IQWiG Reports – V14-02

Systematic guideline search and appraisal, as well as extraction of relevant recommendations, for a DMP "rheumatoid arthritis"[1]

Extract

[1] Translation of Chapters 1 to 6 of the final report *Systematische Leitlinienrecherche und -bewertung sowie Extraktion relevanter Empfehlungen für ein DMP Rheumatoide Arthritis* (Version 1.1; Status: 16 March 2016). 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.

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This report was prepared in collaboration with external experts.

The responsibility for the contents of the report lies solely with IQWiG.

According to §139 b (3) No. 2 of Social Code Book (SGB) V, Statutory Health Insurance, external experts who are involved in the Institute's research commissions must disclose "all connections to interest groups and contract organizations, particularly in the pharmaceutical and medical devices industries, including details on the type and amount of any remuneration received". The Institute received the completed *Form for disclosure of potential conflicts of interest* from each external expert. The information provided was reviewed by a Committee of the Institute specifically established to assess conflicts of interests. The information provided by the external experts on potential conflicts of interest is presented in Chapter A11 of the full report. No conflicts of interest were detected that could endanger professional independence with regard to the work on the present commission.

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Key statement

Research question

The aim of the present investigation is to identify current, topic-relevant, evidence-based guidelines, extract their recommendations and designate those recommendations that are relevant for the care of patients in a disease management programme (DMP) “rheumatoid arthritis” (RA).

Conclusion

On the basis of Grades of Recommendation (GoR) or alternatively of Levels of Evidence (LoE) of extracted recommendations from current evidence-based guidelines, relevant and potentially relevant recommendations on all prespecified healthcare aspects were identified for a DMP “rheumatoid arthritis”, with the exception of the healthcare aspect of rehabilitation.

The recommendations identified on diagnostics refer to the physical examination or the measurement of general and specific inflammatory parameters in the blood.

A treat-to-target therapy is named for the planning of the individual treatment strategy. Remission and/or minimization of disease activity are named as treatment goals.

Recommendations on the design of physiotherapy, on occupational therapy, diet as well as on the use of orthoses were identified in the section “Non-drug therapy and general measures”.

Recommendations on the following subareas were identified for drug therapy:

- Recommendations across drugs for evaluation of the treatment goals “remission” and “reduction in disease activity”, as well as recommendations for regular monitoring of drug therapy.
- Recommendations on disease-modifying antirheumatic drugs (DMARDs): recommendations on the use of conventional synthetic and biological DMARDs (csDMARDs and bDMARDs) are described. The recommendations refer to the selection of suitable drugs and drug combinations depending on disease duration, symptoms, previous treatment attempts, clinical response, and tolerance. Further recommendations refer to the conduct and monitoring of DMARD therapy.
- Recommendations for patients with RA and specific disease constellations or comorbidities.
- Recommendations on symptomatic and anti-inflammatory treatment with glucocorticoids, non-steroid anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 (COX-2) inhibitors, and analgesics as well as on treatment with dietary supplements.

The recommendations identified on the monitoring of disease activity refer to the measurement instrument to be used and the time intervals.

Furthermore, recommendations on the compilation of a multidisciplinary team and on nursing management of RA were identified for the healthcare aspect “cooperation of healthcare sectors”.

The recommendations on patient training refer to the content and design of training.

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List of abbreviations

Abbreviation	Meaning
ACE	angiotensin converting enzyme
ACR	American College of Rheumatology
AGREE	Appraisal of Guidelines for Research & Evaluation
anti-CCP AB	anti-cyclic citrullinated peptide antibodies
bDMARD	biological DMARD
BSR	British Society for Rheumatology
COX-2	cyclooxygenase-2
CRA	Canadian Rheumatology Association
CRP	C-reactive protein
csDMARD	conventional synthetic DMARD
DAS	Disease Activity Score
DGRh	Deutsche Gesellschaft für Rheumatologie (German Rheumatology Association)
DMARD	disease-modifying antirheumatic drugs
DMP	disease management programme
EULAR	European League Against Rheumatism
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GoR	Grade of Recommendation
HBV	hepatitis B virus
i.v.	intravenous
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
JIA	juvenile idiopathic arthritis
LoE	Level of Evidence
NCCCC	National Collaborating Centre for Chronic Conditions
NSAID	non-steroid anti-inflammatory drug
NVL	Nationale VersorgungsLeitlinie (National Care Guideline)
NYHA	New York Heart Association
RA	rheumatoid arthritis
RACGP	Royal Australian College of General Practitioners
RCT	randomized controlled trial
RF	rheumatoid factor
RTX	rituximab
SIGN	Scottish Intercollegiate Guidelines Network

Abbreviation	Meaning
SoR	Strength of Recommendation
T2T	International Task Force of Rheumatologists
TCZ	tocilizumab
TNF	tumour necrosis factor

1 Background

Disease management programmes

Disease management programmes (DMPs) are structured treatment programmes for chronically ill people that are based on the findings of evidence-based medicine. Within the framework of these programmes, treatment methods are primarily used that correspond to the current state of scientific knowledge [1]. Patients thus receive health care that aims to prevent as far as possible the risk of late complications and acute deterioration of the disease and increase their quality of life. The goal of DMPs is, among other things, to optimize treatment, promote collaboration with service providers, and thus better interlink diagnostic and therapeutic procedures [2].

Relevant disorder

Rheumatoid arthritis (RA) is the most common chronic-inflammatory joint disorder in industrial countries with a prevalence of 0.5% to 0.8% in the adult population [3,4]. The prevalence data correspond to the data for Germany [5]. RA is attributed to the autoimmune disorders [6]. RA occurs in adulthood; women are more often affected than men.

The course of disease differs individually and cannot be predicted in individual cases [5,7]. The first 3 to 6 months of the disease represent a “therapeutic window” within which the immunological process can be stopped or permanently changed. Early diagnosis and initiation of treatment are thus of decisive importance for the course of disease [5,8].

