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Biologics for rheumatoid arthritis[1]

Extract

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This report was prepared in collaboration with external experts.

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Key statement

Research question

The aim of the present investigation is

- to assess the benefit of biologics in comparison with each other

in patients with rheumatoid arthritis with regard to patient-relevant outcomes.

Table 1 below shows the biologics included in the benefit assessment (in the respective approved therapeutic indication):

Table 1: Overview of the biologics considered in the present benefit assessment for the treatment of rheumatoid arthritis in the respective approved therapeutic indication

Drug	First-line treatment (with a biologic) (combination with MTX)[a]	Further lines of treatment (with a biologic)[a]	
		Monotherapy	Combination with MTX
Abatacept	●	–	●
Adalimumab	●	●	●
Anakinra	–	–	●
Certolizumab pegol	●	●	●
Etanercept	●	●	●
Golimumab	●	–	●
Infliximab	●	–	●
Rituximab	–	–	●[b]
Tocilizumab	●	●	●

a: First-line treatment with a biologic in monotherapy is not relevant for the comparative benefit assessment of the biologics, since only 1 biologic (etanercept) is approved as first-line treatment without combination with MTX.

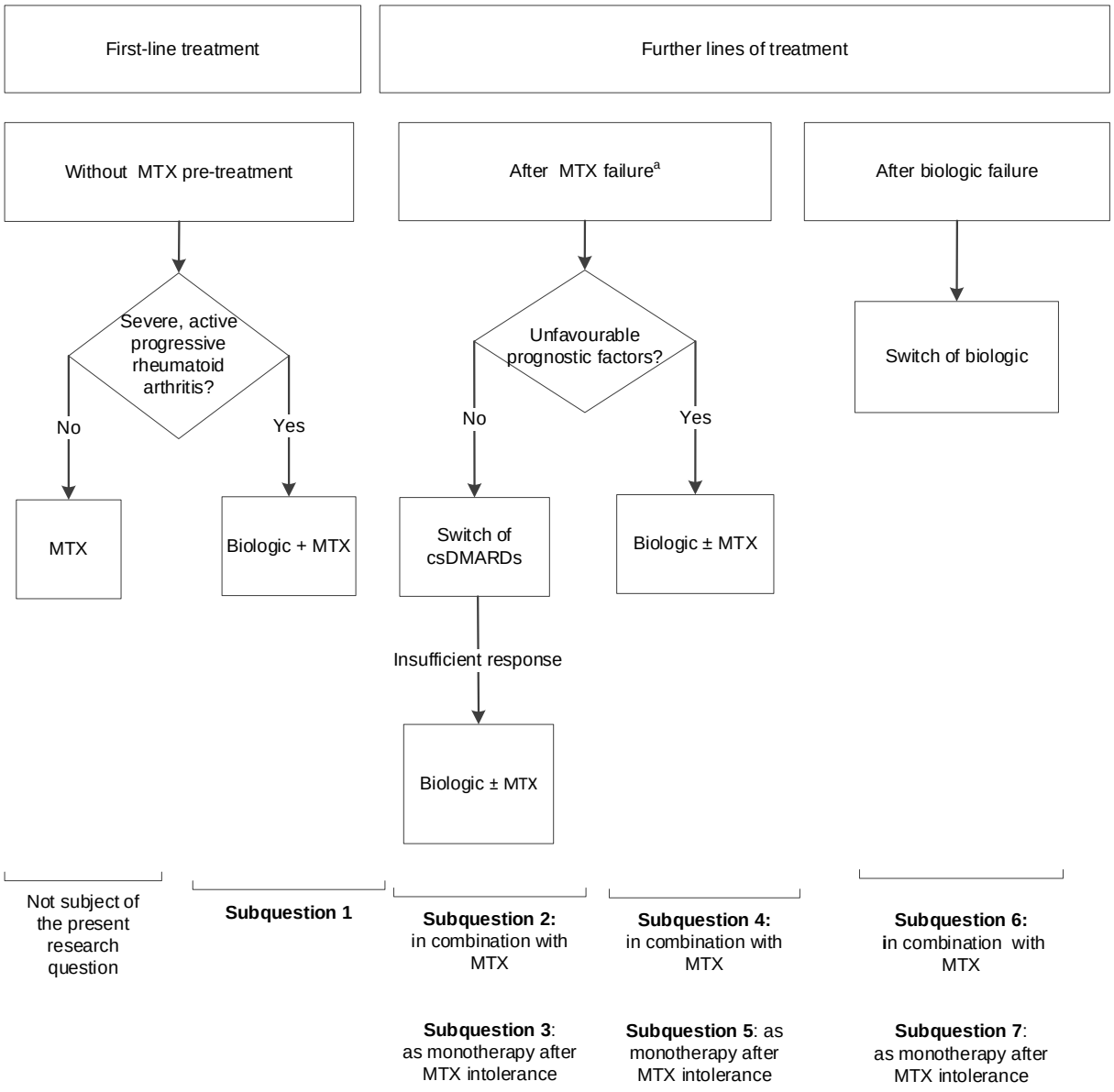
b: Rituximab is approved in patients with inadequate response or intolerance to other DMARDs including 1 or more treatments with TNF inhibitors.

● Approved in the line of treatment (as of 28 June 2017).

- Not approved in the line of treatment (as of 28 June 2017.)

DMARD: disease-modifying antirheumatic drug; MTX: methotrexate; TNF: tumour necrosis factor

Based on the approval of the biologics and the recommendations of EULAR [5], there are 7 subquestions for the present benefit assessment (see Figure 1).



a: After MTX failure, i.e., if clinical remission has not been achieved, MTX is combined with a biologic in further treatment, provided there is no MTX intolerance.

csDMARD: conventional synthetic disease-modifying antirheumatic drug; MTX: methotrexate

Figure 1: Subquestions 1 to 7 based on approval and EULAR recommendations

Conclusion

Combination therapy with methotrexate (MTX) without MTX pretreatment (Subquestion 1)

In the combination therapy with MTX without MTX pretreatment, the following biologics were compared with each other in the present benefit assessment: abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, and tocilizumab. A direct comparative study was not available for any comparison of biologics.

For the combination therapy with MTX without MTX pretreatment, the evidence base is as follows.

- there is no hint of greater or lesser benefit of any biologic versus another biologic for clinical remission (which particularly in this subquestion is the primary treatment goal to be achieved)
- there is a hint of greater benefit of adalimumab and etanercept versus certolizumab pegol and tocilizumab for low disease activity
- there is no hint of greater or lesser benefit of any further biologic versus another biologic for low disease activity
- there is no hint of greater or lesser benefit or harm of any biologic versus another biologic for further patient-relevant outcomes

Combination therapy with MTX after MTX failure (Subquestion 4)

In combination therapy with MTX after MTX failure, the following biologics were compared with each other in the present benefit assessment: abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab and tocilizumab. Only 2 studies with a direct comparison of biologics were available.

For the combination therapy with MTX after MTX failure, the evidence base is as follows:

- there is a hint of greater benefit of adalimumab, certolizumab pegol and golimumab versus anakinra for the primary treatment goal of clinical remission
- there is a hint of greater benefit of abatacept, adalimumab, infliximab, and tocilizumab versus anakinra for low disease activity
- there is hint of greater benefit of abatacept and tocilizumab versus anakinra for pain.
- there is a hint of greater benefit of golimumab versus anakinra for health-related quality of life (physical component summary score of the Short Form 36 - Health Survey)
- there is a hint of greater harm of certolizumab pegol versus all other biologics for 1 or more of the following 3 outcomes: serious adverse events, infections, serious infections. In addition, there is a hint of greater harm of golimumab and tocilizumab versus infliximab for serious infections.
- there is a hint of greater harm of anakinra versus abatacept, adalimumab, etanercept and infliximab as well as of tocilizumab versus abatacept for discontinuations due to adverse events
- there is no hint of greater or lesser benefit or harm of any other biologic versus another biologic for all further outcomes.

Monotherapy after MTX intolerance (Subquestion 5)

In monotherapy after MTX intolerance, the following biologics were compared with each other in the present benefit assessment: adalimumab and tocilizumab. For this comparison, only a single study was available for the direct comparison of both biologics. No study on certolizumab pegol and etanercept was identified that could enable a comparison with other biologics.

For monotherapy after MTX intolerance, the evidence base is as follows:

- there is no hint of greater or lesser benefit or harm of any biologic versus another biologic for the primary treatment goal of clinical remission or other outcomes

Combination therapy with MTX after biologic failure (Subquestion 6)

In the combination therapy with MTX after biologic failure, the following biologics were compared with each other in the present benefit assessment: abatacept, adalimumab, certolizumab pegol, golimumab, rituximab and tocilizumab. No relevant studies were identified for anakinra, etanercept and infliximab, so that no comparison with the other biologics was possible. There was only a single study with a direct comparison of biologics.

For the combination therapy with MTX after biologic failure, the evidence base is as follows:

- there is no hint of greater or lesser benefit or harm of any biologic versus another biologic for the primary treatment goal of clinical remission or other outcomes

Further subquestions

No conclusion was drawn for the following subquestions of the present benefit assessment due to the inadequate data situation:

- combination therapy with MTX after MTX failure and pretreatment with further conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) (Subquestion 2)
- monotherapy after MTX intolerance and pretreatment with further csDMARDs (Subquestion 3)
- monotherapy after MTX intolerance and biologic failure (Subquestion 7).

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List of abbreviations

Abbreviation	Meaning
ACR	American College of Rheumatology
AE	Adverse event
bDMARD	Biological disease-modifying antirheumatic drug
boDMARD	Biological originator disease-modifying antirheumatic drug
bsDMARD	Biosimilar disease-modifying antirheumatic drug
CDAI	Clinical Disease Activity Index
CRP	C-reactive protein
csDMARD	Conventional synthetic disease-modifying antirheumatic drug
DAS	Disease Activity Score
DMARD	Disease-modifying antirheumatic drug
EULAR	European League Against Rheumatism
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
JAK	Janus kinase inhibitor
MTX	Methotrexate
NMA	Network meta-analysis
NSAID	Non-steroidal anti-inflammatory drugs
RCT	Randomized controlled trial
SAE	Serious adverse event
SDAI	Simplified Disease Activity Index
sDMARD	Synthetic disease-modifying antirheumatic drug
SGB	Sozialgesetzbuch (Social Code Book)
TNF	Tumour necrosis factor
tsDMARD	Targeted synthetic disease-modifying antirheumatic drug
VAS	Visual analogue scale

1 Background

Cause and course of rheumatoid arthritis

Rheumatoid arthritis is an autoimmune disease that particularly affects the body's joints [1] and is the most common form of chronic inflammatory joint disease [2]. In most cases, joints distant from the centre of the body are affected, often symmetrically. Chronic inflammation of the synovial membranes leads to destruction of the joints (= cartilage and adjacent bones, capsule and ligamentous apparatus) [1,3]. In order to prevent such damage, treatment of rheumatoid arthritis is recommended as soon as the diagnosis is made [4,5]. The individual burden of disease is characterized by symptoms such as pain, fatigue and exhaustion, depressive mood disorders, functional limitations and the associated loss of independence [6-9].

Treatment goals

The primary goal of the treatment of rheumatoid arthritis is to reduce disease activity to a level at which patients are free of signs and symptoms of significant inflammatory disease activity, called clinical remission [10]. Especially for patients in whom previous treatments have failed, low disease activity is also a treatment goal [5].

Definition of clinical remission

Clinical remission is assessed on the basis of the measurement of disease activity. There are various instruments that measure the status of disease activity, such as the Disease Activity Score (DAS) 28 [11], the Simplified Disease Activity Index (SDAI) [12] and the Clinical Disease Activity Index (CDAI) [13]. Each of these instruments defines clinical remission as well as low, moderate and high disease activity by means of specific thresholds [14,15]. A working group of the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) has developed a definition [16] that defines remission using 2 alternative approaches:

- Index-based definition:
  - SDAI ≤ 3.3

    calculated from the simple sum of the following components: number of painful joints, number of swollen joints, global assessment of disease activity by the patient, global assessment of disease activity by the physician, and C-reactive protein (CRP) value in mg/dl [12].
  - CDAI ≤ 2.8

    calculated from the simple sum of the following components: number of painful joints, number of swollen joints, global assessment of disease activity by the patient, and global assessment of disease activity by the physician [16]
- Definition where all criteria must be met (designated as Boolean definition): ≤ 1 painful joint, ≤ 1 swollen joint, CRP ≤ 1 mg/dl, and global assessment of disease activity by the patient ≤ 1 on a scale of 0 to 10

The use of these two approaches is recommended according to the current European guideline for the definition of clinical remission [5,10]. The ACR/EULAR working group does not consider the definition of a DAS-28 value < 2.6 to be sufficiently stringent to measure clinical remission. This value is considered to also include patients with considerable residual disease activity [10].

Maintaining remission during the course of the disease is also an important treatment goal [10]. If clinical remission persists over a longer period of time, a reduction in medication might be considered [4,5].

Definition of low disease activity

The thresholds for measuring low disease activity are ≤ 10 for the CDAI, ≤ 11 for the SDAI, and < 3.2 for the DAS 28. All 3 instruments describe patients with no more than low disease activity with the corresponding thresholds [15]. According to EULAR recommendations, all of these 3 instruments with the corresponding thresholds are basically suitable for measuring low disease activity [5].

Treatment of rheumatoid arthritis and guideline recommendations

Non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids and disease-modifying antirheumatic drugs (DMARDs) are used in the drug treatment of rheumatoid arthritis [1]. NSAIDs have an analgesic, antipyretic and anti-inflammatory effect. However, they do not influence the long-term course of the disease. DMARDs are available for this purpose. They are currently divided into 2 classes: synthetically produced ("synthetic") DMARDs (sDMARDs) and biotechnologically produced ("biological") DMARDs (bDMARDs). Smolen 2014 [17] proposes the following nomenclature: The sDMARDs are divided into conventional sDMARDs (csDMARDs) and targeted sDMARDs (tsDMARDs). In addition to methotrexate (MTX), csDMARDs include leflunomide and sulfasalazine; tsDMARDs include Janus kinase (JAK) inhibitors. The bDMARDs are divided into original preparations (biological originator DMARDs [boDMARDs]) and biosimilars (bsDMARDs). In this assessment, boDMARDs and bsDMARDs are referred to as "biologics".

At the time of commissioning by the Federal Joint Committee (G-BA), the following biologics (trade name in brackets) were approved in Europe for the treatment of rheumatoid arthritis: abatacept (Orencia), adalimumab (Humira, Amgevita[2], Solymbic[2]), anakinra (Kineret), certolizumab pegol (Cimzia), etanercept (Enbrel, Benepali[2], Erelzi[2]), golimumab (Simponi), infliximab (Remicade, Flixabi[2], Inflectra[2], Remsima[2]), rituximab (MabThera, Truxima[2], Riximyo[2], Rixathon[2]), and tocilizumab (RoActemra) [18-33] (Status of Summary of Product Characteristics: 28 June 2017). In the present assessment, original preparations and biosimilars are combined under the respective designation of the active ingredient.

[2] Biosimilar

Biologics use different mechanisms to influence different parts of the inflammatory process. Most of them belong to the tumour necrosis factor (TNF)-α inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab). There is also an interleukin-1 inhibitor (anakinra) and an interleukin-6 inhibitor (tocilizumab). Rituximab reduces the number of mature B lymphocytes and abatacept inhibits the activation of T lymphocytes by antigen-presenting cells.

The European guideline of 2016 [4,5], which was used when preparing the report plan (protocol) of the present assessment, recommends treatment with csDMARDs as first-line treatment. MTX should be part of first-line treatment (as long as there are no contraindications and no intolerance). The use of further sDMARDs and / or biologics in further treatment lines depends on whether the treatment goal is achieved and on prognostic factors (disease activity, damage to the joints and formation of auto-antibodies). In patients without prognostically unfavourable factors, after the failure of first-line treatment with csDMARDs, a further treatment line with csDMARDs should be considered. When treating patients with prognostically unfavourable factors, however, the addition of a biologic or, more recently, a JAK inhibitor should be considered. In case of an insufficient effect of the second csDMARD in patients without prognostically unfavourable factors, treatment with TNF-α inhibitors, abatacept or tocilizumab or with a JAK inhibitor should be considered according to the guideline.

So far it is unclear how the above-mentioned biologics compare with each other [4,5]. This comparison is the aim of the present assessment.

