Guidelines & Position Statements – restricted to 2016-2021 and scanned for relevancy

0 results

Embase (Ovid): 1974 – 17 March 2021
Searched: 18.3.21

1 rheumatoid arthritis/ (186940)
2 ((Arthrit$ or artrit$ or disease$ or condition$ or nodule$) adj2 (deformans or rheumat$ or reumat$ or revmatoid or revmatic or revmarthrit$)).ti,ab,ot. (195166)
3 (rheumarthritis or (beauvais adj2 disease$)).ti,ab,ot. (8)
4 ((Chronic or rheumatic) adj2 (polyarthritis or poly arthritis or rheumatism)).ti,ab,ot. (1528)
5 Felty syndrome/ (858)
6 Pneumoconiosis/ (5619)
7 (((felty$ or caplan$) adj2 (syndrome$ or disease$)) or lung coniosis or pneumoconiosis or pneumoconiotic lesion$ or pneumokoniosis or pneumonoconiosis or pneumonokoniosis or silicoarthritis).ti,ab,ot. (4902)
8 or/1-7 (248891)
9 *decision making/ or *patient decision making/ or *shared decision making/ (67963)
10 exp *decision support system/ (12877)
11 ((share$ or sharing$ or inform$) adj3 (decision$ or deciding$ or choice$)).ti,ab. (55543)
12 (decision$ adj2 aid$).ti,ab. (9305)
13 ((decision$ or choice$) adj3 (making$ or support$ or behaviour$ or behavior$)).ti,ab. (246374)
14 ((patient$ or consumer$) adj2 (involve$ or involving or participat$)).ti,ab. (102399)
15 ((patient-centred or patient-centered) adj2 care).ti,ab. (9677)
16 (person centred or person centered).ti,ab. (7202)
17 sdm.ti,ab. (3781)
18 or/9-17 (426409)
19 8 and 18 (4443)
20 disease modifying antirheumatic drug/ (18721)
21 (bDMARD$ or tsdmard or "b/tsdmard" or csDMARD).ti,ab,ot. (3198)
22 ((biologic or target$ synthetic or synthetic target$ or conventional synthetic) adj (disease modif$ antirheumatic or disease-modif$ anti-rheumatic) adj (drug$ or agent$)).ti,ab,ot. (2012)
23 ((biologic anti-rheumatic or biologic antirheumatic) adj (drug$ or agent$)).ti,ab,ot. (35)

24 ((target$ synthetic or synethetic target$ or biologic or conventional synthetic) adj dmard).ti,ab,ot. (1028)
25 ("treat to target" or "T2T" or "treatto target").ti,ab,ot. (3568)
26 abatacept/ (9890)
27 (Abatacept or "bms 188667" or "bms188667" or "CTLA4 Ig" or "CTLA4 immunoglobulin" or "CTLA4Ig" or Orencia or "CTLA4 IGG4M" or "RG 1046" or "RG1046" or "RG2077" or "RG 2077" or 332348-12-6).ti,ab,ot,rn. (11095)
28 Rituximab/ (84898)
29 (Rituximab or "abp 798" or "abp798" or blitzima or "ct p 10" or "ctp 10" or "gp 2013" or "gp2013" or "mk8808" or "pf 05280586" or "pf 5280586" or "pf05280586" or "pf5280586" or "r 105" or "r105" or reditux or "rg 105" or "rg105" or ritemvia or ritumax or Rituxan or ritutxin or rituzena or rixathon or riximyo or "ro 452294" or "ro452294" or ruxience or truxima or tuxella or 174722-31-7).ti,ab,ot,rn. (87701)
30 Anakinra/ (3296)
31 (Anakinra or antril or kineret or "recombinant interleukin 1 receptor antagonist$" or recombinant interleukin one receptor antagonist$ or "recombinant interleukin 1 receptor blocker$" or recombinant interleukin one receptor blocker$ or IL-1RA or 143090-92-0).ti,ab,ot,rn. (15303)
32 Antirheumatic agent/ (12345)
33 (Anti-il6 or anti-interleukin-6).ti,ab. (1109)
34 Tocilizumab/ (15241)
35 (Tocilizumab or actemra or actemra200 or atlizumab or lusinex or r-1569 or r1569 or roactemra or 375823-41-9).ti,ab,ot,rn. (15963)
36 Sarilumab/ (965)
37 (Sarilumab or kevzara or regn-88 or regn88 or sar-153191 or sar153191 or 118954ad1-98-7).ti,ab,ot,rn. (994)
38 Tumor necrosis factor inhibitor/ (15173)
39 (Tumo?r necrosis factor inhibitor$ or anti TNF agent$ or anti TNF alpha agent$ or anti tumo?r necrosis factor agent$ or TNF alpha inhibitor$ or TNF inhibitor$ or tumo?r necrosis factor alpha inhibitor$).ti,ab,ot. (15883)
40 Adalimumab/ (35939)
41 (((Adalimumab$ or abp-501 or abp501 or abt-d2e7 or abtd2e7 or adaly or amgevita or amjevita or avt-02 or avt02 or bat-1406 or bat1406 or bax-2923 or bax2923 or bax-923 or bax923 or bi695501 or bi695501 or chs-1420 or chs1420 or ct-p17 or ctp17 or cyltezo or da-3113 or da3113 or dmb-3113 or dmb3113 or examptia or fkb-327 or fkb327 or fyzoclad or gp-2017 or gp2017) and hadlima) or halimatoz or hefiya or hlx-03 or hlx03 or hulio or humira or hyrimoz or ibi-303 or ibi303 or idacio or imraldi or kromeya or lu-200134 or lu200134 or m-923 or m923 or mabura or "monoclonal antibody D2E7" or msb-11022 msb11022 or ons-3010 or ons3010 or pf-06410293 or pf06410293 or pf-6410293 or pf6410293 or raheara or sb-5 or sb5 or solymbic or trudexa or zrc-3197 or zrc3197 or 1446410-95-2 or 331731-18-1).ti,ab,ot,rn. (30083)
42 Certolizumab pegol/ (7156)
43 (Certolizumab or cdp-870 or cdp870 or cimzia or pha-738144 or pha738144).ti,ab,ot,rn. (7733)
44 (pegylated tumo?r necrosis factor alpha adj (antibod$ or anti-bod$)).ti,ab,ot. (0)
45 Golimumab/ (7571)
46 (Golimumab or cnto-148 or cnto148 or Simponi or 476181-74-5).ti,ab,ot,rn. (7697)

