IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A10-01

Biotechnologically produced drugs as second-line therapy for rheumatoid arthritis[1]

Executive Summary

[1] Translation of the executive summary of the final report "Biotechnologisch hergestellte Arzneimittel in der Zweitlinientherapie bei der rheumatoiden Arthritis" (Version 1.0; Status: 28 June 2013). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher:
Institute for Quality and Efficiency in Health Care

Topic:
Biotechnologically produced drugs as second-line therapy for rheumatoid arthritis

Commissioning agency:
Federal Joint Committee

Commission awarded on:
20 May 2010

Internal Commission No.:
A10-01

Address of publisher:
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List of abbreviations

Abbreviation	Meaning
bDMARD	biologic disease modifying anti-rheumatic drug
DMARD	disease modifying anti-rheumatic drug
G-BA	*Gemeinsamer Bundesausschuss* (Federal Joint Committee)
HAQ	Health Assessment Questionnaire
HUI	Health Utility Index
IQWiG	*Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen* (Institute for Quality and Efficiency in Health Care)
LOCF	last observation carried forward
MTX	methotrexate
RA	rheumatoid arthritis
RCT	randomized controlled trial
SF	Health Survey Short Form
TNF	tumour necrosis factor

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Executive summary

In its letter of 21 May 2010 the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) with the assessment of biotechnologically produced drugs in second-line therapy of rheumatoid arthritis (RA).

Research question

The aims of the present investigation were

- to assess the benefit of treatment with biotechnologically produced drugs compared with each other
- to assess the benefit of treatment with biotechnologically produced drugs compared with treatment with non-biotechnologically produced drugs, as well as
- to assess the benefit of treatment with biotechnologically produced drugs compared with treatment without therapy extension (with or without placebo control)

in each case as second-line therapy in patients with RA. The assessment was based on patient-relevant outcomes.

In this context, "treatment extension" is understood as continued therapy initiated as a supplementation to existing therapy.

For the present commission, for biotechnologically produced drugs (biologic disease modifying anti-rheumatic drugs, bDMARDs), second-line therapy, i.e. therapy after failure of previous treatment, was to be distinguished from first-line therapy, i.e. therapy in treatment-naive patients. In the present benefit assessment, the definition of second-line therapy therefore covered the use of biotechnologically produced drugs in persons who had been pretreated with at least one disease-modifying antirheumatic drug, also including biotechnologically produced ones.

Methods

The assessment was conducted on the basis of randomized controlled trials (RCTs) on the research question stated above. For this purpose a systematic literature search was conducted in the following databases: MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (Clinical Trials), and BIOSIS Previews. In addition, a search for relevant systematic reviews was conducted in the following databases: MEDLINE, EMBASE, the Cochrane Database of Systematic Reviews (Cochrane Reviews), the Database of Abstracts of Reviews of Effects (Other Reviews), and the Health Technology Assessment Database (Technology Assessments). The systematic reviews were screened for further relevant studies. The literature search covered the period up to 10 May 2012. In addition, trial registries and publicly accessible regulatory documents were searched, and the manufacturers of the drugs approved in Germany (abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab) were asked to provide relevant published or

unpublished studies. In addition, AstraZeneca GmbH, Merck Serono GmbH and Pfizer Pharma GmbH were asked for an agreement on the complete and regulated transfer of information of clinical study reports on investigations in which their drug was used as a comparator to one of the drugs named above or the drug itself was not relevant for the assessment (tofacitinib, atacicept), but suitable comparator drugs were used.

The results of the search in bibliographic databases and in publicly accessible trial registries, as well as potentially relevant citations from systematic reviews, were assessed with regard to their relevance by 2 reviewers independently of one another. The results from further sources searched were assessed by one reviewer and the result of this assessment was checked by a second reviewer. After an assessment of the risk of bias the results of individual studies were organized according to drugs and outcomes and described.

Results

The overview in Table 1 shows which comparisons were available for the bDMARDs, how many studies for each drug were included in the present benefit assessment, and how many patients were included in each study. A total of 35 studies were identified as relevant for the research question of the present benefit assessment. In part only subpopulations of studies were relevant for the benefit assessment. Most studies investigated the test and control intervention in compliance with the approval status, in each case in combination with methotrexate (MTX) and placebo comparisons.

The bDMARDs adalimumab, etanercept and tocilizumab are also approved for monotherapy: relevant studies for the present benefit assessment were identified in which these drugs were used in monotherapy. Tocilizumab was compared with adalimumab in patients with intolerance to MTX. Etanercept was used in patients with intolerance to MTX and in patients with severe active and progressive RA as monotherapy compared with sulfasalazine or MTX.

The risk of bias at study level was low for the majority of studies (32 studies). For most results, the risk of bias at outcome level was high. In 28 studies, therapy adaptations were possible 4 to 24 weeks after randomization if the response to the intervention was insufficient. From this point in time, the values of these patients were often considered in the analysis as last-observation-carried-forward (LOCF) values or as non-responders. As often markedly different proportions of patients in the treatment groups received therapy adaptation or the study was discontinued due to a lack of efficacy, relevant bias was possible by the use of this approach. If possible, sensitivity analyses were conducted for the present benefit assessment to investigate the impact of bias.

Table 1: Pairwise comparisons of interventions with number of studies and patients

Intervention + MTX[a]	**Control + MTX[a]**	**Number of studies**	**Number of patients[b]**
Abatacept	Placebo	6	2679
Adalimumab	Placebo	6	1508
Anakinra	Placebo	2	1653
Certolizumab pegol	Placebo	4	1286
Etanercept	Placebo	2	548
Etanercept[c] (MTX intolerance)	Sulfasalazine[c]	1	71
Etanercept[c] (patients with severe active and progressive RA)	MTX[c]	1	41
Golimumab (no previous treatment with TNF-α inhibitors)	Placebo	2	401
(previous treatment with TNF-α inhibitors)	Placebo	1	205
Infliximab	Placebo	1	174
Rituximab (no previous treatment with rituximab)	Placebo	1	520
(after a lack of response to a cycle of rituximab)	Placebo	1	475
Tocilizumab (largely no previous treatment with TNF-α inhibitors)	Placebo	5	2836
(previous treatment with TNF-α inhibitors)	Placebo	1	335
Direct comparison:			
Tocilizumab[c] (Patients who were not suitable for further treatment with MTX)	Adalimumab[c]	1	326
Sum:		35	13,058

a: If not otherwise stated.
b: Relevant populations for the present assessment.
c: Monotherapy.
MTX: methotrexate, RA: rheumatoid arthritis, TNF: tumour necrosis factor

In the following text the results are summarized for each drug.

Abatacept

Six studies on abatacept were included for the present research question, in each case for the comparison of abatacept + MTX versus placebo + MTX. In 1 study only a subpopulation was relevant.

Table 2 contains the summary of results of the present benefit assessment for abatacept and information on the number of available studies for the respective outcomes as well as for the outcome-related risk of bias.

Table 2: Summary of results on abatacept

Outcome [if applicable, measurement tool or operationalization]	**Result of the meta-analysis or individual studies/result from assessment of relevance (if conducted) Group difference [95% CI][a] (number of studies with results for the benefit assessment/thereof number of studies with outcome-related high risk of bias)**
Abatacept + MTX versus placebo + MTX	
Remission [DAS 28 (CRP)[b] < 2.6]	Heterogeneous result, effects in the same direction in favour of abatacept + MTX (4/1)
RA symptoms	
Painful joints (number, relative change [%])	Heterogeneous result, effects in the same direction in favour of abatacept + MTX (5/3)
Swollen joints (number, relative change [%])	Heterogeneous result, effects in the same direction in favour of abatacept + MTX (5/3)
Pain (VAS 100 mm, relative change [%])[d]	Heterogeneous result, effects in the same direction and largely statistically significant results in favour of abatacept + MTX/heterogeneous result:[e] the 95% CI of the SMD largely did not lie completely below −0.2 (6/4)
Global assessment of DA by patients (VAS 100 mm, relative change [%])[d]	Heterogeneous result, effects in the same direction and largely statistically significant results in favour of abatacept + MTX/heterogeneous result:[e] the 95% CI of the SMD largely lay completely below −0.2 (6/4). The explanatory factor could be the higher proportion of patients in 1 study with previous treatment with TNF-α inhibitors −0.36 [−0.45; −0.28][c]
Morning stiffness (minutes, absolute change)	Heterogeneous result, effects in the same direction in favour of abatacept + MTX (2/2)
Fatigue (VAS 100 mm, absolute change)[d]	−10.1 [−14.3; −5.91]/−0.40 [−0.56; −0.23][e] (1/1)
Quality of sleep (SPI of MOS sleep, scale 0 to 100, absolute change)[d]	−3.60 [−6.04; −1.17]/−0.24 [−0.41; −0.08][e] (1/1)
Structural changes of joints	Not examined
Status of physical functioning	
Changes (HAQ-DI or mHAQ)[d]	Heterogeneous result, effects in the same direction in favour of abatacept + MTX /−0.50 [−0.59; −0.40][e] (6/4)
Responder analysis (HAQ-DI or mHAQ)	Patients with an improvement of ≤ −0.3: OR: 2.71 [2.15; 3.40] (5/3)
Level of social functioning	Not examined

(continued)

Table 2: Summary of results on abatacept (continued)

Outcome [if applicable, measurement tool or operationalization]	**Result of the meta-analysis or individual studies/result from assessment of relevance (if conducted) Group difference [95% CI][a] (number of studies with results for the benefit assessment/thereof number of studies with outcome-related high risk of bias**
Abatacept + MTX versus placebo + MTX	
Health-related QoL	
Physical health (SF-36, absolute change)[f]	4.47 [3.47; 5.46]/0.50 [0.39; 0.61][e] (5/3)
Mental health (SF-36, absolute change)[f]	3.31 [2.29; 4.32]/heterogeneous result,[e] effects in the same direction; largely the 95% CI of the SMD did not lie completely above 0.2 (5/3)
All-cause mortality (deaths)	RD: −0.00 [−0.01; 0.00] (6/4)
ADR	
Pat. with at least 1 SAE	OR: 0.90 [0.64; 1.26] (5/3)
Study discont. due to AE	OR: 1.15 [0.69; 1.93] (5/3)
Pat. with at least 1 AE	OR: 1.20 [0.95; 1.51] (6/4)
Pat. with at least 1 serious infection	OR: 1.19 [0.56; 2.54] (5/3)
Pat. with at least 1 infection	heterogeneous result, effects not in the same direction and largely not statistically significant (6/4)

a: Mean difference, unless otherwise noted.

b: DAS 28 using the inflammation parameter CRP.

c: Result from a meta-analysis excluding the study with a higher proportion of patients with previous TNF-α inhibitor treatment.

d: Negative effect estimates mean better values under abatacept + MTX.

e: SMD in the form of Hedges' g for the assessment of the relevance of the statistically significant difference. If the 95% CI did not lie completely below the irrelevance threshold of −0.2 or above the irrelevance threshold of 0.2, an irrelevant effect could not be excluded.

f: Positive effect estimates mean better values under abatacept + MTX.

ADR: adverse drug reactions, AE: adverse event, CI: confidence interval, CRP: C-reactive protein, DAS: Disease Activity Score, discont.: discontinued, HAQ-DI: Health Assessment Questionnaire-Disability Index, DA: disease activity, QoL: quality of life, mHAQ: modified HAQ, MOS: Medical Outcomes Study, MTX: methotrexate, OR: odds ratio, Pat.: patients, RA: rheumatoid arthritis, RD: risk difference, SAE: serious adverse event, SF: Health Survey Short Form, SMD: standardized mean difference, SPI: Sleep Problem Index, VAS: Visual Analogue Scale.

At study level all included studies on abatacept + MTX showed a low risk of bias. The risk of bias of the results at outcome level was mostly high, except for the results for the outcome of remission. In the studies assessed, substantially more patients under placebo + MTX discontinued the study due to a lack of efficacy or received therapy adaptation. In most cases statistical replacement procedures were used for patients who discontinued; however, relevant bias leading to a high risk of bias in the assessment was still possible. In these cases sensitivity analyses were conducted for the present benefit assessment to investigate the impact of bias, if possible.

Heterogeneous results were shown for the outcomes “remission” and “status of physical functioning”, whereby the results of the individual studies were in each case statistically significant in favour of abatacept + MTX. For the outcomes of health-related quality of life (in terms of the dimension of physical health) a statistically significant effect was also shown in favour of abatacept + MTX or an irrelevant effect could be excluded. Important heterogeneity of results with a clear direction of results was shown for the outcomes “painful joints” and “morning stiffness”, in each case in favour of abatacept + MTX. A possible explanatory factor for heterogeneity could not be identified. Important heterogeneity of results with a clear direction of results was also shown for the outcomes “swollen joints” and “global assessment of disease activity by the patient”. A potential explanatory factor for heterogeneity for this outcome was in each case the larger proportion of patients in one of the studies who had previously been treated with tumour necrosis factor (TNF)-α inhibitors. A meta-analysis without this study in each case showed no important heterogeneity, with a statistically significant result in favour of abatacept + MTX. Except for the outcome “remission” an outcome-related high risk of bias was consistently or largely shown. On the basis of sensitivity analyses (see above), the results were classified as robust. In each case the data provide proof of a benefit of abatacept.

