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REVISION

EULAR RECOMMENDATIONS FOR THE MANAGEMENT OF RHEUMATOID ARTHRITIS WITH SYNTHETIC AND BIOLOGICAL DISEASE-MODIFYING ANTIRHEUMATIC DRUGS: 2019 UPDATE

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Abstract

Objectives. To provide an update of the EULAR RA management recommendations to account for the most recent developments in the field.

Methods. An international task force considered new evidence supporting or contradicting previous recommendations and novel therapies and strategic insights based on two systematic literature searches on efficacy and safety of disease modifying antirheumatic drugs (DMARDs) since the last update (2016) until 2019,. A predefined voting process was applied, current levels of evidence and strengths of recommendation were assigned and participants ultimately voted independently on their level of agreement with each of the items.

Results. The task force agreed on 5 overarching principles and 12 recommendations concerning use of conventional synthetic (cs) DMARDs (methotrexate (MTX), leflunomide, sulfasalazine); glucocorticoids (GC); biological (b) DMARDs (tumour necrosis factor (TNF)-inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab), abatacept, rituximab, tocilizumab, sarilumab and biosimilar (bs) DMARDs) and targeted synthetic (ts) DMARDs (the Janus kinase (JAK) inhibitors tofacitinib, baricitinib, filgotinib, upadacitinib). There is guidance on monotherapy, combination therapy, treatment strategies (treat-to-target) and tapering upon sustained clinical remission. Cost and sequencing of b/tsDMARDs are addressed. Initially, MTX plus glucocorticoids and upon insufficient response within 3 to 6 months, stratification according to risk factors is recommended. With poor prognostic factors (presence of autoantibodies, high disease activity, early erosions, or failure of 2 csDMARDs), any bDMARD or JAK-inhibitor should be added to the csDMARD. If this fails, any other bDMARD (from another or the same class) or tsDMARD is recommended. Upon sustained remission, DMARDs may be tapered, but not be stopped. Levels of evidence and levels of agreement were mostly high.

Conclusions. These updated EULAR recommendations provide consensus on the management of RA with respect to benefit, safety, preferences and cost.

The European League Against Rheumatism (EULAR) developed its first recommendations for the management of rheumatoid arthritis (RA) with synthetic and biological disease modifying antirheumatic drugs (DMARDs) in 2010.[1] They summarized the state of the art and provided rheumatologists, patients, payers and other stakeholders with the evidence-based views of European experts on the optimal use and sequence of pharmaceutical therapies in patients with RA. Over the course of this decade, the development of new classification criteria for RA,[2] novel information on optimal clinical targets, such as the ACR-EULAR remission definitions,[3] evolution of treatment algorithms and strategies[4;5] and the advent of new drugs,[6;7] already necessitated two updates of the EULAR recommendations.[8;9] The American College of Rheumatology (ACR), The Asian-Pacific League of Associations for Rheumatology (APLAR) and the Pan-American League of Associations for Rheumatology (PANLAR) have published similar guidance documents, albeit using slightly different approaches.[10-12]

Today it is widely accepted that clinical remission is the main therapeutic target for RA patients, with low disease activity (LDA) as a best possible alternative, and that a treat-to-target (T2T) strategy should be applied when treating patients with RA.[1;9-11]

Although relevant data accrue rapidly, several of the recommendations, even in the 2016 update, were based on rather low levels of evidence and many have elicited intense debates because of variable interpretations of evidence and empirical approaches. Three years have passed since the last update.[9] Therefore, it was considered timely to again evaluate information regarding:

- newly licensed drugs;
- long-term efficacy and safety of long approved agents;
- comparative effectiveness studies;
- therapeutic targets; treatment strategies;
- and/or specific items of the 2016 research agenda that have been accomplished during these last few years of the present decade;
- consideration of safety aspects and costs.

The EULAR Executive Committee approved the proposal to update the recommendations. We wished to obtain global input and account for views from regions of the world beyond Europe and invited rheumatologists from Asia, Latin America and North America to contribute to the discussion and phrasing of the recommendations.

The major focus of the EULAR recommendations continues to be pharmacological therapy with DMARDs. The concept of “disease modification” comprises a combination of relief of signs and symptoms; improvement or normalization of physical function, quality of life and social and work

capacity, and most characteristically the inhibition of occurrence or progression of structural damage to cartilage and bone. The latter distinguished DMARDs from mere symptomatic agents, such as non-steroidal antirheumatic drugs (NSAIDs).

The increasing number of effective drugs and modes of action (MOA) has improved the likelihood of reaching the treatment target for individuals with RA, but high drug-costs still limit widespread use and thus contribute to inequity of access to best care across various regions and countries.[13-15] The approval and advent of biosimilar (bs) DMARDs has introduced price competition and led to a considerable reduction of the net costs of biological (b) DMARDs,[16] although this may not be true in all countries and may require further exploration. Nevertheless, access to optimal care is usually poor in low income countries, but even in some affluent countries payers still do not adhere to otherwise widely established standards of care.[17;18] Therefore, recommendations for the management of patients with RA have become increasingly useful in providing physicians, patients, health professionals, payers, regulators and others involved in health care with evidence-based guidance supported by the views of experts involved in generating these novel developments. Consequently, from their outset, EULAR recommendations always addressed cost aspects.[1] Indeed, in the recently updated EULAR standardized operating procedures on the development of recommendations, cost aspects have been included in addition to requiring the assessment of evidence on efficacy and safety as well as expert opinion.[19] This is in line with recommendations by the World Health Organization on rational treatment.[20]

Herein, we provide the 2019 update of the EULAR RA management recommendations.

Methods

After approval by the EULAR Executive Committee, the Convener (JS) and methodologist (RL) invited a Steering Committee and a Task Force to work on this update of the EULAR recommendations for the management of RA. The 2019 update followed the EULAR standardized operating procedures (SOPs) for the development of recommendations[19] which also suggest adherence to the Appraisal of Guidelines for Research & Evaluation (AGREE) recommendations in their updated version (AGREE II).[21]

Steering Committee

The Steering Committee included eight rheumatologists (JB, GB, MD, RL, IM, JS, RvV, DvdH), one patient representative (MdW) and two fellows (AK, AS) who performed the systematic literature

research (SLR). This group initially developed the respective research questions. The SLRs focused on (i) efficacy of DMARDs (as monotherapy or combination therapy, including conventional synthetic [cs] DMARDs, bDMARDs and targeted synthetic [ts] DMARDs), glucocorticoids and treatment strategies; and (ii) safety of DMARDs and glucocorticoids. To this end, the SLRs obtained in 2016[22-24] served as a starting point and a systematic analysis of the literature published between 2016 and March 8th, 2019 was performed. New information on treatment strategies was also evaluated. In contrast to the previous safety SLR which focused on registry data, the current safety SLR also addressed data from randomized controlled trials and extension studies, since for many new agents registry data are still limited. Formal economic analyses were not performed, but cost aspects were considered throughout the process in line with the current state of the art of developing recommendations.[20;25] The two rheumatology fellows exploited existing publication databases on randomized controlled trials for efficacy and safety, and also evaluated recent EULAR and ACR congress abstracts. Summary-of-Findings (SOF) tables were generated, a thorough Risk-of-Bias (RoB) assessment was performed (for details see the publications on these SLRs[26;27]) and levels of evidence (LoE) and strengths of recommendation (SoR) were determined with the standards of the Oxford Centre for Evidence Based Medicine.[28] The two SLRs informing the Task Force and a detailed description of their methods are published separately.[26;27] Of note, in the present publication we also use references from the 2019 Annual European Congress held in June 2019 where it deemed appropriate, or publications that appeared after the deadline of the SLRs, March 8, 2019, when the contents had previously been covered by abstracts addressed in the SLRs, or otherwise newly published information regarding efficacy and especially safety that deemed important to be included as up-to-date information for the readers at the time of submission.