47 Infliximab/ (53113)
48 (Infliximab or abp-710 or abp710 or avakine or ct-p13 or flixabi or gp-1111 or gp1111 or inflectra or ixifi or pf-06438179 or pf06438179 or pf-6438179 or pf6438179 or remicade or remsima or renflexis or revellex or ta-650 or ta650 or zessly or 170277-31-3).ti,ab,ot,rn. (54025)
49 Tumor necrosis factor decoy receptor/ (125)
50 (Tnf decoy receptor$ or tumo?r necrosis factor decoy receptor$ or TNFR$).ti,ab,ot. (12825)
51 Etanercept/ (32728)
52 (Etanercept or avent or benepali or embrel or Enbrel or enerceptan or enia-11 or enia11 or erelzi or eticovo or gp-2015 or gp2015 or infinitam or lifmior or opinercept or recombinant tumo?r necrosis factor receptor Fc fusion protein$ or tnr-001 or tnr001 or tumo?r necrosis factor receptor Fc fusion protein$ or tunex or ylb-113 or ylb113 or 185243-69-0 or 200013-86-1 or 2055118-96-0).ti,ab,ot,rn. (33621)
53 Janus kinase inhibitor/ (3428)
54 (Janus kinase inhibitor$ or jak inhibitor$ or janus tyrosine kinase inhibitor$).ti,ab,ot. (4894)
55 Tofacitinib/ (5270)
56 (Tofacitinib or cp-690-550 or "cp 690,50" or cp-690550 or cp690-550 or "cp690,550" or cp690550 or tasocitinib or xeljanz or 477600-75-2 or 540737-29-9).ti,ab,ot,rn. (5558)
57 Baricitinib/ (1733)
58 (Baricitinib or incb-028050 or incb028050 or incb-28050 or incb28050 or ly-3009104 or ly3009104 or Olumiant or 1187594-09-7).ti,ab,ot,rn. (1778)
59 (Upadacitinib or abt-494 or abt494 or rinvoq or 1310726-60-3 or 1607431-21-9).ti,ab,ot,rn. (668)
60 Filgotinib/ (552)
61 (Filgotinib or g-146034 or g-146034-101 or g146034 or g146034-101 or glpg-0634 or glpg0634 or gs-6034 or gs6034 or 1206161-97-8 or 1540859-07-1 or 1802998-75-9).ti,ab,ot,rn. (577)
62 Methotrexate/ (183061)
63 (Methotrexate or methopterine or ametopterine or abitrexate or amethopterin amethopterine or antifolan or biotrexate or canceren or cl-14377 or cl14377 emtexate or emthexat or emthexate or farmitrexat or farmitrexate or farmotrex or folex or ifamet or imeth or intradose or jylamvo or lantarel or ledertrexate or maxtrex or metex or methoblastin or methohexate or methotrate or methotrexate or methotrexate or methotrexate or methoxtrexate ormethrotrexate or methylaminopterin or methylaminopterine or metical or metoject or metothrexate or metotrexat or methotrexate or metotrexin or metrex or mexate or mpi-5004 or mpi5004 or MTX or neotrexate or nordimet or novatrex or nsc-740 or nsc740 or otrexup or rasuvo or reumatrex or rheumatrex or texate or texorate or trexall or xaken or xatmep or zexate or 15475-56-6 or 59-05-2 or 7413-34-5).ti,ab,ot,rn. (191098)
64 Leflunomide/ (12412)
65 (Leflunomide$ or arava or hwa-486 or hwa486 or repso or rs-34821 or rs34821 or su-101 or su1010 or 75706-12-6).ti,ab,ot,rn. (12754)
66 salazosulfapyridine/ (26190)
67 (Salazosulfapyridine or azlufidine en-tabs or azopyrin or azopyrine or azosulfidine or azulfide or azulfidina or Azulfidine or azulfin or benzosulfa or colo pleon or colopleon or

disalazin or gastropyrin or pleon ra or pyralin en or rorasul or rosulfant or "s.a.s.-500" or salazine or salazo sulfapyridine or salazodin or salazopirina or salazopyridin$ or salazopyrin$ or salazosulfa pyridine or salazosulfpyridine or salicyl azo sulfapyridine or salicylazosulfapyridin$ or salisulf or salopyr or saridine or sas-500 or sas500 or sulcolon or sulfasalazine or sulfasalizine or sulfosalazine or sulphasalazine or zopyrin or 599-79-1).ti,ab,ot,rn. (26977)
68 Hydroxychloroquine/ (31239)
69 (Hydroxychloroquine or chloroquinol or ercoquin or hydrochloroquine or hydrocloroquine or oxychloroquine or sn-8137 or sn8137 or 118-42-3 or 525-31-5).ti,ab,ot,rn. (31862)
70 or/20-69 (407498)
71 19 and 70 (1644)
72 limit 71 to yr="2016 -Current" (816)

MEDLINE, Epub Ahead of Print, In-Process, In-Data_Review & Other Non-Indexed Citations, Daily and Versions (Ovid): 1946 – 17 March 2021