RA predominantly affects the joints of the hands and feet, mostly following a symmetrical pattern [5]. Depending on disease severity, the chronic inflammation of the synovial membranes rapidly or insidiously leads to the destruction of cartilage and the adjoining bone, with the destruction of affected joints, which is visible in X-rays. Typical symptoms are general symptoms of disease such as pain, restriction in mobility, fatigue, as well as inflammations of tendon sheaths, blood vessels, and internal organs [5].

In order to distinguish RA from similar disorders, the classification criteria of the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) from 2010 are used; these also cover the early forms of RA and are considered in guidelines developed after 2010 (see Table 1). Besides these criteria, the classification scheme of the ACR from 1987 [9] is still being used in guidelines.

Table 1: ACR/EULAR classification criteria for rheumatoid arthritis [6] (adapted)

The precondition for the application of the criteria listed in the table below is the existence of at least one case of confirmed synovitis in at least one target joint without indications of a different cause (trauma, other inflammatory or degenerative joint disorders),

If, according to the items in the table, at least 6 points (last column) are achieved then the disease can be classified as RA.

Swelling/ pain	Serology[c]	Acute phase parameters[d]	Symptom duration[e]	Points
≤ 1 large[a]	RF & ACPA negative	CRP & ESR normal	< 6 weeks	0
2–10 large[a]	-	CRP or ESR increased	≥ 6 weeks	1
1–3 small[b]	RF or ACPA low-positive	-	-	2
4–10 small[b]	RF or ACPA high-positive	-	-	3
> 10 joints; of which at least 1 small one is affected	-	-	-	5

a: The definition "large joints" refers to shoulders, elbows, hips, knees and ankles. The initial definition of definitive synovitis does not have to be fulfilled for a joint to be rated as an affected joint; here it refers to any joint from the above list with swelling or tenderness.
b: The definition "small joints" refers to the first to fifth metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints, second to fifth metatarsophalangeal (MTP) joints, thumb interphalangeal joints (IP 1), and wrists. The first carpometacarpal (CMC) joints, the first metatarsophalangeal (MTP) joints, and the distal interphalangeal (DIP) joints are excluded from the assessment.
c: Serology: RF or ACPA are assessed as "high-positive" if the level is more than 3 times above the upper normal level.
d: The criterion for an acute phase response is fulfilled if CRP or ESR is increased. With ESR, physiologically increased levels (age, sex, pregnancy) should be considered and in case of doubt should not be rated.
e: Definition of duration of symptoms: this refers to the joint that, according to the patient's self-report of symptoms, has been affected the longest.
ACR: American College of Rheumatology; ACPA: anti-citrullinated protein antibody; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; EULAR: European League Against Rheumatism; RA: rheumatoid arthritis; RF: rheumatoid factor

Juvenile idiopathic arthritis (JIA) is a chronic autoimmune disorder of unknown aetiology occurring in childhood and adolescence. The disorder is classified in 7 sub-types according to clinical and serological characteristics: systemic arthritis, rheumatoid factor (RF)-negative polyarthritis, RF-positive polyarthritis, oligoarthritis, enthesitis-associated arthritis, psoriasis arthritis, and undifferentiated arthritis [10]. JIA is not addressed in the present report.

Guidelines

For the present report the term "guidelines" is used according to the definition of the Institute of Medicine (IOM): "practice guidelines are systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances" [11] and "include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options" [12].

Guideline authors often award a “Grade of Recommendation” (GoR) and a “Level of Evidence” (LoE). The GoR reflects the strength of a recommendation and is usually based on a weighing of the benefit and risks of a treatment, on each specific healthcare context, as well as on the strength of the underlying evidence or the LoE. The LoE represents an assessment of internal validity of the studies underlying the recommendations; in this context, systematic reviews of randomized controlled trials (RCTs) are generally awarded the highest LoE. However, guideline developers use different systems to grade evidence and, within the LoE, acknowledge a varying importance of the different clinical and epidemiological studies as well as of further potentially biasing factors, if applicable.

2 Research question

The aim of the present investigation is to identify current, topic-relevant, evidence-based guidelines, extract their recommendations and designate those recommendations that are relevant for the care of patients in a DMP “rheumatoid arthritis”.

3 Methods

The investigation included guidelines that had been developed specifically for RA. The target population of the guideline synopsis consisted of patients with RA.

Only evidence-based guidelines applicable to the German healthcare system and published from January 2009 onwards were included. The recommendations had to be clearly designated as such.

For this purpose, a systematic Internet search for guidelines was conducted in guideline databases, as well as on the websites of multidisciplinary and specialist guideline providers. In addition, information was screened from the hearing procedure on the preliminary report plan (protocol) and preliminary report. The selection of relevant guidelines was performed by means of title and abstract screening, with subsequent assessment of the full texts of the potentially relevant guidelines. The title and abstract screening was performed by one reviewer and a second reviewer checked the result. The assessment of the full texts and the selection of the guidelines to be included were performed by 2 reviewers independently of one another. The assessment of the relevance of the additional information from the hearing procedure was also performed by both reviewers; discrepancies were solved through discussion between them.

The methodology of the guidelines included was assessed using the Appraisal of Guidelines for Research & Evaluation (AGREE) II instrument. The AGREE II instrument is used to assess the methodological quality of a guideline and contains a total of 23 appraisal criteria. Six domains are allocated to these criteria, each of which describes a separate dimension of methodological guideline quality. The assessments were performed by 2 reviewers independently of one another. These 2 reviewers then assessed the overall quality of the guidelines. The results of the AGREE II appraisal were not a criterion for the inclusion of guidelines in the investigation, but served to present transparently the methodological strengths or weaknesses of the evidence-based guidelines included.