The Steering Committee discussed the results of the SLRs thoroughly and formulated proposals for an update of the recommendations based on this information. The SLR data and the suggestions of the Steering Committee were presented to the whole Task Force for further discussion, development of the updated recommendations and voting.

Task Force

The Task Force consisted of 47 individuals, including the Steering Committee members. Among the Task Force members were 3 patients, 2 health professionals and 2 delegates of the EULAR young rheumatologists' network EMEUNET. The rheumatologists were all experienced in the treatment of RA and most had previously participated in clinical trials; moreover, several of them were involved in the analysis of data from their countries' patient registries or in various aspects of outcomes research. The patients and health professionals all had a track record of participating in consensus

finding activities, like most of the rheumatologists. Since we also wished the Task Force's work to be informed by rheumatologists from other regions of the world, aside from a broad representation from 15 European countries, two rheumatologists from Asia, two from Latin America and two from North America participated; most had actively participated in developing documents of their regional leagues and/or national societies. All Task Force members disclosed their potential conflicts of interest to the EULAR Executive Committee before the start of the process.

Consensus Finding

A few principal considerations were specified upfront. Firstly, the previous 2016 version of the recommendations (containing 4 overarching principles and 12 recommendations) were key considerations,[9] but were all open to amendment, changes in ordering or deletion where appropriate. Secondly, it was decided that existing recommendations should be discussed in the context of new evidence. If new evidence contradicting a previous recommendation was lacking, the former evidence-base had to be accepted and the recommendation had to be kept unchanged. This approach prevents the intentional or unintentional neglect of previous formal task force decisions, which had been based on a thorough discussion of existing evidence presented at that time, recalibrated and sometimes amended at update-procedures; also, they have always been endorsed by voting among the previous task force members followed by EULAR's executive committee approval. Thirdly, drugs not (yet) approved in Europe but used elsewhere in the world, and unapproved drugs with evidence from phase 3 clinical trials could be considered in the recommendations to allow for some anticipation of a potential future uptake in clinical practice, appreciating all respective caveats. Importantly, drugs can only legally be prescribed after their regulatory approval. Also, whereas the recommendations address some safety aspects, the readers are referred to the summaries of product characteristics (SPCs) for more detailed safety information for each of the drugs. Fourth, registry data were primarily used for assessment of rare safety issues but not efficacy, since the outcomes of patients included in registries are often confounded by indication.

After the presentation of the SLR results and the Steering Committee's proposals for the amendment of the recommendations, the Task Force was divided into 3 breakout groups. One group reviewed new evidence related to treatment strategies and targets, focusing also on the overarching principles; the second group addressed new evidence regarding bDMARDs and tsDMARDs; and the third group dealt with new evidence in relation to the use of csDMARDs (monotherapy or in

combinations) and glucocorticoids. Respective safety aspects were addressed in each of these breakout groups.

After representatives of each breakout group had reported the results of the respective discussions and presented proposals for the wording of individual recommendations to the whole Task Force for further deliberations, voting took place.

For a change of an existing overarching principle or recommendation to be accepted for the final document, a majority of ≥75% of the votes was required. Once such change was accepted, wording details could undergo further voting. A new recommendation was immediately accepted when ≥75% or more of the task force members voted for it. If this result was not achieved, the respective text was amended and subjected to a second ballot, for which a 67% majority was required. If this ballot was not successful, the text was further amended and subjected to a 3rd ballot for which a simple (>50%) was required; failing that, the proposal was rejected. For new or amended items the results of the respective last ballot are shown as percentage of voting members. Notes captured the contents of the discussions and the reasoning behind each decision and these are presented in the comments accompanying the individual items. At every point in time more than 90% of the members participated in the ballots; the percentages shown always relate to percent of present participants in that vote.

After the face-to-face meeting, each recommendations, as agreed by the Task Force, received the appropriate level of evidence and strength of recommendation based on the SLRs. With this information added, the recommendations were subjected to an anonymous electronic assessment (by e-mail) on the levels of agreement (LoA). Each recommendation received an assessment on a scale of 0-10 with 0 meaning no agreement whatsoever and 10 full agreement; the mean values of these votes are presented.

The draft of the manuscript was sent to all Task Force members for their comments. After incorporation of these comments the manuscript was submitted to the EULAR Executive Committee for review and approval. The comments obtained from the Executive Committee were also addressed, and the final version of the manuscript was then submitted to the Journal for peer review.

Results

The 2019 update of the EULAR RA management recommendations reflects the balance of clinical, functional and structural efficacy, safety, costs and patients' perceptions as evaluated by the Task Force. Drug-toxicity was discussed and considered, but the respective data are presented primarily in the Safety SLR,[26] because it is assumed that prescribers should be aware of the safety information provided in the SPCs of the various agents. EULAR has developed a series of documents addressing safety of drugs used for the treatment of RA,[29-35] and various other publications have focused on these aspects.[36-42] In particular, as suggested by the safety SLR, the major risk of bDMARDs and tsDMARDs is related to infections. Recommendations for vaccination[33] as well as a score allowing calculation of the risk of infection in patients exposed to bDMARDs have been developed.[41;43;44] Nevertheless, when toxicity constitutes a major or unexpected problem, a specific warning is provided in this document. Of note, the two SLRs[26;27] as well as the text accompanying each item should be regarded as part and parcel of these recommendations, since the individual bullet points represent only abbreviated versions of the discussions and conclusions.

When classifying DMARDs, the Task Force adhered to the previously used nomenclature[8;45] as shown in Table 1. This Table also provides a glossary of terms employed in the present document. The Task Force did not distinguish between early and established RA but rather between three phases of the treatment process by differentiating between patients who are naïve to any DMARD therapy (phase I), patients who had an insufficient response (IR) to initial course(s) of csDMARDs (phase II) and those who had an IR to bDMARDs (phase III). There is currently no evidence for differential responses solely based on disease duration, apart from differences in baseline damage due to delayed treatment initiation and consequent risk of damage progression. The Task Force also took prognostic factors (Table 1) into account, which have similar predictive power irrespective of disease duration.[46;47] Of note, recommendations for the management of early arthritis, including undifferentiated arthritis, have been updated recently.[48] The present recommendations do not address the management of patients with undifferentiated arthritis or arthralgia in patients who may be at risk of developing RA, but only patients with RA from the time of diagnosis.