Searched: 18.3.21

1 Arthritis, Rheumatoid/ (101059)
2 ((Arthrit$ or artrit$ or disease$ or condition$ or nodule$) adj2 (deformans or rheumat$ or reumat$ or revmatoid or revmatic or revmarthrit$)).ti,ab,ot. (132139)
3 (rheumarthritis or (beauvais adj2 disease$)).ti,ab,ot. (5)
4 ((Chronic or rheumatic) adj2 (polyarthritis or poly arthritis or rheumatism)).ti,ab,ot. (3248)
5 Felty Syndrome/ (719)
6 Pneumoconiosis/ (6675)
7 (((felty$ or caplan$) adj2 (syndrome$ or disease$)) or lung coniosis or pneumoconiosis or pneumoconiotic lesion$ or pneumokoniosis or pneumonoconiosis or pneumonokoniosis or silicoarthritis).ti,ab,ot. (5150)
8 or/1-7 (167854)
9 exp Decision Making/ (208871)
10 exp decision support techniques/ (78900)
11 exp Decision Theory/ (12373)
12 ((share$ or sharing$ or inform$) adj3 (decision$ or deciding$ or choice$)).ti,ab. (40137)
13 (decision$ adj2 aid$).ti,ab. (6340)
14 ((decision$ or choice$) adj3 (making$ or support$ or behaviour$ or behavior$)).ti,ab. (180877)
15 ((patient$ or consumer$) adj2 (involve$ or involving or participat$)).ti,ab. (64961)
16 ((patient-centred or patient-centered) adj2 care).ti,ab. (6961)
17 (person centred or person centered).ti,ab. (5866)
18 sdm.ti,ab. (2905)
19 exp Informed Consent/ (41630)
20 (informed adj3 (consent* or agree* or assent*)).ti,ab. (40044)
21 or/9-20 (572744)
22 8 and 21 (2733)
23 exp Antirheumatic Agents/ (435244)
24 (bDMARD$ or tsdmard or "b/tsdmard" or csDMARD).ti,ab,ot. (887)

25 ((biologic or target$ synthetic or synthetic target$ or conventional synthetic) adj (disease modif$ antirheumatic or disease-modif$ anti-rheumatic) adj (drug$ or agent$)).ti,ab,ot. (957)
26 ((biologic anti-rheumatic or biologic antirheumatic) adj (drug$ or agent$)).ti,ab,ot. (15)
27 ((target$ synthetic or synethetic target$ or biologic or conventional synthetic) adj dmard).ti,ab,ot. (252)
28 ("treat to target" or "T2T" or "treatto target").ti,ab,ot. (1401)
29 Abatacept/ (2989)
30 (Abatacept or "bms 188667" or "bms188667" or "CTLA4 Ig" or "CTLA4 immunoglobulin" or "CTLA4Ig" or Orencia or "CTLA4 IGG4M" or "RG 1046" or "RG1046" or "RG2077" or "RG 2077" or 332348-12-6).ti,ab,ot,rn. (4218)
31 Rituximab/ (15358)
32 (Rituximab or "abp 798" or "abp798" or blitzima or "ct p 10" or "ctp 10" or "gp 2013" or "gp2013" or "mk8808" or "pf 05280586" or "pf 5280586" or "pf05280586" or "pf5280586" or "r 105" or "r105" or reditux or "rg 105" or "rg105" or ritemvia or ritumax or Rituxan or ritutxin or rituzena or rixathon or riximyo or "ro 452294" or "ro452294" or ruxience or truxima or tuxella or 174722-31-7).ti,ab,ot,rn. (25085)
33 Interleukin 1 Receptor Antagonist Protein/ (5298)
34 (Anakinra or antril or kineret or "recombinant interleukin 1 receptor antagonist$" or recombinant interleukin one receptor antagonist$ or "recombinant interleukin 1 receptor blocker$" or recombinant interleukin one receptor blocker$ or IL-1RA or 143090-92-0).ti,ab,ot,rn. (7350)
35 (Anti-il6 or anti-interleukin-6).ti,ab. (607)
36 (Tocilizumab or actemra or actemra200 or atlizumab or lusinex or r-1569 or r1569 or roactemra or 375823-41-9).ti,ab,ot,rn. (4305)
37 (Sarilumab or kevzara or regn-88 or regn88 or sar-153191 or sar153191 or 118954ad1-98-7).ti,ab,ot,rn. (185)
38 Tumor Necrosis Factor Inhibitors/ (783)
39 (Tumo?r necrosis factor inhibitor$ or anti TNF agent$ or anti TNF alpha agent$ or anti tumo?r necrosis factor agent$ or TNF alpha inhibitor$ or TNF inhibitor$ or tumo?r necrosis factor alpha inhibitor$).ti,ab,ot. (7665)
40 Adalimumab/ (5593)
41 (Adalimumab$ or abp-501 or abp501 or abt-d2e7 or abtd2e7 or adaly or amgevita or amjevita or avt-02 or avt02 or bat-1406 or bat1406 or bax-2923 or bax2923 or bax-923 or bax923 or bi695501 or bi695501 or chs-1420 or chs1420 or ct-p17 or ctp17 or cyltezo or da-3113 or da3113 or dmb-3113 or dmb3113 or examptia or fkb-327 or fkb327 or fyzoclad or gp-2017 or gp2017 or hadlima or halimatoz or hefiya or hlx-03 or hlx03 or hulio or humira or hyrimoz or ibi-303 or ibi303 or idacio or imraldi or kromeya or lu-200134 or lu200134 or m-923 or m923 or mabura or "monoclonal antibody D2E7" or msb-11022 msb11022 or ons-3010 or ons3010 or pf-06410293 or pf06410293 or pf-6410293 or pf6410293 or raheara or sb-5 or sb5 or solymbic or trudexa or zrc-3197 or zrc3197 or 1446410-95-2 or 331731-18-1).ti,ab,ot,rn. (9131)
42 Certolizumab Pegol/ (633)
43 (Certolizumab or cdp-870 or cdp870 or cimzia or pha-738144 or pha738144).ti,ab,ot,rn. (1336)
44 (pegylated tumo?r necrosis factor alpha adj (antibod$ or anti-bod$)).ti,ab,ot. (0)
45 (Golimumab or cnto-148 or cnto148 or Simponi or 476181-74-5).ti,ab,ot,rn. (1311)