The guideline recommendations relevant for the research question were extracted into tables, together with the related GoR and LoE for the respective healthcare aspects. In this context, the GoR reflects the strength of a recommendation and is usually based on a weighing of the benefit and risks of treatment, on each specific health care context, as well as on the strength of the underlying evidence or the LoE. The LoE reported by the guideline authors represents an assessment of internal validity of the studies underlying the recommendations; in this context, systematic reviews of RCTs are generally awarded the highest LoE. In addition, when extracting the recommendations for each individual GoR and LoE for the assessment of their DMP relevance, it was reported whether the recommendations were allocated to a high (↑) or low (↓) GoR/LoE.

The guideline recommendations and the definitions of the disorder were summarized in a structured information synthesis. If possible and meaningful, individual recommendations on

overarching topics (of healthcare aspects) were presented conjointly and evaluated with regard to DMP-relevance. The corresponding GoR, or if not reported, alternatively the LoE, were used to evaluate the relevance of recommendations on a topic for a DMP “rheumatoid arthritis”:

- DMP relevance was determined if different guidelines provided consistent recommendations on a topic, with mostly a high GoR, or alternatively with mostly a high LoE.
- Potential DMP relevance was determined for recommendations in which consistent statements were made on a topic, but were only partially and not mostly allocated to a high GoR, or alternatively a high LoE. In the following text, the latter is referred to as an inconsistent GoR or alternatively an inconsistent LoE. In addition, potential DMP relevance was determined if only one guideline provided recommendations on a topic and they were allocated to a high GoR or alternatively a high LoE.
- Further evaluation of DMP relevance was proposed in cases where different guidelines provided inconsistent recommendations on a topic, with at least partially a high GoE or alternatively a high LoE.
- No statement on DMP relevance could be made if no GoR or LoE were provided on a topic for the majority of recommendations or if the GoR or LoE could not be clearly allocated to the recommendations.
- No DMP relevance was determined if a GoR or alternatively an LoE was provided on a topic for at least half of the recommendations, but no high GoR, or alternatively no high LoE, was awarded.

For all (potentially) DMP-relevant recommendations it was evaluated whether contradicting statements existed in IQWiG reports. In addition, in the event of (potentially) DMP-relevant recommendations on drug therapy, the indication-specific prescribability and the approval status in Germany were evaluated.

4 Results

4.1 Results of information retrieval

The systematic Internet search was conducted in November 2014 and the search update was conducted from October 2015 to November 2015. After title and abstract screening it yielded 96 potentially relevant documents, which were screened in full text. After evaluation of the criteria for guideline inclusion, 18 relevant guidelines were included.

Table 2: Abbreviations of the guidelines included and the publishing institutions

Abbreviation	Publisher
ACR 2015 [13]	American College of Rheumatology (ACR)
BSR 2013 TCZ [14]	British Society for Rheumatology (BSR), British Health Professionals in Rheumatology (BHPR)
BSR 2011 RTX [15]	British Society for Rheumatology (BSR), British Health Professionals in Rheumatology (BHPR)
BSR 2010 antiTNF [16]	British Society for Rheumatology (BSR), British Health Professionals in Rheumatology (BHPR)
BSR 2010 bio [17]	British Society for Rheumatology (BSR), British Health Professionals in Rheumatology (BHPR)
CRA 2012 bio [18]	Canadian Rheumatology Association (CRA)
CRA 2012 safety [19]	Canadian Rheumatology Association (CRA)
DGRh 2012 [20]	Deutsche Gesellschaft für Rheumatologie (DGRh), (German Rheumatology Association)
DGRh 2011 [21]	Deutsche Gesellschaft für Rheumatologie (DGRh), (German Rheumatology Association)
EULAR 2014 [22]	European League Against Rheumatism (EULAR)
EULAR 2013 bio [23]	European League Against Rheumatism (EULAR)
EULAR 2013 imaging [24]	European League Against Rheumatism (EULAR)
EULAR 2011 nurse [25]	European League Against Rheumatism (EULAR)
EULAR 2009 CVR [26]	European League Against Rheumatism (EULAR)
NCCCC 2009 [27]	National Collaborating Centre for Chronic Conditions (NCCCC), NICE
RACGP 2009 [28]	Royal Australian College of General Practitioners (RACGP)
SIGN 2011 [7]	Scottish Intercollegiate Guidelines Network (SIGN)
T2T 2010 [29]	International Task Force of Rheumatologists
antiTNF: anti-tumour necrosis factor; bio: biological therapy; CVR: cardiovascular risk; RTX: rituximab; TCZ: tocilizumab	

4.2 Characteristics of the guidelines included

The guidelines included were published by institutions from Germany (n = 2), the United Kingdom (n = 6), a European working group (n = 5), the United States (n = 1), Canada (n = 2), Australia (n = 1), and an international working group (n = 1).

Nine guidelines (ACR 2015, BSR 2013 TCZ, BSR 2011 RTX, BSR 2010 antiTNF, BSR 2010 bio, DGRh 2012, CRA 2012 bio, CRA 2012 safety, and EULAR 2013 bio) are restricted to treatment with selected drugs or drug classes. One of these guidelines (ACR 2015) additionally focuses on the use of conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) and biologics in high-risk patients and on vaccinations in patients treated with DMARDs. Two guidelines (NCCCC 2009 and T2T 2010) include more general treatment aspects. One guideline (EULAR 2013 imaging) exclusively provides recommendations on imaging-based joint diagnostics in patients with RA. The diagnosis and treatment options of early RA are described by 3 guidelines (DGRh 2011, RACGP 2009, and SIGN 2011). A further 3 guidelines address specific topics, such as the definition of the role and tasks of nursing staff in the management of patients with RA (EULAR 2011 nurse), patient training (EULAR 2014) or cardiovascular risk management in patients with chronic-inflammatory joint diseases (EULAR 2009 CVR).

In 13 guidelines patients with RA are the only target population; 5 guidelines (CRA 2012 bio, CRA 2012 safety, EULAR 2014, EULAR 2011 nurse, and EULAR 2009 CVR) also address patients with other chronic-inflammatory joint diseases.