Overarching principles

As before, the Task Force reinforced the necessity to adhere to some general principles when treating patients with RA, the so-called overarching principles (Table 2). These principles constitute the foundation upon which the actual recommendations are based. By their common-sense nature, they cannot be based on specific scientific evidence. Until 2013, there were 3 overarching principles;

Table 1. Glossary and definitions (after[9])

Term	Definition	
Poor prognostic factors	• Persistently moderate or high disease activity (after csDMARD therapy) according to composite measures including joint counts despite csDMARD therapy • High acute phase reactant levels • High swollen joint count • Presence of RF and/or ACPA, especially at high levels • Presence of early erosions • Failure of 2 or more csDMARDs	
Low dose glucocorticoids	• ≤7.5mg/day (prednisone equivalent)	
Tapering	• Reduction of drug dose or increase of application interval • May include cessation (tapering to 0), but then only after slow reduction	
Cessation, stopping	Stopping of a particular drug	
Disease activity states		
Remission	ACR-EULAR remission definition (Boolean or index-based)	
Low disease activity	Low disease activity state according to any of the validated composite disease activity measures that include joint counts	
Moderate, high disease activity	Respective disease activity state according to any of the validated composite disease activity measures that include joint counts	
DMARD nomenclature		
Synthetic DMARDs (sDMARDs)	• Conventional synthetic DMARDs (csDMARDs)	E.g. methotrexate, leflunomide, sulfasalazine, hydroxychloroquine
	• Targeted synthetic DMARDs (tsDMARDs)	E.g. baricitinib, tofacitinib
Biological DMARDs (bDMARDs	• Biological originator DMARDs (boDMARDs)	TNFi: adalimumab, certolizumab, etanercept, golimumab, infliximab; IL-6Ri: sarilumab, tocilizumab; Co-stimulation-i: abatacept; anti-B-cell (CD20): rituximab
	• Biosimilar DMARDs (bsDMARDs), currently for: adalimumab, etanercept, infliximab, rituximab.	

ACPA, anti-citrullinated protein antibody; ACR, American College of Rheumatology; DMARDs, disease-modifying antirheumatic drugs; EULAR, European League Against Rheumatism; RF, rheumatoid factor.

in 2016, the Task Force added a 4th one as overarching principle B. Now yet another item appeared necessary as overarching principle D, resulting in 5 overarching principles for the 2019 update (Table 2).

A. *Treatment of RA patients should aim at the best care and must be based on a shared decision between the patient and the rheumatologist.* This principle remained unchanged in wording and placement. During discussion, the importance of shared decision making was reiterated and the importance of patient education emphasized. Indeed, patient education may increase adherence to medication;[49] moreover, education of rheumatologists may foster adherence to appropriate assessment strategies.[50] There were suggestions made to expand this item by mentioning the importance of patient education separately, but there was ultimate agreement that patient education forms the implicit and inseparable basis for shared decision making. Nevertheless, since shared decision making is so important, communication skills should also be a focus of rheumatologists and other health professionals. This item is also included in a publication on quality indicators that should be incorporated in the decision process.[51] It should also be noted that the focus of the task force was on DMARDs and not on other pharmacological and non-pharmacological therapies which may have to be considered in many patients as adjunctive therapies for best care. The task force agreed at a level of 9.7 (SD 1.1) with this principle.

B. *Treatment decisions are based on disease activity, safety issues and other patient factors, such as comorbidities and progression of structural damage.* Added in 2016 and remaining unchanged, this principle is particularly important when considering the use of bDMARDs and tsDMARDs. The higher risk of Herpes Zoster infections, more pronounced in some Asian countries such as Japan and South Korea, is captured under this principle. The prevalent discussion on the risk of venous thrombo-embolic events (VTEs), such as in relation to obesity or a history of prior VTE events, has also been addressed.[52;53] To this end, there was a debate about whether the term "risk" should be more explicitly added to this overarching principle, but it was then agreed that the terms "comorbidities and safety issues" inherently include risk assessment, and obesity, for example, also constitutes a comorbidity. It was decided to mention these deliberations in the explanatory text and leave the principle unchanged. *LoA 9.8 (0.5).*

C. *Rheumatologists are the specialists who should primarily care for RA patients.* Unchanged from previous recommendations, this principle addresses the importance of specialty care

Table 2. The 2019 updated EULAR RA management recommendations

	Overarching Principles	LoE	SoR	LoA
A	Treatment of RA patients should aim at the best care and must be based on a shared decision between the patient and the rheumatologist.	n.a.	n.a.	9.7
B	Treatment decisions are based on disease activity, safety issues and other patient factors, such as comorbidities and progression of structural damage.	n.a.	n.a.	9.8
C	Rheumatologists are the specialists who should primarily care for RA patients.	n.a.	n.a.	9.9
D	Patients require access to multiple drugs with different modes of action to address the heterogeneity of RA; they may require multiple successive therapies throughout life.	n.a.	n.a.	9.9
E	RA incurs high individual, medical and societal costs, all of which should be considered in its management by the treating rheumatologist.	n.a.	n.a.	9.4
	Recommendations			
1.	Therapy with DMARDs should be started as soon as the diagnosis of RA is made.	1a	A	9.8
2.	Treatment should be aimed at reaching a target of sustained remission or low disease activity in every patient.[1]	1a	A	9.7
3.	Monitoring should be frequent in active disease (every 1–3 months); if there is no improvement by at most 3 months after the start of treatment or the target has not been reached by 6 months, therapy should be adjusted.	2b	B	9.3
4.	MTX should be part of the first treatment strategy.	1a	A	9.4
5.	In patients with a contraindication to MTX (or early intolerance), leflunomide or sulfasalazine should be considered as part of the (first) treatment strategy.	1a	A	9-0
6.	Short term glucocorticoids should be considered when initiating or changing csDMARDs, in different dose regimens and routes of administration, but should be tapered as rapidly as clinically feasible.	1a	A	8.9
7.	If the treatment target is not achieved with the first csDMARD strategy, in the absence of poor prognostic factors[1], other csDMARDs should be considered.	5	D	8.4
8.	If the treatment target is not achieved with the first csDMARD strategy, when and poor prognostic factors[1] are present, a bDMARD[2] or a tsDMARD[3] should be added.	1a	A	9.3
9.	bDMARDs and tsDMARDs should be combined with a csDMARD; in patients who cannot use csDMARDs as comedication, IL-6 pathway inhibitors and tsDMARDs may have some advantages compared to other bDMARDs.	1a	A	8.9
10.	If a bDMARD* or tsDMARD[#] has failed, treatment with another bDMARD[2] or a tsDMARD[3] should be considered; if one TNF inhibitor therapy has failed, patients may receive an agent with another mode of action or a second TNF inhibitor.	*1b #5	A D	8.9
11.	If a patient is in persistent remission after having tapered glucocorticoids, one can consider tapering bDMARDs or	1b	A	9.2

	tsDMARDs, especially if this treatment is combined with a csDMARD.			
12.	If a patient is in persistent remission, tapering the csDMARD could be considered.	2b	B	9.0