46 Infliximab/ (10539)
47 (Infliximab or abp-710 or abp710 or avakine or ct-p13 or flixabi or gp-1111 or gp1111 or inflectra or ixifi or pf-06438179 or pf06438179 or pf-6438179 or pf6438179 or remicade or remsima or renflexis or revellex or ta-650 or ta650 or zessly or 170277-31-3).ti,ab,ot,rn. (15345)
48 Tumor Necrosis Factor Decoy Receptors/ (511)
49 (Tnf decoy receptor$ or tumo?r necrosis factor decoy receptor$ or TNFR$).ti,ab,ot. (8535)
50 Etanercept/ (5973)
51 (Etanercept or avent or benepali or embrel or Enbrel or enerceptan or enia-11 or enia11 or erelzi or eticovo or gp-2015 or gp2015 or infinitam or lifmior or opinercept or recombinant tumo?r necrosis factor receptor Fc fusion protein$ or tnr-001 or tnr001 or tumo?r necrosis factor receptor Fc fusion protein$ or tunex or ylb-113 or ylb113 or 185243-69-0 or 200013-86-1 or 2055118-96-0).ti,ab,ot,rn. (8855)
52 Janus Kinase Inhibitors/ (529)
53 (Janus kinase inhibitor$ or jak inhibitor$ or janus tyrosine kinase inhibitor$).ti,ab,ot. (2338)
54 (Tofacitinib or cp-690-550 or "cp 690,50" or cp-690550 or cp690-550 or "cp690,550" or cp690550 or tasocitinib or xeljanz or 477600-75-2 or 540737-29-9).ti,ab,ot,rn. (1662)
55 (Baricitinib or incb-028050 or incb028050 or incb-28050 or incb28050 or ly-3009104 or ly3009104 or Olumiant or 1187594-09-7).ti,ab,ot,rn. (465)
56 (Upadacitinib or abt-494 or abt494 or rinvoq or 1310726-60-3 or 1607431-21-9).ti,ab,ot,rn. (146)
57 (Filgotinib or g-146034 or g-146034-101 or g146034 or g146034-101 or glpg-0634 or glpg0634 or gs-6034 or gs6034 or 1206161-97-8 or 1540859-07-1 or 1802998-75-9).ti,ab,ot,rn. (120)
58 Methotrexate/ (38529)
59 (Methotrexate or methopterine or ametopterine or abitrexate or amethopterin amethopterine or antifolan or biotrexate or canceren or cl-14377 or cl14377 emtexate or emthexat or emthexate or farmitrexat or farmitrexate or farmotrex or folex or ifamet or imeth or intradose or jylamvo or lantarel or ledertrexate or maxtrex or metex or methoblastin or methohexate or methotrate or methotrexate or methotrexate or methotrexate or methoxtrexate ormethrotrexate or methylaminopterin or methylaminopterine or metical or metoject or metothrexate or metotrexat or methotrexate or metotrexin or metrex or mexate or mpi-5004 or mpi5004 or MTX or neotrexate or nordimet or novatrex or nsc-740 or nsc740 or otrexup or rasuvo or reumatrex or rheumatrex or texate or texorate or trexall or xaken or xatmep or zexate or 15475-56-6 or 59-05-2 or 7413-34-5).ti,ab,ot,rn. (57015)
60 Leflunomide/ (1547)
61 (Leflunomide$ or arava or hwa-486 or hwa486 or repso or rs-34821 or rs34821 or su-101 or su1010 or 75706-12-6).ti,ab,ot,rn. (2632)
62 Sulfasalazine/ (4161)
63 (Salazosulfapyridine or azlufidine en-tabs or azopyrin or azopyrine or azosulfidine or azulfide or azulfidina or Azulfidine or azulfin or benzosulfa or colo pleon or colopleon or disalazin or gastropyrin or pleon ra or pyralin en or rorasul or rosulfant or "s.a.s.-500" or salazine or salazo sulfapyridine or salazodin or salazopirina or salazopyridin$ or salazopyrin$ or salazosulfa pyridine or salazosulfpyridine or salicyl azo sulfapyridine or

salicylazosulfapyridin$ or salisulf or salopyr or saridine or sas-500 or sas500 or sulcolon or sulfasalazine or sulfasalizine or sulfosalazine or sulphasalazine or zopyrin or 599-79-1).ti,ab,ot,rn. (6559)
64 Hydroxychloroquine/ (4442)
65 (Hydroxychloroquine or chloroquinol or ercoquin or hydrochloroquine or hydrocloroquine or oxychloroquine or sn-8137 or sn8137 or 118-42-3 or 525-31-5).ti,ab,ot,rn. (7863)
66 or/23-65 (490317)
67 22 and 66 (955)
68 limit 67 to yr="2016 -Current" (367)

APPENDIX 2: RE-CALCULATIONS WITH REVMAN 5.4.1

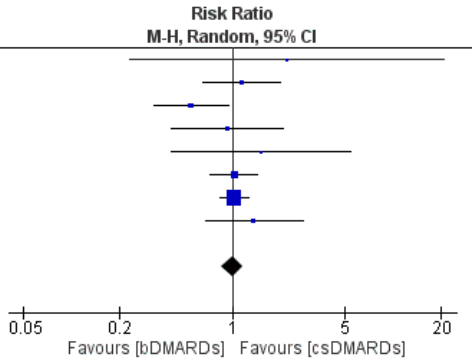
A2.1 CANCER RECURRENCE

Relative risk of (a) solid, (b) skin and (c) breast cancer recurrence between bDMARDs (TNFi) and csDMARDs (recalculated from Xie 2020a[14]; Table 16). Please note that totals refer to patient-years.