2 Research question

The aim of the present investigation is

- to assess the benefit of biologics in comparison with each other

in patients with rheumatoid arthritis with regard to patient-relevant outcomes.

Table 2 below shows the biologics included in the benefit assessment (in the respective approved therapeutic indication):

Table 2: Overview of the biologics considered in the present benefit assessment for the treatment of rheumatoid arthritis in the respective approved therapeutic indication

Drug	**First-line treatment (with a biologic) (combination with MTX)[a]**	**Further lines of treatment (with a biologic)[a]**	
		Monotherapy	**Combination with MTX**
Abatacept	●	–	●
Adalimumab	●	●	●
Anakinra	–	–	●
Certolizumab pegol	●	●	●
Etanercept	●	●	●
Golimumab	●	–	●
Infliximab	●	–	●
Rituximab	–	–	●[b]
Tocilizumab	●	●	●

a: First-line treatment with a biologic in monotherapy is not relevant for the comparative benefit assessment of the biologics, since only 1 biologic (etanercept) is approved as first-line treatment without combination with MTX.

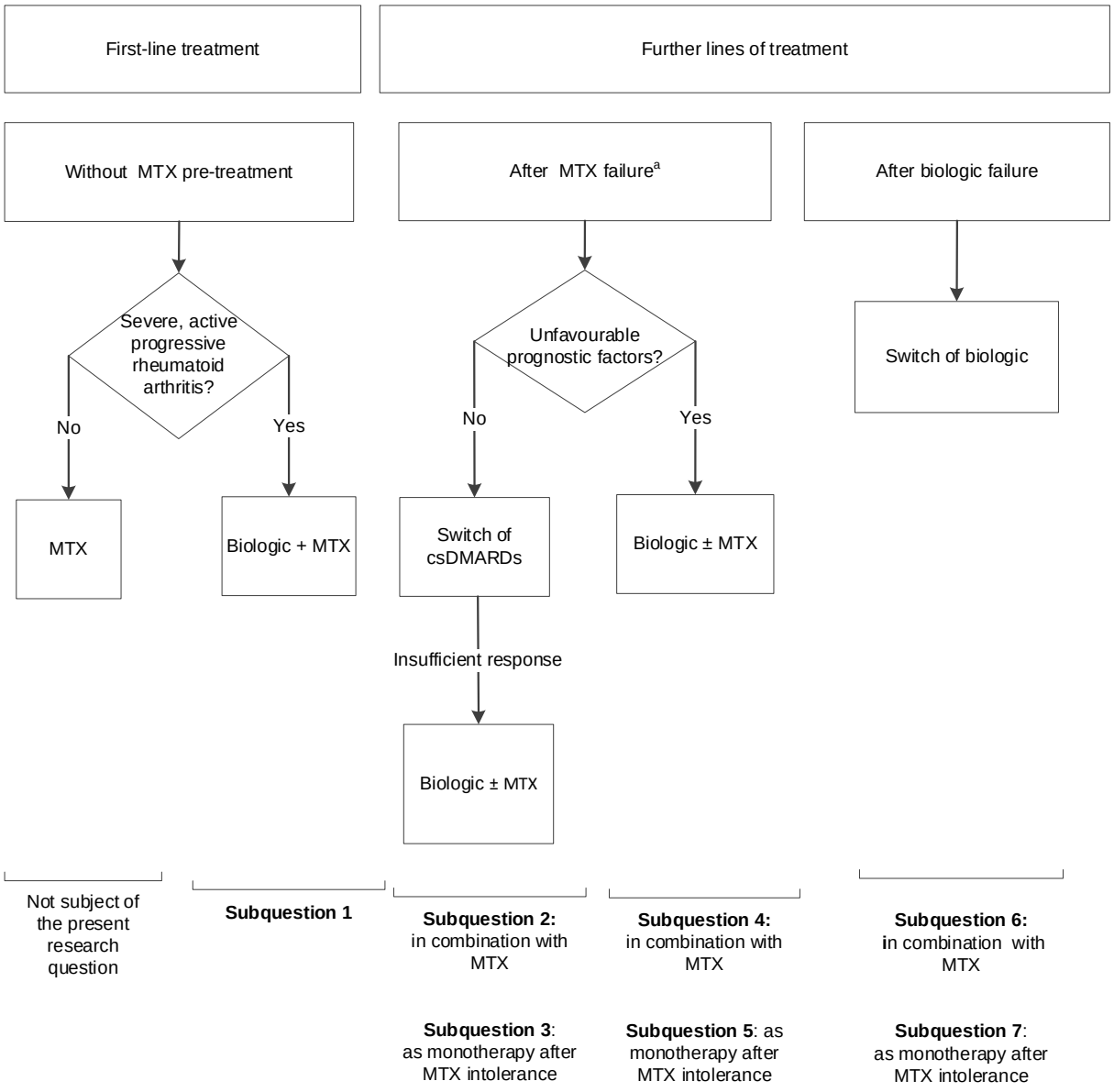
b: Rituximab is approved in patients with inadequate response or intolerance to other DMARDs including 1 or more treatments with TNF inhibitors.

● Approved in the line of treatment (as of 28 June 2017).

- Not approved in the line of treatment (as of 28 June 2017.)

DMARD: disease-modifying antirheumatic drug; MTX: methotrexate; TNF: tumour necrosis factor

Based on the approval of the biologics and the recommendations of EULAR [5], there are 7 subquestions for the present benefit assessment (see Figure 2).



a: After MTX failure, i.e., if clinical remission has not been achieved, MTX is combined with a biologic in further treatment, provided there is no MTX intolerance.

csDMARD: conventional synthetic disease-modifying antirheumatic drug; MTX: methotrexate

Figure 2: Subquestions 1 to 7 based on approval and EULAR recommendations

3 Methods

The target population of the benefit assessment was adult patients (≥ 18 years) with rheumatoid arthritis. All biologics approved at the time of commissioning by the G-BA were to be compared with each other and were therefore both test and control interventions.

The following patient-relevant outcomes were considered for the investigation:

- Clinical remission, defined according to the working group of ACR and EULAR [16] as
  - Index-based definition:
    - SDAI ≤ 3.3 calculated from the simple sum of the following components: number of painful joints, number of swollen joints, global assessment of disease activity by the patient on a scale from 0 to 10, and global assessment of disease activity by the physician on a scale from 0 to 10, and CRP value in mg/dl [12]
    - CDAI ≤ 2.8 calculated from the simple sum of the following components: number of painful joints, number of swollen joints, global assessment of disease activity by the patient on a scale from 0 to 10, and global assessment of disease activity by the physician on a scale from 0 to 10 [16]
  - Definition where all criteria must be met (referred to as Boolean definition): ≤ 1 painful joint, ≤ 1 swollen joint, CRP ≤ 1 mg/dl, and global assessment of disease activity by the patient ≤ 1 on a scale of 0 to 10

  The assessment of remission was primarily based on the CDAI ≤ 2.8.
- Low disease activity

  The assessment of low disease activity was primarily based on the CDAI ≤ 10.
- Symptoms of rheumatoid arthritis: pain, fatigue
- Physical function including activities of daily living
- Social functional level (participation in professional and social life)
- Health-related quality of life
- All-cause mortality
- Adverse effects
  - serious adverse events (SAEs)
  - discontinuation due to adverse events (AEs)
  - infections
  - serious infections

Subjective outcomes (e.g. health-related quality of life) were only considered if they had been measured with valid measurement instruments (e.g. validated scales).

Only randomized controlled trials (RCTs) with a minimum duration of 6 months (24 weeks) were included in the benefit assessment.

A systematic literature search for primary literature was performed in the databases MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials. In parallel, a search for relevant systematic reviews was conducted in the databases MEDLINE, Embase, the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects, and the Health Technology Assessment Database.

In addition, the following information sources and search techniques were considered: study registries, documents from pharmaceutical companies, publicly accessible documents from regulatory authorities, the website of the G-BA and the Institute for Quality and Efficiency in Health Care (IQWiG), as well as the screening of reference lists, documents made available from hearing procedures, and author queries.

The selection of relevant studies was carried out by 2 reviewers independently of each other. Discrepancies were resolved by discussion between them. Data were extracted into standardized tables. In order to assess the qualitative certainty of the results, the risk of bias was evaluated at study and outcome level and classified as low or high. For studies whose control intervention was considered exclusively as a common comparator in a network meta-analysis (NMA), the risk of bias was evaluated only if it was to be examined as a factor in the check of structural quality or if it was decisive for deriving the evidence base (existence of a statistically significant difference on the basis of an indirect comparison in which only one study was available for one or both biologics). The results of the individual studies were described and organized by outcomes.

For each outcome, a conclusion was drawn on the underlying evidence base for the greater or lesser benefit or harm in 4 levels with regard to the respective certainty of the conclusion: There was either proof (highest certainty), an indication (medium certainty), a hint (weakest certainty) or none of these 3 situations. The latter was the case if no data were available or the available data did not allow any of the other 3 conclusions to be drawn. Then the conclusion “there is no hint of greater or lesser benefit or harm” was drawn.

Since the aim of the present benefit assessment was to compare the biologics with each other, only NMAs were calculated in which at least 50% of the biologics approved for a subquestion were represented.

All companies with whom a confidentiality agreement had been concluded and authors with available journal publications and no identifiable company sponsor were asked to submit additional analyses for the following outcomes and operationalizations (baseline data and results after treatment):

- Definitions for remission: CDAI ≤ 2.8, SDAI ≤ 3.3, DAS 28 < 2.6, Boolean definition

- Definitions for low disease activity: CDAI ≤ 10, SDAI ≤ 11, DAS 28 < 3.2

The request contained a detailed description of the content of data submission. Specifically, the studies were named, including the relevant study phase and the study population (total or subpopulations). Results based on definitions for remission and low disease activity that were not primarily used for the present benefit assessment can be found in the tables with results from the individual studies (see full report).

In addition, a further request was made to the companies for the submission of analyses of subpopulations relevant for the present benefit assessment. In addition to clinical remission and low disease activity, all other outcomes relevant for the benefit assessment were the subject of this data request. This request also contained a detailed description of the content of the data submission, including a description of the outcome operationalizations requested.

The individual results were analysed with the aid of NMA if sufficient structural quality existed for the studies within the respective subquestions, i.e. the assumptions of similarity, homogeneity and consistency were met or not obviously violated:

- Assumption of similarity: Clinical factors, so-called effect modifiers (patient, intervention and study characteristics) and methodological factors (e.g. outcome characteristics) were considered for the check of similarity of the studies. When checking the similarity of the studies, factors were identified for which uncertainties regarding similarity remained due to deviations or lack of information. These were not considered so relevant that the corresponding studies were excluded from a study pool, but for these factors it was examined in sensitivity analyses whether the results were robust despite such uncertainties.
- Homogeneity assumption: If at least 2 studies were available for a pairwise comparison (comparison of 1 biologic with 1 biologic or with 1 common comparator), homogeneity was checked for this comparison. The assumption of homogeneity was retained if the effect estimates did not show substantial statistical heterogeneity. If heterogeneous effects were present, it was investigated which factors (including clinical and methodological) could possibly explain this heterogeneity. First, the factors were examined that had already led to uncertainties in the similarity check.
- Consistency assumption: For valid results, consistency within a network is necessary. Consistency is present if the estimates from direct and indirect comparisons agree. In the case of differences, the factors that had already led to uncertainties in the similarity check were first examined.

If there was an obvious violation of one of the 3 assumptions, the studies with the potential explanatory factor were excluded from an NMA.

At least 2 studies must be available to check the homogeneity assumption. Then a homogeneous replication of a study result is possible. As a rule, the prerequisite for checking the consistency

assumption is that, for an indirect comparison of biologics, a corresponding direct comparative study is available in the NMA. Then it can be checked whether estimates from direct and indirect comparisons agree. If the data situation allows both the homogeneity and the consistency assumption to be checked and these checks show neither heterogeneous nor inconsistent results, a moderate or high qualitative certainty of results of the NMA can be achieved, depending on the data constellation. If 1 of the 2 checks is omitted (or both checks), the NMA is still performed, but a high qualitative certainty of results can no longer be achieved. Table 3 shows the minimum requirements for the maximum achievable qualitative certainty of results for the situations arising in the present benefit assessment.

Table 3: Maximum qualitative certainty of results of an NMA that can as a rule be achieved and its minimum requirements for the situations arising in the present benefit assessment

Maximum qualitative certainty of results that can as a rule be achieved from comparisons in NMA	**Standard minimum requirements in NMA**[a]	**Possible certainty of conclusions**
High	▪ Assumptions of homogeneity and consistency are verifiable in each case and not obviously violated ▪ Network includes at least 1 study with a direct comparison of biologics with high qualitative certainty of results, showing a statistically significant result	Proof
Moderate	▪ Assumptions of homogeneity and consistency are verifiable in each case and not obviously violated ▪ At least 1 study with a low risk of bias exists	Indication
Low	▪ Homogeneity and consistency assumption do not have to be verifiable ▪ In case of verifiable homogeneity or consistency assumption: no obvious violation of the respective assumptions ▪ If the homogeneity assumption test is omitted for a pairwise comparison, the existing study must have a low risk of bias.	Hint
a: Similarity assumption: If no or insufficient information is available to check the similarity of studies, they are not included in the NMA. NMA: network meta-analysis		

4 Results

4.1 Results of comprehensive information retrieval

Information retrieval identified 118 RCTs as relevant for the question of the present benefit assessment (see Table 4). The search strategies for bibliographic databases and study registries are included in the appendix. The last search took place on 2 March 2017.

Table 4: Study pool of the benefit assessments (across all subquestions)

Drug	Study	Available documents		
		Full-text publication (in scientific journals)	Results report from study registries	Clinical study report from company documents (not publicly available)
Placebo-controlled				
Abatacept	AGREE	yes [34-37]	yes [38-41]	yes [42]
	AIM	yes [43-45]	yes [46-48]	yes [49]
	ASSURE	yes [50]	yes [51-53]	yes [54]
	ATTAIN	yes [55-59]	yes [60,61]	yes [62]
	ATTEST	yes [63,64]	yes [65-67]	yes [68]
	AVERT	yes [69,70]	yes [71-73]	yes [74]
	IM101071	yes [75]	yes [76,77]	yes [78]
	IM101100	yes [79-84]	yes [85-87]	yes [88]
	IM101124	no	yes [89-91]	yes [92]
Adalimumab	ADMIRE	yes [93]	yes [94,95]	yes [96]
	ARMADA	yes [97]	no	yes [98]
	August II	yes [99]	yes [100]	yes [101]
	CONCERTO	no	yes [102,103]	yes [104]
	DE019	yes [105-108]	yes [109]	yes [110]
	HIT HARD	yes [111]	no	yes [112][a]
	HOPEFUL-1	yes [113,114]	yes [115,116]	yes [117,118]
	IM133001	yes [119]	no	no
	M02-556	yes [120,121]	no	yes [122]
	M10-261	no	yes [123-125]	yes [126]
	MONARCH	yes [127]	no	no
	OPERA	yes [128-138]	no	no
	OPTIMA	yes [139-142]	yes [143-145]	yes [146]
	ORAL STANDARD	yes [147-150]	yes [151,152]	yes [153]
	ORAL STRATEGY	no	no	yes [154]
	OSKIRA-4	yes [155,156]	yes [157-159]	no
	PREMIER	yes [105,160-170]	yes [171,172]	yes [173]
	PROWD	yes [139,174]	no	yes [175]
	RA-BEAM	yes [176]	yes [177]	yes [178]
	RADAR	no	yes [179]	yes [180]
	STAR	yes [181,182]	no	yes [183]
	STRASS[b]	yes [184]	no	no

(continued)

Table 4: Study pool of the benefit assessments (across all subquestions) (continued)