Abbreviations: boDMARDs, biological originator DMARDs; bsDMARD, biosimilar DMARDs; csDMARDs, conventional synthetic DMARDs; DMARDs, disease-modifying antirheumatic drugs; EULAR, European League Against Rheumatism; Jak, Janus kinase; MTX, methotrexate; RA, rheumatoid arthritis; TNF, tumour necrosis factor; tsDMARDs, targeted synthetic DMARDs (currently Janus kinase inhibitors).
[1]For definitions of remission, low disease activity and poor prognostic factors, see Table 1.
[2]Abatacept, rituximab, sarilumab, tocilizumab, and TNF-inhibitors: adalimumab, certolizumab pegol, etanercept, golimumb, infliximab (whether boDMARDs or EMA-approved/FDA-approved bsDMARDs).
[3]Janus kinase inhibitors

for a complex disease like RA,[54-58] since rheumatologists possess the optimal depth and breadth of experience regarding the use of all types of DMARDs, including efficacy outcomes, risk assessment and knowledge of comorbidities (as discussed under item B). Importantly, health professionals such as rheumatology nurse specialists also take care of many aspects related to the management of RA and patient education. The rheumatologist often leads a multidisciplinary team in the course of providing "best care" in accordance with item A. On the other hand, in certain areas of the world Rheumatology training is not sufficiently available and other experts may care for RA patients, hence the term "primarily". Moreover, some comorbidities, such as chronic hepatitis, interstitial lung disease or cardiovascular events, may require consultation with, and treatment by, other specialists. Together with item D, this principle achieved the highest *LoA 9.9 (0.4).*

D. *Patients require access to multiple drugs with different modes of action to address the heterogeneity of RA; they may require multiple successive therapies throughout life.*
Developing this new overarching principle was considered necessary and timely, in view of the increasing number of drugs available to treat RA. We now recognize 5 molecular target families (TNF, IL-6, CD80/86, CD20 and Janus kinases) with multiple drugs for several of these molcules. Treating towards a target of remission or low disease activity (see recommendations 2 and 3) potentially requires switching between drugs (cycling), sometimes even as early as every 3 months if improvement in accordance with strategic principles (see recommendations 2 and 3) is not sufficient. Moreover, it is well established that after failure of one drug, a different drug belonging to the same class, i.e. targeting the

same molecule, can still be efficacious. Therefore, patients, rheumatologists and payers must be aware that multiple successive drug options are often needed to reach the therapeutic goal. This does not necessarily incur extra cost, since continuing a (partially) failing DMARD can be as costly as switching to another DMARD. This item addresses an additional important characteristic: RA is a life-long disease whose cause is unknown and which – like many other chronic disorders – cannot currently be cured in most patients, but can be brought into remission or at least low disease activity in the vast majority of patients with appropriate treatment adaptations using the whole spectrum of therapies available to us today. Thus, remission on drug is the best we can usually achieve, with subsequent dose reduction representing a viable option. While the approach to taper medication is addressed in recommendations 11 and 12, patients, rheumatologists, payers and society must realize that many patients will not be able to stop therapy and may require lifelong treatment. Up to 50% of patients starting a new DMARD must stop it within 12 to 18 months for insufficient efficacy or adverse events.[59;60] Indeed, many patients still do not reach the therapeutic targets, despite all of our modern therapies and therapeutic strategies, but still about 10-20% of patients who fail multiple drugs have a good treatment response to yet another agent.[61] The major weakness of our current treatment approaches is the lack of biomarkers for immediate stratification of an individual patient to the most appropriate drug. Importantly, these considerations emphasize the need to search for predictive markers; however, since a considerable number of patients (about 20-30%) are refractory to all current treatment options, new therapies also need to be developed. Among the task force members, 100% agreed to add this principle and to its wording and placement. *LoA 9.9 (0.4).*

E. *RA incurs high individual, medical and societal costs, all of which should be considered in its management by the treating rheumatologist.* This (unchanged) principle reminds all stakeholders of an important balance. On the one hand, effective RA therapy can reduce the economic burden on individual patients, their families and society. This economic burden not only includes direct medical costs, but also indirect costs due to sick leave, work disability and premature retirement. On the other hand, the high price of many current drugs causes a net increase in the economic burden to society. So when making therapeutic decisions, drugs that are less costly must be preferred over more costly ones, as long as they are similarly efficacious and safe and in line with the therapeutic paradigms.[20] As mentioned in the introduction, in many countries, the high costs of treatment limit the availability of modern therapies (inequity),[14] the availability of biosimilars can address this and provide significant reductions of health care budgets, when their price is sufficiently low and their application is

then reinforced by payers or politicians.[16;62] The task force voted unanimously to place this item as the last overarching principle, without a change in wording. *LoA 9.4 (1.4).*

Individual recommendations

General aspects

The Task Force's discussions resulted in 12 recommendations. The first 7 recommendations as well as recommendations 9 and 12 remain unchanged. The background and evidence for these items have been presented previously, and in this respect the reader is referred to the 2016 update.[9] Each was briefly or more extensively discussed. This was not the case for the aforementioned 9 unchanged items. Note that the evidence-base was carried forward from last time (or when new data were available adapted accordingly) and that all items whether changed or unchanged underwent a new assessment for the LoA.

As before, the recommendations are ordered in a way that allows their sequential use, and the respective algorithm is depicted in Figure 1. The recommendations start with the approach to patients with newly diagnosed RA, then address both specific drugs and treatment strategies for these patients as well as those who already failed specific therapies, and end with proposals for tapering therapy under appropriate preconditions.

1. *Therapy with DMARDs should be started as soon as the diagnosis of RA is made.* This unchanged item represents the basic principle of RA treatment that initiation of DMARD therapy should be immediate, since the disease will not remit spontaneously. *LoE 1a, SoR A, LoA 9.8 (0.6)*.

2. *Treatment should be aimed at reaching a target of sustained remission or low disease activity in every patient.* (Unchanged.) This is a central theme in the care of patients with RA, and in line with the treat-to-target recommendations by an international task force.[5] The instruments that should be used to define remission or low disease activity were not any more discussed (Table 1) and the reader is referred to the treat-to-target recommendations and previous deliberations.[3;5;9] Indeed, ACR and EULAR have agreed on the Boolean- and index-based remission definitions (the latter using the simplified or clinical disease activity index, SDAI/CDAI).[3] As set forth as principle A, the treatment target has to be agreed in a process of shared decision making. *LoE 1a, SoR A, LoA 9.7 (0.6).*