(a)

Study or Subgroup	bDMARDs (TNFi) Events	Total	csDMARDs Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Aaltonen 2015	3	233	1	169	0.5%	2.18 [0.23, 20.74]
Mamtani 2016	17	764	48	2466	7.7%	1.14 [0.66, 1.98]
Mercer 2012	29	627	23	276	8.3%	0.56 [0.33, 0.94]
Philips 2010	7	256	35	1195	3.6%	0.93 [0.42, 2.08]
Raaschou 2013	3	271	10	1370	1.4%	1.52 [0.42, 5.47]
Raaschou 2018	42	2471	155	9394	20.3%	1.03 [0.73, 1.44]
Scott 2016	109	1465	335	4631	53.5%	1.03 [0.84, 1.27]
Strangfeld 2013	18	367	13	361	4.7%	1.36 [0.68, 2.74]
Total (95% CI)		**6454**		**19862**	**100.0%**	**1.00 [0.86, 1.17]**
Total events	228		620			

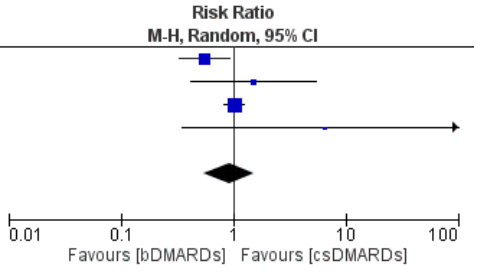
Heterogeneity: Tau² = 0.00; Chi² = 6.74, df = 7 (P = 0.46); I² = 0%
Test for overall effect: Z = 0.05 (P = 0.96)



(b)

Study or Subgroup	bDMARDs (TNFi) Events	Total	csDMARDs Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Mercer 2012	29	627	23	276	34.7%	0.56 [0.33, 0.94]
Raaschou 2013	3	271	10	1370	12.6%	1.52 [0.42, 5.47]
Scott 2016	109	1465	335	4631	49.8%	1.03 [0.84, 1.27]
Strangfeld 2013	3	30	0	28	3.0%	6.55 [0.35, 121.37]
Total (95% CI)		**2393**		**6305**	**100.0%**	**0.92 [0.55, 1.55]**
Total events	144		368			

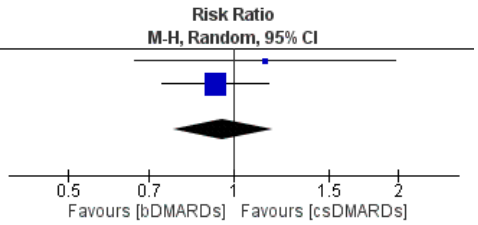
Heterogeneity: Tau² = 0.13; Chi² = 6.71, df = 3 (P = 0.08); I² = 55%
Test for overall effect: Z = 0.31 (P = 0.76)



(c)

Study or Subgroup	bDMARDs (TNFi) Events	Total	csDMARDs Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Mamtani 2016	17	764	48	2466	14.4%	1.14 [0.66, 1.98]
Raaschou 2015	120	592	120	550	85.6%	0.93 [0.74, 1.16]
Total (95% CI)		**1356**		**3016**	**100.0%**	**0.96 [0.78, 1.18]**
Total events	137		168			