All guidelines use classification systems for the LoE and/or GoR. One guideline only provides an LoE (NCCCC 2009) and one only a GoR (DGRh 2011). In 3 EULAR guidelines (EULAR 2013 bio, EULAR 2013 imaging, and EULAR 2011 nurse) and in the guideline DGRh 2012 a GoR classification system was used that could not be applied to the procedure of the German National Care Guideline (NVL).

4.3 Methodological quality of the guidelines

4.3.1 Results of the appraisal with AGREE

Overall, the guidelines received on average the highest standardized domain scores in the domains "clarity and presentation" as well as "scope and purpose". The clearest deficits were visible in the domain "applicability". This means that insufficient information was provided in the guidelines on the support of their implementation, on beneficial and obstructive factors, as well as on resource needs and on audit criteria.

In the overall assessment, guidelines DGRh 2011, CRA 2012 bio, SIGN 2011, and NCCCC 2009 received the best ratings. Guideline DGRh 2011 stands out, as it received the best ratings in 3 out of 6 domains.

4.3.2 Guideline authors' handling of unpublished or incompletely published data

Of the 18 guidelines included, 13 contained details on information retrieval of unpublished or incompletely published data. Specific details about the handling of unpublished or incompletely published data, and about how these data potentially influence the statements of single recommendations, are provided by 5 guidelines.

4.4 Synthesis of recommendations

The guideline synopsis is based on the analysis of 18 guidelines. Most of these guidelines address drug therapy of patients with RA. Recommendations on the following healthcare aspects were identified in the guidelines: definition, diagnostics, therapeutic measures (drug and non-drug), cardiovascular risk management in patients with RA, monitoring, patient training, and cooperation of healthcare sectors.

In the following text only those guideline recommendations are summarized for the single healthcare aspects, for which, according to the methodology applied, a relevance or potential relevance for a DMP “rheumatoid arthritis” was determined (see Chapter 3).

4.4.1 Definition of rheumatoid arthritis

Eight guidelines contain information on definitions of RA.

The definitions of RA presented in the guidelines are not designated as recommendations. For the understanding of the recommendations presented in this report, the definitions reported by the guidelines are briefly described in the following text.

None of the guidelines included provided a coherent presentation of aetiology, pathogenesis, symptoms and course of disease. The main component is chronic joint inflammation accompanied by swelling, restrictions in movement, and progressive joint destruction. The joints primarily affected are the small joints of the hands and feet, often with a symmetrical pattern of distribution. Furthermore, some guidelines refer to a systemic character of the disease, which can also affect other organ systems beyond the joints and lead to reduced life expectancy.

In part the guidelines distinguish between early and established RA by means of the temporal course of the disease; however, these distinctions are not made consistently.

The guidelines describe 2 different systems both still used in the guidelines to classify RA: the ACR/EULAR classification from 2010 already presented in Chapter 1 and the older ACR version of 1987, which comprises 7 criteria (see Table 3).

Table 3: Classification criteria for rheumatoid arthritis (1987) [9]

Criteria*	Classification
1	morning stiffness in and around joints lasting at least 1 hour before maximal improvement
2	soft tissue swelling (arthritis) of 3 or more joint areas observed by a physician
3	swelling (arthritis) of the proximal interphalangeal, metacarpophalangeal, or wrist joints
4	symmetric swelling (arthritis)
5	rheumatoid nodules
6	the presence of rheumatoid factor
7	radiographic erosions and/or periarticular osteopenia in hand and/or wrist joints
*Criteria 1 through 4 must have been present for at least 6 weeks.	

4.4.2 Diagnostics of rheumatoid arthritis

A total of 5 guidelines contain recommendations on the diagnostics of RA.

Physical examination

One guideline recommends diagnosing RA as early as possible, so that a preferably positive course of disease can be achieved for patients. Three guidelines recommend early referral of patients with suspected RA to a rheumatologist (recommendations are potentially DMP-relevant).

Blood tests

In the event of suspected RA, 2 guidelines recommend determining the following laboratory parameters (i) erythrocyte sedimentation rate (ESR) (ii) C-reactive protein (CRP), (iii) anti-cyclic citrullinated peptide antibodies (anti-CCP AB), and (iv) RFs (recommendations are potentially DMP-relevant).

4.4.3 Treatment goals

A total of 4 guidelines contain recommendations on treatment goals for patients with RA.

A treat-to-target strategy is recommended by 2 guidelines, independently of whether early or established RA is present. Three guidelines define remission of RA as the supreme treatment goal. If no remission can be achieved, minimization of disease activity is aspired. Criteria for these treatment goals are named (recommendations are potentially DMP-relevant).

4.4.4 Therapeutic measures

4.4.4.1 Non-drug therapy and general measures

A total of 4 guidelines contain recommendations on non-drug therapy.

Physiotherapy / sports

Two guidelines recommend that all patients with RA and functional restrictions should receive physiotherapy. In this context, one guideline names the goals and content of physiotherapy: (i) improvement of general fitness and motivation for regular physical activity, (ii) teaching of exercises that improve joint flexibility and muscle power and address other functional limitations, as well as (iii) teaching of physical therapy methods for short-term reduction in pain (recommendations are potentially DMP-relevant).

Occupational therapy

In patients with RA who complain of functional restrictions, 2 guidelines recommend referral to an occupational therapist (recommendation is potentially DMP-relevant).

Orthoses / bandages / orthopaedic shoe fittings

One guideline provides the recommendation that stiff or functional orthoses can be used in patients with RA to alleviate pain (recommendation is potentially DMP-relevant).

Dietary recommendations

One guideline recommends a Mediterranean diet for patients with RA who would like to change their eating habits because of their disease. However, the physician should inform them that there is no direct relation between a certain type of diet and an improvement in RA symptoms. Studies merely show a positive effect on the general state of health (recommendation is potentially DMP-relevant).

4.4.4.2 Drug therapy

A total of 14 guidelines provide recommendations on drug therapy.