Drug	Study	Available documents		
		Full-text publication (in scientific journals)	Results report from study registries	Clinical study report from company documents (not publicly available)
Placebo-controlled				
Anakinra	990145	yes [185]	no	yes [186]
	990757	yes [187-189]	no	yes [190]
	20000198	no	no	yes [191]
	20000223	yes [192]	no	yes [193]
Certolizumab pegol	C-EARLY	yes [194]	yes [195-197]	yes [198,199]
	CERTAIN	yes [200]	yes [201-203]	yes [204]
	C-OPERA	yes [205]	yes [206]	yes [207]
	HIKARI	yes [208,209]	yes [210]	yes [211]
	RA0025	no	yes [212]	yes [213]
	RAPID 1	yes [214-222]	yes [223,224]	yes [225]
	RAPID 2	yes [222,226,227]	yes [228,229]	yes [230]
Etanercept	0881A1-309	yes [231,232]	no	yes [233]
	0881A1-4532	yes [234,235]	yes [236]	yes [237,238]
	16.0014	yes [239,240]	no	yes [241]
	COMET	yes [242-248]	yes [249,250]	yes [251,252]
	D1520C00001	yes [253]	yes [254,255]	no
	ENCOURAGE	yes [256]	no	no
	Gashi 2014	yes [257]	no	no
	GISEA	yes [258]	no	no
	JESMR	yes [259,260]	yes [261]	no
	Johnsen 2006	yes [262]	no	no
	Kavanaugh 2010	yes [263]	no	no
	Liu 2013	yes [264]	no	no
	PRECEPT	yes [265]	no	no
	RACAT	yes [266,267]	yes [268]	no
	Raffeiner 2015	yes [269]	no	no
	Sun 2016	yes [270]	no	no
	TEAR	yes [271-279]	yes [280]	no
	TEMPO	yes [281-294]	no	yes [295-297]
	Wada 2012	yes [298]	no	no

(continued)

Table 4: Study pool of the benefit assessments (across all subquestions) (continued)

Drug	Study	Available documents		
		Full-text publication (in scientific journals)	Results report from study registries	Clinical study report from company documents (not publicly available)
Placebo-controlled				
Golimumab	C0524T28	yes [299]	yes [300,301]	yes [302,303]
	CD-IA-CAM-3001-1107	no	yes [304,305]	no
	GO-AFTER	yes [306-311]	yes [312-314]	yes [315,316]
	GO-BEFORE	yes [306,317-330]	yes [331,332]	yes [333,334]
	GO-FORTH	yes [335-338]	no	yes [339]
	GO-FORWARD	yes [306,325,340-349]	yes [350-352]	yes [353]
	GO-MORE	yes [306,354]	yes [355]	yes [356]
	GO-SAVE	yes [357]	yes [358-360]	yes [361,362]
Infliximab	Atteritano 2016	yes [363]	no	no
	ATTRACT	yes [348,364-370]	yes [371]	yes [372-374]
	BeSt	yes [375-407]	no	no
	CIERA	yes [408]	no	no
	IDEA	yes [409,410]	yes [411]	no
	NEO-RACo	yes [412-418]	no	no
	P01222	no	no	yes [419]
	P04280	yes [420]	no	yes [421]
	Quinn 2005	yes [422,423]	no	no
	RISING	yes [424,425]	yes [426]	no
	SWEFOT	yes [427-439]	no	no
	Tam 2012	yes [440]	no	no
Rituximab	DANCER	yes [441,442]	no	yes [443-445]
	EXTRRA	yes [446]	no	no
	IMPRESS	yes [447]	no	no
	MIRROR	yes [448]	yes [449,450]	yes [451-453]
	REFLEX	yes [454-457]	yes [458]	yes [459,460]
	SIERRA	no	yes [461]	yes [462]
	SMART	yes [463-466]	yes [467]	yes [468]
	SUNRISE	yes [469]	yes [470]	yes [471-473]
	WA16291	yes [474-476]	no	yes [477]

(continued)

Table 4: Study pool of the benefit assessments (across all subquestions) (continued)

Drug	Study	Available documents		
		Full-text publication (in scientific journals)	Results report from study registries	Clinical study report from company documents (not publicly available)
Placebo-controlled				
Tocilizumab	ACT FAST	no	yes [478,479]	yes [480]
	ACTEMAB	no	yes [481]	yes [482]
	ACT-RAY	yes [483-488]	yes [489,490]	yes [491]
	ACT-STAR	yes [492]	yes [493]	yes [494]
	ACT-TIME	no	yes [495]	yes [496]
	CWP-TCZ301	yes [497]	no	yes [498]
	FUNCTION	yes [499]	yes [500,501]	yes [502,503]
	Lindegaard 2016	yes [504]	no	no
	LITHE	yes [505-512]	yes [513]	yes [514-517]
	MEASURE	yes [518,519]	yes [520]	yes [521]
	MRA230TW	no	no	yes [522]
	OPTION	yes [511,523,524]	yes [525]	yes [526]
	PORTRAIT	no	yes [527]	yes [528]
	RADIATE	yes [511,529-532]	yes [533]	yes [534]
	ROSE	yes [535,536]	yes [537]	yes [538]
	Shi 2013	yes [539]	no	no
	SURPRISE	yes [540]	no	no
	TOWARD	yes [511,541,542]	yes [543]	yes [544]
	TRACE	no	yes [545]	yes [546]
	U-ACT-EARLY	yes [547]	yes [548,549]	yes [550]
Direct comparison of biologics				
Abatacept; adalimumab	AMPLE	yes [551-556]	yes [557,558]	yes [559,560]
Adalimumab; certolizumab pegol	EXXELERATE	yes [561-563]	yes [564,565]	yes [566]
Adalimumab; etanercept	De Stefano 2010	yes [567]	no	no
	RED SEA	yes [568]	no	no
Adalimumab; tocilizumab	ACT-FIRST	no	yes [569,570]	yes [571]
	ADACTA	yes [572,573]	yes [574,575]	yes [576]
Etanercept; tocilizumab	WA25204	no	yes [577]	yes [578]
Abatacept; adalimumab; certolizumab pegol; etanercept; infliximab; golimumab; rituximab	DREAM / TIME	yes [579]	no	no

a: Clinical study report of a study group.

b: The patients in both study arms received either adalimumab or etanercept as monotherapy or in combination with MTX and / or leflunomide.

Table 5 provides an overview of the documents identified on the relevant studies.

Table 5: Number of relevant studies and identified documents (summary)

Studies / documents	
Studies	118 Industry-sponsored: 84 / 118 (71%) IITs: 34 / 118 (29%)
Full publication (in scientific journal)	318[a] for 100 / 118 studies (85%)
Study registry	Entries on study registration: 159 for 96 / 118 studies (81%) Results report from study registries: 124 for 69 / 118 studies (58%)
Clinical study report from company documents (not publicly accessible)	for 80 / 118 studies (68%) for 80 / 84 industry-sponsored studies (95%)
Clinical study report of a study group (not publicly accessible)	for 1 / 118 studies (0.8%) for 1 / 34 IITs (2.9%)
a: 317 from bibliographic search and 1 from author enquiries. IIT: investigator-initiated trial	

After identifying the available studies and documents on the studies, the study pool was divided into Subquestions 1 to 7 for further processing. No studies were assigned to Subquestions 2, 3 and 7. One further subquestion was identified. Moreover, some of the available studies could not be assigned to any question. This is explained in the following text.

Subquestions 2 and 3 (combination therapy after MTX failure or monotherapy after MTX intolerance, each with pretreatment with further csDMARDs)

Subquestions 2 and 3 refer to patients without unfavourable prognostic factors. According to EULAR recommendations, after MTX failure and before switching to a biologic, this population should first be switched to another csDMARD. However, the study documents available for the benefit assessment did not provide sufficient information on the type of pretreatment depending on the prognostic factors in order to differentiate between studies for Subquestions 2 or 3 and 4 or 5. For this reason, no studies were assigned to Subquestions 2 or 3, but only to Subquestions 4 or 5 (population with unfavourable prognostic factors). In the similarity check of the studies, aspects that might result from this were examined. Subquestions 2 and 3 are not addressed any further.

Subquestion 7 (monotherapy after MTX intolerance and biologic failure)

No relevant studies on monotherapy after MTX intolerance and biologic failure (Subquestion 7) were identified via information retrieval. This subquestion is therefore not addressed any further.

Subquestion 8 (discontinuation attempt of a biologic)

From the studies identified via information retrieval, the additional subquestion was derived, which refers to discontinuation attempts of biologics or reduction of previous treatment in

patients in clinical remission. This subquestion was examined as Subquestion 8, but only as supplementary information, due to the insufficient data situation. It is therefore not described further in this Chapter 4, but only in the section on supplementary information in the full report.

Studies that could not be assigned to a subquestion

A total of 35 studies could not be assigned to a subquestion: For 28 studies, the control interventions were not a suitable common comparator in the study pool, since no other study included a sufficiently similar control intervention. For 7 studies, no allocation was possible due to a lack of information in the available documents.

4.2 Number of studies per subquestion and result of the similarity check of the studies

Most studies were available on the combination therapy with MTX after MTX failure (45 studies, Subquestion 4). For Subquestions 1 and 6, 3 sufficiently similar study pools each resulted from the check of similarity of the studies; for Subquestion 4, 4 study pools were created. For all 3 subquestions, there was only 1 study pool each that comprised over 50% of the biologics approved for the subquestions (Study Pools 1.1, 4.1 and 6.1). The other study pools for these subquestions were not further investigated.

For Subquestion 5 (monotherapy after MTX intolerance), 2 relevant studies were identified: 1 study with a direct comparison of biologics and 1 study with a comparison of a biologic with a placebo. The control treatment of this study therefore did not form a common comparator for a comparison with the biologics investigated in the other study. The study was therefore excluded from the further checks for Subquestion 5. Since only 1 study on a direct comparison of biologics remained for Study Pool 5, the similarity check for Subquestion 5 was omitted.

Table 6 shows the number of studies per subquestion and an overview of the study pools resulting from the similarity check.

Table 6: Number of studies for Subquestions 1, 4, 5, 6 with the respective result of the check of similarity of the studies

Subquestions **Number of studies (n)**	**Sufficiently similar study pools per subquestion to examine further methodological prerequisites for the NMA** **Number of available studies in study pool (n)**			
Subquestion 1	**Study Pool 1.1**	**Study Pool 1.2**	**Study Pool 1.3**	-
Combination therapy with MTX without MTX pretreatment n = 24 including 0 studies with direct comparison of biologics / MTX	Combination therapy with MTX without MTX pretreatment[a] n = 19 (overall n = 20[b]; exclusion from further checks: n = 1[c])	Combination therapy with MTX without MTX pretreatment Disease duration > 1 year n = 0 (overall n = 3[b]; exclusion from further checks: n = 3[c])	Combination therapy with MTX without MTX pretreatment, extensive use of corticosteroids n = 3 (overall n = 4; exclusion from further checks: n = 1[d])	-
Subquestion 4	**Study Pool 4.1**	**Study Pool 4.2**	**Study Pool 4.3**	**Study Pool 4.4**
Combination therapy with MTX after MTX failure n = 45 including 4 studies with direct comparison of biologics / MTX	Combination therapy with MTX after MTX failure[e] n = 38 (overall n = 42[f, g]; exclusion from further checks: n = 2[c], n = 2[d])	Combination therapy with MTX after MTX failure, Disease duration < 1 year n = 1 (overall n = 2[g]; exclusion from further checks: n = 1[c])	Combination therapy with MTX after MTX failure, Combination with other sDMARDs n = 0 (overall n = 6[f], exclusion from further checks: n = 6[c])	Combination therapy with MTX after MTX failure, extensive use of corticosteroids n = 0 (overall n = 2, exclusion from further checks: n = 2[c])
Subquestion 5	**Study Pool 5**			
Monotherapy after MTX intolerance n = 2 including 1 study with direct comparison of biologics (exclusion from further checks: n = 1[h])	Monotherapy after MTX intolerance No similarity check, as n = 1			

(continued)

Table 6: Number of studies for Subquestions 1, 4, 5, 6 with the respective result of the check of similarity of the studies (continued)

Subquestions **Number of studies [n]**	**Sufficiently similar study pools per subquestion to examine further methodological prerequisites for the NMA** **Number of available studies in the study pool [n]**			
Subquestion 6	**Study Pool 6.1**	**Study Pool 6.2**	**Study Pool 6.3**	-
Combination therapy with MTX after biologic failure n = 20 including 2 studies with direct comparison of biologics / MTX	Combination therapy with MTX after biologic failure[i] n = 16 (overall n = 18, exclusion from further checks: n = 2[c])	Combination therapy with MTX after biologic failure, intensive pretreatment with biologics n = 0 (overall n = 1, exclusion from further checks: n = 1[j])	Combination therapy with MTX after biologic failure, unrestricted concomitant therapy / treatment adjustments n = 0 (overall n = 1, exclusion from further checks: n = 1[c])	-

a: Disease duration < 1 year; compared with Study Pool 1.3, less corticosteroid use

b: Double-mentioning of 3 studies, each comprising disjunctive subpopulations for Study Pools 1.1 and 1.2.

c: No data for relevant subpopulation.

d: No relevant common comparator within the study pool.

e: Disease duration > 1 year; no combination with other sDMARDs; compared with Study Pool 4.4, less corticosteroid use.

f: Double-mentioning of 6 studies, each comprising disjunctive subpopulations for Study Pools 4.1 and 4.3.

g: Double-mentioning of 1 study, each comprising disjunctive subpopulations for Study Pools 4.1 and 4.2.

h: No relevant common comparator within the subquestion.

i: Compared with Study Pool 6.2, less intensive pretreatment with biologics; limited concomitant therapy / treatment adjustments.

j: No NMA possible because only 1 study is available to compare biologic / MTX vs. placebo / MTX.

MTX: methotrexate; NMA: network meta-analysis; sDMARDs: synthetic disease-modifying antirheumatic drug

4.3 Subquestion 1: Combination therapy with MTX without MTX pretreatment

4.3.1 Study design und study populations (Study Pool 1.1)

After completion of the similarity check of the 24 studies identified for Subquestion 1 (see Table 25 of the full report), Study Pool 1.1 consisted of 20 sufficiently similar studies to investigate combination therapy with MTX without MTX pretreatment (see Table 194 of the full report). Data for an NMA were in principle available for 19 of the 20 studies. Most of them were described as double-blind. There was no study with a direct comparison of biologics. The mean age of patients in most studies was about 50 years. In almost all studies, about three quarters of the study population were women. The mean duration of the disease was less than 1 year, usually less than half a year. Based on available information on disease-specific characteristics (e.g. DAS 28, existing erosions and immunological as well as prognostic factors), severe rheumatoid arthritis could be assumed for the population of all studies at baseline. The populations of 4 studies showed on average a slightly less severe disease compared with the other studies in Study Pool 1.1. For a further study, there was little information to estimate the severity of the disease.

Explicit information on pretreatment with MTX was missing in 1 of the 19 studies. Based on the study objective and the mean short disease duration of the study population, it was assumed for the present benefit assessment that the patients included had not yet been pretreated with MTX.

The uncertainties described above in the similarity of the studies regarding disease severity or pretreatment were not considered to be so relevant that the studies were subsequently excluded from the study pool. However, they were as a rule examined in sensitivity analyses.

4.3.2 Overview of outcomes relevant for the assessment

Data on patient-relevant outcomes were extracted from all 19 studies, if usable data were available. For each patient-relevant outcome, Table 7 shows the number of studies and biologics included in the NMA. Table 8 shows the data per biologic included in the analyses for each patient-relevant outcome.

Table 7: Combination therapy with MTX without MTX pretreatment, number of studies and biologics per NMA (Study Pool 1.1)

	Outcomes[a]										
	Clinical remission (CDAI ≤ 2,8)	**Low disease activity (CDAI ≤ 10)**	**Pain (VAS)**	**Fatigue**	**Physical function (HAQ-DI)**	**Health-related quality of life (SF-36)**	**All-cause mortality**	**SAEs**	**Discontinuation due to AEs**	**Infections**	**Serious infections**
Studies, related to 20 available studies in Study Pool 1.1											
Number of studies without data for relevant subpopulation	1	1	1	1	1	1	1	1	1	1	1
Number of studies without (usable) data	5	5	7	10	2	8	5	6	4	7	7
Number of studies with exclusion because of: violation of homogeneity or consistency assumption or lack of robustness of results in sensitivity analyses to check similarity assumptions	0	0	4	n. c.[b]	5	2	4	3	4	2	2
Number of studies in NMA	14	14	8	n. c.[b]	12	9	10	10	11	10	10
Biologics in NMA, related to 7 relevant biologics for Subquestion 1[c]											
Number of biologics	6	6	5	n. c.[b]	6	6	6	6	7	6	6

a: Insufficient data were available for the planned outcome "social functional level", so that the validity of the instruments used was not examined for the present benefit assessment. Therefore, this outcome is not presented in the table.

b: Less than 50% of approved biologics for the present subquestion; information on the remaining 9 studies with usable data: VAS: 4 studies (3 biologics), BRAF-MDQ / FACIT-Fatigue: 5 studies (3 biologics); results of the VAS cannot be combined with results of the BRAF MDQ / FACIT Fatigue.

c: Anakinra and rituximab are not approved for Subquestion 1.