3. *Monitoring should be frequent in active disease (every 1-3 months); if there is no improvement by at most 3 months after the start of treatment or the target has not been reached by 6 months, therapy should be adjusted.* (Unchanged.) One should consider the desired treatment target as well as various patient factors, including comorbidities, when making treatment adaptations. A rapid attainment of the selected target endpoint is now regarded as being of critical importance: while direct evidence for the question of the best time point for decision making regarding change of therapy is still lacking, it is known thatif disease activity fails to improve by at least 50% within 3 months, the probability of reaching the treatment goal of remission (or low disease activity) is low.[63;64] Also, the decision to use specific instruments should take into account the direct effects of IL-6 and Janus kinase inhibitors on the production of acute phase reactants (potentially independent of clinical improvements, but more reflecting pharmacodynamic effects).[65;66] This recommendation remained unchanged. *LoE 2b, SoR B, LoA 9.3 (0.8).*

4. *Methotrexate should be part of the first treatment strategy.* (Unchanged.) MTX remains the anchor drug in RA; not only is it an efficacious csDMARD by itself, but it is also the basis for combination therapies, either with glucocorticoids or with other csDMARDs, bDMARDs or tsDMARDs. It is important to reiterate that MTX (whether administered orally or subcutaneously) should be escalated to a weekly dose of 0.3mg/kg[67] and that this escalation should be done within 4-6 weeks. In the Western hemisphere, the optimal therapeutic dose will be around 20-25mg[68] per week, while in Asia – in line with a lower body weight and possibly different pharmacogenetics in the East Asian population – the maximum dose will be lower, such as 16mg in Japan.[69] The importance of folic acid supplementation is another central aspect of MTX therapy. Patients often associate MTX with a variety of adverse events that are primarily related to its use as medication for malignancies at high doses; therefore, in the course of the shared decision-making process patient education and information, including addressing fears of potential side effects, is as important for this “old” drug as it is for novel agents.

   As in the past, there were some discussions whether the first treatment strategy should already potentially include a bDMARD or tsDMARD, but this was not further pursued since no new evidence has been seen suggesting that the current approach – especially considering recommendation 6 – should be changed. Indeed, no bDMARD plus MTX has yet shown superiority compared with MTX plus glucocorticoids in MTX-naïve patients,[70;71] and tsDMARDs have not yet been compared to MTX plus glucocorticoids as starting therapy.

Moreover, there is no longer-term disadvantage taking this approach, since initiation of MTX in early RA patients and subsequent addition of a TNF-inhibitor (TNFi) at 6 months in case of an insufficient response confers similar overall results as using the combination of MTX and a TNFi from the start, with many patients having already achieved the therapeutic target without the use of a bDMARD.[72] Thus, this decision was based on both economic considerations and on the evidence base regarding efficacy and safety of different initial therapeutic approaches in patients with early RA. *LoE 1a, SoR A, LoA 9.4 (1.2).*

5. *In patients with a contraindication to MTX (or early intolerance), leflunomide or sulfasalazine should be considered as part of the (first) treatment strategy.* (Unchanged.)There was a brief discussion whether a direct step to a bDMARD or tsDMARD should be considered if MTX was contraindicated, but no evidence comparing any of these agents in monotherapy with leflunomide or sulfasalazine in combination with glucocorticoids is currently available. It was also suggested that antimalarials should be added to this recommendation. Indeed, as discussed in previous documents, antimalarials and especially hydroxychloroquine, have a limited place, mainly reserved for patients with mild RA. As no new evidence regarding a good efficacy of hydroxychloroquine was found for RA in general and the historic studies had shown only weak clinical and no structural efficacy,[73] it was decided to keep the focus on sulfasalazine and leflunomide. In some countries, especially in Asia, also other agents like bucillamine or iguratimode have been approved for RA, but these drugs were not considered here given insufficient data in other regions. *LoE 1a, SoR A, LoA 9.0 (1.2).*

6. *Short term glucocorticoids should be considered when initiating or changing csDMARDs, in different dose regimens and routes of administration, but should be tapered as rapidly as clinically feasible.* (Unchanged.)There was much less discussion on the use of glucocorticoids than ever before in the history of these recommendations, and there was unanimity that they should primarily be used as bridging therapy until csDMARDs exhibit their efficacy and that tapering glucocorticoids rapidly (aiming at discontinuation within about 3 months) is important. Failure to sustain the treatment target upon tapering or withdrawal of glucocorticoids after the bridging phase should be regarded as failure of this therapeutic phase and thus elicit the institution of a bDMARD or a tsDMARD added to the csDMARD. Regarding the debate over whether treatment with bDMARDs or tsDMARDs should be preferred to csDMARDs plus glucocorticoids, at least 3 trials have shown similar responses when MTX plus GC was compared with MTX plus bDMARDs[70;71;74] and no new data conflicting

with this view have been published since then; tsDMARDs have not yet been compared to MTX plus glucocortiocids. *LoE 1a, SoR A, LoA 8.9 (1.3).*

7. *If the treatment target is not achieved with the first csDMARD strategy, in the absence of poor prognostic factors, other csDMARDs should be considered.* (Unchanged.) Poor prognostic factors were defined many years ago and are shown in Table 1. They include high disease activity, presence of erosions and autoantibody-positivity at high titers, but also failure to achieve low disease activity after the application of at least two csDMARDs. It was suggested that failure of an initial treatment with MTX plus GC was also included in this list; however, this proposal did not find sufficient backing by the task force. Since the addition of glucocorticoids both to a first csDMARD and to a subsequent csDMARD therapy is highly recommended (see #6: "or changing csDMARDs"), consideration of "other csDMARDs" here means either switching to, or addition of another csDMARD. As detailed in 2016, combinations of csDMARDs are not regarded as superior to MTX monotherapy by the task force, especially if MTX is combined with glucocorticoids.[75] One study (CareRA) evaluated early RA patients with high and low risk and showed that a milder intervention (MTX compared with MTX+glucocorticoids) also resulted in similar outcomes,[75] but there are no studies available that have evaluated such a strategy in patients who have failed MTX. On the other hand, it is known that patients who fail MTX often do respond to a subsequent csDMARD course.[76] *LoE 5, SoR D, LoA 8.4 (1.6).*

8. *If the treatment target is not achieved with the first csDMARD strategy and poor prognostic factors are present, a bDMARD or a tsDMARD should be added.* In 2016, this recommendation read as follows: "If the treatment target is not achieved with the first csDMARD strategy, when poor prognostic factors (Table 1) are present, addition of a bDMARD or a tsDMARD should be considered; current practice would be to start a bDMARD." In previous years the SLRs have revealed evidence of similar efficacy among the bDMARDs,[23] and this obviously includes biosimilars approved by EMA or FDA.[27] Thus, there are two major changes in the 2019 update. First, the task force revised the preference of bDMARDs over tsDMARDs because of new evidence regarding the successful long-term efficacy and safety of JAK inhibitors.[77-79] Second, it recommended that a bDMARD should be "added" rather than "considered". Regarding the first change, the task force also agreed that bDMARDs and tsDMARDs have on average similar efficacy and, therefore, no preference can be given to any of these agents for reasons of efficacy. While two studies designed as non-inferiority trials have shown statistical superiority of baricitinib or upadacitinib compared

with adalimumab (all in combination with MTX),[80;81] a third study using tofacitinib+MTX did not show similar superiority;[82] thus, the overall clinical relevance of small differences in clinical trials was not considered convincing enough for the task force to prefer tsDMARDs over bDMARDs. This conclusion is further supported by recently presented data revealing that filgotinib+MTX met non-inferiority for DAS28<3.2, but not superiority criteria, when compared with adalimumab, a pre-specified endpoint, although superiority was observed for some of the secondary endpoints.[83] Importantly, in these studies various inflammatory markers, such as swollen joint counts, did not differ among the groups, in line with the hitherto unknown clinical relevance mentioned above.