4.4.4.2.1 General treatment recommendations

A total of 6 guidelines provide general treatment recommendations.

Until the treatment goal is reached, 3 guidelines recommend regular evaluation of drug therapy depending on disease severity, and, if necessary, implementation of required treatment adaptions (recommendations are potentially DMP-relevant). Six guidelines provide recommendations for the regular evaluation of disease activity and name different periods for this evaluation, depending on the severity of RA (recommendations are potentially DMP-relevant).

4.4.4.2.2 Disease-modifying drugs

A total of 12 guidelines provide recommendations on DMARDs.

Basic medication

Treatment goal

Six guidelines define remission or achievement of lower disease activity as the treatment goal of DMARD therapy in patients with RA and recommend starting treatment as early as possible after the diagnosis is made (recommendations are DMP-relevant).

Treatment duration

Two guidelines provide recommendations on lifelong DMARD therapy and on regular evaluation to ensure continuous suppression of disease activity (recommendations are potentially DMP-relevant).

Treatment adaption

One guideline provides a recommendation on treatment adaption in the event of insufficient response to treatment (recommendation is potentially DMP-relevant).

4.4.4.2.2.1 Initial csDMARD therapy

A total of 8 guidelines provide recommendations on initial therapy with csDMARDs.

Monotherapy

One guideline provides a recommendation to use csDMARD monotherapy over dual or triple combination therapy in DMARD-naive patients with early RA and low disease activity. As initial therapy for DMARD-naive patients, one guideline generally recommends the use of csDMARDs independently of additional treatment with glucocorticoids (recommendations are potentially DMP-relevant).

Six guidelines recommend using csDMARDs as initial therapy in RA. In this context, methotrexate[3] is named as the treatment of first choice. In the event of contraindications or intolerance to methotrexate, 2 guidelines also alternatively recommend sulfasalazine or leflunomide as initial therapy; besides methotrexate, a further guideline also names sulfasalazine as treatment of choice (recommendations are DMP-relevant).

One guideline provides a recommendation to use csDMARD monotherapy over tumour necrosis factor (TNF)-α-antagonists in DMARD-naive patients with established RA and low disease activity (recommendation is potentially DMP-relevant).

Until initial (mono- or combination) therapy achieves an effect, 2 guidelines recommend additional glucocorticoids. However, depending on clinical symptoms, glucocorticoids should be tapered as rapidly as is feasible (recommendations are DMP-relevant).

[3] Not all methotrexate agents are approved for treatment of RA or only some pharmaceutical companies have an approval for all forms of administration for the therapeutic indication of RA (see, for example, [30-32]).

Combination therapy of several csDMARDs

Two guidelines recommend combination therapy[4] of csDMARDs if monotherapy is insufficient. In this context, one of the csDMARDs should be methotrexate[3], but only if no contraindications exist (recommendations are DMP-relevant).

Due to the increased toxicity compared with other combination therapies, one guideline recommends the cautious use of methotrexate[3] in combination with leflunomide (recommendation is potentially DMP-relevant).

In the event of combination therapy[4] in DMARD-naive patients (independently of glucocorticoid therapy), one guideline recommends the use of csDMARDs (recommendation is potentially DMP-relevant).

Four guidelines recommend favouring combination therapy[4] with csDMARDs in patients with insufficient response to initial therapy (monotherapy). In this context, one guideline also refers to the advantages of sequential monotherapy (recommendation is DMP-relevant).

4.4.4.2.2.2 Combination therapy of csDMARDs and bDMARDs

A total of 6 guidelines provide recommendations on combination therapy of csDMARDs and biologic DMARDs (bDMARDs).

In the event of an insufficient response to (mono- or combination) csDMARD therapy, 5 guidelines recommend a combination[4] of csDMARDs and bDMARDs. The decision that this treatment is indicated should be made by a rheumatologist. Two guidelines explicitly recommend the combination of methotrexate[3] and a biologic (recommendations are DMP-relevant).

One guideline recommends that patients with established RA who still show moderate or high disease activity under monotherapy with TNF-α antagonists should additionally receive at least one csDMARD (recommendation is potentially DMP-relevant).

4.4.4.2.2.3 bDMARD therapy

A total of 9 guidelines provide recommendations on bDMARD therapy.

One guideline provides a negative recommendation on treatment with TNF-α antagonists in patients with severe, active-inflammatory and established RA in patients who had not received prior treatment with methotrexate[3] or other csDMARDs (recommendation is potentially DMP-relevant).

[4] It must be evaluated in each individual case whether the drugs are also approved for the respective combination therapies mentioned in the guidelines. According to the information from a comment on the preliminary report, in Germany, for the combination with a bDMARD only methotrexate is approved.

To control disease activity, one guideline recommends treatment with intravenous (i.v.) tocilizumab in patients who have moderate to severe RA and cannot tolerate methotrexate[3]. In contrast, patients who do not respond sufficiently to methotrexate but do not show intolerance reactions should further be treated with methotrexate (recommendations are potentially DMP-relevant).

One guideline recommends treatment with TNF-α antagonists for DMARD-naive patients with high disease activity and the presence of unfavourable prognostic factors or for patients with insufficient response to csDMARD therapy (recommendations are potentially DMP-relevant).

In patients with early RA who, despite csDMARD monotherapy, still show moderate to high disease activity, one guideline recommends switching to a TNF-α antagonist or a non-TNF-α biologic (recommendation is potentially DMP-relevant).

Three guidelines recommend switching treatment from TNF-α antagonists to biologics with other modes of action or to other TNF-α antagonists if the first named are insufficiently effective or treatment has to be discontinued due to side effects (recommendations are DMP-relevant).

Two guidelines recommend the use of tofacitinib[5] in patients with RA if all treatment attempts with bDMARD have been exhausted and still no improvement is visible (recommendation is potentially DMP-relevant).