AE: adverse event; BRAF-MDQ: Bristol Rheumatoid Arthritis Fatigue-Multidimensional Questionnaire; CDAI: Clinical Disease Activity Index; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy Fatigue; HAQ-DI: Health Assessment Questionnaire Disability Index; MTX: methotrexate; n. c.: not calculated; NMA: network meta-analysis; SAE: serious adverse event; SF 36: Short Form 36 - Health Survey; VAS: visual analogue scale; vs: versus

Table 8: Combination therapy with MTX without MTX pretreatment, matrix of available patient-relevant outcomes and biologics per NMA (Study Pool 1.1)

Biologic[a] + MTX vs. placebo + MTX	**Outcomes[b]**										
	Clinical remission (CDAI ≤ 2,8)	**Low disease activity (CDAI ≤ 10)**	**Pain (VAS)**	**Fatigue**	**Physical function (HAQ-DI)**	**Health-related quality of life (SF-36)**	**All-cause mortality**	**SAEs**	**Discontinuation due to AEs**	**Infections**	**Serious infections**
Abatacept	●	●	-	n. c.[c]	●	●	●	●	●	●	●
Adalimumab	●	●	●		●	●	●	●	●	●	●
Certolizumab pegol	●	●	●		●	●	●	●	●	●	●
Etanercept	●	●	●		●	●	●	●	●	●	●
Golimumab	●	●	●		●	●	●	●	●	●	●
Infliximab	-	-	(●)		**(●)**	(●)	**(●)**	**(●)**	●	(●)	**(●)**
Tocilizumab	●	●	●		●	●	●	●	●	●	●

a: Anakinra and rituximab are not listed as they are not approved for Subquestion 1.

b: Insufficient data were available for the planned outcome "social functional level", so that the validity of the instruments used was not examined for the present benefit assessment. Therefore, this outcome is not presented in the matrix.

c: Less than 50% of the approved biologics for the present subquestion.

● Data were reported and were usable.

(●) Data were reported and would have been usable in principle, but excluded after the homogeneity assumption and consistency assumption had been checked or after the conduct of sensitivity analyses to check the similarity assumption.

- No data were reported.

AE: adverse event; CDAI: Clinical Disease Activity Index; HAQ-DI: Health Assessment Questionnaire Disability Index; MTX: methotrexate; n. c.: not calculated; NMA: network meta-analysis; SAE: serious adverse event; SF 36: Short Form 36 - Health Survey; VAS: visual analogue scale; vs.: versus

Of the 4 studies on infliximab / MTX, 3 studies showed uncertainties in disease severity, which was a factor for the sensitivity analyses. In sensitivity analyses to examine the robustness of the results regarding this factor, these 3 studies were excluded. Since the sole study without this uncertainty only provided data on discontinuation due to AEs, infliximab / MTX was part of the corresponding analyses only for this outcome.

4.3.3 Results on patient-relevant outcomes (Study Pool 1.1)

Results of the check of the homogeneity and consistency assumption for the NMA

Provided that at least 2 studies on a biologic were available for the check of the homogeneity assumption, substantial heterogeneity was not found for any of the outcomes in the pairwise

meta-analyses of the studies. Thus, no study was excluded from the NMA study pool due to heterogeneity. The homogeneity assumption was not checked for pairwise comparisons with only 1 available study, so that for NMA comparisons including such a pairwise comparison, at most a low qualitative certainty of results could be achieved.

Since no study with a direct comparison of biologics was available for the combination therapy with MTX without MTX pretreatment, the consistency assumption was not checked in the network, so that at most a low qualitative certainty of results could be achieved.

Maximum possible evidence base on the basis of the available data

On the basis of the available data for the combination therapy with MTX without MTX pretreatment, at most hints of greater or lesser benefit or harm could be derived. The reason for this is that the consistency assumption was not checked. Furthermore, in a data constellation for an indirect comparison with only 1 study available for at least 1 of the 2 biologics of the comparison, no hint can be derived if this study has a high risk of bias.

Analysis times considered

For some of the studies, analyses were available for all outcomes for several times of analysis (between 24 and 52 weeks, rarely also for observation periods of more than 1 year). For the present benefit assessment, times between 24 and 52 weeks were considered sufficiently similar to be analysed in a common NMA. Since for the majority of the studies the data at the 24- or 30-week time of analysis were more meaningful due to fewer treatment and/or study discontinuations than those at later times, these were preferred for all outcomes (apart from all-cause mortality and AE outcomes), if available.

For all-cause mortality and AE outcomes, only 1 time of analysis was available for the majority of the studies. For most studies, data were available at times between 24 and 52 weeks (in the majority of cases 52 weeks); for 3 studies only data at 2 years were available. Due to insufficient similarity between the 2-year time of analysis and times up to 1 year, the 2-year data were not considered. As data were available at 52 weeks for the majority of the studies, if several times of analysis were available, the 52-week data were preferred for all-cause mortality and AE outcomes.

Subgroup characteristics and other effect modifiers

For combination therapy with MTX without MTX pretreatment, analyses were only available in isolated studies for the investigation of subgroup characteristics and other effect modifiers and, moreover, only for isolated biologics. Analyses for more than 1 biologic were not available for any outcome. For pain, fatigue and health-related quality of life there were no subgroup analyses in the included studies. Due to the data situation, no potential effect modifiers were investigated for combination therapy with MTX without MTX pretreatment.

Positive and negative effects for comparison of biologics with each other in combination therapy with MTX without MTX pretreatment

For combination therapy with MTX without MTX pretreatment, Table 9 shows for which outcomes positive or negative effects were present, on the basis of which conclusions for greater or lesser benefit or harm were derived.

For infliximab / MTX, except for discontinuation due to AEs, data were not included in the NMA for any other outcomes (no data available on clinical remission and low disease activity based on CDAI, outcome not measured in the study or studies excluded in a previous analysis step).

Table 9: Combination therapy with MTX without MTX pretreatment, positive and negative effects from NMAs (Study Pool 1.1)

Comparisons[a]	Outcome: Effect estimate from the NMA (biologic in bold font vs. biologic in normal font), RR [95% CI]	
	To the advantage of the biologic in bold font	**To the disadvantage of the biologic in bold font**
Abatacept + MTX vs.		
Adalimumab + MTX	-	-
Certolizumab pegol + MTX	-	-
Etanercept + MTX	-	-
Golimumab + MTX	-	-
Infliximab + MTX	-	-
Tocilizumab + MTX	-	-
Adalimumab + MTX vs.		
Abatacept + MTX	-	-
Certolizumab pegol + MTX	Low disease activity (CDAI ≤ 10): 1.23 [1.06; 1.42]	-
Etanercept + MTX	-	-
Golimumab + MTX	-	-
Infliximab + MTX	-	-
Tocilizumab + MTX	Low disease activity (CDAI ≤ 10): 1.22 [1.04; 1.43]	-
Certolizumab pegol + MTX vs.		
Abatacept + MTX	-	-
Adalimumab + MTX	-	Low disease activity (CDAI ≤ 10): 0.82 [0.70; 0.95]
Etanercept + MTX	-	Low disease activity (CDAI ≤ 10): 0.79 [0.65; 0.97]
Golimumab + MTX	-	-
Infliximab + MTX	-	-
Tocilizumab + MTX	-	-
Etanercept + MTX vs.		
Abatacept + MTX	-	-
Adalimumab + MTX	-	-
Certolizumab pegol + MTX	Low disease activity (CDAI ≤ 10): 1.26 [1.03; 1.54]	-
Golimumab + MTX	-	-
Infliximab + MTX	-	-
Tocilizumab + MTX	Low disease activity (CDAI ≤ 10): 1.25 [1.02; 1.54]	-

(continued)

Table 9: Combination therapy with MTX without MTX pretreatment, positive and negative effects from NMAs (Study Pool 1.1) (continued)

Comparisons[a]	Outcome: Effect estimate from the NMA (biologic in bold font vs. biologic in normal font), RR [95% CI]	
	To the advantage of the biologic in bold font	**To the disadvantage of the biologic in bold font**
Golimumab + MTX vs.		
Abatacept + MTX	-	-
Adalimumab + MTX	-	-
Certolizumab pegol + MTX	-	-
Etanercept + MTX	-	-
Infliximab + MTX	-	-
Tocilizumab + MTX	-	-
Infliximab + MTX vs.		
Abatacept + MTX	-	-
Adalimumab + MTX	-	-
Certolizumab pegol + MTX	-	-
Etanercept + MTX	-	-
Golimumab + MTX	-	-
Tocilizumab + MTX	-	-
Tocilizumab + MTX vs.		
Abatacept + MTX	-	-
Adalimumab + MTX	-	Low disease activity (CDAI ≤ 10): 0.82 [0.70; 0.96]
Certolizumab pegol + MTX	-	-
Etanercept + MTX	-	Low disease activity (CDAI ≤ 10): 0.80 [0.65; 0.98]
Golimumab + MTX	-	-
Infliximab + MTX	-	-

- No hint of greater or lesser benefit or harm; for information on for which outcomes data were available in the NMA, see Table 8.

a: Anakinra and rituximab are not listed as they are not approved for Subquestion 1.

CDAI: Clinical Disease Activity Index; CI: confidence interval; MTX: methotrexate; NMA: network meta-analysis; RR: relative risk; vs.: versus

For the combination therapy with MTX without MTX pretreatment, only effects on low disease activity were observed (CDAI ≤ 10). The results were in favour of adalimumab + MTX versus certolizumab pegol + MTX and tocilizumab + MTX. The results were also in favour of etanercept + MTX versus certolizumab pegol / MTX and tocilizumab / MTX. Thus, for adalimumab + MTX and etanercept + MTX there is a hint of greater benefit versus certolizumab pegol + MTX and tocilizumab + MTX.

4.3.4 Evidence map (Study Pool 1.1)

Since no studies with a direct comparison of biologics were available for the combination therapy with MTX without MTX pretreatment (Study Pool 1.1), no consistency check was possible. For this reason, at most hints of greater or lesser benefit or harm could be derived.

For combination therapy with MTX without MTX pretreatment, the following evidence map (Table 10) shows for which patient-relevant outcomes there is greater or lesser benefit or harm.

Table 10: Combination therapy with MTX without MTX pretreatment, evidence map for greater or lesser benefit or harm (Study Pool 1.1)

Comparisons[a]	Clinical remission (CDAI ≤ 2.8)	Low disease activity (CDAI ≤ 10)	Pain (VAS)	Fatigue	Physical function (HAQ-DI)	Social functional level	Health-related quality of life		All-cause mortality	SAEs	Discontinuation due to AEs	Infections	Serious infections
							SF-36, mental summary score	SF-36, physical summary score					
Abatacept + MTX vs.													
Adalimumab + MTX	-	-	-[b]	Not calculated[c]	-	Not calculated[d]	-	-	-	-	-	-	-
Certolizumab pegol + MTX	-	-	-[b]		-		-	-	-	-	-	-	-
Etanercept + MTX	-	-	-[b]		-		-	-	-	-	-	-	-
Golimumab + MTX	-	-	-[b]		-		-	-	-	-	-	-	-
Infliximab + MTX	-[b]	-[b]	-[b]		-[b]		-[b]	-[b]	-[b]	-[b]	-	-[b]	-[b]
Tocilizumab + MTX	-	-	-[b]		-		-	-	-	-	-	-	-
Adalimumab + MTX vs.													
Abatacept + MTX	-	-	-[b]	Not calculated[c]	-	Not calculated[d]	-	-	-	-	-	-	-
Certolizumab pegol + MTX	-	⇗	-		-		-	-	-	-	-	-	-
Etanercept + MTX	-	-	-		-		-	-	-	-	-	-	-
Golimumab + MTX	-	-	-		-		-	-	-	-	-	-	-
Infliximab + MTX	-[b]	-[b]	-[b]		-[b]		-[b]	-[b]	-[b]	-[b]	-	-[b]	-[b]
Tocilizumab + MTX	-	⇗	-		-		-	-	-	-	-	-	-
Certolizumab pegol + MTX vs.													
Abatacept + MTX	-	-	-[b]	Not calculated[c]	-	Not calculated[d]	-	-	-	-	-	-	-
Adalimumab + MTX	-	⇘	-		-		-	-	-	-	-	-	-
Etanercept + MTX	-	⇘	-		-		-	-	-	-	-	-	-
Golimumab + MTX	-	-	-		-		-	-	-	-	-	-	-
Infliximab + MTX	-[b]	-[b]	-[b]		-[b]		-[b]	-[b]	-[b]	-[b]	-	-[b]	-[b]
Tocilizumab + MTX	-	-	-		-		-	-	-	-	-	-	-

(continued)

Table 10: Combination therapy with MTX without MTX pretreatment, evidence map for greater or lesser benefit or harm (Study Pool 1.1) (continued)

Comparisons[a]	Clinical remission (CDAI ≤ 2.8)	Low disease activity (CDAI ≤ 10)	Pain (VAS)	Fatigue	Physical status (HAQ-DI)	Social functional level	Health-related quality of life: SF-36, mental summary score	Health-related quality of life: SF-36, physical summary score	All-cause mortality	SAE	Discontinuation due to AEs	Infections	Serious infections
Etanercept + MTX vs.													
Abatacept + MTX	-	-	-[b]	Not calculated[c]	-	Not calculated[d]	-	-	-	-	-	-	-
Adalimumab + MTX	-	-	-		-		-	-	-	-	-	-	-
Certolizumab pegol + MTX	-	⇗	-		-		-	-	-	-	-	-	-
Golimumab + MTX	-	-	-		-		-	-	-	-	-	-	-
Infliximab + MTX	-[b]	-[b]	-[b]		-[b]		-[b]	-[b]	-[b]	-[b]	-	-[b]	-[b]
Tocilizumab + MTX	-	⇗	-		-		-	-	-	-	-	-	-
Golimumab + MTX vs.													
Abatacept + MTX	-	-	-[b]	Not calculated[c]	-	Not calculated[d]	-	-	-	-	-	-	-
Adalimumab + MTX	-	-	-		-		-	-	-	-	-	-	-
Certolizumab pegol + MTX	-	-	-		-		-	-	-	-	-	-	-
Etanercept + MTX	-	-	-		-		-	-	-	-	-	-	-
Infliximab + MTX	-[b]	-[b]	-[b]		-[b]		-[b]	-[b]	-[b]	-[b]	-	-[b]	-[b]
Tocilizumab + MTX	-	-	-		-		-	-	-	-	-	-	-
Infliximab + MTX vs.													
Abatacept + MTX	-[b]	-[b]	-[b]	Not calculated[c]	-[b]	Not calculated[c]	-[b]	-[b]	-[b]	-[b]	-	-[b]	-[b]
Adalimumab + MTX	-[b]	-[b]	-[b]		-[b]		-[b]	-[b]	-[b]	-[b]	-	-[b]	-[b]
Certolizumab pegol + MTX	-[b]	-[b]	-[b]		-[b]		-[b]	-[b]	-[b]	-[b]	-	-[b]	-[b]
Etanercept + MTX	-[b]	-[b]	-[b]		-[b]		-[b]	-[b]	-[b]	-[b]	-	-[b]	-[b]
Golimumab + MTX	-[b]	-[b]	-[b]		-[b]		-[b]	-[b]	-[b]	-[b]	-	-[b]	-[b]
Tocilizumab + MTX	-[b]	-[b]	-[b]		-[b]		-[b]	-[b]	-[b]	-[b]	-	-[b]	-[b]

(continued)

Table 10: Combination therapy with MTX without MTX pretreatment, evidence map for greater or lesser benefit or harm (Study Pool 1.1) (continued)

Comparisons[a]	Clinical remission (CDAI ≤ 2.8)	Low disease activity (CDAI ≤ 10)	Pain (VAS)	Fatigue	Physical status (HAQ-DI)	Social functional level	Health-related quality of life		All-cause mortality	SAEs	Discontinuation due to AEs	Infections	Serious infections
							SF-36, mental summary score	SF-36, physical summary score					
Tocilizumab + MTX vs.													
Abatacept + MTX	-	-	-[b]	Not calculated[c]	-	Not calculated[d]	-	-	-	-	-	-	-
Adalimumab + MTX	-	↘	-		-		-	-	-	-	-	-	-
Certolizumab pegol + MTX	-	-	-		-		-	-	-	-	-	-	-
Etanercept + MTX	-	↘	-		-		-	-	-	-	-	-	-
Golimumab + MTX	-	-	-		-		-	-	-	-	-	-	-
Infliximab + MTX	-[b]	-[b]	-[b]		-[b]		-[b]	-[b]	-[b]	-[b]	-	-[b]	-[b]

a: Anakinra and rituximab are not listed as they are not approved for Subquestion 1.

b: No data for the comparison of biologics in the NMA.

c: Less than half of approved biologics for the subquestions in potential NMA.

d: Insufficient data were available for the planned outcome "social functional level", so that the validity of the instruments used was not examined for the present benefit assessment.