A statistically significant result in favour of abatacept + MTX was shown for the outcome “fatigue”, whereby it could be excluded that this lay in a certainly irrelevant range. As the result was based on a study with an outcome-related high risk of bias, this provides a hint of a benefit of abatacept.

No proof of benefit or harm was provided for the other outcomes, as either the results were not statistically significant or an irrelevant effect could not be excluded because important heterogeneity of results existed without a clear direction of results or data were missing.

Relevant subgroup analyses were available for the Health Assessment Questionnaire (HAQ) “response” for the potential effect modifiers “age” and “sex”, but they did not provide proof of different effects in younger and older patients or in women and men.

Table 13 presents the evidence map for abatacept.

Adalimumab

Six studies on adalimumab were included for the present research question, in each case for the comparison of adalimumab + MTX versus placebo + MTX. For 1 study solely a subpopulation was relevant. Table 3 contains the summary of the present benefit assessment of adalimumab and information on the number of studies for the respective outcomes as well as on the outcome-related risk of bias.

Table 3: Summary of results on adalimumab

Outcome [if applicable, measurement tool or operationalization]	**Result of the meta-analysis or individual studies/result from assessment of relevance (if conducted) Group difference [95% CI][a] (number of studies with results for the benefit assessment/thereof number of studies with outcome-related high risk of bias)**
Adalimumab + MTX versus placebo + MTX	
Remission (DAS [CRP] < 2.6)[b]	OR: 4.20 [2.72; 6.47] (6/0)
RA symptoms	
Painful joints (number, absolute change)[c]	Heterogeneous result, effects in the same direction in favour of adalimumab + MTX (5/5)
Swollen joints (number, absolute change)[c]	Heterogeneous result, effects in the same direction in favour of adalimumab + MTX (5/5)
Pain (VAS 100 mm, absolute change)[c]	−14.98 [−18.53; −11.44]/heterogeneous result,[d] same direction of effects, the 95% CI of the SMD largely lay completely below 0.2 (5/5)
Global assessment of DA by patients (VAS 100 mm, absolute change)[c]	−15.22 [−18.62; −11.81]/−0.60 [−0.73; −0.47][d] (5/5)
Morning stiffness	
Duration (minutes, absolute change)[c]	−24.12 [−45.37; −2.88] (2/2)
Responder analysis (no morning stiffness)	Patients without morning stiffness: OR: 2.82 [1.91; 4.71] (2/2)
Fatigue (FACIT-F, absolute change)[e]	4.25 [3.03; 5.47]/0.46 [0.33; 0.59][d] (4/4)
Quality of sleep (SPI II of MOS sleep, scale 0 to 100, absolute change)[c]	−4.02 [−8.32; 0.27] (1/1)
Structural changes of joints	Not examined
Status of physical functioning (HAQ-DI or modified kHAQ)	
Absolute change[c]	Heterogeneous result, effects in the same direction in favour of adalimumab + MTX/heterogeneous result,[c] effects in the same direction, the 95% CI of the SMD largely lay completely below 0.2 (5/5)
Responder analysis (HAQ-DI)	Patients with an improvement of: ≤ −0.22: OR: 2.40 [1.75; 3.29] (2/2) ≤ −0.3: OR: 1.64 [1.10; 2.42] (2/2) ≤ −0.5: heterogeneous result, effects in the same direction in favour of adalimumab + MTX (2/2)
Level of social functioning	
Work limitations (WLQ, absolute change)[c]	−0.26 [−2.49; 1.97] (1/1)

(continued)

Table 3: Summary of results on adalimumab (continued)

Outcome [if applicable, measurement tool or operationalization	**Result of the meta-analysis or individual studies/result from assessment of relevance (if conducted) Group difference [95% CI][a] (number of studies with results for the benefit assessment/thereof number of studies with outcome-related high risk of bias)**
Adalimumab + MTX versus placebo + MTX	
Health related quality of life	
Physical health (SF-36, absolute change)[e]	Heterogeneous result, effects in the same direction in favour of adalimumab + MTX/heterogeneous result,[c] effects in the same direction, the 95% CI of the SMD largely lay completely above 0.2 (3/3)
Mental health (SF-36, absolute change)[e]	2.13 [0.72; 3.55]/0.21 [0.07; 0.35][d] (3/3)
HUI 2[e] (absolute change)	0.10 [0.06; 0.14]/0.41 [0.24; 0.59][d] (2/2)
HUI 3[e] (absolute change)	Heterogeneous result, effects in the same direction and results statistically significant in favour of adalimumab + MTX/ 0.48 [0.23; 0.73][d] (2/2)
EQ-5D	Result not interpretable[f] (1/1)
All-cause mortality (deaths)	RD: 0.01 [−0.00; 0.01] (6/5)
ADR	
Pat. with at least 1 SAE	OR: 0.96 [0.56; 1.64] (5/4)
Study discont. due to AE	OR: 1.49 [0.93; 2.36] (6/5)
Pat. with at least 1 AE	OR: 1.45 [1.06; 1.99] (5/4) under consideration of different discontinuation rates due to a lack of efficacy or important differences in proportions of patients with therapy adaptation in 3 studies, the effect cannot be rated as robust. OR: 1.29 [0.94; 1.78].
Pat. with at least 1 serious infection	OR: 2.74 [1.12; 6.69] (6/5)
Pat. with at least 1 infection	OR: 1.45 [1.15; 1.83] (5/4) under consideration of different discontinuation rates due to a lack of efficacy or important differences in proportions of patients with therapy adaptation in 3 studies, the effect cannot be rated as robust. OR: 1.25 [0.99, 1.58].

a: Mean difference, unless otherwise noted.

b: DAS using the inflammation parameter CRP.

c: Negative effect estimates mean better values under adalimumab + MTX.

d: SMD in the form of Hedges' g for the assessment of the relevance of the statistically significant difference. If the 95% CI did not lie completely below the irrelevance threshold of −0.2 or above the irrelevance threshold of 0.2, an irrelevant effect could not be excluded.

e: Positive effect estimates mean better values under adalimumab + MTX.

f: For the EQ-5D only results of the total score are available. Due to missing results for the Single Utility Index, the results for the EQ-5D are not assessable.

ACR: American College Of Rheumatology, ADR: adverse drug reactions, AE: adverse event, CI: confidence interval, CRP: C-reactive protein, DA: disease activity, discont.: discontinued, EQ-5D: EuroQol-5D, FACIT-F: Functional assessment of chronic illness therapy – Fatigue, HAQ-DI: Health Assessment Questionnaire-Disability Index, HUI: Health Utility Index, kHAQ: Korean version of HAQ, LOCF: last observation carried forward, MOS: Medical Outcomes Study, MTX: methotrexate, OR: odds ratio, Pat.: patients, RA: rheumatoid arthritis, RD: risk difference, SF: Health Survey Short Form, SMD: standardized mean difference, SAE: serious adverse event, SPI: Sleep Problem Index, VAS: Visual Analogue Scale, WLQ: Work Limitations Questionnaire

At study level 5 of the included studies on adalimumab + MTX showed a low risk of bias. Except for the results for the outcome of remission, the risk of bias of the results at outcome level was predominantly high. In most cases this was because substantially more patients in the placebo + MTX group discontinued the study prematurely due to lack of efficacy. Although statistical replacement procedures were used for the patients who discontinued, relevant bias could still occur. If possible, in these cases sensitivity analyses were conducted for the present benefit assessment to investigate the impact of bias.

Statistically significant results were shown or an irrelevant effect could be excluded or, with important heterogeneity of results, a clear direction of results was shown in each case in favour of adalimumab + MTX for each of the outcomes of remission, painful/swollen joints, pain, global assessment of disease activity by the patient, morning stiffness, fatigue, status of physical functioning and health-related quality of life in terms of the dimension "physical health" measured with the Health Survey Short Form (SF)-36, as well as other dimensions of health-related quality of life measured with the Health Utility Index (HUI). Except for the outcome "remission", the outcome-related risk of bias was consistently high. On the basis of sensitivity analyses (see above), the results were classified as robust. In each case the data provide proof of a benefit of adalimumab.

The meta-analysis showed a statistically significant result for the outcome "patients with at least one serious infection". The outcome-related risk of bias was predominantly high, but on the basis of a sensitivity analysis the effect was classified as robust. This provides proof of harm of adalimumab.

There was a statistically significant result to the disadvantage of adalimumab + MTX both for the overall rate of adverse events and also for the overall rate of infections. In view of the mostly high outcome-related risk of bias, in each case there was an indication of harm of adalimumab.

For the remaining outcomes there was no proof either of benefit or harm, because the results were not statistically significant or it could not be excluded that an effect lay in a certainly irrelevant range, or because data were missing.

Relevant subgroup analyses were available for the outcomes "swollen joints", "painful joints" and "HAQ (changes)" in terms of the potential effect modifier "sex". However, as no interaction was found there is no proof of differing effects in women and men.

Table 13 presents the evidence map for adalimumab.

Anakinra

Two studies on anakinra were included for the present research question, in each case for the comparison of anakinra + MTX with placebo + MTX. From one study, only one

subpopulation was relevant, for which, however, solely data for the overall rate of serious infections were available.

Table 4 contains the summary of the results of the present benefit assessment of anakinra and information on the number of available studies for the respective outcomes and on the outcome-related risk of bias.

Table 4: Summary of the results on anakinra

Outcome [if applicable, measurement tool or operationalization]	**Result of the meta-analysis or individual studies/result from assessment of relevance (if conducted) Group differences [95% CI][a] (number of studies with results for the benefit assessment/thereof number of studies with outcome-related high risk of bias)**
Anakinra + MTX versus placebo + MTX	
Remission	Not examined
RA symptoms	
Painful joints (number, absolute change)[b]	−2.10 [−4.26; −0.06] (1/0)
Swollen joints (number, absolute change)[b]	−2.04 [−3.58; −0.50] (1/0)
Pain (VAS 100 mm, absolute change)[b]	−5.16 [−9.46; −0.86]/−0.22 [−0.40; −0.04][c] (1/0)
Global assessment of DA by the patient (VAS 100 mm, absolute change)[b]	−8.17 [−12.26; −4.08]/−0.26 [−0.39; −0.13][c] (1/0)
Morning stiffness (minutes, absolute change)[b]	−4.15 [−19.15; 10.85] (1/0)
Structural joint changes	Not examined
Status of physical functioning	
Changes (HAQ-DI)	An adequate responder analysis was also available for the individual study, which was the primary relevant analysis for the present benefit assessment.
Responder analysis (HAQ-DI)	Patients with an improvement of ≤ −0.22: OR: 1.83 [1.36; 2.46] (1/1)
Level of social functioning	Not examined
Health-related quality of life	
Physical health (SF-36, absolute change)[d]	2.78 [1.30; 4.26]/0.35 [0.16; 0.54][c] (1/0)
Mental health (SF-36, absolute change)[d]	0.09 [−1.64; 1.82] (1/0)
All-cause mortality (deaths)	p = 0.671[e] (1/1)
ADR	
Pat. with at least 1 SAE	p = 0.951[e] (1/1)
Study discontinuation due to AE	p = 0.429[e] (1/1)
Pat. with at least 1 AE	p = 0.069[e] (1/1)
Pat. with at least 1 serious infection	Heterogeneous result (no results in the same direction or statistically significant) (2/2)
Pat. with at least 1 infection	p = 0.391[e] (1/1)

(continued)

Table 4: Summary of the results on anakinra (continued)

a: Mean difference, unless otherwise noted. b: Negative effect estimates mean better values under anakinra + MTX. c: SMD in the form of Hedges' g for the assessment of the relevance of the statistically significant difference. If the 95% CI did not lie completely below the irrelevance threshold of −0.2 or above the irrelevance threshold of 0.2, an irrelevant effect could not be excluded. d: Positive effective estimates mean better values under anakinra + MTX. e: Solely p-value taken into account in the present benefit assessment ADR: adverse drug reactions, AE: adverse event, CI: confidence interval, DA: disease activity, HAQ-DI: Health Assessment Questionnaire-Disability Index, MTX: methotrexate, OR: odds ratio, Pat.: patients, RA: rheumatoid arthritis, SAE: serious adverse event, SF: Health Survey Short Form, SMD: standardized mean difference, VAS: Visual Analogue Scale

At study level there was a high risk of bias for one of the two studies. At outcome level it was low solely for the outcomes with continuous level of measurement, because these were reported only for the study with a low risk of bias at study level.