A third JAK inhibitor, peficitinib, has meanwhile been approved in Japan where clinical trials revealed significant efficacy;[84;85] in a global study efficacy was not similarly apparent possibly due to high placebo effects.[86]

A fourth JAK inhibitor, upadacitinib, has undergone testing in phase 3 trials in different RA populations as combination and monotherapy,[27] adding to the documented efficacy of this class of drugs; upadacitinib has meanwhile been approved at 15mg daily by the Food and Drug Administration of the USA with a variety of warnings added to the prescribing information, including a warning that thromboses have occurred in patients treated with JAK inhibitors;[87] also EMA has given a positive opinion on upadacitinib.

For a fifth JAK inhibitor, filgotinib, publication of further phase 3 trial results is awaited and the drug is currently undergoing regulatory evaluation.

With respect to safety, beyond what was known to the last task force, such as an increased risk of Herpes Zoster infections, and further corroborated in the course of the current safety SLR,[26] a new safety issue, namely thromboembolic events including pulmonary embolism, has emerged for both baricitinib (4mg daily)[88] and tofacitinib (at both 5mg and especially 10mg bid particularly in patients with risks of thromboembolic events and higher age)[89] These latter data are derived from an interim analysis of study A3921133 (NCT02092467), an ongoing study that compares tofacitinib at 5 and 10 mg twice daily with TNF inhibition regarding major cardiovascular events and malignancy in patients with rheumatoid arthritis and at least one cardiovascular risk factor.[90] Thromboembolic events have also been observed with upadacitinib.[91;92] They are seen especially in patients with a high risk for these events (see safety SLR), auch as those with a past history of thromboembolic events, those with high body mass index, those with hormone replacement therapy and higher age.[88;93] Therefore, JAK- inhibitors should be used with caution in patients with high risk of TE events. Moreover, currently information regarding this risk is not yet final and further accruing, and

it is not understood which mechanisms may drive this risk; this should become a major target of research.

Thus, the decision which drug to prescribe when a patient has failed to reach the treatment target with the first therapeutic strategy and has unfavourable prognostic markers should be based on an aggregate of contraindications, patient preference and costs.

The second change that a bDMARD or tsDMARD should be "added" rather than "considered" constitutes a stronger support for combination therapy (item 9) than before.

No new studies on the efficacy of csDMARDs after prior failure of MTX (or other csDMARDs) have been performed since the last update, but during the discussions of the last update sufficient evidence was found showing that the benefit of this approach is limited and progression of damage may accrue.[94;95] Given that the costs of bDMARD and tsDMARD have decreased in many countries since the advent of biosimilars, the task force members felt that this recommendation should be reinforced. Some participants suggested applying a similar recommendation even for patients who do not exhibit poor prognostic factors (item 7), but this suggestion did not find sufficient resonance in the task force. On the other hand, although this question was part of the research agenda for many years, no study has directly compared the benefit that exists when MTX-IR patients with or without poor prognostic factors receive add-on bDMARDs or tsDMARDs compared with add-on csDMARDs; this continues to be part of the research agenda. The new wording was approved by 95% of the participants. *LoE for general efficacy: 1a (regarding its primary use in patients with poor prognostic factors: 5), SoR A (D), LoA 9.3 (1.0).*

9. *bDMARDs and tsDMARDs should be combined with a csDMARD; in patients who cannot use csDMARDs as co-medication, IL-6 pathway inhibitors and tsDMARDs may have some advantages compared to other bDMARDs.* (Unchanged.) The task force reiterated that – in contrast to clinical practice where up to 40% of patients are on bDMARD monotherapy – combination therapy is advantageous with respect to efficacy compared to monotherapy for all bDMARDs and tsDMARDs and with respect to immunogenicity for allbDMARDs. When MTX is part of such combination therapy, high doses may not be necessary: in combination with TNFi (and presumably other therapies), 10mg/week may be sufficient[96;97] to increase the efficacy of the bDMARD. Tocilizumab and sarilumab as monotherapy are more efficacious than adalimumab monotherapy and JAK inhibitor monotherapy generally also has good clinical efficacy. In light of these observations, the task force discussed if the second part of the sentence should read "should be preferred" rather than "may have some

advantages", but this proposal did not reach a 75% majority; in the second ballot, 68% of the members voted for the final version. *LoE 1a, SoR A; LoA 8.9 (1.1).*

10. *If a bDMARD or tsDMARD has failed, treatment with another bDMARD or a tsDMARD should be considered; if one TNF inhibitor therapy has failed, patients may receive an agent with another mode of action or a second TNF inhibitor.* The first part of this recommendation remains unchanged. The second part underwent a slight modification by changing the sequence: the task force now placed "another mode of action" before "a second TNFi". This amendment was based on some reports from registry data, observational studies and a randomized controlled trial suggesting that using another mode of action leads to better efficacy than a second TNFi.[98-100] However, these and similar other studies may have had a high risk of bias and, as detailed in the previous SLR, a meta-analysis of randomized controlled trials performed in patients with an insufficient response to TNFis did not reveal differences in efficacy between switching to a second TNFi and using a different drug class,[23] although these were separate and not head-to-head studies. This recommendation does not only relate to failure of TNFi, but rather to failure of any bDMARD or tsDMARD. While data for the efficacy of TNFi after failure of another TNFi have been available for long,[101-103] a recent post-hoc analysis of a clinical trial suggested also some efficacy of sarilumab after failure of tocilizumab.[104] At the time of the SLRs no data were available regarding studies of (i) IL-6R inhibitors after prior failure of another such compound (e.g. sarilumab after failure of tocilizumab), (ii) JAK inhibitors after failure of another one (e.g. baricitinib after insufficient response to tofacitinib or (iii) bDMARDs after failure of tsDMARDs. However, since then a study using a TNFi after insufficient response to a JAK-inhibitor was published, revealing similar overall outcomes as switching from a TNFi to a JAK inhibitor.[105] Needless to say that the term "second TNF-inhibitor" does not relate to a biosimilar of the failed compound but to a molecularly different TNFi. Among the task force members, 84% agreed with this change. The LoE continues to be 1a for patients who did not sufficiently respond to TNFis (SoR A); JAK inhibition was studied in RCTs after failure of several bDMARDs.[91;106] *LoE 1a, SoR A; LoA 8.9 (1.2).*