⇗: Hint of greater benefit or hint of lesser harm.

↘: Hint of lesser benefit or hint of greater harm.

- No hint, indication or proof of greater or lesser benefit or harm.

AE: adverse event; CDAI: Clinical Disease Activity Index; HAQ-DI: Health Assessment Questionnaire Disability Index; MTX: methotrexate; NMA: network meta-analysis; SAE: serious adverse event; SF-36: Short Form 36 - Health Survey; VAS: visual analogue scale; vs.: versus

4.4 Subquestion 4: Combination therapy with MTX after MTX failure

4.4.1 Study design and study populations (Study Pool 4.1)

After completion of the similarity check of the 45 studies identified for Subquestion 4 (see Table 25 of the full report), Study Pool 4.1 consisted of 42 sufficiently similar studies to investigate combination therapy with MTX after MTX failure (see Table 241 of the full report). Data for an NMA were in principle available for 38 of the 42 trials. Most of these studies were described as double-blind. Among the 38 studies, there were 2 studies with a direct comparison of biologics. All other studies investigated the comparison with placebo / MTX. The mean age of the patients in most studies was between 50 and 60 years. In the majority of the studies, approximately 75% to 90% of the study population were women. The mean duration of the disease was usually between 6 and 12 years. Only in 2 studies was it markedly shorter with

about 2 years. On the basis of the available information on disease-specific characteristics (e.g. DAS 28, existing erosions and immunological as well as prognostic factors), severe rheumatoid arthritis with an unfavourable prognosis could be assumed for the populations of most studies at baseline. Only 3 studies included populations with less severe disease on average. For 1 study, disease severity could not be reliably estimated due to a lack of information and it was unclear whether the study population had an unfavourable prognosis.

In 5 studies, between 5% and 20% of the study population had already been pretreated with biologics. Data were available for 4 of the 5 studies for the relevant subpopulation without pretreatment with biologics, but not for all outcomes for 1 of these studies. For 1 of the 5 studies, data on pretreatment with biologics were missing for the relevant subpopulation (patients with combination therapy with MTX after MTX failure); only data on the total population were available. A corresponding uncertainty remained for this study. For a further study, data were missing on whether the study population had been pretreated with biologics.

For a total of 3 studies, important information on disease severity and pretreatment with biologics was missing.

The above-mentioned uncertainties in the similarity of the studies regarding disease severity or pretreatment were not classified as so relevant that the studies were excluded from the study pool. However, they were as a rule examined in sensitivity analyses.

4.4.2 Overview of outcomes relevant for the assessment

Data on patient-relevant outcomes were extracted from all 38 studies, if usable data were available. For each patient-relevant outcome, Table 11 shows the number of studies and biologics included in the NMA. Table 12 shows the data per biologic included in the analyses for each patient-relevant outcome.

Table 11: Combination therapy with MTX after MTX failure, number of studies and biologics per NMA (Study Pool 4.1)

	Outcomes[a]										
	Clinical remission (CDAI ≤ 2.8)	**Low disease activity (CDAI ≤ 10)**	**Pain (VAS)**	**Fatigue (VAS / NRS) / (BRAF-MDQ / FACIT-Fatigue)[b]**	**Physical function (HAQ-DI)**	**Health-related quality of life (SF-36)**	**All-cause mortality**	**SAEs**	**Discontinuation due to AEs**	**Infections**	**Serious infections**
Studies, related to 42 available studies for Study Pool 4.1											
Number of studies without data for relevant subpopulation or without relevant common comparator in Study Pool 4.1	4	4	4	4	4	4	4	4	4	4	4
Number of studies without (usable) data	4	5	8	19	5	15	4	4	2	3	5
Number of studies with exclusion because of: breach of homogeneity or consistency assumption or lack of robustness of results in sensitivity analyses to check similarity assumptions	0	6	18	0	4	1	0	3	6	4	3
Number of studies in NMA	34	27	12	7 / 13[c]	29	22	34	31	30	31	30
Biologics in NMA, related to 8 relevant biologics for Subquestion 4[d]											
Number of biologics	8	8	6	4 / 4[c]	8	7	8	8	8	8	8

a: Insufficient data were available for the planned outcome "social functional level", so that the validity of the instruments used was not examined for the present benefit assessment. Therefore, this outcome is not presented in the table.

b: For the outcome "fatigue", separate NMAs were calculated for sufficiently similar operationalizations: 1 NMA for the operationalizations VAS and NRS and 1 NMA for the operationalizations FACIT-Fatigue and BRAF-MDQ.

c: Number in NMA of VAS and NRS / number in NMA of BRAF-MDQ and FACIT-Fatigue.

d: Rituximab is not approved for Subquestion 4.

AE: adverse event; BRAF-MDQ: Bristol Rheumatoid Arthritis Fatigue-Multidimensional Questionnaire; CDAI: Clinical Disease Activity Index; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy Fatigue; HAQ-DI: Health Assessment Questionnaire Disability Index; MTX: methotrexate; NMA: network meta-analysis; NRS: numerical rating scale; SAE: serious adverse event; SF 36: Short Form 36 - Health Survey; VAS: visual analogue scale; vs.: versus

Table 12: Combination therapy with MTX after MTX failure, matrix of available patient-relevant outcomes and biologics per NMA (Study Pool 4.1)

Biologic[a] + MTX	**Outcomes[b]**										
	Clinical remission (CDAI ≤ 2.8)	**Low disease activity (CDAI ≤ 10)**	**Pain (VAS)**	**Fatigue (VAS / NRS) / (BRAF-MDQ / FACIT-Fatigue)[b]**	**Physical function (HAQ-DI)**	**Health-related quality of life (SF-36)**	**All-cause mortality**	**SAEs**	**Discontinuation due to AEs**	**Infections**	**Serious infections**
Comparison with placebo + MTX											
Abatacept	●	●	●	●[d]	●	●	●	●	●	●	●
Adalimumab	●	●	●	●[e]	●	●	●	●	●	●	●
Anakinra	●	●	●	-	●	●	●	●	●	●	●
Certolizumab pegol	●	●	(●)	●[f]	●	●	●	●	●	●	●
Etanercept	●	●	●	-	●	-	●	●	●	●	●
Golimumab	●	●	-	●[e]	●	●	●	●	●	●	●
Infliximab	●	●	●	●[d]	●	●	●	●	●	●	●
Tocilizumab	●	●	●	●[e]	●	●	●	●	●	●	●
Direct comparison of biologics											
Abatacept vs. adalimumab	●	●	●	●[d]	●	●	●	●	●	●	●
Certolizumab pegol vs. adalimumab	●	(●)	(●)	●[f, g]	●	●	-[h]	-[h]	-[h]	-[h]	-[h]

(continued)

Table 12: Combination therapy with MTX after MTX failure, matrix of available patient-relevant outcomes and biologics per NMA (Study Pool 4.1) (continued)

a: Rituximab is not listed as it is not approved for Subquestion 4.

b: Insufficient data were available for the planned outcome "social functional level", so that the validity of the instruments used was not examined for the present benefit assessment. Therefore, this outcome is not presented in the matrix.

c: For the outcome "fatigue", separate NMAs were calculated for sufficiently similar operationalizations: 1 NMA for the operationalizations VAS and NRS and 1 NMA for the operationalizations FACIT-Fatigue and BRAF-MDQ.

d: VAS.

e: FACIT Fatigue.

f: Fatigue Assessment Scale (NRS).

g: BRAF-MDQ.

h: Only analysis times at 2 years or more were available; due to the lack of similarity to the majority of available times from other studies, this later time was not taken into account in the analysis.

● Data were reported and were usable.

(●) Data were reported and would have been usable in principle, but excluded after the homogeneity assumption and consistency assumption had been checked or after the conduct of sensitivity analyses to check the similarity assumption.

- No data were reported.

AE: adverse event; BRAF-MDQ: Bristol Rheumatoid Arthritis Fatigue-Multidimensional Questionnaire; CDAI: Clinical Disease Activity Index; FACIT-Fatigue: Functional-Assessment-of-Chronic-Illness-Therapy-Fatigue; HAQ-DI: Health Assessment Questionnaire Disability Index; MTX: methotrexate; NMA: network meta-analysis; NRS: numerical rating scale; SAE: serious adverse event; SF 36: Short Form 36 - Health Survey; VAS: visual analogue scale; vs.: versus

4.4.3 Results on patient-relevant outcomes (Study Pool 4.1)

Results of the check of the homogeneity and consistency assumption for the NMA

Occasionally, only 1 study was available for the comparison of the corresponding outcome, so that the homogeneity assumption was not checked. Most outcomes were affected for the comparison of infliximab / MTX with placebo / MTX. For these comparisons, at most a low qualitative certainty of results could thus be achieved on the basis of the NMA.

For comparisons for which more than 1 study was available, checking the homogeneity assumption in pairwise meta-analyses showed substantial heterogeneity for the following 5 comparisons of biologics / MTX with placebo / MTX: abatacept / MTX, etanercept / MTX, tocilizumab / MTX (all for pain), anakinra / MTX (discontinuation due to AEs), certolizumab pegol / MTX (low disease activity). Possible reasons for heterogeneity were investigated and described separately for each outcome. After excluding studies for which there were uncertainties in disease severity, the comparisons of abatacept / MTX and certolizumab pegol / MTX with placebo / MTX showed no substantial heterogeneity anymore. For the comparisons of anakinra / MTX, etanercept / MTX and tocilizumab / MTX with placebo / MTX, only 1 study was available in each case due to the exclusion of studies with possible explanatory factors, so that the homogeneity assumption could no longer be checked. In particular, these factors were

exceptional disease severity (etanercept / MTX) and high risk of bias (anakinra / MTX, tocilizumab / MTX).

In principle, the consistency assumption for the study pool on combination therapy with MTX after MTX failure could only be checked for comparisons with the biologics abatacept / MTX, adalimumab / MTX and certolizumab pegol / MTX with each other, since a direct comparative study was available for each of the comparisons of abatacept / MTX with adalimumab / MTX and of certolizumab pegol / MTX with adalimumab / MTX. After checking the consistency assumption, the outcomes low disease activity and pain showed inconsistency in the closed comparison (loop) of certolizumab pegol / MTX, adalimumab / MTX and placebo / MTX with each other. None of the following factors investigated was a possible reason for inconsistency (factors leading to uncertainties in the similarity check, exceptional disease severity, study initiation before 2004). Finally, the risk of bias was investigated and studies with a high risk of bias were excluded. Thus, among others, the study with the direct comparison of certolizumab pegol / MTX with adalimumab / MTX was excluded. Therefore, there were no further checks of the consistency assumption. Thus, for this comparison based on the NMA, at most a low qualitative certainty of results could be achieved for low disease activity and pain.

Maximum possible evidence base on the basis of the available data

Comparisons of biologics for which a direct comparison was available

For comparisons of biologics for which a direct comparison was available, on the basis of the available data on combination therapy with MTX after MTX failure at most proof of greater or lesser benefit or harm could be derived. However, at least one condition for this was never met: There was no statistically significant effect from a direct comparison with a high certainty of results that was confirmed by indirect evidence with at least a moderate certainty of results.

Comparisons of biologics for which no direct comparison was available

For comparisons of biologics for which no direct comparison was available, on the basis of the available data on combination therapy with MTX after MTX failure at most hints of greater or lesser benefit or harm could be derived. The reason for this is that in the absence of direct comparisons of biologics, it was not possible to check the consistency assumption. Furthermore, in a data constellation for an indirect comparison with only 1 study for at least 1 of the 2 biologics of the comparison, no hint can be derived if there is a high risk of bias for this study.

Analysis times considered

For all-cause mortality and the AE outcomes, analyses were available for 1 time only (between 24 and 52 weeks) for most of the studies; several analysis times were available for only 4 studies. For all other outcomes, several analysis times were available for a larger part of the studies (between 24 and 52 weeks, rarely also for observation periods of more than 1 year). For the present benefit assessment, times between 24 and 52 weeks were considered sufficiently similar to be analysed in a common NMA. Since for the vast majority of the studies, the data at

24 or 30 weeks were more meaningful than those at later analysis times due to fewer treatment and/or study discontinuations, these were preferred if they were available.

In addition, for 1 study, only data at 2 years and onwards were available for all-cause mortality and AE outcomes. Such data were not considered due to insufficient similarity of this analysis time versus those times available in the majority of other studies.

Subgroup characteristics and other effect modifiers

For combination therapy with MTX after MTX failure, data on less than half of the biologics / MTX relevant for Subquestion 4 were available for the investigation of subgroup characteristics and other effect modifiers for all outcomes, except for physical function. For this outcome, there were subgroup analyses in studies covering a total of 4 biologics; for 1 of the biologics (tocilizumab / MTX), however, corresponding analyses were available for only 1 study for which there were uncertainties regarding similarity that were found to be relevant in sensitivity analyses. Thus, also for the subgroup analyses on physical function, data on only less than half of the biologics / MTX relevant for Subquestion 4 would have been available. There were no subgroup analyses in any of the included studies for pain, fatigue and health-related quality of life. Due to the data situation, no potential effect modifiers were investigated for combination therapy with MTX after MTX failure.

Positive and negative effects for comparison of biologics with each other in combination therapy with MTX after MTX failure

For combination therapy with MTX after MTX failure, Table 13 shows for which outcomes there were positive or negative effects on the basis of which conclusions of greater or lesser benefit or harm were derived.