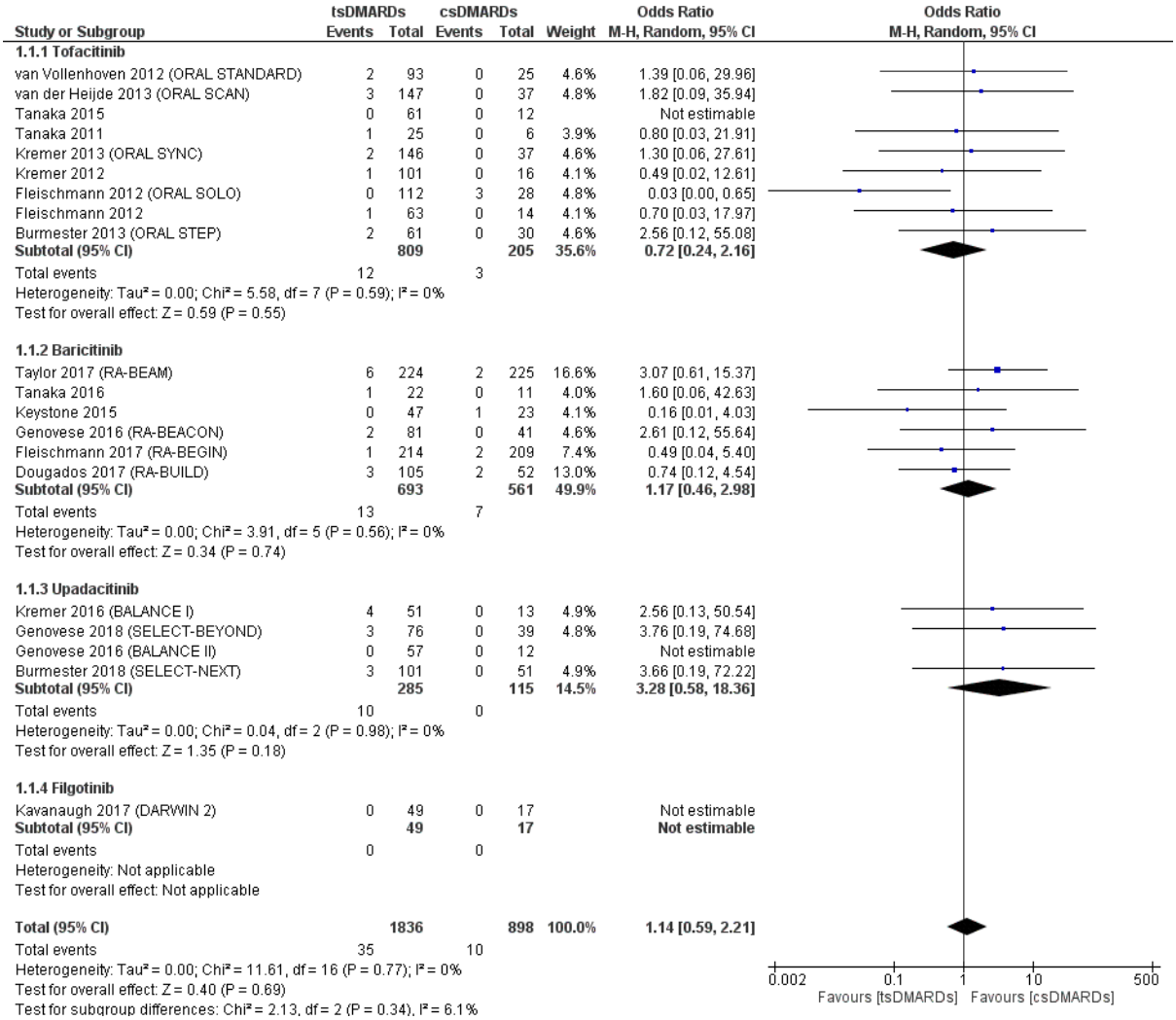
Heterogeneity: Tau² = 0.00; Chi² = 0.47, df = 1 (P = 0.49); I² = 0%
Test for overall effect: Z = 0.41 (P = 0.68)



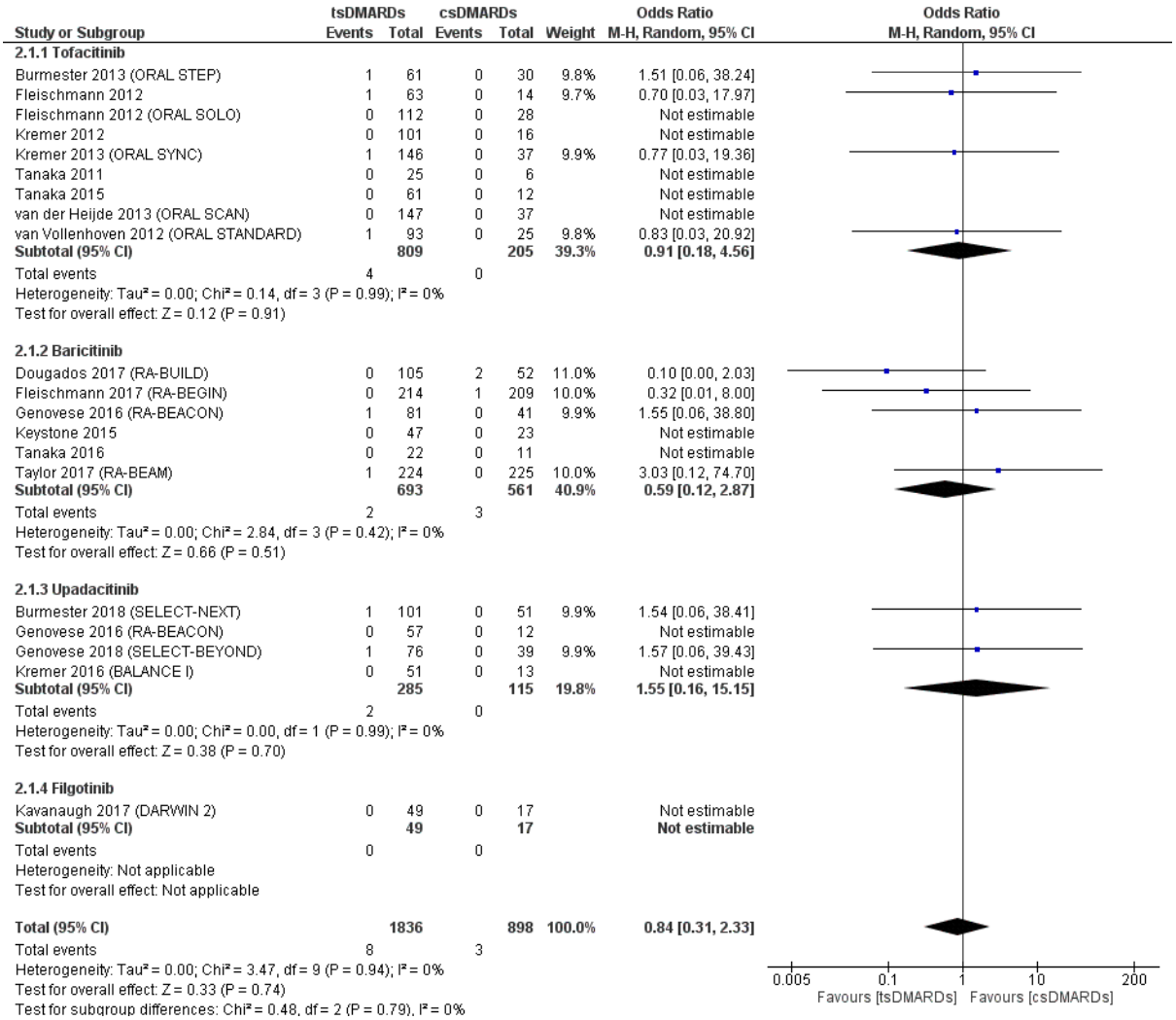
A2.2 CARDIOVASCULAR EVENTS

Odds ratio of (a) all CVEs, (b) all MACEs and (c) VTEs between tsDMARDs and csDMARDs (recalculated from Xie 2019[21]; Table 12). Please note that totals refer to patient-years.