A statistically significant effect in favour of anakinra + MTX was shown for each of the outcomes "painful joints", "swollen joints" and "status of physical functioning". The respective results on the joints were based on a study with a low outcome-related risk of bias. The result for the status of physical functioning was based on an adequate responder analysis, also from one study, but with high outcome-related risk of bias. The high risk of bias was substantially due to the unclear replacement procedure. A sensitivity analysis as part of the present benefit assessment confirmed the existence of an effect, so the result was regarded as robust. This provides an indication of a benefit of anakinra in each case.

For the other outcomes there is no proof of benefit or harm either because the results were not statistically significant or it could not be excluded that an effect lay in a certainly irrelevant range, a substantial heterogeneity in the meta-analysis of the results existed without a clear direction of results, or data were missing.

No relevant subgroup analyses were available.

Table 13 presents the evidence map for anakinra.

Certolizumab pegol

Four studies on certolizumab pegol were included for the present research question, in each case for the comparison of certolizumab pegol + MTX versus placebo + MTX.

Table 5 contains the summary of the results of the present benefit assessment of certolizumab pegol and information on the number of available studies for the respective outcomes as well as on the outcome-related risk of bias.

Table 5: Summary of results on certolizumab pegol

Outcome [if applicable, measurement tool or operationalization]	**Result of the meta-analysis or individual studies/result from assessment of relevance (if conducted) Group differences [95% CI][a] (number of studies with results for the benefit assessment/thereof number of studies with outcome-related high risk of bias)**
Certolizumab + MTX versus placebo + MTX	
Remission (DAS 28 [ESR][b] < 2.6)	OR: 10.35 [4.70; 22.75] (3/0)
RA symptoms	
Painful joints (number, absolute change)[c]	Heterogeneous result, effects in the same direction in favour of certolizumab + MTX (4/3); possibly because DMARDs other than MTX were sometimes administered in one of the studies: −11.57 [−13.70; −9.44][d]
Swollen joints (number, absolute change)[c]	Heterogeneous result, effects in the same direction in favour of certolizumab + MTX (4 /3); possibly because DMARDs other than MTX were sometimes administered in one of the studies: −9.25 [−10.71; −7.79][d]
Pain (VAS 100 mm, absolute change)[c]	−16.66 [−20.16; −13.17]/ −0.55 [−0.67; −0.43][e] (4/3)
Responder analysis (VAS 100 mm)[f]	OR: 2.61 [1.42; 4.81] (1/0)
Global assessment of DA by the patient (VAS 100 mm, absolute change)[c]	Heterogeneous result, effects in the same direction in favour of certolizumab + MTX/−0.57 [−0.69; −0.45][e] (4/3)
Morning stiffness (hours, absolute change)	Heterogeneous result, effects in the same direction in favour of certolizumab pegol + MTX. Result was not confirmed in a sensitivity analysis (3/3)
Fatigue (FAS, absolute change)[c]	−0.96 [−1.34; −0.58]/ −0.29 [−0.42; −0.17][e] (3/2)
Structural joint changes	Not examined
Status of physical functioning	
(HAQ-DI, absolute change)[c]	Heterogeneous result, effects in the same direction in favour of certolizumab + MTX / −0.48 [−0.61; −0.35][e] (4/3)
Responder analysis	Patients with an improvement of: ≤ −0.22: OR: 1.85 [1.02; 3.45] (1/0)

(continued)

Table 5: Summary of results on certolizumab pegol (continued)

Outcome [if applicable, measurement tool or operationalization]	**Result of the meta-analysis or individual studies/result from assessment of relevance (if conducted) Group differences [95% CI][a] (number of studies with results for the benefit assessment/thereof number of studies with outcome-related high risk of bias)**
Level of social functioning (WPAI-RA, absolute changes)[c]	
Absenteeism	-15.14 [-33.83; 3.55] (1/1)[g]
Presenteeism	-15.5 [-30.93; -0.07] (1/1)[g]
Work productivity loss	-13.01 [-31.65; 5.63] (1/1)[g]
Activity impairment	-15.19 [-22.25; -8.12] (1/1)
Health-related quality of life	
Physical health (SF-36, absolute change)[f]	3.32 [2.04; 4.60]/ 0.30 [0.18; 0.42][e] (4/3)
Mental health (SF-36, absolute change)[f]	2.47 [0.67; 4.27]/ Heterogeneous result, the 95% CI of the SMD largely did not lie completely above 0.2 (4/3)
EQ-5D-VAS 20 cm (range of 0 - 100, absolute change)[f]	Result not interpretable
All-cause mortality (deaths)	RD: 0.00 [−0.01; 0.01] (4/3)
Certolizumab + MTX versus placebo + MTX	
ADR	
Pat. with at least 1 SAE	OR: 1.86 [0.95; 3.65] (4/3)
Study discontinuation due to AE	OR: 1.76 [0.89; 3.48] (4/3)
Pat. with at least 1 AE	Heterogeneous result, effects in the same direction, of which one statistically significantly to the disadvantage of certolizumab pegol + MTX (4/3)
Pat. with at least 1 serious infection	OR: 4.34 [1.48; 12.69] (4/3) Under consideration of differential discontinuation rates due to a lack of efficacy or important differences in proportions of patients with therapy adaptation in 3 studies the effect cannot be classified as robust: OR: 1.54 [0.77; 3.11].
Pat. with at least 1 infection	Heterogeneous result, effects not in the same direction, of which one statistically significantly (52 W) to the disadvantage of certolizumab pegol + MTX. Sensitivity analysis not robust (4/3)

(continued)

Table 5: Summary of results on certolizumab pegol (continued)

a: Mean difference, unless otherwise noted.
b: DAS 28 using the inflammatory parameter ESR.
c: Negative effect estimates mean better values under certolizumab pegol + MTX.
d: Result from meta-analysis without studies in which DMARDs other than MTX were sometimes used.
e: SMD in the form of Hedges' g for the assessment of the relevance of the statistically significant difference. If the 95% CI did not lie completely below the irrelevance threshold of −0.2 or above the irrelevance threshold of 0.2, an irrelevant effect could not be excluded.
f: Positive effective estimates mean better values under certolizumab pegol + MTX.
g: Results not interpretable, because unclear whether enough patients were included in the assessment.
ADR: adverse drug reactions, AE: adverse event, CI: confidence interval, DA: disease activity, DAS: Disease Activity Score, DMARD: Disease-Modifying Antirheumatic Drug, EQ-5D: EuroQol-5D, ESR: erythrocyte sedimentation rate, FAS: Fatigue Assessment Scale, HAQ-DI: Health Assessment Questionnaire-Disability Index, MTX: methotrexate, OR: odds ratio, Pat.: patients, RA: rheumatoid arthritis, RD: risk difference, SAE: serious adverse event, SF: Health Survey Short Form, SMD: standardized mean difference, VAS: Visual Analogue Scale, WPAI-RA: Work Productivity and Activity Impairment-rheumatoid arthritis

At study level all studies showed a low risk of bias. The risk of bias at outcome level was generally high except for the results for the outcome of remission and the results of Study C870-076, although patients who discontinued treatment were included in the analysis. If possible, sensitivity analyses were conducted in these cases to investigate the impact of bias.

Certolizumab pegol + MTX

In the combination therapy "certolizumab pegol + MTX" a statistically significant difference in favour of certolizumab pegol + MTX was shown for the outcome "remission" based on 3 studies with a low risk of bias. For the outcomes "painful joints", "swollen joints", "pain", "global assessment of disease activity by the patient" and "status of physical functioning", statistically significant results were also shown or an irrelevant effect could be excluded or results showed important heterogeneity with a clear direction of effect, in each case in favour of certolizumab pegol + MTX. A potential explanation for this heterogeneity in the outcomes "painful joints" and "swollen joints" could be that sometimes DMARDs other than MTX were administered in one of the included studies. The risk of bias for these outcomes, in each case outcome-related, was high in 3 of the 4 studies. On the basis of sensitivity analyses (see above), the results were classified as robust. A statistically significant responder analysis was also present for the outcome "pain". This provides proof of a benefit of certolizumab pegol in each case. The results for "morning stiffness" were not confirmed in the sensitivity analysis and therefore only an indication of a benefit of certolizumab pegol is derived.

There was a statistically significant difference to the disadvantage of certolizumab pegol + MTX for serious infections. Due to the consistent outcome-related high risk of bias, there is an indication of harm of certolizumab pegol. The results for the overall rate of adverse events showed important heterogeneity. This might have been due to the differing study durations. In the only 52-week study, the result was statistically significant and was to the disadvantage of certolizumab pegol + MTX. This provides a hint of harm of certolizumab.

For all investigated individual outcomes of the outcome “level of social functioning” there was a high risk of bias with results from one study. Except for the individual outcome “impairment of daily activities by the disease”, the results were not interpretable because it was unclear whether enough patients were actually included in the analysis. Accordingly, for “impairment of daily activities by the disease” there is a hint of a benefit, whereas due to inadequate data, for all other individual outcomes there is no proof of benefit.

No proof of benefit or harm was provided for the other outcomes, as either the results were not statistically significant or it could not be excluded that an effect lay in a certainly irrelevant range, or data were missing or could not be evaluated.

No relevant subgroup analyses were available.

Table 13 presents the evidence map for certolizumab pegol.

Etanercept

Four studies on etanercept were included for the present research question. In 2 studies etanercept + MTX was compared with placebo + MTX. In addition, the use of etanercept in monotherapy was investigated in one study compared with sulfasalazine and in another compared with MTX in patients with intolerance of MTX or severe active and progressive RA.

Table 6 and Table 7 contain the summary of the results of the present benefit assessment on etanercept and information about the number of available studies for each of the outcomes as well as the outcome-related risk of bias. Since the duration of the studies on etanercept + MTX varied considerably, the results were not summarised in a meta-analysis.

Table 6: Summary of results on etanercept (comparison etanercept + MTX vs. placebo + MTX)

Outcome [if applicable, measurement tool or operationalization]	**Result of the meta-analysis or individual studies/result from assessment of relevance (if conducted) Group differences [95% CI][a,b] (number of studies with results for the benefit assessment/thereof number of studies with outcome-related high risk of bias)**	
	24 weeks	**164 weeks**
Etanercept + MTX versus placebo + MTX		
Remission (DAS 28 [ESR][c] < 2.6)	OR: 2.57 [0.52; 12.75] (1/1)	OR: 2.90 [1.90; 4.43] (1/0)
RA symptoms		
Painful joints (number, relative change [%])[d]	−31.4 [−47.26; −15.54] (1/1)	−16.2 [−28.48; −3.92] (1/1)
Swollen joints (number, relative change [%])[d]	−33.7 [−52.24; −15.16] (1/1)	−16.4 [−28.82; −3.97] (1/1)
Pain (VAS 100 mm)[d]	[Relative change (%)] −56.4 [−92.32; −20.48] / −0.68 [−1.14; −0.23][e] (1/1)	[Absolute change] −14.72 [−25.87; −3.57]/ −0.24 [−0.42; −0.06][e] (1/1)
Global assessment of DA by the patient (VAS 100 mm)[d]	[Relative change (%)] −37.6 [−61.2; −14.00] / −0.69 [−1.15; −0.24][e] (1/1)	[Absolute change] −14.7 [−25.8; −3.6] / −0.24 [−0.43; −0.06][e] (1/1)
Assessment of general health by the patient (VAS 100 mm)[d]	Not examined	[Absolute change] −19.0 [−33.40; −4.60]/ −0.24 [−0.42; −0.06][e] (1/1)
Morning stiffness (minutes)[d]	p < 0.001[f] (difference in favour of etanercept + MTX) (1/1)	[Absolute change] −104 [−182.81; −25.19] (1/1)
Structural joint changes	Not examined	
Status of physical functioning		
Absolute change (HAQ-DI)[d]	−0.50 [−0.79; −0.21]/ −0.75 [−1.20; −0.30][e] (1/1)	−1.0 [−1.76; −0.24][f] (1/1)
Responder analysis (HAQ-DI)	Not examined	Patients with an improvement of: ≤ −0.22: OR: 2.49 [1.53; 4.05] ≤ −0.5: OR: 2.88 [1.96; 4.23] ≤ −0.8: OR: 3.03 [2.07; 4.43] (1/1)
Level of social functioning	Not examined	
Ended work		No evaluable results
Reduction in working days		No evaluable results
Work loss		No evaluable results

(continued)

Table 6: Summary of results on etanercept (comparison etanercept + MTX vs. placebo + MTX) (continued)

Outcome [if applicable, measurement tool or operationalization]	**Result of the meta-analysis or individual studies/result from assessment of relevance (if conducted) Group differences [95% CI][a,b] (number of studies with results for the benefit assessment/thereof number of studies with outcome-related high risk of bias)**	
	24 weeks	**164 weeks**
Etanercept + MTX versus placebo + MTX		
Health-related quality of life (EQ-5D-VAS 20 cm [range from 0–100, absolute change])[g]	Not examined	−12.8 [−22.50; −3.10]/ 0.24 [0.06; 0.42][e] (1/1)
All-cause mortality (deaths)	p = 1[h] (1/1)	p = 0.585[h] (1/1)
ADR		
Pat. with at least 1 SAE	p = 0.228[h] (1/1)	p = 0.214[h] (1/1)
Study discontinuation due to AE	p = 1.000[h] (1/1)	p = 0.123[h] (1/1)
Pat. with at least 1 AE	p = 0.403[h] (1/1)	p = 0.636[h] (1/1)
Pat. with at least 1 serious infection	p = 0.496[h] (1/1)	p = 0.768[h] (1/1)
Pat. with at least 1 infection	p = 0.315[h] (1/1)	p = 0.538[h] (1/1)

a: Mean difference, unless otherwise noted.
b: Results not summarised in meta-analysis because study durations very different.
c: DAS 28 using the inflammatory parameter ESR.
d: Negative effect estimates mean better values under etanercept + MTX.
e: SMD in the form of Hedges' g for assessing the relevance of the statistically significant difference. If the 95% CI did not lie completely below the irrelevance threshold of −0.2 or above the irrelevance threshold of 0.2, an irrelevant effect could not be excluded.
f: Relevance not assessed because a responder analysis was available for the identical study pool.
g: Positive effect estimates mean better values under etanercept + MTX.
h: Solely p-value taken into account in the present benefit assessment.