11. *If a patient is in persistent remission after having tapered glucocorticoids, one can consider tapering bDMARDs or tsDMARDs, especially if this treatment is combined with a csDMARD.* In this update, the term "tsDMARD" was now included, based on respective trial data.[107] Otherwise the recommendation remained unchanged. In the discussions, the task force members reinforced the proposed sequence (stopping glucocorticoids first and

subsequently, when the treatment target is sustained, reducing bDMARDs or tsDMARDs). With the reiteration of this principle ("persistent remission" recommended before starting drug tapering) which has been introduced already in 2010 and maintained ever since, because no conflicting data became available, the task force explicitly affirmed the requirement of persistent remission before initiation of dose reduction or interval increase of bDMARDs or tsDMARDs. It is important to mention that discontinuation of bDMARDs is frequently associated with flares (increasing with time since discontinuation) and that, therefore, many task force members would have preferred to see tapering just as a dose reduction or interval increase rather than leading to discontinuation; however, the vast majority (>80%) of patients who flare can regain a good outcome upon reinstitution of the previous treatment.[107;108]

A definition for the term persistent is not available, since no study investigated whether 3, 6 or 12 month of stringent remission is more appropriate for such definition; in some studies 6 months of remission was used for this purpose, but this needs to be part of the research agenda. Several studies showed a clear correlation of flare risk with failure to achieve "deep" or "stringent" remission prior to bDMARD tapering;[107;109-112] however, this was not definitely established in a recent systematic literature review because of conflicting study data,[113]

Flares after bDMARD tapering are associated with a progression of joint damage, especially when leading to long-term increase in disease activity,[114;115] whilst progression of damage may not be seen with short lived flares.[115] Importantly, also small increases in joint damage may become significant over years and lead to irreversible disability.[115]

Thus, overall persistent ACR-EULAR remission is associated with lowest risk of flares and tapering while in low disease activity (including other, less stringent states previously termed remission) is not recommended because of a higher risk of flares.[116] Further, tapering may have to be approached particularly carefully in patients who have joint damage, since these patients have a high risk of damage progression upon withdrawal of bDMARDs, similar to patients with elevated levels of acute phase reactants or residual (low) disease activity, which is not seen upon dose reduction.[116] As an additional discussion point in this respect, it was suggested to consider continuing the bDMARD (or tsDMARDs) while stopping the accompanying csDMARD. However, a recent randomized trial investigating this question yielded no difference in outcomes between these 2 strategies;[117] thus, for cost and safety reasons the committee still supported that bDMARD and tsDMARD rather than csDMARDs should be tapered first. Among the participants, 93% approved this change. *LoE 1b, SoR A, LoA 9.2 (1.0).*

12. *If a patient is in persistent remission, tapering the csDMARD could be considered.* While combining recommendations 11 and 12 was discussed, the ultimate decision of the task force was to leave them separate and not change this item. This point relates primarily to two aspects: (i) in patients who have responded well to a csDMARD and did not need addition of a bDMARD or tsDMARD, the csDMARD dose may be reduced in persistent remission; (ii) if in a patient who was on combination therapy slow dose reduction or interval increase of a bDMARD or tsDMARD has ultimately resulted in cessation of this added therapy and persistent remission is maintained, one may consider also reducing the csDMARD dose. However, one needs to bear in mind that RA is regarded a usually incurable disease and that, therefore, a drug that has proven efficacy and is tolerated by the patient should not be stopped. With regards to the question of stopping versus continuing csDMARDs in remission, no new trials have been found in the current SLR, an older trial comparing withdrawal versus continuation of csDMARDs in patients in remission found a significant increase in flare rate and restitution to the situation prior to discontinuation may not be as successful with csDMARDs as with bDMARD or tsDMARD reinstitution, since only half of the patients regained the previous state.[118;119] Dose reduction, however, can be considered. *LoE 2b, SoR B, LoA 9.0 (1.1).*

Figure 1 depicts the algorithm based on the updated recommendations. The figure is an abbreviated version of Table 2 and the footnotes explain the definitions used. The research agenda (Table 3) is an update of the previous version, of which several questions have been addressed over the last 3 years.

Table 3. Research Agenda

1. Do we have enough data to recommend a specific treatment in patients with pre-RA at high risk to develop RA?
2. Is the application of a TNF-inhibitor after abatacept, tocilizumab, rituximab or a Jak-inhibitor has failed, safe and efficacious?
3. How safe and efficacious are abatacept, tocilizumab and rituximab after any of the other non-TNF-inhibitor-bDMARDs or a tsDMARD has failed?
4. How safe and efficacious is the use of an IL-6 pathway inhibitor if another IL-6 pathway inhibitor/a JAK-inhibitor has failed?
5. How safe and efficacious is the use of a JAK-inhibitor after another Jak-inhibitor has failed?
6. How safe and efficacious is the combination of a JAK-inhibitor with a bDMARD, such as a TNF-inhibitor?
7. Does the risk stratification for bDMARD/tsDMARD initiation based on presence of good or bad prognostic factors as recommended by EULAR translate into improved outcomes for both prognosis groups?
8. Do patients who lack poor prognostic factors benefit as much from a switch or addition of a csDMARD as from the addition of a bDMARD?

9. Is tapering of bDMARD monotherapy possible?
10. Will RCTs on tapering of bDMARDs and tsDMARDs designed to following predefined predictors for maintenance of good outcomes after withdrawal of bDMARDs show success?
11. How good is patient adherence to a bDMARD or tsDMARD and can non-adherence explain secondary loss of efficacy?
12. How can refractory RA be best defined, and what is the optimal treatment approach?
13. Can we identify new biomarkers to stratify patients and to predict therapeutic response and pending lack of response?
14. Which other factors, e.g. life-style characteristics, treatment history, allow to make the best possible therapeutic decisions?
15. Do JAKi confer specific safety signals of concern?
16. What are the molecular pathways associated with thromboembolism when using JAKi?
17. Can the identification of disease phenotypes inform tailored therapeutic use?
18. Do the different bDMARD/tsDMARD lead to comparable improvements in co/multimorbidities?
19. Does the concomitant use of glucocorticoids at very low doses (1-3mg prednisone equivalent) increase therapeutic success without producing unacceptable side effects?
20. Will therapeutic drug monitoring improve disease course and outcome and support decisions about switching within or between drugs?
21. Is leflunomide equivalent to MTX as first line csDMARD therapy?
22. For active RA patients who have failed multiple drugs, are there combinations that may be more successful such as JAK-inhibitor with bDMARD?
23. Is secondary loss of efficacy dues to non-adherence or a consequence of true loss of efficacy of a given drug and if the latter, what is the reason for this loss of efficacy?
24. How long should the duration of persistent remission or requirements be before csDMARD can be tapered?
25. Are the Boolean remission criteria sufficiently well defined?
26. Can taxonomy of RA be improved to guide therapeutic decisions?

DISCUSSION

Since the 2016 update, several new drugs have been approved in Europe. These new drugs are all within classes that had already been licensed for use in RA patients, such as additional bsDMARDs inhibiting TNF; sarilumab, an anti-IL-6 receptor antibody that targets the same molecule as tocilizumab; and tofacitinib and baricitinib, two JAK inhibitors of which tofacitinib had already long been used in the USA and other regions of the world. Thus, major changes of these recommendations were not to be expected, but revisiting recommendations with respect to their timeliness is important to ensure that their evidence is maintained or strengthened or, when contradicting data become apparent, that they are amended to reflect the latest knowledge and evidence-base.