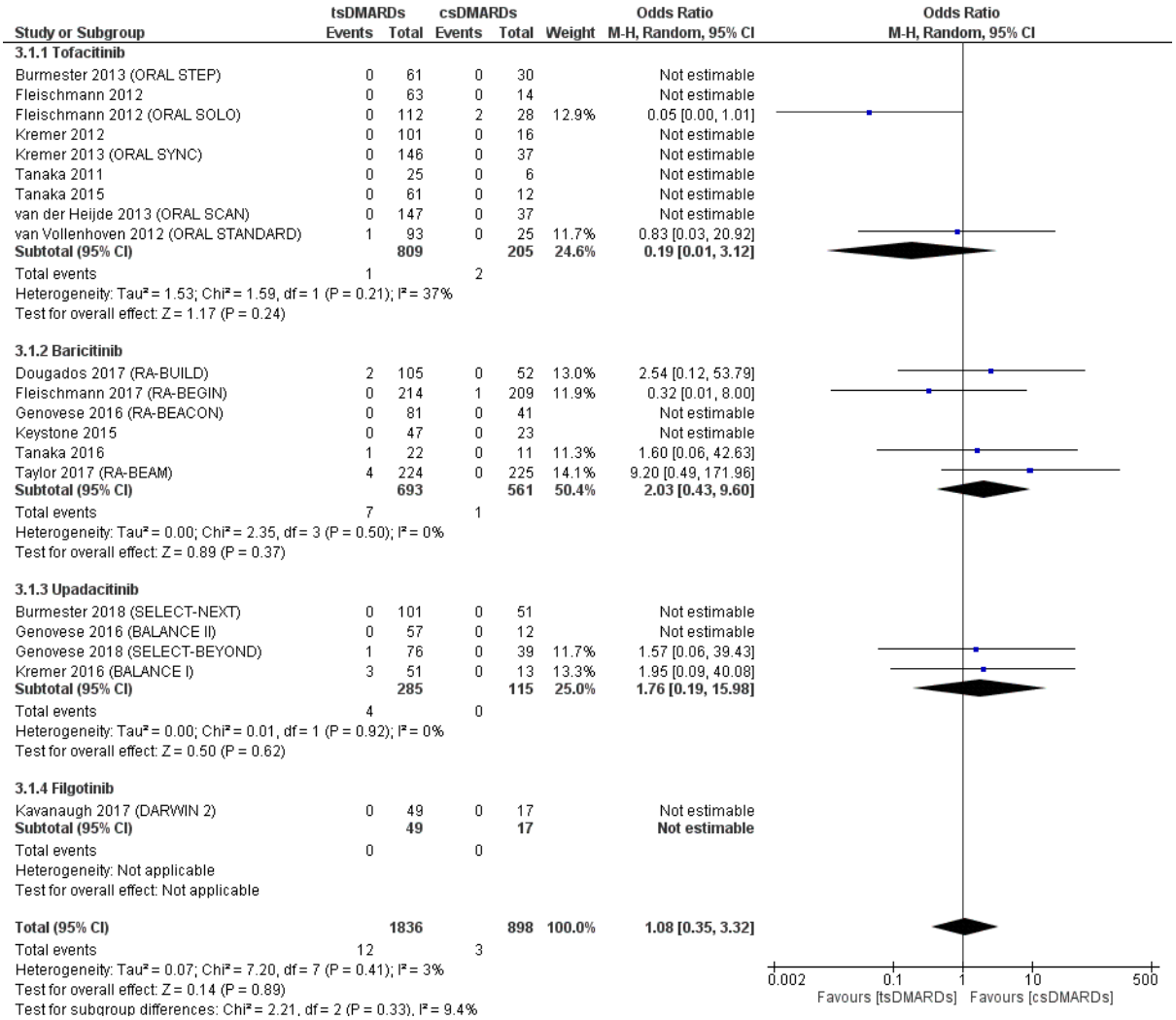
(a)



(b)