Two guidelines provide recommendations for treatment with rituximab[6]. Rituximab is recommended for patients with contraindications to TNF-α antagonists and for patients with high disease activity in whom treatment with one or more biologics was unsuccessful. One guideline refers to the particular effectiveness of rituximab in patients with positive RF or positive anti-CCP AB (recommendations are DMP-relevant).

4.4.4.2.2.4 Conduct / monitoring and safety aspects of DMARD therapy

A total of 11 guidelines provide recommendations on monitoring and on safety aspects of DMARD therapy.

csDMARDs

One guideline recommends the individual calculation of the methotrexate[3] dose for each patient. Methotrexate should be given orally or, if not tolerated, parenterally and increased relatively rapidly to the maximum dose of 25 mg per week (recommendations are potentially DMP-relevant).

[5] Tofacitinib is not approved in Germany for the therapeutic indication of RA [33,34].

[6] According to the summary of product characteristics, rituximab is only approved in Germany as i.v. administration for the therapeutic indication of RA [35].

Two guidelines recommend that due to its toxicity, DMARD therapy should be initiated and accompanied by a rheumatologist (recommendation is potentially DMP-relevant).

For patients with established RA who show low disease activity, one guideline recommends continuing csDMARD or bDMARD therapy (recommendations are potentially DMP-relevant).

For patients with established RA in remission, one guideline recommends not completely discontinuing DMARD therapy (recommendation is potentially DMP-relevant).

bDMARDs

Rituximab therapy

According to one guideline, the success of rituximab therapy[6] should be evaluated not earlier than 16 weeks following the start of treatment. Ideally, the evaluation should be performed after 24 weeks. If no improvement has been shown at this time, treatment should be discontinued (recommendation is potentially DMP-relevant).

4.4.4.2.3 Indication for treatment for specific disease constellations / comorbidities

A total of 4 guidelines provide recommendations on specific disease constellations and comorbidities.

Malignancies

Two guidelines recommend rituximab[6] therapy in patients with a history of lymphoproliferative malignancies. Alternatively, treatment with csDMARD combinations, abatacept or tocilizumab is primarily recommended instead of treatment with TNF-α antagonists (recommendations are potentially DMP-relevant).

One guideline notes that before treatment with TNF-α antagonists the patients should be informed that there is currently no indication of an increased tumour risk, but increased vigilance is nevertheless advisable (recommendation is potentially DMP-relevant).

Heart failure

Two guidelines provide recommendations on treatment with TNF-α antagonists in patients with heart failure. One of these guidelines explicitly advises against the use of TNF-α antagonists for patients with New York Heart Association (NYHA) stage III/IV. TNF-α antagonists should be used with caution in patients with NYHA stage I/II. The other guideline recommends primarily using csDMARDs, non-TNF-α antagonists or tofacitinib[5] instead of TNF-α antagonists in RA patients with heart failure (recommendations are potentially DMP-relevant).

Vaccinations

Three guidelines recommend that patients treated with TNF-α antagonists should receive a pneumococcal and influenza vaccination. One guideline further recommends a hepatitis B virus (HBV) vaccination (recommendations are potentially DMP-relevant).

Three guidelines recommend that patients treated with non-TNF-α biologics should receive a pneumococcal and influenza vaccination (in this context one guideline only addresses treatment with tocilizumab). One guideline further recommends an HBV vaccination (recommendations are potentially DMP-relevant).

Hepatitis

Two guidelines recommend that RA patients with a treated HBV infection should be treated just like those without such an infection (recommendation is potentially DMP-relevant).

Perioperative infections

One guideline recommends that patients with RA can continue treatment with methotrexate[3] despite planned surgery (recommendation is potentially DMP-relevant).

4.4.4.2.4 Symptomatic and anti-inflammatory therapy

A total of 7 guidelines provide recommendations on symptomatic and anti-inflammatory therapy.

Glucocorticoids

One guideline recommends always discussing the use of glucocorticoids with a rheumatologist and, when deciding on whether such treatment is indicated, to consider the risk profile and any comorbidities of the patients (recommendation is potentially DMP-relevant).

Five guidelines recommend using low-dose glucocorticoids in combination with DMARD as the initial treatment strategy for patients with RA (recommendation is DMP-relevant). Furthermore, 4 guidelines recommend using glucocorticoids until DMARDs are effective or for symptom control (recommendation is potentially DMP-relevant). According to one guideline, as soon as the patient's clinical state allows, glucocorticoids should be tapered (recommendation is potentially DMP-relevant).

Non-steroid anti-inflammatory drugs

Four guidelines recommend the use of non-steroid anti-inflammatory drugs (NSAIDs) or cyclooxygenase (COX)-2 inhibitors to treat pain and joint stiffness in patients with RA. The drug should be chosen depending on the respective risk profile and comorbidities of the patient. Patients should be informed about potential side effects (recommendations are potentially DMP-relevant).

Analgesics (pure analgesics)

In the event of insufficient control of pain, 2 guidelines recommend the use of analgesics. Different drugs are named by the respective guidelines in this regard. In this context, one guideline recommends the use of analgesics to prevent or shorten long-term treatment with NSAIDs or COX-2 inhibitors (recommendations are DMP-relevant).

Dietary supplements

For patients with RA, one guideline recommends diet supplementation with omega-3 fatty acids to alleviate pain and reduce joint stiffness (recommendation is potentially DMP-relevant).

4.4.4.3 Cardiovascular risk management in patients with rheumatoid arthritis

No DMP-relevant or potentially DMP-relevant recommendations were identified on this healthcare aspect.

4.4.5 Monitoring

A total of 8 guidelines provide recommendations on monitoring.

Disease activity

Six guidelines provide recommendations regarding at what intervals and in which disease stages disease activity should be determined. Disease activity should be determined every 1 to 3 months in patients with established RA and monthly in patients with early RA or moderate to strong disease activity. In well-adjusted patients or in patients in remission, monitoring can be performed at greater intervals (recommendations are potentially DMP-relevant).