The 2019 update of these recommendations, therefore, consolidates the previous efforts whilst adding one overarching principle (item D).

As before, the recommendations are ordered in terms of a sequential treatment strategy from the time point of diagnosis and the requirement to immediately start a DMARD therapy (#1) to the tapering of treatment once a stringent remission has been achieved (#11, 12). Nine of the specific recommendations were not changed (1-7, 9 and 12).The recommendation to use MTX plus glucocorticoids as an initial treatment strategy (# 5 and #6), while unchanged, has been reinforced by the task force; indeed, an abstract presented after the task force meeting revealed that MTX plus glucocorticoid is non-inferior to three bDMARD modes of action combined with MTX, namely certolizumab (TNF), tocilizumab (IL-6R) and abatacept (co-stimulation),[71] confirming and further strengthening the task forces long-standing recommendation in this respect. This recommendation relates to the initiation of csDMARD therapy and bridging therapy with glucocorticoids, not to long-term use of glucocorticoids after the bridging period which may be afflicted with cardiovascular and other risks.[34;120-122] In early RA patients who fail MTX by 6 months, addition of bDMARDs/tsDMARDs is associated with a similar overall rate of low disease activity or remission at 12 months from treatment start as immediately starting an TNFi plus MTX;[72] it is conceivable that this also pertains to other agents, although such data are currently lacking. Thus, the reduced response rates mentioned above are primarily due to the long disease duration and failure of several csDMARDs before initiation of a bDMARD or tsDMARD and not primarily a consequence of failing MTX.[123]

The task force maintained its recommendation to stratify patients who failed to attain the treatment target with the first treatment strategy into those with and those without poor prognostic factors. The task force also reiterated its previous decision that bDMARDs and tsDMARDs should primarily be combined with csDMARDs, such as MTX, a decision now strengthened by the new SLR data allowing the level of evidence to rise from 1b to 1a also for tsDMARDs.

No evidence is available for switches between IL-6 receptor inhibitors or between JAK inhibitors. However, the task force assumed that these are similarly efficacious to switches for which direct evidence exists. This assumption was partly confirmed in a recent trial showing efficacy of a bDMARD after an insufficient response to a tsDMARD.[124]

Whereas the first 10 items address therapeutic strategies for patients with active RA from the time of diagnosis to failure of sequential therapies, the last two recommendations deal with patients in whom remission was attained. Tapering of bDMARDs and tsDMARDs should be cautious and only be started when stringent remission, such as based on the ACR-EULAR definitions, is sustained. It should be noted that flares are frequent after withdrawal of bDMARDs and tsDMARDs and increase with time from cessation. Clear evidence base to withdraw csDMARDs first are lacking, as also revealed by a recent trial comparing these two strategies.[125] Thus, maintaining a bDMARD or tsDMARD at a reduced dose or an expanded interval may be prudent.

Overall, the 2019 update reveals that various principles, such as the principle of (early) remission induction by virtue of T2T and the value of glucocorticoids and csDMARDs in this trajectory are firmly established. The ongoing development of new bDMARDs and tsDMARDs has allowed for an increasing proportion of patients to attain the treatment target. On the other hand, new bDMARDs and tsDMARDs primarily have access to the affluent markets because of their high price, thereby continuing to leave an unmet need in RA patients in less affluent countries (most countries of the world) or in less affluent patients in high income countries (such as in the USA). The task force considers this a challenge to organisations like EULAR, APLAR, PANLAR and ACR. Moreover, it appears that the financial benefits brought by the advent of more affordable bsDMARD to most EU countries have not been seen in other regions to a nearly similar extent.

While recommendations presented in this update summarize the state of art from an evidence-driven point of view, they will always be aspirational in nature. They reflect 'best-practice', provided in an ideal world in which physicians adhere to the principle of assessing the patients regularly and making decisions driven by these assessments. They assume that rheumatologists are aware of the various drugs' safety issues, such as the risk of thromboembolic events upon use of JAKi, especially in patients with cardiovascular risk factors, that was recently reported by by regulators.[53;88;93] They also assume patients adhere to the medication selected and prescribed in a shared decision process. In this imaginary world of 'best practice' costs are not a limiting factor. Such aspirational recommendations should be read as an encouragement to all that are involved in improving access to health care in less affluent situations.

Aspirational recommendations may have their downsides. They may inadvertently contribute to what is called by some "the race to the end": the infinite search for ever subtler improvements in efficacy and safety at ever higher expenses and attainable for ever fewer patients. Moreover, overdiagnosis and overtreatment[126] may add to treatment inefficiency, risks and costs. It is the responsibility of the national and international professional societies to provide sufficient postgraduate education and information on benefits and risks of available drugs, so that appropriate RA treatment is applied and thus not only stays manageable in terms of costs, but also becomes attainable to those living in less affluent situations. This is conveyed with the present EULAR recommendations. Another good example of activities is the EULAR-initiative to provide recommendations for difficult-to-treat RA,[127] which will address the question if a once established diagnosis continues to be correct and will point to distinctions between inflammatory and non-inflammatory symptoms when deciding about T2T. In this respect, it is important to note that we are encountering an increasing number of patients who are "refractory" to treatment or "difficult to treat",[127;128] and for whom the current recommendations also apply, provided a correct diagnosis and

assessment of ongoing disease activity have been made. A correct diagnosis is key for the correct application of recommendations and appropriate use of medicines,[20] which in RA means to combat inflammation. However, since refractoriness appears to be associated with treatment delays and high initial inflammatory load,[128] rapid institution of appropriate treatment strategies once the diagnosis is made (recommendation 1) is of crucial importance.

In summary, the 2019 update of the EULAR recommendations provides rheumatologists, patients, health professionals and other stakeholders with the most recent evidence regarding the management of patients with rheumatoid arthritis. Adhering to these recommendations, which are based on systematic literature reviews and opinions of experts from around the world, will allow optimal treatment of RA patients at the beginning of the 3rd decade of this century. Using the many therapeutic options available, the treatment target can be reached in most patients, however, about 20-30% remain refractory to current therapies.[128] For these, new treatment options, but also better insights into the pathogenesis of RA will be needed. The research agenda points to unresolved questions and enables future task forces to further improve the EULAR recommendations.

As reflected by the current update in comparison with the previous one, for most of the therapeutic aspects of RA, we have reached a steady state of the evidence base for patients with established RA, although still some needs remain unmet,[129] including the need to cure the disease. With the current rate of evidence development, we expect an update of the recommendations to be necessary in about 3-4 years.

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Figure Legend.

Presentation of the 2019 update of the EULAR RA management recommendations in form of an algorithm. This is an abbreviated version aiming to provide a general overview, but it must be borne in mind that the algorithm cannot be separated from the details presented in the discussion of the individual recommendations in the paper which are part and parcel of these recommendations.

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