ADR: adverse drug reactions, AE: adverse event, CI: confidence interval, DA: disease activity, DAS: Disease Activity Score, EQ-5D: EuroQol-5D, ESR: erythrocyte sedimentation rate, HAQ-DI: Health Assessment Questionnaire-Disability Index, MTX: methotrexate, OR: odds ratio, Pat.: patients, RA: rheumatoid arthritis, SMD: standardized mean difference, SAE: serious adverse event, VAS: Visual Analogue Scale, vs.: versus

Table 7: Summary of results on etanercept (etanercept monotherapy)

Outcome [if applicable, measurement tool or operationalization]	**Result of the meta-analysis or individual studies/result from assessment of relevance (if conducted) Group differences [95% CI][a,b] (number of studies with results for the benefit assessment/thereof number of studies with outcome-related high risk of bias)**	
	vs. sulfasalazine (MTX-intolerance)	**vs. MTX (severe active and progressive RA)**
Etanercept monotherapy		
Remission (DAS 28 [ESR][c] < 2.6)	OR: 8.60 [0.47; 156.13] (1/1)	OR: 14.00 [1.53; 128.49] (1/1)
RA symptoms		
Painful joints (number, relative change [%])[d]	–45.99 [–67.55; –24.43] (1/1)	–31.9 [–54.86; –8.96] (1/1)
Swollen joints (number, relative change [%])[d]	–34.47 [–62.48; –6.46] (1/1)	–35.9 [–64.46; –7.34] (1/1)
Pain (VAS 100 mm [absolute change])[d]	–44.84 [–70.90; –18.78]/–0.87 [–1.40; –0.34][e] (1/1)	–42.7 [–69.54; –15.85]/ –0.96 [–1.62; –0.31][e] (1/1)
Global assessment of DA by the patient (VAS 100 mm [absolute change])[d]	–34.31 [–51.90; –16.72] / –0.98 [–1.52; –0.45][e] (1/1)	–38.4 [–64.25; –12.50]/ –0.90 [–1.55; –0.25][e] (1/1)
Assessment of general health by the patient (VAS 100 mm [absolute change])[d]	–37.90 [–58.33; –17.47]/ –0.94 [–1.47; –0.40][e] (1/1)	–36.4 [–61.88; –10.83]/ –0.86 [–1.51; –0.22][e] (1/1)
Morning stiffness (minutes, absolute change)[d]	–297.51 [–491.96; –103.06] (1/1)	–229.7 [–418.63; –40.74] (1/1)
Structural joint changes	Not examined	
Status of physical functioning		
relative change (HAQ-DI)[d]	–30.71 [–53.96; –7.46][f] (1/1)	–54.9 [–97.78; –11.92]/ –0.77 [–1.41; –0.13][e] (1/1)
Responder analysis (HAQ-DI)	Patients with an improvement of: ≤ −0.22: OR: 4.67 [1.57; 13.89] (1/1)	Not examined
Level of social functioning	Not examined	Not examined
Health-related quality of life	Not examined	Not examined
All-cause mortality (deaths)	Result not adequately presented (1/1)	p > 0.999[h] (1/1)

(continued)

Table 7: Summary of results on etanercept (etanercept monotherapy) (continued)

ADR		
Pat. with at least 1 SAE	p > 0.999[h] (1/1)	p = 0.86[h] (1/1)
Study discontinuation due to AE	p = 0.88[h] (1/1)	p = 0.70[h] (1/1)
Pat. with at least 1 AE	p = 0.30[h] (1/1)	p = 0.35[h] (1/1)
Pat. with at least 1 serious infection	p > 0.999[h] (1/1)	p > 0.999[h] (1/1)
Pat. with at least 1 infection	p = 0.45[h] (1/1)	p = 0.57[h] (1/1)

a: Mean difference, unless otherwise noted.
b: Results not summarised in meta-analysis because study durations very different.
c: DAS 28 using the inflammatory parameter ESR.
d: Negative effect estimates mean better values under etanercept + MTX.
e: SMD in the form of Hedges' g for assessing the relevance of the statistically significant difference. If the 95% CI did not lie completely below the irrelevance threshold of −0.2 or above the irrelevance threshold of 0.2, an irrelevant effect could not be excluded.
f: Relevance not assessed because a responder analysis was available for the identical study pool.
g: Positive effect estimates mean better values under etanercept + MTX.
h: Solely p-value taken into account in the present benefit assessment.

ADR: adverse drug reactions, AE: adverse event, CI: confidence interval, DA: disease activity, DAS: Disease Activity Score, ESR: erythrocyte sedimentation rate, HAQ-DI: Health Assessment Questionnaire-Disability Index, MTX: methotrexate, OR: odds ratio, Pat.: patients, RA: rheumatoid arthritis, SAE: serious adverse event, SMD: standardized mean difference, VAS: Visual Analogue Scale; vs.: versus

Etanercept + MTX

At study level both studies showed a low risk of bias. The risk of bias of the results at outcome level was generally high, except for the results for the outcome "remission" in Study 0881A1-308-EU/AU (TEMPO). One of the reasons that applied in most cases and to both studies was that under placebo + MTX substantially more patients discontinued the studies prematurely due to lack of efficacy. Although statistical replacement procedures were used for the patients who discontinued, relevant bias could still occur. If possible, in these cases sensitivity analyses were conducted for the present benefit assessment to investigate the impact of bias.

A statistically significant effect with a low risk of bias was shown for the outcome "remission" in the larger of the two studies. The result of the smaller study with a high risk of bias was not statistically significant, but the effect was in the same direction. There is therefore an indication of a benefit of etanercept + MTX for the outcome "remission".

Statistically significant results were shown or an irrelevant effect could be excluded for the outcomes "painful joints", "swollen joints", "morning stiffness" and "status of physical functioning". There was an outcome-related high risk of bias in each case. In both studies, a statistically significant result in favour of etanercept + MTX was also shown for the outcome "morning stiffness". Since the data of the much smaller studies could not be clearly interpreted, but the effect was in the same direction as that of the larger study, the result of the larger study was not questioned. The result of the assessment was thus primarily based on a study with an outcome-related high risk of bias. On the basis of a sensitivity analysis (see

above), the effect was classified as robust. For each of the above-named outcomes, there is an indication of a benefit of etanercept.

No proof of benefit or harm was provided for the other outcomes, as either the results were not statistically significant or an irrelevant effect could not be excluded, the results were without a clear direction of effect, or data were missing.

Etanercept versus sulfasalazine

Results were available from one study with a low risk of bias at study level. However at outcome level, the risk of bias was consistently assessed as high. With the exception of remission, this was because of the lack of information as to how many patients from the treatment groups discontinued the study because of lack of efficacy and whether or how these patients were taken into account in the analysis. Accordingly, no sensitivity analyses could be conducted either. For the outcome "remission" it was unclear whether the outcome assessors were blinded.

Statistically significant results were shown or an irrelevant effect could be excluded for the outcomes "painful joints", "swollen joints", "pain", "global assessment of disease activity by the patient", "general health", "morning stiffness" and "status of physical functioning". For each of these outcomes there was a hint of an added benefit of etanercept compared with sulfasalazine in patients with intolerance of MTX.

For the other outcomes, there is no proof of added benefit or greater harm, because the results were not statistically significant or data were missing.

Etanercept versus MTX

Results of one study with a low risk of bias at study level were available. However at outcome level, the risk of bias was consistently assessed as high. With the exception of remission, the reason was the lack of information as to how many patients from the treatment groups discontinued the study because of lack of efficacy and whether or how these patients were taken into account in the analysis. For the outcome "remission" it was unclear whether the outcome assessors were blinded.

Statistically significant results were shown or an irrelevant effect could be excluded for the outcomes "remission", "painful joints", "swollen joints", "pain", "global assessment of disease activity by the patient", "general health" and "morning stiffness". For each of these outcomes there was a hint of an added benefit of etanercept compared with MTX in patients with severe active and progressive RA.

For the other outcomes there is no proof of added benefit or greater harm, because the results were not statistically significant, or an irrelevant effect could not be excluded, or because data were missing.

No relevant subgroup analyses were available.

Table 13 presents the evidence map for etanercept.

Golimumab

Three studies on golimumab were included for the present research question, in each case for the comparison of golimumab + MTX versus placebo + MTX. In contrast to the other two studies, one study investigated a population previously treated with TNF-α inhibitors. In addition, solely a subpopulation was relevant from this study.

Table 8 contains the summary of the results of the present benefit assessment of golimumab and information on the number of studies for the respective outcomes as well as on the outcome-related risk of bias. The populations with and without previous treatment with TNF-α inhibitors were not regarded as comparable so that the results were not summarised in a meta-analysis.

Table 8: Summary of results on golimumab

Outcome [if applicable, measurement tool or operationalization]	**Result of the meta-analysis or individual studies/result from assessment of relevance (if conducted) Group differences [95% CI][a, b] (number of studies with results for the benefit assessment/thereof number of studies with outcome-related high risk of bias)**	
Golimumab + MTX versus placebo + MTX		
	No previous treatment with TNF-α inhibitors	**Previous treatment with TNF-α inhibitors**
Remission (DAS 28 [ESR][c] < 2.6)	OR: 5.28 [2.78; 10.05] (2/0)	OR: 5.45 [1.52; 19.6] (1/1)
RA symptoms		
Painful joints (number, relative change [%])[e]	−30.58 [−41.29; −19.87] (2/2)	–49.36 [–72.75; –25.98] (1/1)
Swollen joints (number, relative change [%])[e]	−24.96 [−34.43; −15.50] (2/2)	–45.43 [–70.79; –20.06] (1/1)
Pain (VAS 100 mm, relative change [%])	Heterogeneous result[f], statistically significant results in the same direction in favour of golimumab + MTX Relevance assessment[g]: heterogeneous result, same direction of effects (2/2)	–59.44 [–134.9; 16.05] (1/1)
Global assessment of DA by the patient (VAS 100 mm, relative change [%])	Heterogeneous result[f], effects in the same direction, of which one statistically significant in favour of golimumab + MTX; relevance assessment[g]: heterogeneous result (2/2)	–31.88 [–48.87; –14.9]/ –0.54 [–0.83; –0.24] (1/1)
Fatigue (FACIT-F, relative change [%])[h]	5.14 [2.69; 7.60]/0.57 [0.29; 0.84][g] (1/1)	19.62 [–2.63; 41.87] (1/1)
Structural joint changes	Not examined	Not examined[d]
Status of physical functioning		
Absolute changes (HAQ-DI)[e]	−0.31 [−0.41; −0.21]/ −0.60 [−0.81; −0.40][g] (2/2)	–2.47 [–31.9; 27.0] (1/1)
Responder analysis (HAQ-DI)[h]	Patients with an improvement of: ≤ −0.25: OR: 3.41 [1.92; 6.05] ≤ −0.3: OR: 2.24 [1.28; 3.91] (1/1)	Patients with an improvement of: ≤ −0.22: OR: 1.79 [1.03; 3.11]

(continued)

Table 8: Summary of results on golimumab (continued)

Outcome [if applicable, measurement tool or operationalization]	**Result of the meta-analysis or individual studies/result from assessment of relevance (if conducted) Group differences [95% CI][a] [b] (number of studies with results for the benefit assessment/thereof number of studies with outcome-related high risk of bias)**	
Golimumab + MTX versus placebo + MTX		
	No previous treatment with TNF-α inhibitors	**Previous treatment with TNF-α inhibitors**
Level of social functioning		
Performance (VAS 10 cm)[e]	[Absolute change] −1.52 [−2.34; −0.70]/ −0.50 [−0.77; −0.22][g] (1/1)	[Relative change] –26.64 [–60.65; 7.37] (1/1)
Work loss[e] (days[i])	[Absolute change] −4.85 [−9.49; −0.21] (1/1)	Not examined[d]
Unfit to work/ fit to work[j]	p = 0.452[k]/p = 0.178[k] (1/1)	[WLQ, relative change] –14.9 [–43.08; 13.28] (1/1)
Health-related quality of life		
Physical health (SF-36, absolute change)[h]	5.74; [3.50; 7.98]/0.70 [0.42; 0.98][g] (1/1)	Not examined[d]
Mental health (SF-36, absolute change)[h]	p = 0.339[k] (1/1)	Not examined[d]
All-cause mortality (deaths)	RD: 0.00 [−0.01; 0.01] (2/2)	p = 0.343[k] (1/1)
ADR		
Pat. with at least 1 SAE	OR: 1.89 [0.64; 5.62] (2/2)	p = 0.300[k] (1/1)
Study discontinuation due to AE	Heterogeneous result,[f] no results in the same direction or statistically significant (2/2)	p = 0.264[k] (1/1)
Pat. with at least 1 AE	OR: 1.32 [0.84; 2.10] (2/2)	p = 1.000[k] (1/1)
Pat. with at least 1 serious infection	RD: 0.00 [−0.01; 0.02] (2/2)	p = 0.699[k] (1/1)
Pat. with at least 1 infection	OR: 1.04 [0.68; 1.58] (2/2)	p = 0.529[k] (1/1)

a: Mean difference, unless otherwise noted.
b: Results not summarised in meta-analysis and interpreted separately because populations were different.
c: DAS 28 using the inflammatory parameter ESR.
d: For the relevant study population of the present report.
e: Negative effect estimates mean better values under golimumab.
f: Although a possible reason for the heterogeneity could be that solely Japanese took part in the study, patients from study centres throughout Asia also took part in Study C0524T06, so this cannot fully explain the heterogeneity.
g: SMD in the form of Hedges' g for assessing the relevance of the statistically significant difference. If the 95% CI did not lie completely below the irrelevance threshold of −0.2 or above the irrelevance threshold of 0.2, an irrelevant effect could not be excluded.