Three guidelines recommend the Disease Activity Score (DAS)-28 instrument to record and document disease activity (recommendation is DMP-relevant).

4.4.6 Cooperation of healthcare sectors

A total of 8 guidelines provide recommendations on the cooperation of healthcare sectors.

Multidisciplinary treatment / DMP

Even though the recommendations of 4 guidelines on the involvement of a multidisciplinary therapy team are not DMP-relevant, 3 guidelines nevertheless provide detailed recommendations on professions that should be represented in such a team for the care of patients with RA, whereby only one guideline’s recommendation on physiotherapists is supported by a high LoE (recommendations are potentially DMP-relevant).

Nursing management of RA

One guideline provides recommendations on the management of patients with chronic-inflammatory joint diseases by specially trained nurses. The provision of continuous care by the same nurse for the whole duration of treatment is recommended. As a result, on the one

hand better communication, continuity, and treatment satisfaction should be achieved for the patients, while on the other, nursing staff should be involved in comprehensive disease management targeted towards controlling disease activity, reducing symptoms, and thus achieving the desired treatment goal. One guideline recommends delegating examinations and the monitoring of comprehensive disease management to nursing staff in order to control costs (recommendations are potentially DMP-relevant).

4.4.7 Patient training

A total of 5 guidelines provide recommendations on patient training.

Four guidelines recommend offering participation in training programmes to patients with RA or encouraging patients to participate in them. Two guidelines recommend tailoring the content of training to the individual patient and his or her needs. One guideline recommends a theory- and evidence-based patient training as individual or group training. Different contact strategies (personally, online or by phone) and ways of communicating information (information brochures or multimedia information services) are recommended in this context (recommendations are potentially DMP-relevant).

5 Classification of the work result

Healthcare aspects

The focus of the extracted guideline recommendations that are relevant or potentially relevant for a DMP “rheumatoid arthritis” is on drug therapy. Eight out of 18 of the guideline documents scrutinized focus exclusively on drug therapy of patients with RA. Only 4 guidelines address several healthcare aspects, including diagnostics, non-drug therapies and cross-sectional healthcare. It is noticeable that it must be concluded that the healthcare sector “rehabilitation” does not seem to be covered by the guideline recommendations extracted, even though RA is a disorder characterized by chronicity and imminent functional restrictions. This apparent imbalance is caused by the fact that on the one hand, interventions that are typically components of rehabilitation programmes (such as exercise therapy, occupational therapy, or dietary recommendations) are addressed by the guidelines as single measures under non-drug treatment procedures. On the other, recommendations on the range of treatments as they are typically offered in German rehabilitation facilities [36,37] are allocated to the healthcare aspect “multidisciplinary treatment/DMP”. However, it should be noted that the relevant and potentially relevant recommendations in this area do not reach the same degree of detail as the recommendations on drug therapy.

Guideline statements without recommendatory character

The guidelines provide different descriptions of the disorder of RA, which particularly differ in their completeness of content. In this context the different interpretation of the distinction between “early” and “established” RA used by some of the guidelines is particularly notable. In the whole report we therefore dispensed with a distinction according to “early” and “established” RA. Within the recommendations these terms nevertheless appear and, in cases of doubt, any ambiguities should be solved with the aid of the definition from the corresponding guideline document.

In addition, the guidelines name 2 different classification systems for RA: the traditional ACR criteria from 1987 [9] and the ACR/EULAR classification criteria from 2010 [6]. Whereas the older system is primarily suitable for classifying advanced disease stages and is still used by most of the guidelines cited here, the newer one can also be applied for early RA [36]. As the definitions and classification systems are not recommendations, in the synthesis they are not classified as relevant aspects for a DMP directive.

With its “good practice points”, the guideline of the Royal Australian College of General Practitioners (RACGP) provides additional information on recommendations without providing a GoR or LoE for them. This additional information is presented in the synthesis, insofar as it contains aspects not covered by recommendations from other guidelines supported by a GoR or LoE. For instance, in the area of diagnostics this applies to the interpretation of findings or in the area of drug therapy to dosages, contraindications, side effects, and advice on drug monitoring.

Imaging diagnostics

The guideline recommendations on imaging diagnostics (EULAR 2013 imaging) contain no or no potentially relevant information for a potential DMP. The lack of relevance for a DMP is due to the fact that a GoR is available in the form of the Strength of Recommendation (SoR) grading used by the EULAR guidelines, but that this GoR is not applicable to the NVL procedure. Therefore, the available but lower LoE were drawn upon here. However, as the X-ray findings of the affected joints (fingers, feet) are needed to use the traditional ACR classification (which for their part are the basis for the formulation of treatment recommendations in some guidelines), a discrepancy is noticeable between the non-applicable SoR and the low LoE, which should be further evaluated (e.g. by means of the primary literature).

Malignancies under TNF-α antagonists (DMARD therapy)

Several guidelines provide recommendations addressing the connection between treatment with TNF-α antagonists and the risk of developing a malignant tumour or the risk of exacerbation of an existing malignant tumour (ACR 2015, CRA 2012 safety, BSR 2010 antiTNF). Only 2 statements were made with high GoR and on the basis of an evidence base described as high quality by the guideline authors. One statement refers to the avoidance of TNF-α in patients with lymphoproliferative malignancies (ACR 2015). A further guideline notes that according to the current data no clear connection between tumour risk and treatment with TNF-α antagonists can be determined; however, patients and treating physicians are called on to show increased vigilance. Closer examination of the evidence base named in the guideline for this recommendation shows that, to support this statement, the results of a meta-analysis of 9 RCTs were discarded and instead, the results of 5 observational or registry studies were used (BSR 2010 antiTNF). All other statements on DMARD therapy (in particular with TNF-α antagonists) in patients with malignancies are not supported by high GoR and/or high LoE and thus do not lead to a (potentially) DMP-relevant classification. To clarify a connection between bDMARD therapy and an induction or worsening of malignant tumours it would potentially be meaningful to scrutinize primary data.