Table 13: Combination therapy with MTX after MTX failure, positive and negative effects from NMAs (Study Pool 4.1)

Comparisons[a]	Outcome: Effect estimate from the NMA (biologic in bold font vs. biologic in normal font), RR [95% CI]	
	To the advantage of the biologic in bold font	To the disadvantage of the biologic in bold font
Abatacept + MTX vs.		
Adalimumab + MTX	-	-
Anakinra + MTX	▪ Low disease activity: (CDAI ≤ 10): 1.46 [1.01; 2.09] ▪ Pain (VAS): ▫ MD [95% CI]: −12.24 [−16.37; −8.11] ▫ SMD [95% CI]: −0.50 [−0.65; −0.34] ▪ Discontinuation due to AEs: 0.12 [0.02; 0.61]	-
Certolizumab pegol + MTX	▪ SAEs: 0.42 [0.23; 0.78] ▪ Infections: 0.73 [0.56; 0.95] ▪ Serious infections: 0.22 [0.06; 0.85]	-
Etanercept + MTX	-	-
Golimumab + MTX	-	-
Infliximab + MTX	-	-
Tocilizumab + MTX	▪ Discontinuation due to AEs: 0.41 [0.18; 0.93]	-
Adalimumab + MTX vs.		
Abatacept + MTX	-	-
Anakinra + MTX	▪ Clinical remission (CDAI ≤ 2.8): 3.60 [1.16; 11.22] ▪ Low disease activity (CDAI ≤ 10): 1.55 [1.08; 2.21] ▪ Discontinuation due to AEs: 0.18 [0.04; 0.87]	-
Certolizumab pegol + MTX	▪ SAEs: 0.41 [0.22; 0.75]	-
Etanercept + MTX	-	-
Golimumab + MTX	-	-
Infliximab + MTX	-	-
Tocilizumab + MTX	-	-

(continued)

Table 13: Combination therapy with MTX after MTX failure, positive and negative effects from NMAs (Study Pool 4.1) (continued)

Comparisons[a]	Outcome: Effect estimate from the NMA (biologic in bold font vs. biologic in normal font), RR [95% CI]	
	To the advantage of the biologic in bold font	**To the disadvantage of the biologic in normal font**
Anakinra + MTX vs.		
Abatacept + MTX	-	▪ Low disease activity (CDAI ≤ 10): 0.69 [0.48; 0.99] ▪ Pain (VAS): ▫ MD [95% CI]: 12.24 [8.11; 16.37] ▫ SMD [95% CI]: 0.50 [0.34; 0.65] ▪ Discontinuation due to AEs: 8.27 [1.64; 41.61]
Adalimumab + MTX	-	▪ Clinical remission (CDAI ≤ 2.8): 0.28 [0.09; 0.86] ▪ Low disease activity (CDAI ≤ 10): 0.65 [0.45; 0.92] ▪ Discontinuation due to AEs: 5.54 [1.15; 26.63]
Certolizumab pegol + MTX	▪ SAEs: 0.43 [0.23; 0.81] ▪ Infections: 0.67 [0.51; 0.89] ▪ Serious infections: 0.21 [0.05; 0.86]	▪ Clinical remission (CDAI ≤ 2.8): 0.25 [0.08; 0.79]
Etanercept + MTX	-	▪ Discontinuation due to AEs: 10.58 [1.71; 65.41]
Golimumab + MTX	-	▪ Clinical remission (CDAI ≤ 2.8): 0.21 [0.06; 0.81] ▪ Health-related quality of life (SF-36, physical component summary score): ▫ MD [95% CI]: −3.74 [−5.61; −1.88]; ▫ SMD [95% CI]: −0.56 [−0.78; −0.33]
Infliximab + MTX	-	▪ Low disease activity (CDAI ≤ 10): 0.35 [0.14; 0.86] ▪ Discontinuation due to AEs: 8.68 [1.48; 50.90]
Tocilizumab + MTX	-	▪ Low disease activity (CDAI ≤ 10): 0.58 [0.39; 0.85] ▪ Pain (VAS): ▫ MD [95% CI]: 16.72 [6.49; 26.94] ▫ SMD [95% CI]: 0.71 [0.27; 1.14]

(continued)

Table 13: Combination therapy with MTX after MTX failure, positive and negative effects from NMAs (Study Pool 4.1) (continued)

Comparisons[a]	Outcome: Effect estimate from the NMA (biologic in bold font vs. biologic in normal font), RR [95% CI]	
	To the advantage of the biologic in bold font	**To the disadvantage of the biologic in bold font**
Certolizumab pegol + MTX vs.		
Abatacept + MTX	-	▪ SAEs: 2.36 [1.29; 4.31] ▪ Infections: 1.37 [1.06; 1.77] ▪ Serious infections: 4.52 [1.17; 17.41]
Adalimumab + MTX	-	SAEs: 2.46 [1.33; 4.56]
Anakinra + MTX	▪ Clinical remission (CDAI ≤ 2.8): 3.99 [1.26; 12.63]	▪ SAEs: 2.33 [1.24; 4.38] ▪ Infections: 1.49 [1.13; 1.97] ▪ Serious infections: 4.75 [1.16; 19.49]
Etanercept + MTX	-	▪ SAEs: 2.39 [1.04; 5.52] ▪ Infections: 1.53 [1.12; 2.08]
Golimumab + MTX	-	▪ Infections: 1.47 [1.02; 2.12]
Infliximab + MTX	-	▪ SAEs: 3.88 [1.71; 8.82] ▪ Serious infections: 15.72 [2.75; 89.92]
Tocilizumab + MTX	-	▪ Infections: 1.35 [1.02; 1.77]
Etanercept + MTX vs.		
Abatacept + MTX	-	-
Adalimumab + MTX	-	-
Anakinra + MTX	▪ Discontinuation due to AEs: 0.09 [0.02; 0.58]	-
Certolizumab pegol + MTX	▪ SAEs: 0.42 [0.18; 0.96] ▪ Infections: 0.65 [0.48; 0.89]	-
Golimumab + MTX	-	-
Infliximab + MTX	-	-
Tocilizumab + MTX	-	-

(continued)

Table 13: Combination therapy with MTX after MTX failure, positive and negative effects from NMAs (Study Pool 4.1) (continued)

Comparisons[a]	Outcome: Effect estimate from the NMA (biologic in bold font vs. biologic in normal font), RR [95% CI]	
	To the advantage of the biologic in bold font	**To the disadvantage of the biologic in bold font**
Golimumab + MTX vs.		
Abatacept + MTX	-	-
Adalimumab + MTX	-	-
Anakinra + MTX	▪ Clinical remission (CDAI ≤ 2.8): 4.68 [1.24; 17.66] ▪ Health-related quality of life (SF-36, physical component summary score): ▫ MD [95% CI]: 3.74 [1.88; 5.61]; ▫ SMD [95% CI]: 0.56 [0.33; 0.78]	-
Certolizumab pegol + MTX	▪ Infections: 0.68 [0.47; 0.98]	-
Etanercept + MTX	-	-
Infliximab + MTX	-	▪ Serious infections: 11.89 [1.23; 115.02]
Tocilizumab + MTX	-	-
Infliximab + MTX vs.		
Abatacept + MTX	-	-
Adalimumab + MTX	-	-
Anakinra + MTX	▪ Low disease activity (CDAI ≤ 10): 2.87 [1.17; 7.06] ▪ Discontinuation due to AEs: 0.12 [0.02; 0.67]	-
Certolizumab pegol + MTX	▪ SAEs: 0.26 [0.11; 0.59] ▪ Serious infections: 0.06 [0.01; 0.36]	-
Etanercept + MTX	-	-
Golimumab + MTX	▪ Serious infections: 0.08 [0.01; 0.81]	-
Tocilizumab + MTX	▪ Serious infections: 0.21 [0.05; 0.997]	-

(continued)

Table 13: Combination therapy with MTX after MTX failure, positive and negative effects from NMAs (Study Pool 4.1) (continued)

Comparisons[a]	Outcome: Effect estimate from the NMA (biologic in bold font vs. biologic in normal font), RR [95% CI]	
	To the advantage of the biologic in bold font	**To the disadvantage of the biologic in bold font**
Tocilizumab + MTX vs.		
Abatacept + MTX	-	▪ Discontinuation due to AEs: 2.46 [1.07; 5.67]
Adalimumab + MTX	-	-
Anakinra + MTX	▪ Low disease activity (CDAI ≤ 10): 1.73 [1.18; 2.53] ▪ Pain (VAS): ▫ MD [95% CI]: −16.72 [−26.94; −6.49] ▫ SMD [95% CI]: −0.71 [−1.14; −0.27]	-
Certolizumab pegol + MTX	▪ Infections: 0.74 [0.56; 0.98]	-
Etanercept + MTX	-	-
Golimumab + MTX	-	-
Infliximab + MTX	-	▪ Serious infections 4.67 [1.003; 21.77]

- No hint of greater or lesser benefit or harm; for information on which outcomes had data in the NMA, see Table 10.

a: Rituximab is not listed as it is not approved for Subquestion 4.

AE: adverse event; CDAI: Clinical Disease Activity Index; CI: confidence interval; MD: mean difference; MTX: methotrexate; NMA: network meta-analysis; RR: relative risk; SAE: serious adverse event; SF-36: short form 36 - health survey; SMD: standardized mean difference (Hedges' g); VAS: visual analogue scale; vs.: versus

In combination therapy with MTX after MTX failure, adalimumab / MTX, certolizumab pegol / MTX, and golimumab / MTX each showed positive effects versus anakinra / MTX for clinical remission. Thus, for this outcome, there is a hint of greater benefit of these 3 biologics (each in combination with MTX) compared with anakinra / MTX.

In combination therapy with MTX after MTX failure, abatacept / MTX, adalimumab / MTX, infliximab / MTX, and tocilizumab / MTX each showed positive effects versus anakinra / MTX for low disease activity. Thus, for this outcome, there is a hint of greater benefit of these 4 biologics (each in combination with MTX) compared with anakinra / MTX.

Abatacept / MTX and tocilizumab / MTX each showed positive effects versus anakinra / MTX for pain. Thus, for this outcome, there is hint of greater benefit of these 2 biologics (each in combination with MTX) compared with anakinra / MTX.

Certolizumab pegol / MTX showed negative effects versus all other biologics / MTX for SAEs, infections and / or serious infections. Thus, for harm outcomes, there is a hint of greater harm of certolizumab pegol / MTX compared with abatacept, adalimumab, anakinra, etanercept, golimumab, infliximab and tocilizumab (each in combination with MTX).

Anakinra / MTX showed negative effects versus abatacept / MTX, adalimumab / MTX, etanercept / MTX, and infliximab / MTX for discontinuation due to AEs. Thus, for this outcome, there is a hint of greater harm of anakinra / MTX compared with these 4 biologics (each in combination with MTX).

In addition, only isolated effects were shown: For golimumab / MTX and tocilizumab / MTX there were negative effects (hint of greater harm) for serious infections compared with infliximab / MTX; for health-related quality of life (physical component summary score of SF-36) an effect in favour of golimumab / MTX (hint of greater benefit) versus anakinra / MTX was shown. For tocilizumab / MTX, there was also a negative effect (hint of greater harm) for discontinuation due to AEs versus abatacept / MTX. For all other outcomes, there were neither positive nor negative effects in the comparisons of biologics in combination therapy with MTX after MTX failure.

4.4.4 Evidence map (Study Pool 4.1)

For the combination therapy with MTX after MTX failure (Study Pool 4.1), no corresponding study with a direct comparison was available in the NMA for an indirect comparison for which a positive or negative effect was derived. Therefore, no consistency check was possible, and for this reason, at most hints of greater or lesser benefit or harm could be derived.

For combination therapy with MTX after MTX failure, the following evidence map (Table 14) shows for which patient-relevant outcomes there is greater or lesser benefit or harm.

Table 14: Combination therapy with MTX after MTX failure, evidence map for greater or lesser benefit or harm (Study Pool 4.1)

Comparisons[a]	Clinical remission (CDAI ≤ 2.8)	Low disease activity (CDAI ≤ 10)	Pain (VAS)	Fatigue (VAS / NRS; BRAF-MDQ / FACIT-Fatigue)[b]	Physical function (HAQ-DI)	Social functional level	Health-related quality of life		All-cause mortality	SAEs	Discontinuations due to AEs	Infections	Serious infections
							SF-36, mental summary score	SF-36, physical summary score					
Abatacept + MTX vs.													
Adalimumab + MTX	-	-	-	-	-	Not calculated[c]	-	-	-	-	-	-	-
Anakinra + MTX	-	⇗	⇗	-[d]	-		-	-	-	-	⇗	-	-
Certolizumab pegol + MTX	-	-	-[d]	-	-		-	-	-	⇗	-	⇗	⇗
Etanercept + MTX	-	-	-	-[d]	-		-[d]	-[d]	-	-	-	-	-
Golimumab + MTX	-	-	-[d]	-[d]	-		-	-	-	-	-	-	-
Infliximab + MTX	-	-	-	-	-		-	-	-	-	-	-	-
Tocilizumab + MTX	-	-	-	-[d]	-		-	-	-	-	⇗	-	-
Adalimumab + MTX vs.													
Abatacept + MTX	-	-	-	-	-	Not calculated[c]	-	-	-	-	-	-	-
Anakinra + MTX	⇗	⇗	-	-[d]	-		-	-	-	-	⇗	-	-
Certolizumab pegol + MTX	-	-	-[e]	-	-		-	-	-	⇗	-	-	-
Etanercept + MTX	-	-	-	-[d]	-		-[d]	-[d]	-	-	-	-	-
Golimumab + MTX	-	-	-[d]	-	-		-	-	-	-	-	-	-
Infliximab + MTX	-	-	-	-	-		-	-	-	-	-	-	-
Tocilizumab + MTX	-	-	-	-	-		-	-	-	-	-	-	-
Anakinra + MTX vs.													
Abatacept + MTX	-	⇘	⇘	-[d]	-	Not calculated[c]	-	-	-	-	⇘	-	-
Adalimumab + MTX	⇘	⇘	-	-[d]	-		-	-	-	-	⇘	-	-
Certolizumab pegol + MTX	⇘	-	-[d]	-[d]	-		-	-	-	⇗	-	⇗	⇗
Etanercept + MTX	-	-	-	-[d]	-		-[d]	-[d]	-	-	⇘	-	-
Golimumab + MTX	⇘	-	-[d]	-[d]	-		-	⇘	-	-	-	-	-
Infliximab + MTX	-	⇘	-	-[d]	-		-	-	-	-	⇘	-	-
Tocilizumab + MTX	-	⇘	⇘	-[d]	-		-	-	-	-	-	-	-

(continued)

Table 14: Combination therapy with MTX after MTX failure, evidence map for greater or lesser benefit or harm (Study Pool 4.1) (continued)

Comparisons[a]	Clinical remission (CDAI ≤ 2.8)	Low disease activity (CDAI ≤ 10)	Pain (VAS)	Fatigue (VAS / NRS; BRAF-MDQ / FACIT-Fatigue)[b]	Physical function (HAQ-DI)	Social functional level	Health-related quality of life		All-cause mortality	SAEs	Discontinuations due to AEs	Infections	Serious infections
							SF-36, mental summary score	SF-36, physical summary score					
Certolizumab pegol + MTX vs.													
Abatacept + MTX	-	-	-[d]	-	-	Not calculated[c]	-	-	-	⇓	-	⇓	⇓
Adalimumab + MTX	-	-	-[e]	-	-		-	-	-	⇓	-	-	-
Anakinra + MTX	⇑	-	-[d]	-[d]	-		-	-	-	⇓	-	⇓	⇓
Etanercept + MTX	-	-	-[d]	-[d]	-		-[d]	-[d]	-	⇓	-	⇓	-
Golimumab + MTX	-	-	-[d]	-	-		-	-	-	-	-	⇓	-
Infliximab + MTX	-	-	-[d]	-	-		-	-	-	⇓	-	-	⇓
Tocilizumab + MTX	-	-	-[d]	-	-		-	-	-	-	-	⇓	-
Etanercept + MTX vs.													
Abatacept + MTX	-	-	-	-[d]	-	Not calculated[c]	-[d]	-[d]	-	-	-	-	-
Adalimumab + MTX	-	-	-	-[d]	-		-[d]	-[d]	-	-	-	-	-
Anakinra + MTX	-	-	-	-[d]	-		-[d]	-[d]	-	-	⇑	-	-
Certolizumab pegol + MTX	-	-	-[d]	-[d]	-		-[d]	-[d]	-	⇑	-	⇑	-
Golimumab + MTX	-	-	-[d]	-[d]	-		-[d]	-[d]	-	-	-	-	-
Infliximab + MTX	-	-	-	-[d]	-		-[d]	-[d]	-	-	-	-	-
Tocilizumab + MTX	-	-	-	-[d]	-		-[d]	-[d]	-	-	-	-	-
Golimumab + MTX vs.													
Abatacept + MTX	-	-	-[d]	-[d]	-	Not calculated[c]	-	-	-	-	-	-	-
Adalimumab + MTX	-	-	-[d]	-	-		-	-	-	-	-	-	-
Anakinra + MTX	⇑	-	-[d]	-[d]	-		-	⇑	-	-	-	-	-
Certolizumab pegol + MTX	-	-	-[d]	-	-		-	-	-	-	-	⇑	-
Etanercept + MTX	-	-	-[d]	-[d]	-		-[d]	-[d]	-	-	-	-	-
Infliximab + MTX	-	-	-[d]	-[d]	-		-	-	-	-	-	-	⇓
Tocilizumab + MTX	-	-	-[d]	-	-		-	-	-	-	-	-	-

(continued)

Table 14: Combination therapy with MTX after MTX failure, evidence map for greater or lesser benefit or harm (Study Pool 4.1) (continued)

Comparisons[a]	Clinical remission (CDAI ≤ 2.8)	Low disease activity (CDAI ≤ 10)	Pain (VAS)	Fatigue (VAS / NRS; BRAF-MDQ / FACIT-Fatigue)[b]	Physical function (HAQ-DI)	Social functional level	Health-related quality of life		All-cause mortality	SAEs	Discontinuations due to AEs	Infections	Serious infections
							SF-36, mental summary score	SF-36, physical summary score					
Infliximab + MTX vs.													
Abatacept + MTX	-	-	-	-	-	Not calculated[c]	-	-	-	-	-	-	-
Adalimumab + MTX	-	-	-	-	-		-	-	-	-	-	-	-
Anakinra + MTX	-	⇗	-	-[d]	-		-	-	-	-	⇗	-	-
Certolizumab pegol + MTX	-	-	-[d]	-	-		-	-	-	⇗	-	-	⇗
Etanercept + MTX	-	-	-	-[d]	-		-[d]	-[d]	-	-	-	-	-
Golimumab + MTX	-	-	-[d]	-[d]	-		-	-	-	-	-	-	⇗
Tocilizumab + MTX	-	-	-	-[d]	-		-	-	-	-	-	-	⇗
Tocilizumab + MTX vs.													
Abatacept + MTX	-	-	-	-[d]	-	Not calculated[c]	-	-	-	-	⇘	-	-
Adalimumab + MTX	-	-	-	-	-		-	-	-	-	-	-	-
Anakinra + MTX	-	⇗	⇗	-[d]	-		-	-	-	-	-	-	-
Certolizumab pegol + MTX	-	-	-[d]	-	-		-	-	-	-	-	⇗	-
Etanercept + MTX	-	-	-	-[d]	-		-[d]	-[d]	-	-	-	-	-
Golimumab + MTX	-	-	-[d]	-	-		-	-	-	-	-	-	-
Infliximab + MTX	-	-	-	-[d]	-		-	-	-	-	-	-	⇘

(continued)

Table 14: Combination therapy with MTX after MTX failure, evidence map for greater or lesser benefit or harm (Study Pool 4.1) (continued)

a: Rituximab is not listed as it is not approved for Subquestion 4.

b: For the outcome "fatigue", separate NMAs were calculated for sufficiently similar operationalizations: 1 NMA for the operationalizations VAS and NRS and 1 NMA for the operationalizations FACIT-Fatigue and BRAF-MDQ.

c: Insufficient data were available for the planned outcome "social functional level", so that the validity of the instruments used was not examined for the present benefit assessment.

d: No data for the comparison of biologics in the NMA.

e: No data for the comparison of biologics in the NMA, derivation of the evidence base exclusively on the basis of a study with a direct comparison of biologics.