(continued)

Table 8: Summary of results on golimumab (continued)

h: Positive effect estimates mean better values under golimumab. i: Working days that could not be worked on due to illness. j: Patients who were fit to work at the start of the study, with RA-related inability to work at the end of the study/patients who were unfit at the start of the study, fit to work by the end. k: Solely p-value taken into account in the present benefit assessment. ADR: adverse drug reactions, AE: adverse event, CI: confidence interval, DA: disease activity, DAS: Disease Activity Score, ESR: erythrocyte sedimentation rate, FACIT-F: Functional Assessment of Chronic Illness Therapy – Fatigue, HAQ-DI: Health Assessment Questionnaire-Disability Index, MTX: methotrexate, OR: odds ratio, Pat.: Patients, RA: rheumatoid arthritis, RD: Risk difference, SAE: serious adverse event, SF: Health Survey Short Form, SMD: standardized mean difference, TNF: tumour necrosis factor, VAS: Visual Analogue Scale, WLQ: Work Limitations Questionnaire

Population without previous treatment with TNF-α inhibitors

At study level both studies showed a low risk of bias. The risk of bias at outcome level was exclusively high, except for the outcome of remission. This was because substantially more patients in the control group had received therapy adaptation. If statistical replacement procedures were used for patients who discontinued therapy, relevant bias could occur. If possible, in these cases sensitivity analyses were conducted for the present benefit assessment to investigate the impact of bias. Bias due to possible overlapping effects of the randomized therapy and of treatment under therapy adaptation could also not be excluded for the case of separate analyses. However, bias would probably tend to have an impact to the disadvantage of the test intervention and was therefore classified as conservative bias.

A statistically significant result in favour of golimumab + MTX was shown for the outcome “remission” with an outcome-related low risk of bias. Statistically significant results in favour of golimumab + MTX were also shown or an irrelevant effect could be excluded for the outcomes “painful joints”, “swollen joints” and “status of physical functioning”. A heterogeneous result was obtained for the outcome “pain”, whereby the larger of 2 studies showed a certainly not irrelevant effect. The outcome-related risk of bias for these outcomes was high. On the basis of sensitivity analyses (see above), the results were, however, classified as robust. In each case, the data provide proof of a benefit of golimumab.

Statistically significant results were also shown or an irrelevant effect could be excluded for the outcome “fatigue” and the dimension “physical health” of “health-related quality of life”. Due to the consistent outcome-related high risk of bias in the meta-analysis, or from robust results after sensitivity analyses in individual studies, in each case there is an indication of a benefit of golimumab.

A not irrelevant effect was shown for the outcome “level of social functioning”. As this result was based on a single study with an outcome-related high risk of bias, this provides a hint of a benefit of golimumab.

No proof of benefit or harm was provided for the other outcomes, as either the results were not statistically significant, important heterogeneity of results existed without a clear direction of results, or data were missing.

Relevant subgroup analyses were conducted in one study for adverse events with regard to the potential effect modifier "age". No proof was shown for different effects in younger and older patients.

Population with previous treatment with TNF-α inhibitors

The risk of bias in the study that examined the population previously treated with TNF-α inhibitors was low. The outcome-related risk of bias was generally high, because it was unclear whether or how patients with therapy adaption were included in the analysis or which replacement procedure was used.

A statistically significant result was shown for the outcome "remission". Although the risk of bias was high, the certainty of results can be assumed to be high because a possible bias would tend to have a negative effect on golimumab. This provides an indication of a benefit of golimumab.

As statistically significant results were also shown or an irrelevant effect could be excluded for the outcomes "painful joints", "swollen joints", "global assessment of disease activity by the patient" and "status of physical functioning" (responder analyses), this provides a hint of a benefit of golimumab + MTX for each of the outcomes mentioned.

No proof of benefit or harm was provided for the other outcomes, as either the respective results were not statistically significant or no data were available.

No relevant subgroup analyses were available.

Table 13 presents the evidence map for golimumab.

Infliximab

One study on infliximab was included for the present research question that compared infliximab + MTX against placebo + MTX.

Table 9 contains the summary of the results of the present benefit assessment of infliximab and information about the outcome-related risk of bias.

Table 9: Summary of results on infliximab

Outcome [if applicable, measurement tool or operationalization]	**Result of the meta-analysis or individual studies/result from assessment of relevance (if conducted) Group differences [95% CI][a, b] (number of studies with results for the benefit assessment/thereof number of studies with outcome-related high risk of bias)**
Infliximab + MTX versus placebo + MTX	
Remission (DAS < 2.6)	OR: 7.71 [0.93; 64.05]; p = 0.03[c] (1/0)
RA symptoms	
Painful joints (number, relative change [%])[d]	–26.0 [–43.28; –8.72] (1/0)
Swollen joints (number, relative change [%])[d]	–24.4 [–42.86; –5.94] (1/0)
Pain (VAS 100 mm, relative change [%])	–17 [–32.16; –1.84]/-0.34 [–0.64; –0.03] (1/0)
Global assessment of DA by the patient (VAS 100 mm, relative change [%])	–35.2 [–64.41; –5.99]/–0.36 [–0.67; –0.06] (1/0)
Morning stiffness (minutes, relative change [%])	p = 0.031[e] (difference in favour of infliximab + MTX) (1/0)
Fatigue (VAS 100 mm, relative change [%])	p = 0.021[e] (difference in favour of infliximab + MTX) (1/0)
Structural joint changes	Not examined
Status of physical functioning	
Relative change (HAQ-DI)[d]	p = 0.081[e] (1/1)
Responder analyses (HAQ-DI)	Patients with an improvement of: ≤ −0.22: OR: 3.16 [1.69; 5.91]
Level of social functioning	Not examined
Health-related quality of life	
Physical health (SF-36, absolute change)	1.5; [–2.91; 5.91] (1/1)
Mental health (SF-36, absolute change)	0.1; [–4.48; 4.68] (1/1)
All-cause mortality (deaths)	Results not adequately presented
ADR	
Pat. with at least 1 SAE	p = 0.093[e] (1/1)
Study discontinuation due to AE	p = 0.541 (1/1)
Pat. with at least 1 AE	p = 0.668[e] (1/1)
Pat. with at least 1 serious infection	p = 0.085[e] (1/1)
Pat. with at least 1 infection	p = 0.300[e] (1/1)

(continued)

Table 9: Summary of results on infliximab (continued)

a: Mean difference, unless otherwise noted.
b: Results not summarised in meta-analysis because comparator groups were different.
c: The p-value is relevant for the assessment. The differing significances (p-value vs. OR) are probably due to the asymptotic distribution of the OR, which can lead to a conservative estimate of the CI.
d: Negative effect estimates mean better values under infliximab.
e: Solely p-value taken into account in the present benefit assessment.
ADR: adverse drug reactions, AE: adverse event, CI: confidence interval, DA: disease activity, DAS: Disease Activity Score, HAQ-DI: Health Assessment Questionnaire-Disability Index, MTX: methotrexate, Pat.: patients, RA: rheumatoid arthritis, RD: risk difference, SAE: serious adverse event, SF: Health Survey Short Form, VAS: Visual Analogue Scale

At study level the study showed a low risk of bias.

A statistically significant result in favour of infliximab + MTX for the outcomes "remission" and "symptoms of RA" relating to "painful joints", "swollen joints", "morning stiffness" and "fatigue" was shown with a low risk of bias. A statistically significant result in favour of infliximab + MTX was also shown for the outcome "status of physical functioning" (responder analyses). This result was based on a single study with an outcome-related high risk of bias caused by the differing discontinuation rates between the patients who were treated with infliximab + MTX and those given MTX + placebo. As the result in the sensitivity analysis was robust, this provides an indication of a benefit of infliximab in each case.

No proof of benefit or harm was provided for the other outcomes, as either the results were not statistically significant, an irrelevant effect could not be excluded or data were missing.

Table 13 presents the evidence map for infliximab.

Rituximab

Two studies on rituximab were included for the present research question, each on the comparison of rituximab + MTX versus placebo + MTX. Both studies exclusively enrolled patients who had shown an inadequate response to TNF-α inhibitors before the start of the study. One of the two studies examined the question of the repeated administration of a rituximab cycle after lack of response to a first cycle of rituximab.

Table 10 contains the summary of the results of the present benefit assessment of rituximab and information on the number of available studies for the respective outcomes as well as on the outcome-related risk of bias. As different research questions were examined in the two studies, from which different populations resulted for the present benefit assessment, the results were not summarised in a meta-analysis.

Table 10: Summary of results on rituximab

Outcome [if applicable, measurement tool or operationalization]	**Result of the meta-analysis or individual studies/result from assessment of relevance (if conducted) Group differences [95% CI][a, b] (number of studies with results for the benefit assessment/thereof number of studies with outcome-related high risk of bias)**	
Rituximab + MTX versus placebo + MTX		
	Without previous treatment with rituximab	**After no response to one cycle of rituximab**
Remission (DAS 28 [ESR][c] < 2.6)	OR: 19.12 [2.57; 142.06] (1/0)	OR: 1.98 [0.79; 4.96] (1/1)
RA symptoms		
Painful joints (number, absolute change)[d]	−5.94 [−7.29; −4.59] (1/1)	−1.6 [−4.90; 1.70] (1/1)
Swollen joints (number, absolute change)[d]	−4.65 [−5.71; −3.60] (1/1)	−1.5 [−3.63; 0.63] (1/1)
Pain (VAS 100 mm, absolute change)[d]	−21.12 [−25.50; −16.75][e]/ −0.86 [−1.05; −0.68] (1/1)	−3.4 [−8.84; 2.04] (1/1)
Global assessment of DA by the patient (VAS 100 mm, absolute change)[d]	−21.16 [−25.60; −16.72] / −0.85 [−1.04; −0.66][e] (1/1)	−3.4 [−8.59; 1.79] (1/1)
Fatigue (FACIT-F, absolute change)[f]	−8.58 [−10.40; −6.76]/ −0.84 [−1.03; −0.66][e] (1/1)	0 [−2.02; 2.02] (1/1)
Structural joint changes	Not examined	Not examined
Status of physical functioning		
Changes (HAQ-DI)[d]	An adequate responder analysis was also available for the single study, which was the primary relevant analysis for the present benefit assessment.	An adequate responder analysis was also available for the single study, which was the primary relevant analysis for the present benefit assessment.
Responder analysis (HAQ-DI)	Patients with an improvement of: ≤ −0.22: OR: 3.68 [2.52; 5.37] ≤ −0.25: OR: 4.13 [2.73; 6.26] (1/1)	Patients with an improvement of: ≤ −0.22: OR: 0.99 [0.67; 1.45] ≤ −0.3: OR: 1.18 [0.80; 1.74] (1/1)
Level of social functioning	Not examined	Not examined

(continued)

Table 10: Summary of results on rituximab (continued)