Applicability

In the implementation of recommendations on the use of methotrexate it should be considered that only individual pharmaceutical companies have approval for all methotrexate agents for the treatment of RA. This statement is relevant insofar as, besides being used as an immunosuppressive drug for inflammatory rheumatic diseases, methotrexate is also used as a cytostatic drug in cancer therapy. The doses used for cancer therapy are 400 to a 1000 times higher than those used in RA therapy (5000 mg per week vs. 5 to 25 mg per week) [30-32,38]. Rituximab is only approved for RA therapy for i.v. use [35].

The Janus kinase inhibitor tofacitinib, which is used as a bDMARD in patients with RA, is not approved in Germany for this therapeutic indication [39]. The treatment recommendations

designated as relevant or potentially relevant are thus currently not implementable in the German healthcare context.

Amendments on the basis of comments and the scientific debate

In the following text, aspects are addressed that are included in the guideline synopsis, but for which no DMP-relevance was inferred due to low GoR / LoE. Persons submitting comments evaluated the aspects mentioned here as aspects with a need for supplementation or modification with regard to DMP relevance and were in each case supported by literature citations. For the reasons mentioned above, these aspects were not considered in the assessment of DMP relevance, but due to their clinical relevance are described here for further evaluation by the G-BA.

Sports and exercises for patients with RA

Four guidelines provide guidelines on the item "sports and exercises". However, only one recommendation, which names the content and goals of physiotherapy, could be classified as potentially DMP-relevant. Due to low GoR and/or low LoE, all other recommendations on the topic are not DMP-relevant. However, one person submitting comments referred to 9 studies and reviews [40-48] suggesting that sport and exercise programmes reduce pain and fatigue syndromes and improve functionality and performance.

Administration and dosage of methotrexate

One of the guidelines included recommends increasing the methotrexate dose (oral or parenteral) relatively quickly until the usual maximum dose of 25 mg per week is reached. One person submitting comments referred to current study results showing that the threshold dose of bioavailability of methotrexate when administered orally is 15 mg per week [49] and noted that therefore, a dose increase beyond 15 mg only has an added value if the drug is administered parenterally.

Administration of tocilizumab

Furthermore, one guideline recommends i.v. administration of tocilizumab in patients with RA. Persons submitting comments noted that tocilizumab could also be applied subcutaneously. However, they failed to provide literature citations in this regard.

Co- and multimorbidity

With a low GoR and/or LoE, 2 guidelines recommend a routine examination with regard to the existence of latent tuberculosis before the start of treatment with TNF-α antagonists. This recommendation was classified as not DMP-relevant. However, one person submitting comments referred to the key role TNF-α plays in the formation of the granuloma that keeps the mycobacterial infection in the latent phase and thus prevents active tuberculosis [50].

With a low GoR and/or LoE, 2 guidelines provide recommendations on cardiovascular risk management in patients with RA. These recommendations were classified as not DMP-

relevant. However, one person submitting comments noted that cardiovascular diseases are among the most commonly occurring comorbidities [51-54].

With a missing GoR and LoE, one guideline recommends annual check-ups, including ophthalmological consultations. No DMP relevance could be determined for this recommendation. One person submitting comments referred to the high proportion of patients with RA (up to 25%) [55] with involvement of the eye and consequences for their vision [56]. Furthermore, the possibility of complications of the eye (retinal damage, glaucoma) in connection with chloroquine or low-dose glucocorticoids was pointed out [57,58].

Glucocorticoid injections

With a low GoR and/or LoE, 3 guidelines recommend intra-articular glucocorticoid injections for rapid symptom control. This recommendation was classified as not DMP-relevant. One person submitting comments referred to 2 studies [59,60] showing the positive short- and long-term effect of this treatment. Furthermore, it was noted that this type of injection was a fixed component in daily health care.

Instruments to measure disease activity

Three guidelines recommend using the DAS28 instrument within monitoring to measure disease activity. This represents a DMP-relevant recommendation. However, one person submitting comments noted that important organizations (ACR and EULAR) favour the application of the Clinical Disease Activity Index (CDAI) or a Boolean approach to measure disease activity [61], even though they do not explicitly recommend this in their guidelines.

6 Conclusion

On the basis of GoR or alternatively of LoE of extracted recommendations from current evidence-based guidelines, relevant and potentially relevant recommendations on all prespecified healthcare aspects were identified for a DMP “rheumatoid arthritis”, with the exception of the healthcare aspect of rehabilitation.

The recommendations identified on diagnostics refer to the physical examination or the measurement of general and specific inflammatory parameters in the blood.

A treat-to-target therapy is named for the planning of the individual treatment strategy. Remission and/or minimization of disease activity are named as treatment goals.

Recommendations on the design of physiotherapy, on occupational therapy, diet as well as on the use of orthoses were identified in the section “Non-drug therapy and general measures”.

Recommendations on the following subareas were identified for drug therapy:

- Recommendations across drugs for evaluation of the treatment goals “remission” and “reduction in disease activity”, as well as recommendations for regular monitoring of drug therapy.
- Recommendations on DMARDs: recommendations on the use of csDMARDs and bDMARDs are described. The recommendations refer to the selection of suitable drugs and drug combinations depending on disease duration, symptoms, previous treatment attempts, clinical response, and tolerance. Further recommendations refer to the conduct and monitoring of DMARD therapy.
- Recommendations for patients with RA and specific disease constellations or comorbidities.
- Recommendations on symptomatic and anti-inflammatory treatment with glucocorticoids, NSAIDs, COX-2 inhibitors, and analgesics as well as on treatment with dietary supplements.

The recommendations identified on the monitoring of disease activity refer to the measurement instrument to be used and the time intervals.

Furthermore, recommendations on the compilation of a multidisciplinary team and on nursing management of RA were identified for the healthcare aspect “cooperation of healthcare sectors”.

The recommendations on patient training refer to the content and design of training.

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Please see full final report for full reference list.

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