tsDMARDs
csDMARDs
Odds Ratio
Odds Ratio
Study or Subgroup
Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
2.1.1 Tofacitinib
Burmester 2013 (ORAL STEP) 1 61 0 30 9.8% 1.51 [0.06, 38.24]
Fleischmann 2012 1 63 0 14 9.7% 0.70 [0.03, 17.97]
Fleischmann 2012 (ORAL SOLO) 0 112 0 28 Not estimable
Kremer 2012 0 101 0 16 Not estimable
Kremer 2013 (ORAL SYNC) 1 146 0 37 9.9% 0.77 [0.03, 19.36]
Tanaka 2011 0 25 0 6 Not estimable
Tanaka 2015 0 61 0 12 Not estimable
van der Heijde 2013 (ORAL SCAN) 0 147 0 37 Not estimable
van Vollenhoven 2012 (ORAL STANDARD) 1 93 0 25 9.8% 0.83 [0.03, 20.92]
Subtotal (95% CI) 809 205 39.3% 0.91 [0.18, 4.56]
Total events 4 0
Heterogeneity: Tau² = 0.00; Chi² = 0.14, df = 3 (P = 0.99); I² = 0%
Test for overall effect: Z = 0.12 (P = 0.91)
2.1.2 Baricitinib
Dougados 2017 (RA-BUILD) 0 105 2 52 11.0% 0.10 [0.00, 2.03]
Fleischmann 2017 (RA-BEGIN) 0 214 1 209 10.0% 0.32 [0.01, 8.00]
Genovese 2016 (RA-BEACON) 1 81 0 41 9.9% 1.55 [0.06, 38.80]
Keystone 2015 0 47 0 23 Not estimable
Tanaka 2016 0 22 0 11 Not estimable
Taylor 2017 (RA-BEAM) 1 224 0 225 10.0% 3.03 [0.12, 74.70]
Subtotal (95% CI) 693 561 40.9% 0.59 [0.12, 2.87]
Total events 2 3
Heterogeneity: Tau² = 0.00; Chi² = 2.84, df = 3 (P = 0.42); I² = 0%
Test for overall effect: Z = 0.66 (P = 0.51)
2.1.3 Upadacitinib
Burmester 2018 (SELECT-NEXT) 1 101 0 51 9.9% 1.54 [0.06, 38.41]
Genovese 2016 (RA-BEACON) 0 57 0 12 Not estimable
Genovese 2018 (SELECT-BEYOND) 1 76 0 39 9.9% 1.57 [0.06, 39.43]
Kremer 2016 (BALANCE I) 0 51 0 13 Not estimable
Subtotal (95% CI) 285 115 19.8% 1.55 [0.16, 15.15]
Total events 2 0
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.99); I² = 0%
Test for overall effect: Z = 0.38 (P = 0.70)
2.1.4 Filgotinib
Kavanaugh 2017 (DARWIN 2) 0 49 0 17 Not estimable
Subtotal (95% CI) 49 17 Not estimable
Total events 0 0
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Total (95% CI) 1836 898 100.0% 0.84 [0.31, 2.33]
Total events 8 3
Heterogeneity: Tau² = 0.00; Chi² = 3.47, df = 9 (P = 0.94); I² = 0%
Test for overall effect: Z = 0.33 (P = 0.74)
Test for subgroup differences: Chi² = 0.48, df = 2 (P = 0.79), I² = 0%
0.005
0.1
1
10
200
Favours [tsDMARDs]
Favours [csDMARDs]

(c)


tsDMARDs
csDMARDs
Odds Ratio
Odds Ratio
Study or Subgroup
Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
3.1.1 Tofacitinib
Burmester 2013 (ORAL STEP) 0 61 0 30 Not estimable
Fleischmann 2012 0 63 0 14 Not estimable
Fleischmann 2012 (ORAL SOLO) 0 112 2 28 12.9% 0.05 [0.00, 1.01]
Kremer 2012 0 101 0 16 Not estimable
Kremer 2013 (ORAL SYNC) 0 146 0 37 Not estimable
Tanaka 2011 0 25 0 6 Not estimable
Tanaka 2015 0 61 0 12 Not estimable
van der Heijde 2013 (ORAL SCAN) 0 147 0 37 Not estimable
van Vollenhoven 2012 (ORAL STANDARD) 1 93 0 25 11.7% 0.83 [0.03, 20.92]
Subtotal (95% CI) 809 205 24.6% 0.19 [0.01, 3.12]
Total events 1 2
Heterogeneity: Tau² = 1.53; Chi² = 1.59, df = 1 (P = 0.21); I² = 37%
Test for overall effect: Z = 1.17 (P = 0.24)
3.1.2 Baricitinib
Dougados 2017 (RA-BUILD) 2 105 0 52 13.0% 2.54 [0.12, 53.79]
Fleischmann 2017 (RA-BEGIN) 0 214 1 209 11.9% 0.32 [0.01, 8.00]
Genovese 2016 (RA-BEACON) 0 81 0 41 Not estimable
Keystone 2015 0 47 0 23 Not estimable
Tanaka 2016 1 22 0 11 11.3% 1.60 [0.06, 42.63]
Taylor 2017 (RA-BEAM) 4 224 0 225 14.1% 9.20 [0.49, 171.96]
Subtotal (95% CI) 693 561 50.4% 2.03 [0.43, 9.60]
Total events 7 1
Heterogeneity: Tau² = 0.00; Chi² = 2.35, df = 3 (P = 0.50); I² = 0%
Test for overall effect: Z = 0.89 (P = 0.37)
3.1.3 Upadacitinib
Burmester 2018 (SELECT-NEXT) 0 101 0 51 Not estimable
Genovese 2016 (BALANCE II) 0 57 0 12 Not estimable
Genovese 2018 (SELECT-BEYOND) 1 76 0 39 11.7% 1.57 [0.06, 39.43]
Kremer 2016 (BALANCE I) 3 51 0 13 13.3% 1.95 [0.09, 40.08]
Subtotal (95% CI) 285 115 25.0% 1.76 [0.19, 15.98]
Total events 4 0
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.92); I² = 0%
Test for overall effect: Z = 0.50 (P = 0.62)
3.1.4 Filgotinib
Kavanaugh 2017 (DARWIN 2) 0 49 0 17 Not estimable
Subtotal (95% CI) 49 17 Not estimable
Total events 0 0
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Total (95% CI) 1836 898 100.0% 1.08 [0.35, 3.32]
Total events 12 3
Heterogeneity: Tau² = 0.07; Chi² = 7.20, df = 7 (P = 0.41); I² = 3%
Test for overall effect: Z = 0.14 (P = 0.89)
Test for subgroup differences: Chi² = 2.21, df = 2 (P = 0.33), I² = 9.4%
0.002
0.1
1
10
500
Favours [tsDMARDs]
Favours [csDMARDs]