Outcome [if applicable, measurement tool or operationalization]	**Result of the meta-analysis or individual studies/result from assessment of relevance (if conducted) Group differences [95% CI][a, b] (number of studies with results for the benefit assessment/thereof number of studies with outcome-related high risk of bias)**	
Rituximab + MTX versus Placebo + MTX		
	Without previous treatment with rituximab	**After no response to one cycle of rituximab**
Health-related quality of life		
Physical health (SF-36, absolute change)[h]	4.92 [3.61; 6.24]/ 0.67 [0.48; 0.85][e] (1/1)	0.1 [−1.71; 1.91]
Mental health (SF-36, absolute change)[h]	3.43 [1.63; 5.23]/ 0.34 [0.16; 0.52][e] (1/1)	0.1 [−2.47; 2.67]
All-cause mortality (deaths)	p = 1[i] (1/1)	p = 0.818[i] (1/1)
ADR		
Pat. with at least 1 SAE	p = 0.313[i] (1/1)	p = 0.600[i] (1/1)
Study discontinuation due to AE	p = 0.077[i] (1/1)	p = 0.302[i] (1/1)
Pat. with at least 1 AE	p = 0.416[i] (1/1)	p = 0.035[i] (1/1)
Pat. with at least 1 serious infection	p = 0.474[i] (1/1)	p = 0.894[i] (1/1)
Pat. with at least 1 infection	p = 0.491[i] (1/1)	p = 0.541[i] (1/1)

a: Mean difference, unless otherwise noted.
b: Results were not summarised in a meta-analysis and were interpreted separately from each other because the research questions of the studies differed, resulting in different populations for the present benefit assessment.
c: DAS 28 using the inflammatory parameter ESR.
d: Negative effect estimates mean better values under rituximab + MTX.
e: SMD in the form of Hedges' g for assessing the relevance of the statistically significant difference. If the 95% CI did not lie completely below the irrelevance threshold of −0.2 or above the irrelevance threshold of 0.2, an irrelevant effect could not be excluded.
f: Negative data were reported in the study report as improvement, which actually means the opposite for the tool used.
g: No relevance assessment, because a responder analysis was available for the identical study pool
h: Positive effect estimates mean better values under rituximab + MTX.
i: Solely p-value taken into account in the present benefit assessment.
ADR: adverse drug reactions, AE: adverse event, CI: confidence interval, DA: disease activity, DAS: Disease Activity Score, ESR: erythrocyte sedimentation rate, FACIT-F: Functional assessment of chronic illness therapy – Fatigue, HAQ-DI: Health Assessment Questionnaire-Disability Index, MTX: methotrexate, OR: Odds Ratio, Pat.: patients, RA: rheumatoid arthritis, SAE: serious adverse event, SF: Health Survey Short Form, SMD: standardized mean difference, VAS: Visual Analogue Scale

Population not previously treated with rituximab

The risk of bias at study level was low. At outcome level the study showed a low risk of bias for the outcome "remission"; for all other outcomes a high one. This was always due to substantially more patients of the placebo + MTX group having discontinued the study prematurely. Although statistical replacement procedures were used for patients who

discontinued, relevant bias could still occur. If possible, in these cases sensitivity analyses were conducted for the present benefit assessment to investigate the impact of bias.

A statistically significant result in favour of rituximab + MTX was shown for the outcome "remission". As this result is based on a study with an outcome-related low risk of bias, this provides an indication of a benefit of rituximab.

Statistically significant results in each case were also shown in favour of rituximab + MTX, or an irrelevant effect could be excluded for the outcomes "status of physical functioning", "painful joints", "swollen joints", "pain", "global assessment of disease activity by the patient" and "fatigue". The respective results were each based on a single study with an outcome-related high risk of bias. On the basis of sensitivity analyses (see above), the effects were classified as robust. This provides an indication of a benefit of rituximab.

A statistically significant result was also shown in favour of rituximab + MTX or an irrelevant effect could be excluded for the dimension "physical health" of the outcome "health-related quality of life". As the result was based on a single study with an outcome-related high risk of bias, this provides a hint of a benefit of rituximab.

No proof of benefit or harm was provided for the other outcomes, as either the results were not statistically significant or it could not be excluded that an effect lay in a certainly irrelevant range, or data were missing.

No relevant subgroup analyses were available.

After no response to one cycle of rituximab

For this study there was also a low risk of bias at study level and a consistently high risk of bias at outcome level. Once again, this was always due to substantially more patients having discontinued the study prematurely in the placebo + MTX group. Although statistical replacement procedures were used for patients who discontinued, relevant bias could still occur.

No proof of benefit or harm was provided, as either the results were not statistically significant or data were missing. Although a statistically significant difference in favour of rituximab + MTX was shown in terms of the overall rate of adverse events, this difference was largely based on events that portray the severity of the underlying disease. Therefore the result does not permit any conclusions about the harm of rituximab + MTX.

No relevant subgroup analyses were available.

Table 13 presents the evidence map for rituximab.

Tocilizumab

Six studies on tocilizumab were included for the present research question, in each case for the comparison of tocilizumab + MTX with placebo + MTX. From one study, solely a subpopulation was relevant. Moreover, in contrast to the other 5 studies, in one study patients with inadequate response to TNF-α inhibitors were examined.

Table 11 contains a summary of the results of the present benefit assessment of tocilizumab and information on the number of available studies for the respective outcomes as well as on the outcome-related risk of bias. The populations with and without previous treatment with TNF-α inhibitors were not regarded as comparable and therefore the results were not summarised in a meta-analysis.

Table 11: Summary of results on tocilizumab

Outcome [if applicable, measurement tool or operationalization]	**Result of the meta-analysis or individual studies/result from assessment of relevance (if conducted) Group differences [95% CI][a] (number of studies with results for the benefit assessment/thereof number of studies with outcome-related high risk of bias)**	
Tocilizumab + MTX versus placebo + MTX		
	Majority without previous treatment with TNF-α inhibitors	**Previous treatment with TNF-α inhibitors**
Remission (DAS 28 [ESR][b] < 2.6)	OR: 19.36 [11.23; 33.39] (2/0)	OR: 46.08 [6.24; 340.29] (1/0)
RA symptoms		
Painful joints (number, absolute change)[c]	Heterogeneous result, statistically significant results in the same direction in favour of tocilizumab + MTX (4/4); explanatory factor could be the study duration: −7.48 [−9.86; −5.10][d]	−15.1 [−18.8; −11.4] (1/1)
Swollen joints (number, absolute change)[c]	Heterogeneous result, statistically significant results in the same direction in favour of tocilizumab + MTX (4/4); explanatory factor could be the study duration: −5.64 [−7.17; −4.10][d]	−7.2 [−9.9; −4.5] (1/1)
Pain (VAS 100 mm, absolute change)[c]	−17.67 [−20.64; −14.71]/ −0.68 [−0.79; −0.56][e] (2/2)	−19.3 [−26.1; −12.6]/ −0.62 [−0.85; −0.40][e] (1/1)

(continued)

Table 11: Summary of results on tocilizumab (continued)

Outcome [if applicable, measurement tool or operationalization]	**Result of the meta-analysis or individual studies/result from assessment of relevance (if conducted) Group differences [95% CI][a] (number of studies with results for the benefit assessment/thereof number of studies with outcome-related high risk of bias)**	
Tocilizumab + MTX versus placebo + MTX		
	Majority without previous treatment with TNF-α inhibitors	**Previous treatment with TNF-α inhibitors**
Global assessment of DA by the patient (VAS 100 mm, absolute change)[c]	−17.37 [−20.42; −14.32]/ −0.65 [−0.77; −0.53][e] (2/2)	−18.3 [−25.1; −11.4]/ −0.58 [−0.80; −0.36][e] (1/1)
Morning stiffness	–[f]	Not examined
Fatigue (FACIT-F, absolute change)[g]	4.99 [3.63; 6.35]/ 0.50 [0.37; 0.63][e] (2/2)	7.19 [4.71; 9.67]/ 0.64 [0.41; 087][e] (1/1)
Sleep quality	–[f]	Not examined
Structural joint changes	Not examined	Not examined
Status of physical functioning (HAQ-DI)		
(HAQ-DI, absolute change)[c]	−0.36 [−0.42; −0.29]/ −0.63 [−0.75; −0.51][e] (2/2)	−0.36 [−0.47; −0.26]/ −0.74 [−0.97; −0.52][e] (1/1)
Responder analysis (HAQ-DI)	Patients with an improvement of: ≤ −0.25: OR: 2.76 [2.05; 3.72] ≤ −0.3: OR: 2.68 [1.98; 3.61] ≤ −0.5: OR: 2.92 [2.14; 3.98] ≤ −0.75: OR: 3.13 [2.14; 4.57] (1/1)	–[f]
Level of social functioning	–[f]	Not examined
Health-related quality of life		
Physical health (SF-36, absolute change)[g]	4.92 [3.58; 6.26]/ 0.56 [0.43; 0.69][e] (2/2)	7.06 [5.08; 9.04]/ 0.80 [0.57; 1.04][e] (1/1)
Mental health (SF-36, absolute change)	Heterogeneous result, statistically significant results in the same direction in favour of tocilizumab + MTX/heterogeneous result, the 95% CI of the SMD in 1 study did not lie completely above 0.2 (2/2)	2.44 [–0.46; 5.34] (1/1)
EQ-5D	–[f]	Not examined
All-cause mortality (deaths)	RD: 0.00 [−0.00; 0.01] (4/4)	p > 0.999[h] (1/1)

(continued)

Table 11: Summary of results on tocilizumab (continued)

ADR		
Pat. with at least 1 SAE	OR: 1.66 [1.16; 2.38] (5/5) OR: 1.08 [0.77, 1.51][i]	p = 0.110[h] (1/1)
Study discontinuation due to AE	OR: 2.85 [1.80; 4.51] (4/4)	p = 0.783[h] (1/1)
Pat. with at least 1 AE	Heterogeneous result, results in same direction and in the majority of cases statistically significant to the disadvantage of tocilizumab + MTX (5/5)[i]	p = 0.486[h] (1/1)
Pat. with at least 1 serious infection	OR: 2.76 [1.32; 5.75] (4/4) OR: 1.66 [0.90; 3.06][i]	p = 0.731[h] (1/1)
Pat. with at least 1 infection	OR: 1.36 [1.15, 1.61] (5/5) OR: 0.92 [0.72; 1.17][i]	p = 0.169[h] (1/1)

a: Mean difference, unless otherwise noted.
b: DAS 28 using the inflammatory parameter ESR.
c: Negative effect estimates mean better values under tocilizumab + MTX.
d: Result from meta-analysis without 52-week study.
e: SMD in the form of Hedges' g for assessing the relevance of the statistically significant difference. If the 95% CI did not lie completely below the irrelevance threshold of −0.2 or above the irrelevance threshold of 0.2, an irrelevant effect could not be excluded.
f: Proportion of patients not considered in the analysis > 30% or group difference in the proportion of patients not considered in the analysis ≥ 15%: data not included in the present benefit assessment.
g: Positive effect estimates mean better values under tocilizumab + MTX.
h: Solely p-value taken into account in the present benefit assessment.
i: In view of differential discontinuation rates due to lack of efficacy, or important differences in the proportion of patients with therapy adaptation, in 4 studies the result is not classified as robust.

ADR: adverse drug reactions, AE: adverse event, CI: confidence interval, DA: disease activity, DAS: Disease Activity Score, EQ-5D: EuroQol-5D, ESR: erythrocyte sedimentation rate, FACIT-F: Functional assessment of chronic illness therapy – Fatigue, HAQ-DI: Health Assessment Questionnaire-Disability Index, MTX: methotrexate, OR: Odds Ratio, Pat.: patients, RA: rheumatoid arthritis, RD: risk difference, SAE: serious adverse event, SF: Health Survey Short Form, SMD: standardized mean difference

Population in the majority of cases without previous treatment with TNF-α inhibitors

At study level all included studies showed a low risk of bias. At outcome level this was consistently high except for the outcome "remission". This was because of marked differences between the treatment groups regarding the need for therapy adaptation. Although statistical replacement procedures were used for patients who discontinued, relevant bias could still occur. If possible, in these cases sensitivity analyses were conducted for the present benefit assessment to investigate the impact of bias.

A statistically significant result in favour of tocilizumab + MTX was shown for the outcome "remission" that was based on 2 studies with a low risk of bias. Statistically significant results in each case in favour of tocilizumab + MTX were also shown or an irrelevant effect could be excluded for the outcomes "pain", "global assessment of disease activity by the patient", "fatigue", "status of physical functioning" and "health-related quality of life" relating to the dimension "physical health" measured with the Health Survey Short Form (SF)-36. For the

outcomes “swollen joints” and “painful joints”, important heterogeneity of results existed with a clear direction of results, also in favour of tocilizumab + MTX. One explanation for the existing heterogeneity could be different study durations (52 weeks versus 24 weeks). There was a consistent, outcome-related high risk of bias for these outcomes. On the basis of sensitivity analyses (see above), the effects were, however, classified as robust. The data provide proof of a benefit of tocilizumab in each case.

