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EULAR RECOMMENDATIONS FOR THE MANAGEMENT OF RHEUMATOID ARTHRITIS WITH SYNTHETIC AND BIOLOGICAL DISEASE-MODIFYING ANTIRHEUMATIC DRUGS: 2016 UPDATE

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Short title: 2016 Update of EULAR RA management recommendations

Abstract

Recent insights in RA necessitated updating the EULAR RA management recommendations. A large international Task Force based decisions on evidence from 3 systematic literature reviews, developing 4 overarching principles and 12 recommendations (versus 3 and 14, respectively, in 2013). The recommendations address conventional synthetic (cs) DMARDs (methotrexate [MTX], leflunomide, sulfasalazine); glucocorticoids (GC); biological (b) DMARDs (TNF-inhibitors [adalimumab, certolizumab pegol, etanercept, golimumab, infliximab], abatacept, rituximab, tocilizumab, clazakizumab, sarilumab and sirukumab and biosimilar (bs) DMARDs; and targeted synthetic (ts) DMARDs (Janus kinase [Jak] inhibitors tofacitinib, baricitinib). Monotherapy, combination therapy, treatment strategies (treat-to-target) and the targets of sustained clinical remission (as defined by ACR-EULAR Boolean or index criteria) or low disease activity are discussed. Cost aspects were taken into consideration.

As first strategy, the Task Force recommends MTX (rapid escalation to 25mg/week) plus short-term GC, aiming at >50% improvement within 3 and target attainment within 6 months. If this fails stratification is recommended. Without unfavorable prognostic markers, switching to – or adding – another conventional synthetic (cs) DMARDs (plus short-term GC) is suggested. In the presence of unfavorable prognostic markers (autoantibodies, high disease activity, early erosions, failure of 2 csDMARDs), any bDMARD (current practice) or Jak inhibitor should be added to the csDMARD. If this fails, any other bDMARD or targeted synthetic (ts) DMARD is recommended. If a patient is in sustained remission, bDMARDs can be tapered.

For each recommendation, levels of evidence and Task Force agreement are provided, both mostly very high. These recommendations intend informing rheumatologists, patients, national rheumatology societies, hospital officials, social security agencies and regulators

about EULAR's most recent consensus on the management of RA, aimed at attaining best outcomes with current therapies.

The management of rheumatoid arthritis (RA) has changed dramatically over the past thirty years. Few therapeutic agents existed then, which were either minimally or not efficacious, because of toxicity and the fact that optimal dosing and onset of action had not yet been elucidated for some agents.[1-4] Available therapies were started late rather than early in the course of the disease.[5;6] Early arthritis clinics were emerging,[7-9] and their successes fueled reappraisal of the classification criteria then available that focused primarily upon long-standing disease.[10] A therapeutic target had not yet been defined, because relief of symptoms appeared to be the most important goal and the concept of aiming at disease states like remission or low disease activity was at best aspirational.[11]

To date, we have available numerous efficacious agents. Among the conventional synthetic (cs) disease modifying antirheumatic drugs (DMARDs)[12] we adopted MTX, upon its optimal use, as the anchor drug;[4] in addition, a number of biological (b) DMARDs have been approved, more recently followed (in many countries) by approval of the first targeted synthetic (ts) DMARD, with more in development.[13] Today, new classification criteria for RA promote the study of patients earlier in their disease course than before[14] and recommendations have been developed to treat RA patients via strategic algorithms targeting an optimal outcome, irrespective of the types of available therapies.[15-17]

A limited number of measures to assess response in clinical trials and follow disease activity in clinical practice are widely used[18-21] and the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) have jointly developed new definitions for remission which provide an optimal clinical outcome and can be achieved in a significant proportion of patients in trials and practice.[22] Attaining remission according to these criteria, index-based or Boolean, will prevent joint destruction or at least progression of

joint damage irrespective of residual subclinical changes,[23;24] optimize physical function, improve quality of life and work capacity,[25;26] and reduce comorbidity risks.[27;28]