⇗: Hint of greater benefit or hint of lesser harm.

⇘: Hint of lesser benefit or hint of greater harm.

-No hint, indication or proof of greater or lesser benefit or harm

AE: adverse event; BRAF-MDQ: Bristol Rheumatoid Arthritis Fatigue - Multidimensional Questionnaire; CDAI: Clinical Disease Activity Index; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy Fatigue; HAQ DI: Health Assessment Questionnaire Disability Index; MTX: methotrexate; NMA: network meta-analysis; NRS: numeric rating scale; SAE: serious adverse event; SF 36: Short Form 36 - Health Survey; VAS: visual analogue scale; vs.: versus

4.5 Subquestion 5: Monotherapy after MTX intolerance

4.5.1 Study design and study populations (Study Pool 5)

For Subquestion 5, 2 studies were included that were to be checked for similarity (see Table 25 of the full report): 1 study with a direct comparison of biologics and 1 study with a comparison of a biologic with a placebo. The control treatment of this study therefore does not provide a common comparator for comparison with the biologics investigated in the other study. The study was therefore excluded from the further evaluations for Subquestion 5. Since only 1 study on a direct comparison of biologics remained for Study Pool 5 (see Table 307 of the full report), the similarity check for Subquestion 5 was omitted. In the remaining study the direct comparison of the biologics adalimumab and tocilizumab was investigated. The study was described as double-blind. In this study, the subpopulation that was relevant for the present benefit assessment was the subpopulation consisting of patients who had MTX intolerance and for whom continuation of MTX was inappropriate or not possible. The mean age of these patients was about 54 years and about 83% were women. The mean duration of the disease was about 8 years. On the basis of available information on disease-specific characteristics (e.g. on DAS 28 and on immunological and prognostic factors), severe rheumatoid arthritis could be assumed for the relevant subpopulation of the study.

4.5.2 Overview of the outcomes relevant for the assessment

Data on patient-relevant outcomes were extracted from the study with a direct comparison of biologics, if usable data were available. The study included 2 of 4 biologics approved for Subquestion 5. For each patient-relevant outcome, Table 15 shows the data per biologic included in the analyses.

Table 15: Monotherapy after MTX intolerance, matrix of available patient-relevant outcomes and biologics (Study Pool 5)

Biologic[a]	Outcomes[b]											
	Clinical remission (CDAI ≤ 2.8)	Low disease activity (CDAI ≤ 10)	Pain (VAS)	Fatigue (FACIT-Fatigue)	Physical function (HAQ-DI)	Social functional level	Health-related quality of life (SF-36)	All-cause mortality	SAEs	Discontinuation due to AEs	Infections	Serious infections
Comparison with common comparator												
Adalimumab	No studies on adalimumab were identified for Study Pool 5.											
Certolizumab pegol	No studies on certolizumab pegol were identified for Study Pool 5.											
Etanercept	No studies on etanercept were identified for Study Pool 5.											
Tocilizumab	No studies on tocilizumab were identified for Study Pool 5.											
Direct comparison of biologics												
Adalimumab vs. tocilizumab	●	●	●	●	●	-	●	●	●	●	●	●

a: Abatacept, anakinra, golimumab, infliximab and rituximab are not listed, as they are not approved for Subquestion 5.

● Data were reported and were usable.

- No data were reported.

AE: adverse event; CDAI: Clinical Disease Activity Index; FACIT-Fatigue: Functional-Assessment-of-Chronic-Illness-Therapy-Fatigue; HAQ-DI: Health Assessment Questionnaire Disability Index; MTX: methotrexate; SAE: serious adverse event; SF-36: Short Form 36 – Health Survey; VAS: visual analogue scale

4.5.3 Results on patient-relevant outcomes (Study Pool 5)

Maximum possible evidence base on the basis of available data

On the basis of the available data at most indications of, for example, greater benefit could be derived for clinical remission, low disease activity and all-cause mortality and all AE outcomes; due to a high risk of bias at most hints of, for example, greater benefit could be derived for pain, fatigue, physical function status and health-related quality of life.

Analysis times considered

Since only 1 analysis time was examined in the included study on monotherapy after MTX intolerance, only data at 24 weeks were available for all outcomes.

Subgroup characteristics and other effect modifiers

For the included study on monotherapy after MTX intolerance, no subgroup analyses were available for the relevant subpopulation. Due to the data situation, it was therefore not possible to investigate potential effect modifiers.

Positive and negative effects for the comparison of biologics with each other in monotherapy after MTX intolerance

For monotherapy after MTX intolerance, a positive or negative effect of one biologic versus another was not shown for any outcome. There is thus no numerical presentation of positive and negative effects.

Overall, for monotherapy after MTX intolerance there is no hint of greater or lesser benefit or harm of any biologic versus another biologic.

4.5.4 Evidence map (Study Pool 5)

An evidence map for patient-relevant outcomes has been omitted for monotherapy after MTX intolerance because there are no hints of greater or lesser benefit or harm.

4.6 Subquestion 6: Combination therapy with MTX after biologic failure

4.6.1 Study design and study populations (Study Pool 6.1)

After completion of the similarity check of the 20 studies identified for Subquestion 6 (see Table 25 of the full report), the study pool for the investigation of combination therapy with MTX after biologic failure consisted of 18 sufficiently similar studies (see Table 333 of the full report). Data for an NMA were in principle available for 16 of the 18 studies. 14 of the 16 studies were described as double-blind and 1 study as open. These studies examined the comparison with placebo / MTX. For the last of the 16 studies, the only one with a direct comparison of biologics, blinding was abolished by amendment.

The mean age of patients in most studies was between 50 and 55 years. In only 1 study, the mean age was about 40 years. In the majority of studies, slightly more than three-quarters of the study population were women. The gender ratio was reversed in only 1 study; about a quarter of the study population were women. The mean duration of the disease in the majority of the studies was between about 10 and 12 years. On the basis of available information on disease-specific characteristics (e.g. DAS 28, existing erosions and immunological as well as prognostic factors), severe rheumatoid arthritis could be assumed for study populations at baseline.

In contrast to Study Pools 1.1 and 4.1, following the similarity check of the studies there were no uncertainties in Study Pool 6.1 that had to be investigated in sensitivity analyses.

4.6.2 Overview of the outcomes relevant for the assessment

Data on patient-relevant outcomes were extracted from all 16 studies, if usable data were available. For each patient-relevant outcome, Table 16 shows the number of studies and biologics included in the NMA. Table 17 shows the data per biologic included in the analyses for each patient-relevant outcome.

Table 16: Combination therapy with MTX after biologic failure, number of studies and biologics per NMA (Study Pool 6.1)

	Outcomes[a]										
	Clinical remission (CDAI ≤ 2.8)	**Low disease activity (CDAI ≤ 10)**	**Pain (VAS)**	**Fatigue (FACIT-Fatigue)**	**Physical function (HAQ-DI)**	**Health-related quality of life (SF-36)**	**All-cause mortality**	**SAEs**	**Discontinuation due to AEs**	**Infections**	**Serious infections**
Studies, related to 18 available studies for Study Pool 6.1											
Number of studies without data for relevant subpopulation	2	2	2	2	2	2	2	2	2	2	2
Number of studies without (usable) data	2	2	5	8	6	9	1	0	0	0	0
Number of studies with exclusion because of: breach of homogeneity or consistency assumption or lack of robustness of results in sensitivity analyses to check similarity assumptions	0	0	6	n. c.[b]	3	0	0	0	0	3	0
Number of studies in NMA	14	14	n. c.[c]	n. c.[b]	7	7	15	16	16	13	16
Biologics in NMA, related to 9 relevant biologics for Subquestion 6											
Number of biologics	6	6	n. c.[c]	n. c.[b]	6	5	6	6	6	5	6

a: Insufficient data were available for the planned outcome "social functional level", so that the validity of the instruments used was not checked for the present benefit assessment. Therefore, this outcome is not presented in the table.

b: Less than 50% of the approved biologics for this subquestion with sufficiently similar operationalizations.

c: Less than 50% of the approved biologics for this subquestion, as data were excluded in the course of analyses for checking structural quality.

AE: adverse event; CDAI: Clinical Disease Activity Index; HAQ-DI: Health Assessment Questionnaire Disability Index; MTX: methotrexate; n. c.: not calculated; NMA: Network meta-analysis; SAE: serious adverse event; SF 36: Short Form 36 - Health Survey; VAS: visual analogue scale; vs.: versus

Table 17: Combination therapy with MTX after biologic failure, matrix of patient-relevant outcomes and biologics per NMA (Study Pool 6.1)

Biologic + MTX	**Outcome[a]**										
	Clinical remission (CDAI ≤ 2.8)	**Low disease activity (CDAI ≤ 10)**	**Pain (VAS)**	**Fatigue (FACIT-Fatigue)**	**Physical function (HAQ-DI)**	**Social functional level**	**Health-related quality of life (SF-36)**	**All-cause mortality**	**SAEs**	**Discontinuation due to AEs**	**Infections**
Comparison with placebo + MTX											
Abatacept	●	●	○	○[b]	●	●	●	●	●	●	●
Adalimumab	●	●	(●)	○[c]	●	●	●	●	●	●	●
Anakinra	No studies on anakinra were identified for Study Pool 6.1.										
Certolizumab pegol	●	●	○	-	●	●	●	●	●	●	●
Etanercept	No studies on etanercept were identified for Study Pool 6.1.										
Golimumab	●	●	○	○[c]	●	-	●	●	●	●	●
Infliximab	No studies on infliximab were identified for Study Pool 6.1.										
Rituximab	●	●	○	○[c]	●	●	●	●	●	(●)	●
Tocilizumab	●	●	(●)	○[c]	(●)	●	●	●	●	●	●
Direct comparison of biologics											
Adalimumab vs. tocilizumab	●	●	(●)	○[c]	●	-	●	●	●	●	●

a: Insufficient data were available for the planned outcome social functional level, so that the validity of the instruments used was not examined for the present benefit assessment. Therefore, this outcome is not presented in the matrix.

b: VAS

c: FACIT Fatigue

● Data were reported and were usable.

(●) Data were reported and would have been usable in principle, but excluded after the homogeneity or consistency assumption had been checked.

○ Data were reported, but were not usable for the benefit assessment: less than 50% of the approved biologics for the present subquestion.

- No data were reported.

AE: adverse event; CDAI: Clinical Disease Activity Index; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy Fatigue; HAQ-DI: Health Assessment Questionnaire Disability Index; MTX: methotrexate; NMA: network meta-analysis; SAE: serious adverse event; SF 36: Short Form 36 - Health Survey; VAS: visual analogue scale; vs.: versus

All 9 biologics investigated in this benefit assessment are approved for combination therapy with MTX after biologic failure. For Study Pool 6.1, however, studies on combination therapy

with MTX after biologic failure were identified only for the 6 biologics abatacept, adalimumab, certolizumab pegol, golimumab, rituximab and tocilizumab.

4.6.3 Results on patient-relevant outcomes (Study Pool 6.1)

Results of the check of the homogeneity and consistency assumption for the NMA

For the comparisons of adalimumab / MTX, certolizumab pegol / MTX, and golimumab / MTX (each with placebo / MTX), the homogeneity assumption was not checked because only a single study was available for each comparison. For the same reason, the homogeneity assumption was not checked in isolated cases for outcomes investigated in other comparisons. For these comparisons, it was therefore possible to achieve at most a low qualitative certainty of results on the basis of the NMA. For comparisons for which more than 1 study was available, the check of the homogeneity assumption in pairwise meta-analyses showed substantial heterogeneity for 2 comparisons of biologics / MTX with placebo / MTX for 1 outcome in each case: rituximab / MTX (infections) and tocilizumab / MTX (physical function). The possible reasons for heterogeneity were investigated and described separately for each outcome. Since no factors resulting in sensitivity analyses were identified in the check of similarity of the studies, there were no possible explanations for substantial heterogeneity; thus, all studies with a high risk of bias were excluded from the comparisons concerned. As a result, all studies of the pairwise comparisons were excluded from the respective NMAs.

In principle, checking the consistency assumption for the study pool on combination therapy with MTX after biological failure was only possible in the closed comparison (loop) of adalimumab / MTX, tocilizumab / MTX and placebo / MTX, since a direct comparative study was available for the comparison of adalimumab / MTX with tocilizumab / MTX. After checking the consistency assumption for the preliminary analysis, inconsistency was found for pain (VAS) in this closed comparison (loop) comparing adalimumab / MTX, tocilizumab / MTX and placebo / MTX with each other. Since no factors resulting in sensitivity analyses were identified in the check of similarity of the studies, there were no possible explanations for inconsistency; thus, all studies with a high risk of bias were excluded from the comparisons. This led to the exclusion of the entire closed comparison from the network, which meant that no further checks of the consistency assumption were carried out. In addition, since data on less than half of the biologics approved for Subquestion 6 were available after exclusion of the loop for the comparisons of the biologics with each other, no analyses were performed for pain (VAS).

Maximum possible evidence base on the basis of available data

Comparisons of biologics for which a direct comparison was available

For comparisons of biologics for which a direct comparison was available, on the basis of the available data for combination therapy with MTX after biologic failure at most proof of greater or lesser benefit or harm could be derived. However, the prerequisites for this were not met: There was no statistically significant effect from a direct comparison with a high certainty of results that was confirmed by indirect evidence with at least a moderate certainty of results.

Comparisons of biologics for which no direct comparison was available

For comparisons of biologics for which no direct comparison was available, on the basis of the available data for combination therapy with MTX after biologic failure at most hints of greater or lesser benefit or harm could be derived. The reason is that in the absence of direct comparisons of biologics, it was not possible to check the consistency assumption. Furthermore, in a data constellation for an indirect comparison with only 1 study for at least 1 of the 2 biologics of the comparison, no hint can be derived if there is a high risk of bias for this study.

Analysis times considered

For all-cause mortality and the AE outcomes, analyses were available for the majority of the studies at 24 weeks only. More analysis times were only available for 1 study (24 and 52 weeks). The results for week 24 were used for the present benefit assessment because results were reported for the majority of the studies at this time. For all other outcomes, usable data were only available at 24 weeks. These were therefore used for the present benefit assessment.

Subgroup characteristics and other effect modifiers

For combination therapy with MTX after biologic failure there were no subgroup analyses available for any of the outcomes relevant for the present benefit assessment. Due to the data situation, potential effect modifiers could not be investigated for this type of therapy.