A statistically significant result to the disadvantage of tocilizumab + MTX was shown for discontinuations due to adverse events. There was an outcome-related high risk of bias. On the basis of sensitivity analyses (see above), the effect was classified as robust and therefore this provides proof of a harm of tocilizumab.

A statistically significant result to the disadvantage of tocilizumab + MTX was shown for the overall rates of serious adverse events, serious infections and infection” respectively. The meta-analysis for adverse events showed a relevant heterogeneity with the same direction of effects and a majority of statistically significant results to the disadvantage of tocilizumab + MTX. On the basis of the consistent outcome-related high risk of bias, this provides an indication of harm of tocilizumab for each of these outcomes.

No proof of benefit or harm was provided for the other outcomes, as either the results were not statistically significant, the proportions of patients not considered in the analysis (= non-considered proportions) were too high or data were missing.

Relevant subgroup analyses were available for changes in status of physical functioning, but were not considered further due to the high proportion of patients not considered in the analysis. Relevant subgroup analyses for adverse events for the potential effect modifiers “age” and “sex” showed no proof of different effects in older or younger patient or women or men.

Population with pretreatment with TNF-α inhibitors

Here too, at study level there was a low risk of bias and at outcome level, except for the outcome “remission”, the risk of bias was consistently high. In this study this was likewise due to marked differences between the treatment groups regarding the need for therapy adaptation. Although statistical replacement procedures were used for patients who discontinued, relevant bias could still occur. If possible, sensitivity analyses were also conducted in these cases to investigate the impact of bias for the present benefit assessment.

A statistically significant result in favour of tocilizumab + MTX was shown for the outcome “remission” on the basis of a study with a low risk of bias. Likewise, statistically significant results in each case in favour of tocilizumab + MTX were shown or an irrelevant effect could be excluded for the outcomes “painful joints”, “swollen joints”, “pain”, “global assessment of disease activity by the patient”, “fatigue”, “status of physical functioning” and “health-related quality of life” relating to the dimension “physical health” measured with the SF-36. The

results on each of these outcomes were based on a single study with an outcome-related high risk of bias. However, on the basis of sensitivity analyses (see above), the effects were consistently classified as robust and in each case provide an indication of a benefit of tocilizumab.

No proof of benefit or harm was provided for the other outcomes, as either the results were not statistically significant, the proportions of patients not considered in the analysis (= non-considered proportions) were too high or data were missing.

Relevant subgroup analyses were available for adverse events and serious adverse events, that were conducted concerning the potential effect modifiers “age”, “sex” and “number of TNF-α inhibitors previously taken”. No proof was shown of differing effects between younger and older patients or between men and women. There was an indication of different effects concerning adverse events for the potential effect modifier “number of TNF-α inhibitors previously taken”. The subgroup analysis showed no statistically significant result for the patients who had previously been treated with 2 or 3 TNF-α inhibitors, but there was a statistically significant result for the group previously treated with one TNF-α inhibitor to the disadvantage of tocilizumab + MTX. The result was based on a study with an outcome-related high risk of bias and there was only an indication of an effect modification. Because of the uncertainty of the results, this provides no proof of harm in these patients.

Table 13 presents the evidence map for tocilizumab.

Direct comparison: tocilizumab vs. adalimumab

One relevant study was included for the direct comparison of tocilizumab versus adalimumab.

Table 12 contains the summary of the results of the present benefit assessment for the direct comparison of tocilizumab versus adalimumab in patients who were unsuitable for further treatment with MTX and information about the number of available studies for the respective outcomes as well as the outcome-related risk of bias.

Table 12: Summary of results on the comparison of tocilizumab vs. adalimumab in patients who were unsuitable for further treatment with MTX

Outcome [if applicable, measurement tool or operationalization]	**Result of the meta-analysis or individual studies/(if conducted) Group differences [95% CI][a] (number of studies with results for the benefit assessment/thereof number of studies with outcome-related high risk of bias)**
Tocilizumab vs. adalimumab – patients who were unsuitable for further treatment with MTX	
Remission (DAS 28 [ESR] < 2.6)	OR: 5.69 [3.14; 10.30] (1/0)
RA symptoms	
Painful joints (number, absolute change [%])[b]	–2.8 [–6.4; 0.8] (1/0)
Swollen joints (number, absolute change [%])[b]	–0.3 [–2.4; 1.8] (1/0)
Pain (VAS 100 mm, absolute change [%])[b]	–11.3 [–18.3; –4.3]/−0.39 [−0.64; −0.15][c](1/1)
Global assessment of DA by the patient (VAS 100 mm, absolute change [%])[b]	–10.5 [–17.7; –3.3]/−0.35 [−0.60; −0.11][c] (1/1)
Fatigue (FACIT-F, absolute change)[d]	2.49 [–0.26; 5.24] (1/1)
Structural joint changes	Not examined
Status of physical functioning	
Changes (HAQ)	An adequate responder analysis was also available for the single study, which was the primary relevant analysis for the present benefit assessment.
Responder analysis (HAQ)	Patients with an improvement of: ≤ −0.22: OR: 1.23 [0.80; 1.91] (1/1) ≤ −0.3: OR: 1.17 [0.76; 1.81] (1/1)
Level of social functioning	Not examined
Health-related quality of life	
Physical health (SF-36, absolute change)[d]	1.6 [–0.6; 3.8] (1/1)
Mental health (SF-36, absolute change)[d]	2.9 [0.0; 5.9]/0.24 [–0.01; 0.48][c] (1/1)
All-cause mortality (deaths)	p = 0.208[e] (1/0)

(continued)

Table 12: Summary of results on the comparison of tocilizumab vs. adalimumab in patients who were unsuitable for further treatment with MTX (continued)

ADR	
Pat. with at least 1 SAE	p = 0.675[e] (1/0)
Study discontinuation due to AE	p > 0.999[e] (1/0)
Pat. with at least 1 AE	p = 0.933[e] (1/0)
Pat. with at least 1 serious infection	p > 0.999[e] (1/0)
Pat. with at least 1 infection	p = 0.370[e] (1/0)

a: Mean difference, unless otherwise noted.
b: Negative effect estimates mean better values under tocilizumab.
c: SMD in the form of Hedges' g for assessing the relevance of the statistically significant difference. If the 95% CI did not lie completely below the irrelevance threshold of −0.2 or above the irrelevance threshold of 0.2, an irrelevant effect could not be excluded.
d: Positive effect estimates mean better values under tocilizumab.
e: Solely p-value taken into account in the present benefit assessment.
ADR: adverse drug reactions, CI: confidence interval, DA: disease activity, DAS: Disease Activity Score, ESR: erythrocyte sedimentation rate, FACIT-F: Functional Assessment of Chronic Illness Therapy – Fatigue, HAQ: Health Assessment Questionnaire, MTX: methotrexate, OR: odds ratio, Pat.: patients, RA: rheumatoid arthritis, RD: risk difference, SMD: standardized mean difference, VAS: Visual Analogue Scale, vs.: versus

The risk of bias at study level was low. At outcome level the risk of bias for the outcomes "pain", "global assessment of disease activity", "fatigue" and "health-related quality of life" was assessed as high. A statistically significant result in favour of tocilizumab was shown for the outcome "remission". As the results were based on a single study with an outcome-related low risk of bias, this provides an indication of an added benefit of tocilizumab over adalimumab in patients who were not suitable for further treatment with MTX.

No proof of added benefit or greater harm of one of the two interventions is provided for the other outcomes, as either the results were not statistically significant, an irrelevant effect could not be excluded or data were missing.

No relevant subgroup analyses were available.

Table 13 presents the evidence map for the direct comparison.

Table 13: Evidence map of all drugs

Test intervention	Remission	Symptoms of rheumatoid arthritis								Structural joint changes	Status of physical functioning	Level of social functioning	Quality of life			All-cause mortality	Adverse drug reactions				
		Painful joints	Swollen joints	Pain	Global assessment of DA by the patient	General health	Morning stiffness	Fatigue	Sleep quality				SF-36: physical health/mental health[a]	HUI[a]	EQ-5D		Serious AE	Discontinuation due to AE	AE	Serious infections	Infections
ABA	⇑⇑	⇑⇑	⇑⇑	⇑⇓	⇑⇑	-	⇑⇑	⇗	⇔	-	⇑⇑	-	⇑⇑ / ⇑⇓	-	-	⇔	⇔	⇔	⇔	⇔	⇑⇓
ADA	⇑⇑	⇑⇑	⇑⇑	⇑⇑	⇑⇑	-	⇑⇑	⇑⇑	⇔	-	⇑⇑	⇔	⇑⇑ / ⇔	⇑⇑	-[b]	⇔	⇔	⇔	⇓	⇓⇓	⇓
ANA	-	⇑	⇑	⇔	⇔	-	⇔	-	-	-	⇑	-	⇔ / ⇔	-	-	⇔	⇔	⇔	⇔	⇑⇓	⇔
CER	⇑⇑	⇑⇑	⇑⇑	⇑⇑	⇑⇑	-	⇑	⇔	-	-	⇑⇑	⇗ (⇔)[c]	⇔ / ⇔	-	-[b]	⇔	⇔	⇔	↘	⇓	⇑⇓
ETA 1	⇑	⇑	⇑	⇔	⇔	⇔	⇑	-	-	-	⇑	-[e]	-	-	-[b]	⇔	⇔	⇔	⇔	⇔	⇔
ETA 2	⇔	⇗	⇗	⇗	⇗	⇗	⇗	-	-	-	⇗	-	-	-	-	(⇔)	⇔	⇔	⇔	⇔	⇔
ETA 3	⇗	⇗	⇗	⇗	⇗	⇗	⇗	-	-	-	⇔	-	-	-	-	⇔	⇔	⇔	⇔	⇔	⇔

(continued)

Table 13: Evidence map of all drugs (continued)

Test intervention	Remission	Symptoms of rheumatoid arthritis								Structural joint changes	Status of physical functioning	Level of social functioning	Quality of life			All-cause mortality	Adverse drug reactions				
		Painful joints	Swollen joints	Pain	Global assessment of DA by the patient	General health	Morning stiffness	Fatigue	Sleep quality				SF-36: physical health/mental health[a]	HUI[a]	EQ-5D		Serious AE	Discontinuation due to AE	AE	Serious infections	Infections
GOL 1	⇑⇑	⇑⇑	⇑⇑	⇑⇑	⇔	-	-	⇑	-	-	⇑⇑	⇗	⇑ / ⇔	-	-	⇔	⇔	⇔	⇔	⇔	⇔
GOL 2	⇑	⇗	⇗	⇔	⇗	-	-	⇔	-	-	⇗	⇔	-	-	-	⇔	⇔	⇔	⇔	⇔	⇔
INF	⇑	⇑	⇑	⇔	⇔	-	⇑	⇑	-	-	⇑	-	⇔ / ⇔	-	-	⇔	⇔	⇔	⇔	⇔	⇔
RIT 1	⇑	⇑	⇑	⇑	⇑	-	-	⇑	-	-	⇑	-	⇗ / ⇔	-	-	⇔	⇔	⇔	⇔	⇔	⇔
RIT 2	⇔	⇔	⇔	⇔	⇔	-	-	⇔	-	-	⇔	-	⇔ / ⇔	-	-	⇔	⇔	⇔	⇔	⇔	⇔
TOC 1	⇑⇑	⇑⇑	⇑⇑	⇑⇑	⇑⇑	-	-[e]	⇑⇑	-[d]	-	⇑⇑	-[e]	⇑⇑ / ⇑⇓	-	-[e]	⇔	⇓	⇓⇓	⇓	⇓	⇓
TOC 2	⇑	⇑	⇑	⇑	⇑	-	-	⇑	-	-	⇑	-	⇑ / ⇔	-	-	⇔	⇔	⇔	⇔	⇔	⇔
DC[g]	⇑	⇔	⇔	⇔	⇔	-	-	⇔	-	-	⇔	-	⇔ / ⇔	-	-	⇔	⇔	⇔	⇔	⇔	⇔

(continued)

Table 13: Evidence map of all drugs (continued)

a: Measured with HUI 2 and HUI 3.
b: The results on EQ-5D cannot be estimated because results on the Single Utility Index are missing.
c: Hint of a benefit of certolizumab pegol for the individual outcome "impairment of daily activities by the disease"; for all other individual outcomes, no proof of benefit.
d: The results were based on only 21% of the relevant population, because the outcome had been defined in an amendment and the questions could no longer be handed out to all patients.
e: No data included in the benefit assessment, because the proportion of non-considered patients was > 30%.
f: In favour of etanercept.
g: Tocilizumab is the test intervention, adalimumab the comparator medication.
⇑⇑: Proof of (added) benefit or proof of lesser harm of the test intervention
⇓⇓: Proof of lesser benefit or proof of (greater) harm of the test intervention
⇑: Indication of (added) benefit or indication of lesser harm of the test intervention
⇓: Indication of lesser benefit or indication of harm of the test intervention
⇗: Hint of benefit or hint of lesser harm of the test intervention
⇘: Hint of lesser benefit or hint of greater harm of the test intervention
⇔: No hint, indication, proof of (added) benefit or lesser harm of the test intervention
(⇔): No hint, indication, proof of (added) benefit or lesser harm of the test intervention, but data insufficient
⇑⇓: No hint, indication, proof of (added) benefit or lesser harm of the test intervention, heterogeneous result or an irrelevant effect cannot be excluded
-: No data reported
ABA: abatacept, ADA: adalimumab, AE: adverse event(s), ANA: anakinra, CER: certolizumab pegol, DA: disease activity, DC: direct comparison tocilizumab vs. adalimumab in patients, who were unsuitable for further treatment with MTX, ETA: etanercept, ETA 1: with MTX, ETA 2: MTX-intolerant patients, ETA 3: patients with severe active and progressive rheumatoid arthritis, EQ-5D: EuroQol-5D, GOL: golimumab, GOL 1: no previous treatment with TNF-α inhibitors; GOL 2: previous treatment with TNF-α inhibitors, HUI: Health Utility Index, INF: infliximab, RIT: rituximab, RIT 1: no previous treatment with rituximab, RIT 2: after no response to one cycle of rituximab, SF: Health Survey Short Form, TNF: tumour necrosis factor, TOC 1: in the majority of cases without previous treatment with TNF-α inhibitors, TOC 2: previous treatment with TNF-α inhibitors, VAS: Visual Analogue Scale

Conclusions

The conclusions of the present benefit assessment for each bDMARD are presented separately and in alphabetical order below. A total of one study on the comparison of 2 bDMARDs (tocilizumab versus adalimumab) was available. The majority of the included studies were placebo-controlled. The conclusions on the evidence map for the patient-relevant outcomes are presented per test intervention, divided according to proof, indication, hint and no proof. The conclusions on harm follow those on benefit.