With this recent evolution of evidence supporting stringent disease control to improve outcomes, interest in purely symptomatic drugs has significantly decreased today and disease modification has become the pivotal attribute of all modern drugs and treatment strategies. Nevertheless, symptomatic agents as well as physical measures, psychological support and surgery may and do have a place in the overall management of RA. However, disease modification is the mainstay of RA treatment and constitutes an amalgam of characteristics: relief of signs and symptoms; normalization – or at least important improvement – of impairment in physical function, quality of life and social and work capacity; and – as the foremost distinguishing characteristic of DMARDs compared to symptomatic agents – inhibition of structural damage to cartilage and bone. Therefore, showing inhibition of damage progression by radiography is still a pivotal outcome for the classification of a drug as a DMARD, since radiographs can depict bony and cartilage damage and have proven sensitivity to change even over short-term intervals and at very low levels of overall progression in a population.[29;30] Rapid attainment of the targeted endpoint is now critical, and to achieve the treatment goal of remission or at least low disease activity within the time frame of 6 months, at least 50% clinical improvement within 3 months is desirable.[31]

With rising standards of care and outcomes, RA management has become increasingly complex over the last decade. Despite the availability of many efficacious agents, treatment strategies that have been developed, and outcomes assessments that allow effective follow-up, the high costs of novel therapies have limited the widespread use of these therapeutic

options, creating a significant extent of inequity. Therefore, management recommendations on the approach to treating patients with RA have become increasingly useful in providing physicians, patients, payers, regulators and other health care suppliers with evidence-based guidance supported by the views of experts involved in many of these novel developments. Indeed, EULAR has recently updated the standardized operating procedures on the development of recommendations which include cost aspects in addition to accounting for the assessment of evidence and expert opinion.[32]

EULAR developed a first set of recommendations for the management of RA with DMARDs in 2010 and updated them in 2013. They were originally based on the evidence provided by five (2010) and three (2013)[33-35] systematic literature reviews (SLRs). The EULAR recommendations have been widely used. They have been referred to by national rheumatology societies and regional leagues to inform the development of their own recommendations (such as Canadian, French, German, Mexican, APLAR, PANLAR), as well as by regulatory authorities.[36-42]

Consistent with our approach to providing recommendations based on the latest evidence, we have continued to evaluate the literature on clinical trials of new agents, new information on established drugs, new strategic studies, new perceptions on outcomes assessments and new insights related to the research agenda[16] over the last three years. An abundance of new information motivated us to now further update the EULAR recommendations for the management of RA with DMARDs.

Methods

After approval by the EULAR Executive Committee, the Convenor (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 2010 recommendations and their 2013 update adhered to the original EULAR standardized operating procedures for the development of recommendations;[43] the 2016 update followed the recently amended version of these standards,[32] which also suggest adherence to the Appraisal of Guidelines for Research & Evaluation (AGREE) recommendations in its updated version (AGREE II).[44]

Steering Committee

The Steering Committee included 7 rheumatologists, 1 patient representative and 3 fellows. This group initially developed the research questions for the 3 SLRs (SLRs). These SLRs focused on (i) efficacy of sDMARDs (as monotherapy or combination therapy, including both conventional synthetic [cs] DMARDs and targeted synthetic [ts] DMARDs), and glucocorticoids; (ii) efficacy of bDMARDs (as monotherapy or combined with csDMARDs); and (iii) safety aspects of sDMARDs and biological [b] DMARDs. To this end, the original SLRs obtained in 2013[33-35] served as a starting point and an update on the literature published between 2013 and 2016 was performed. New information on treatment strategies was also evaluated in the present SLRs. 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,[45;46] EULAR's own previous SLR on cost aspects in the context of DMARD therapy[47] and the advent of biosimilars.[48] The three rheumatology fellows (KC, JN, SR) performed the SLRs (and checked each other's work) exploiting existing publication databases on randomized controlled trials for efficacy and registry data for safety, and also

evaluating recent EULAR and ACR congress abstracts. Summary-of-Findings (SOF) tables were generated and levels of evidence (LoE) were determined using the standards of the Oxford Centre for Evidence Based Medicine.[49] The three SLRs informing the Task Force and a detailed description of their methods are published separately.[50-52]

The SoFs of the SLRs were presented to the Steering Committee that formulated a proposal for an update of the recommendations based on this information. The SLR data and the proposals of the Steering Committee were subsequently presented to the whole Task Force for further discussions and ultimately development of the updated recommendations.

Task Force

The Task Force consisted of 50 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 frequently participated in clinical trials; moreover, several of them had experience in patient registries of their countries or in various aspects of outcomes research. The patients and health professionals all had experience in consensus finding activities, as well as 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 14 European countries, 2 colleagues from Asia, 1 from Australia, 2 from Latin America and 2 from North America were invited to participate. Several of them had actively participated in developing documents of their

regional leagues and/or national societies. All Task Force members declared their potential conflicts of interest before the start of the process.