Positive and negative effects for the comparison of biologics with each other in combination therapy with MTX after biologic failure

For combination therapy with MTX after biologic failure, no biologic showed a positive or negative effect compared with another biologic for any outcome. There is thus no numerical presentation of positive and negative effects. Overall, for this type of therapy, there is no hint of greater or lesser harm of any biologic compared with any other biologic.

4.6.4 Evidence map (Study Pool 6.1)

An evidence map for patient-relevant outcomes is omitted for combination therapy with MTX after failure of biologics because there are no hints of greater or lesser benefit or harm.

5 Classification of the assessment result

The vast majority of the studies available for the NMAs examined biologics in comparison with placebo. Thus, for the majority of the comparisons of biologics, it was not possible to check the consistency assumption. It was also not possible to check the homogeneity assumption for all pairwise comparisons in the NMAs, since often only 1 study was available for the respective comparisons. Results from NMAs for which corresponding checks were not possible are therefore less reliable.

The predominant lack of long-term studies and the reduced certainty of results of data from placebo-controlled studies (due to large proportions of treatment switches) led to the NMAs of the present benefit assessment being based on data of a maximum period of up to 1 year (mostly 24 weeks).

With the predominant lack of direct comparative studies and of long-term studies, the present benefit assessment has again identified relevant deficiencies in the data basis for the treatment of patients with rheumatoid arthritis, which have already been described in the literature [580,581]. In view of the numerous available active ingredients and the large number of affected patients, it is not understandable why the situation with regard to studies is so inadequate.

NMAs were only performed if at least half of the biologics approved for a subquestion were included. As a result, for example, smaller study pools (even if these consisted of a direct comparison of 2 biologics) as well as less common individual outcomes, operationalizations of outcomes or analysis times were not investigated. In all subquestions this applied to the outcome “social functional level” (apart from Study Pool 5: no measurement of the outcome); for both combination therapy with MTX without MTX pretreatment and for combination therapy with MTX after biologic failure this also applied to the outcome “fatigue”.

The extensive data requests in the present benefit assessment allowed the assessment to be performed on the basis of results that go beyond the analyses available in the study documents. For instance, the currently recommended operationalizations based on the CDAI were used for clinical remission and low disease activity. These operationalizations did not correspond to the study protocol, especially in older studies, but were submitted by the study sponsors for the vast majority of the studies. Overall, analyses based on the CDAI were missing only sporadically for studies that were included in NMAs. These analyses were completely missing only for infliximab for the combination therapy with MTX without MTX pretreatment (in Study Pool 1.1). For the other biologics in Study Pool 1.1 and all biologics for combination therapy with MTX after MTX failure (Study Pool 4.1), it is not assumed that the few missing analyses of clinical remission or low disease activity according to the current operationalizations lead to a relevant bias in the results. For monotherapy after MTX intolerance (Study Pool 5) and combination therapy with MTX after biologic failure (Study Pool 6.1) corresponding analyses were presented by the study sponsors for all studies that were included in the respective study pool. The present benefit assessment thus for the first time systematically provides

comprehensive results based on the currently recommended operationalizations of clinical remission and low disease activity.

Using the data provided on low disease activity, a comparison of results was also possible for the operationalizations "CDAI ≤ 10" and "DAS 28 < 3.2". For tocilizumab, for all study pools containing sufficient data for the present benefit assessment, clearly more positive results were found for low disease activity if the outcome was measured using the DAS 28 < 3.2 instead of the CDAI ≤ 10. The different results for the two operationalizations can presumably be attributed to the inflammation parameter contained in the DAS 28. Previous positive results for tocilizumab compared with other biologics based on DAS 28 must therefore be questioned.

By providing data on subpopulations, which were also predominantly provided by the study sponsors, the present benefit assessment also includes extensive results for further patient-relevant outcomes. Only for Study Pool 4.1, data on 2 studies were not submitted. It is also not assumed here that the missing analyses of subpopulations for Study Pool 4.1 lead to a relevant bias of the results. Due to the data provided, results for all outcomes that were not available in the study documents were available for the first time at all for the investigations of the Subquestions 5 and 6. The investigations of Study Pools 1.1 and 4.1 could also be considerably enriched because of the systematic provision of data on relevant subpopulations. Thus data on other biologics are now also available. Overall, for the first time, analyses of relevant subpopulations not available in conventional study documents were made available for the present benefit assessment.

6 Conclusion

Combination therapy with MTX without MTX pretreatment (Subquestion 1)

In the combination therapy with MTX without MTX pretreatment, the following biologics were compared with each other in the present benefit assessment: abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, and tocilizumab. A direct comparative study was not available for any comparison of biologics.

For the combination therapy with MTX without MTX pretreatment, the evidence base is as follows.

- there is no hint of greater or lesser benefit of any biologic versus another biologic for clinical remission (which particularly in this subquestion is the primary treatment goal to be achieved)
- there is a hint of greater benefit of adalimumab and etanercept versus certolizumab pegol and tocilizumab for low disease activity
- there is no hint of greater or lesser benefit of any further biologic versus another biologic for low disease activity
- there is no hint of greater or lesser benefit or harm of any biologic versus another biologic for further patient-relevant outcomes

Combination therapy with MTX after MTX failure (Subquestion 4)

In combination therapy with MTX after MTX failure, the following biologics were compared with each other in the present benefit assessment: abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab and tocilizumab. Only 2 studies with a direct comparison of biologics were available.

For the combination therapy with MTX after MTX failure, the evidence base is as follows:

- there is a hint of greater benefit of adalimumab, certolizumab pegol and golimumab versus anakinra for the primary treatment goal of clinical remission
- there is a hint of greater benefit of abatacept, adalimumab, infliximab, and tocilizumab versus anakinra for low disease activity
- there is hint of greater benefit of abatacept and tocilizumab versus anakinra for pain.
- there is a hint of greater benefit of golimumab versus anakinra for health-related quality of life (physical component summary score of the Short Form 36 - Health Survey)
- there is a hint of greater harm of certolizumab pegol versus all other biologics for 1 or more of the following 3 outcomes: serious adverse events, infections, serious infections. In addition, there is a hint of greater harm of golimumab and tocilizumab versus infliximab for serious infections.

- there is a hint of greater harm of anakinra versus abatacept, adalimumab, etanercept and infliximab as well as of tocilizumab versus abatacept for discontinuations due to adverse events
- there is no hint of greater or lesser benefit or harm of any other biologic versus another biologic for all further outcomes.

Monotherapy after MTX intolerance (Subquestion 5)

In monotherapy after MTX intolerance, the following biologics were compared with each other in the present benefit assessment: adalimumab and tocilizumab. For this comparison, only a single study was available for the direct comparison of both biologics. No study on certolizumab pegol and etanercept was identified that could enable a comparison with other biologics.

For monotherapy after MTX intolerance, the evidence base is as follows:

- there is no hint of greater or lesser benefit or harm of any biologic versus another biologic for the primary treatment goal of clinical remission or other outcomes

Combination therapy with MTX after biologic failure (Subquestion 6)

In the combination therapy with MTX after biologic failure, the following biologics were compared with each other in the present benefit assessment: abatacept, adalimumab, certolizumab pegol, golimumab, rituximab and tocilizumab. No relevant studies were identified for anakinra, etanercept and infliximab, so that no comparison with the other biologics was possible. There was only a single study with a direct comparison of biologics.

For the combination therapy with MTX after biologic failure, the evidence base is as follows:

- there is no hint of greater or lesser benefit or harm of any biologic versus another biologic for the primary treatment goal of clinical remission or other outcomes

Further subquestions

No conclusion was drawn for the following subquestions of the present benefit assessment due to the inadequate data situation:

- combination therapy with MTX after MTX failure and pretreatment with further csDMARDs (Subquestion 2)
- monotherapy after MTX intolerance and pretreatment with further csDMARDs (Subquestion 3)
- monotherapy after MTX intolerance and biologic failure (Subquestion 7).

7 References for English extract

Please see full final report for full reference list.

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Appendix A – Search strategies

A.1 – Searches in bibliographic databases

1. Embase

Search interface: Ovid

- Embase 1974 to 2017 February 21

The following filters were adopted:

- Systematic review: Wong [582] – High specificity strategy
- RCT: Wong [582] – Strategy minimizing difference between sensitivity and specificity

#	**Searches**
1	exp Rheumatoid Arthritis/
2	(rheuma* adj6 arthritis).ab,ti.
3	1 or 2
4	(Rituximab* or Abatacept* or Etanercept* or Infliximab* or Adalimumab* or Certolizumab* or Golimumab* or Anakinra* or Tocilizumab*).mp.
5	"recombinant interleukin 1 receptor blocking agent"/
6	or/4-5
7	and/3,6
8	(random* or double-blind*).tw.
9	placebo*.mp.
10	or/8-9
11	(meta analysis or systematic review or MEDLINE).tw.
12	7 and (10 or 11)
13	12 not medline*.cr.
14	13 not (exp animal/ not exp humans/)
15	14 not (Conference Abstract or Conference Review).pt.
16	15 not Editorial.pt.

2. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations February 17, 2017
- Ovid MEDLINE(R) 1946 to February Week 2 2017
- Ovid MEDLINE(R) Daily Update February 17, 2017
- Ovid MEDLINE(R) Epub Ahead of Print February 17, 2017

The following filters were adopted:

- Systematic review: Wong [582] – High specificity strategy
- RCT: Lefebvre [583] – Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing

#	**Searches**
1	exp Arthritis, Rheumatoid/
2	(rheuma* adj6 arthritis).ab,ti.
3	1 or 2
4	(Rituximab* or Abatacept* or Etanercept* or Infliximab* or Adalimumab* or Certolizumab* or Golimumab* or Anakinra* or Tocilizumab*).mp.
5	"Interleukin 1 Receptor Antagonist Protein"/
6	4 or 5
7	3 and 6
8	randomized controlled trial.pt.
9	controlled clinical trial.pt.
10	randomized.ab.
11	placebo.ab.
12	clinical trial as topic/
13	randomly.ab.
14	trial.ti.
15	or/8-14
16	exp animals/ not humans.sh.
17	15 not 16
18	cochrane database of systematic reviews.jn.
19	(search or MEDLINE or systematic review).tw.
20	meta analysis.pt.
21	or/18-20
22	7 and (17 or 21)
23	22 not (editorial or comment).pt.

3. PubMed

Search interface: NLM

- PubMed – as supplied by publisher
- PubMed – in process
- PubMed – pubmednotmedline

Search	Query
#18	Search (rheuma* [TIAB] AND arthritis [TIAB])
#19	Search (Rituximab OR Abatacept OR Etanercept OR Infliximab OR Adalimumab OR Certolizumab OR Golimumab OR Anakinra OR Tocilizumab)
#20	Search "Interleukin 1 Receptor Antagonist Protein"[Mesh]
#21	Search (clinical trial*[tiab] or random*[tiab] or placebo[tiab] or trial[ti])
#22	Search (search[tiab] or meta analysis[tiab] or MEDLINE[tiab] or systematic review[tiab])
#23	Search (#18 AND (#19 OR #20) AND (#21 OR #22))
#24	Search (#23 NOT medline[sb])

4. The Cochrane Library

Search interface: Wiley

- Cochrane Database of Systematic Reviews: Issue 2 of 12, February 2017
- Database of Abstracts of Reviews of Effect: Issue 2 of 4, April 2015
- Cochrane Central Register of Controlled Trials: Issue 1 of 12, January 2017
- Health Technology Assessment Database: Issue 4 of 4, October 2016

ID	Search
#1	[mh "Arthritis, Rheumatoid"]
#2	(rheuma* near/6 arthritis):ti,ab
#3	#1 or #2
#4	Rituximab* or Abatacept* or Etanercept* or Infliximab* or Adalimumab* or Certolizumab* or Golimumab* or Anakinra* or Tocilizumab*
#5	[mh "Interleukin 1 Receptor Antagonist Protein"]
#6	#4 or #5
#7	#3 and #6 Publication Year from 2012 to 2016, in Cochrane Reviews (Reviews and Protocols) and Trials
#8	rheuma* near/6 arthritis
#9	(#1 or #8) and #6 Publication Year from 2012 to 2016, in Other Reviews and Technology Assessments

A.2 – Searches in study registries

1. ClinicalTrials.gov

Provider: U.S. National Institutes of Health

- URL: http://www.clinicaltrials.gov
- Type of search: Expert Search

Suchstrategie
Rheumatoid arthritis AND (Abatacept OR BMS 188667 OR Adalimumab OR ABTD2E7 OR D2E2 OR Anakinra OR rHIL-1ra OR Certolizumab OR CDP 870 OR Etanercept OR TNFR:Fc OR WAY_143050 OR SB4 OR Golimumab OR cnto 148 OR rTNV148B OR SCH 900259 OR Infliximab OR SB2 OR cA2 OR CT-P13 OR Rituximab OR RO45-2294 OR CT-P10 OR Tocilizumab OR RO4877533 OR myeloma receptor antibody)

2. EU Clinical Trials Register

Provider: European Medicines Agency

- URL: https://www.clinicaltrialsregister.eu/ctr-search/search
- Type of search: Basic Search

Suchstrategie
(Abatacept OR "BMS 188667" OR "BMS188667" OR Adalimumab OR ABTD2E7 OR D2E2 OR "ABP 501" OR ABP501 OR Anakinra OR "rHIL-1ra" OR "rHIL1ra" OR Certolizumab OR "CDP 870" OR "CDP870" OR Etanercept OR "TNFR:Fc" OR "WAY_143050" OR SB4 OR Golimumab OR "cnto 148" OR "cnto148" OR "rTNV148B" OR "SCH 900259" OR "SCH900259" OR Infliximab OR SB2 OR cA2 OR "CT-P13" OR "CTP13" OR Rituximab OR "RO45-2294" OR "RO452294" OR "CT-P10" OR "CTP10" OR Tocilizumab OR RO4877533 OR "myeloma receptor antibody") AND arthritis

3. International Clinical Trials Registry Platform Search Portal

Provider: World Health Organization

- URL: http://apps.who.int/trialsearch/
- Type of search: Standard Search

Suchstrategie
Abatacept AND arthritis OR "BMS 188667" AND arthritis OR "BMS188667" AND arthritis OR Adalimumab AND arthritis OR ABTD2E7 AND arthritis OR D2E2 AND arthritis OR "ABP 501" AND arthritis OR Anakinra AND arthritis OR "rHIL-1ra" AND arthritis OR "rHIL1ra" AND arthritis OR Certolizumab AND arthritis OR "CDP 870" AND arthritis OR "CDP870" AND arthritis OR Etanercept AND arthritis OR "TNFR:Fc" AND arthritis OR "WAY_143050" AND arthritis OR SB4 AND arthritis OR Golimumab AND arthritis OR "cnto 148" AND arthritis OR "cnto148" AND arthritis OR "rTNV148B" AND arthritis OR "SCH 900259" AND arthritis OR "SCH900259" AND arthritis OR Infliximab AND arthritis OR SB2 AND arthritis OR "CT-P13" AND arthritis OR "CTP13" AND arthritis OR Rituximab AND arthritis OR "RO45-2294" AND arthritis OR "RO452294" AND arthritis OR "CT-P10" AND arthritis OR "CTP10" AND arthritis OR Tocilizumab AND arthritis OR RO4877533 AND arthritis OR "myeloma receptor antibody" AND arthritis

4. Clinical Study Report (CSR) Synopses

Provider: AbbVie

- URL: https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/clinical-study-report-csr-synopses.html

Suchstrategie
List of products alphabetized by generic name: Adalimumab – Humira Studied Indications or Disease: Rheumatoid Arthritis

5. Our Clinical Studies

Provider: UCB

- URL: http://www.ucb.com/our-science/Our-clinical-studies

Suchstrategie
Compounds / Cimzia (certolizumab pegol) Disease area studied / Rheumatoid Arthritis

6. Trials

Provider: Yale University

- URL: http://yoda.yale.edu/browsetrials/generic-name
- Type of search: Advanced Search

Suchstrategie
Trials By Generic Name / Advanced Search / OR Filter by: / Condition Studied / Arthritis, Rheumatoid

7. Clinical Trial Results

Provider: Bristol-Myers Squibb

- URL: http://www.bms.com/clinical_trials/results/Pages/therapeutic_areas.aspx

Suchstrategie
Select a therapeutic area: Immunoscience / Disease Area Studied / Rheumatoid Arthritis Select a therapeutic area: Immunoscience / Disease Area Studied / Undifferentiated Arthritis