If not otherwise described, the test and control interventions were used in the studies in each case in combination with MTX.

For the bDMARDs adalimumab, etanercept and tocilizumab that are also approved as monotherapy, relevant studies were additionally identified for the present benefit assessment in which these drugs were used as monotherapy. Tocilizumab was compared with adalimumab in patients with intolerance to MTX. Etanercept was used in patients with intolerance to MTX and in patients with severe active and progressive RA as monotherapy in comparison with sulfasalazine or MTX.

Abatacept

For abatacept there is (in comparison with placebo)

- Proof of benefit in terms of remission, in terms of the symptoms of RA with regard to painful joints, swollen joints, the global assessment of disease activity by the patient and morning stiffness, in terms of the status of physical functioning and in terms of the dimension “physical health” of health-related quality of life,
- A hint of benefit in terms of RA symptoms with regard to fatigue,
- No proof of benefit in terms of symptoms of RA with regard to pain and sleep quality, in terms of structural joint changes (such as deformities, stiffness, contractures) due to missing data, in terms of the level of social functioning also due to missing data and in terms of the dimension “mental health” of health-related quality of life as well as
- No proof of harm regarding all-cause mortality, serious adverse events, study discontinuations due to adverse events, overall rate of adverse events, serious infections and overall rate of infections.

Adalimumab

For adalimumab there is (in comparison with placebo)

- Proof of benefit in terms of remission, symptoms of RA with regard to painful joints, swollen joints, pain, the global assessment of disease activity by the patient, morning stiffness and fatigue, in terms of the status of physical functioning and in terms of health-related quality of life with regard to the dimension of physical health, as well as other dimensions, measured with the HUI,

- No proof of benefit in terms of sleep quality, structural joint changes (such as deformities, stiffness, contractures) due to missing data, in terms of the level of social functioning and the level of social functioning as well as in terms of the dimension “mental health” of health-related quality of life,
- Proof of harm in terms of serious infections, whereby there is no proof of harm for overall rate of serious adverse events,
- An indication of harm regarding overall rate of adverse events and overall rate of infections,
- No proof of harm regarding all-cause mortality as well as study discontinuations due to adverse events.

Anakinra

For anakinra there is (in comparison with placebo)

- An indication of benefit in terms of symptoms of RA with regard to painful joints and swollen joints as well as in terms of the status of physical functioning,
- No proof of benefit in terms of remission due to missing data, in terms of symptoms of RA with regard to pain, the global assessment of disease activity by the patient and morning stiffness, in terms of structural joint changes (such as deformities, stiffness, contractures) due to missing data, in terms of the level of social functioning also due to missing data and in terms of of health-related quality of life as well as
- No proof of harm regarding all-cause mortality, serious adverse events, study discontinuations due to adverse events, overall rate of adverse events, serious infections and overall rate of infections.

Certolizumab pegol

For certolizumab pegol there is (in comparison with placebo)

- Proof of benefit in terms of remission, in terms of symptoms of RA with regard to painful joints, swollen joints, pain and the global assessment of disease activity by the patient as well as in terms of the status of physical functioning,
- An indication of benefit in terms of symptoms of RA with regard to morning stiffness,
- A hint of benefit in terms of the level of social functioning with regard to the impairment of daily activities by the disease,
- No proof of benefit in terms of symptoms of RA with regard to fatigue in terms of structural joint changes (such as deformities, stiffness, contractures) due to missing data and in terms of health-related quality of life,
- An indication of harm regarding overall rate of serious infections,

- A hint of harm regarding overall rate of adverse events and
- No proof of harm regarding all-cause mortality, serious adverse events, study discontinuations due to adverse events and overall rate of infections.

Etanercept

For etanercept there is (in comparison with placebo)

- An indication of benefit in terms of remission and symptoms of RA with regard to painful joints, swollen joints and morning stiffness as well as in terms of the status of physical functioning,
- No proof of benefit in terms of symptoms of RA with regard to pain, the global assessment of disease activity by the patient and general health, in terms of structural joint changes (such as deformities, stiffness, contractures) due to missing data, in terms of the level of social functioning and of health-related quality of life due to non-evaluable data and
- No proof of harm regarding all-cause mortality, serious adverse events, study discontinuations due to adverse events, overall rate of adverse events, serious infections and overall rate of infections.

For etanercept there is (in comparison with sulfasalazine) in patients with intolerance to MTX

- A hint of added benefit of etanercept over sulfasalazine in terms of symptoms of RA with regard to painful joints and swollen joints, pain, the global assessment of disease activity by the patient and general health as well as in terms of morning stiffness and status of physical functioning,
- No proof of added benefit in terms of remission and in terms of structural joint changes (such as deformities, stiffness, contractures), level of social functioning and health-related quality of life due to missing data as well as
- No proof of lesser or greater harm through one of the two test interventions regarding all-cause mortality and regarding serious adverse events, study discontinuations due to adverse events, overall rate of adverse events, serious infections and overall rate of infections.

For etanercept there is (in comparison with MTX) in patients with severe active and progressive RA

- A hint of added benefit of etanercept over sulfasalazine in terms of remission, in terms of symptoms of RA with regard to painful joints, swollen joints, pain, the global assessment of disease activity by the patient, general health as well as morning stiffness,
- No proof of added benefit in terms of structural joint changes (such as deformities, stiffness, contractures) due to missing data, in terms of the status of physical functioning,

the level of social functioning and of health-related quality of life in each case due to missing data as well as

- No proof of lesser or greater harm through one of the two test interventions regarding all-cause mortality and regarding serious adverse events, study discontinuations due to adverse events, overall rate of adverse events, serious infections and overall rate of infections.

Golimumab

For golimumab there is (in comparison with placebo) for a population not previously treated with TNF-α inhibitors

- Proof of benefit in terms of remission, in terms of symptoms of RA with regard to painful joints, swollen joints and pain as well as in terms of the status of physical functioning,
- An indication of benefit in terms of symptoms of RA with regard to fatigue and in terms of the dimension “physical health” of health-related quality of life,
- A hint of benefit in terms of the level of social functioning,
- No proof of benefit in terms of symptoms of RA with regard to the global assessment of disease activity by the patient, in terms of structural joint changes (such as deformities, stiffness, contractures) due to missing data as well as in terms of the dimension “mental health” of health-related quality of life and
- No proof of harm regarding all-cause mortality, serious adverse events, study discontinuations due to adverse events, overall rate of adverse events, serious infections and overall rate of infections.

For golimumab there is (in comparison with placebo) for a population previously treated with TNF-α inhibitors

- An indication of benefit in terms of remission,
- A hint of benefit in terms of symptoms of RA with regard to painful joints, swollen joints and the global assessment of disease activity by the patient as well as in terms of the status of physical functioning,
- No proof of benefit in terms of symptoms of RA with regard to pain and fatigue as well as in terms of the level of social functioning – due to missing data there is also no proof of benefit for structural joint changes (such as deformities, stiffness, contractures) and health-related quality of life – and
- No proof of harm regarding all-cause mortality, serious adverse events, study discontinuations due to adverse events, overall rate of adverse events, serious infections and overall rate of infections.

Infliximab

For infliximab there is (in comparison with placebo)

- An indication of benefit in terms of remission, in terms of symptoms of RA with regard to painful joints, swollen joints, morning stiffness and fatigue as well as in terms of the status of physical functioning,
- No proof of benefit in terms of symptoms of RA with regard to pain and the global assessment of disease activity by the patient, in terms of structural joint changes (such as deformities, stiffness, contractures) due to missing data, in terms of the level of social functioning due to missing data and in terms of health-related quality of life as well as
- No proof of harm regarding all-cause mortality, serious adverse events, study discontinuations due to adverse events, overall rate of adverse events as well as serious infections and infections.

Rituximab

For rituximab there is (in comparison with placebo) for a population not previously treated with rituximab

- An indication of benefit in terms of remission, in terms of symptoms of RA with regard to painful joints, swollen joints, pain, the global assessment of disease activity by the patient as well as fatigue and in terms of the status of physical functioning,
- A hint of benefit in terms of the dimension “physical health” of health-related quality of life,
- No proof of benefit in terms of structural joint changes (such as deformities, stiffness, contractures) due to missing data, in terms of the level of social functioning also due to missing data and in terms of the dimension “mental health” of health-related quality of life,
- No proof of harm regarding all-cause mortality, serious adverse events, study discontinuations due to adverse events, overall rate of adverse events, serious infections and overall rate of infections.

For rituximab there is (in comparison with placebo) for a population that has shown no response to a cycle of rituximab

- No proof of benefit regarding the patient-relevant outcomes considered in the present benefit assessment (no data available either for structural joint changes [such as deformities, stiffness, contractures] or for the level of social functioning) as well as
- No proof of harm regarding all-cause mortality, serious adverse events, study discontinuations due to adverse events, overall rate of adverse events, serious infections and overall rate of infections.

Tocilizumab

For tocilizumab there is (in comparison with placebo) for a population in the majority of cases not previously treated with TNF-α inhibitors

- Proof of benefit in terms of remission, in terms of symptoms of RA with regard to painful joints, swollen joints, pain, the global assessment of disease activity by the patient and fatigue, in terms of the status of physical functioning und in terms of the dimension "physical health" of health-related quality of life,
- No proof of benefit in terms of symptoms of RA with regard to morning stiffness and sleep quality due to non-evaluable data, in terms of structural joint changes (such as deformities, stiffness, contractures) due to missing data, in terms of the level of social functioning and in terms of the dimension "mental health" of health-related quality of life,
- Proof of harm regarding study discontinuations due to adverse events,
- An indication of harm regarding serious adverse events, adverse events, serious infections and overall rate of infections as well as
- No proof of harm regarding all-cause mortality.

For tocilizumab there is (in comparison with placebo) for a population previously treated with TNF-α inhibitors

- An indication of benefit in terms of remission, in terms of symptoms of RA with regard to painful joints, swollen joints, pain, the global assessment of disease activity by the patient and fatigue, in terms of the status of physical functioning and in terms of the dimension "physical health" of health-related quality of life,
- No proof of benefit in terms of structural joint changes (such as deformities, stiffness, contractures) due to missing data, in terms of the level of social functioning also due to missing data and in terms of the dimension "mental health" of health-related quality of life as well as
- No proof of harm regarding all-cause mortality, serious adverse events, study discontinuations due to adverse events, overall rate of adverse events, serious infections and overall rate of infections.

For tocilizumab in comparison with adalimumab in patients, who were not suitable for further treatment with MTX, there is

- An indication of added benefit in terms of remission,
- No proof of added benefit in terms of symptoms of RA with regard to painful joints, swollen joints, pain, the global assessment of disease activity by the patient and fatigue, in terms of the status of physical functioning and in terms of health-related quality of life –

no data were available for structural joint changes (such as deformities, stiffness, contractures) and for the level of social functioning – as well as

- No proof of greater or lesser harm regarding all-cause mortality, serious adverse events, study discontinuations due to adverse events, overall rate of adverse events, serious infections and overall rate of infections.

Keywords: abatacept, adalimumab, anakinra, arthritis – rheumatoid, benefit assessment, certolizumab pegol, etanercept, golimumab, infliximab, interleukin 1 receptor antagonist protein, rituximab, systematic review, TNFR-Fc fusion protein, tocilizumab

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