The Task Force agreed upon a few principal considerations upfront. Firstly, all recommendations needed to be discussed in the context of new evidence; where no new evidence was available, the former evidence base was followed. Secondly, any of the previous recommendations (4 overarching principles and 14 recommendations) could be maintained as they had been presented in the 2013 version, amended, shifted in sequence or deleted. Thirdly, drugs that were not (yet) approved in Europe but used elsewhere in the world, or drugs that had not yet undergone regulatory assessment but for which evidence from clinical trials was available, could be considered in recommendations to allow for some anticipation of a potential uptake in clinical practice, with all respective caveats. Finally, there was agreement that all recommendations of 2013, which were either further supported by new evidence or lacked novel information, should be incorporated as previously worded, unless certain components were now considered inappropriate.

After the presentation of the SLR results and the Steering Committee's proposals for the amendment of the recommendations, the Task Force was split into 4 breakout groups. One group reviewed bDMARDs, the second group csDMARDs, the third tsDMARDs, and the fourth glucocorticoids; all groups proposed draft language for respective recommendations to the whole Task Force. Safety aspects were addressed in each of these breakout groups.

Consensus Finding

Representatives of each breakout group reported the results of the respective deliberations and presented proposals for the wording of individual recommendations to the whole Task Force. Thereafter the voting process took place.

For an overarching principle or recommendation to be accepted for the final document without further change, a majority of 75% of the votes was required in the first ballot. 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, further textual changes were proposed until a ≥50% majority was attained. The recommendations are presented as finally voted upon. The results of the respective last ballot are presented as percentage of voting members. Notes captured the contents of the discussions and the reasoning behind each decision to be presented in the comments accompanying the individual items. For various reasons, not every Task Force member was present in the room throughout the whole meeting and, therefore, there were slight variations in the numbers of votes. However, at every point in time more than 90% of the members participated in the ballots.

After the face-to-face meeting, the recommendations, as agreed by the Task Force, were subjected to an anonymous vote (by e-mail) on the levels of agreement (LoA). Each recommendation received an adjudication on a scale of 0-10, 0 meaning no agreement whatsoever and 10 absolute agreement. During this process, several weeks after the meeting, one individual withdrew from the Task Force, because the inclusion of csDMARD combination therapy in the recommendations had not found a majority during the preceding voting process. This colleague had been present and voted throughout the face-to-face meeting and the respective votes regarding all recommendations are accounted for

accordingly, but ultimately the person declined authorship and no vote was cast on the level of agreement.

The draft of the manuscript was sent to all Task Force members for their comments. After incorporation of these comments it was submitted to the EULAR Executive Committee for review and approval; at this time it was again sent to the Task Force members. Final remarks were obtained from members of the Task Force and the Executive Committee and addressed in the manuscript which was then submitted with approval by the EULAR Executive Committee.

Results

General aspects

As before, the 2016 update of the EULAR RA management recommendations reflects the balance of clinical, functional and structural efficacy, safety, costs and patients' perceptions as perceived by the Task Force. Aspect of drug-toxicity were considered in the overall wording of the recommendations, but data are presented only in the Safety SLR because it is assumed that prescribers are aware of the safety information provided in the manufacturers' package inserts of the various agents. Also, EULAR has developed a series of documents dealing with safety aspects of RA drugs,[53-58] and various other publications have addressed these aspects.[59-62] In particular, as also suggested by the safety SLR,[50] the major risk of bDMARDs (and also tsDMARDs) is related to infections, and recommendations for

vaccination[56] as well as a score allowing to calculate the risk of infection in patients exposed to bDMARDs have been recently developed.[63;64] For all medications discussed in this paper, the summary of product characteristics (SPC) document provides valuable information on risks, side effects, and need for monitoring. The recommendations given here should in no way be construed so as to detract from that information. In any case, when toxicity constitutes a major issue, a specific warning is provided within the respective recommendation or the accompanying comments. Of note, the 3 SLRs as well as the text accompanying each item should be regarded as part and parcel of the recommendation. The individual bullet points represent abbreviated conclusions from the discussions and, as such, do not capture all aspects related to a particular theme; rather, such aspects are elucidated in more detail in the respective explanatory part of the Results section.

When classifying DMARDs, the Task Force adhered to the previously used nomenclature[12;16] as shown in Table 1. This Table also provides a glossary for terms employed in the recommendations. The Task Force did not distinguish between early and established RA regarding the recommendation of the types of drugs, but rather discerned phases of the treatment process by differentiating between patients who are naïve to any DMARD therapy, patients who had an insufficient response (IR) to initial course(s) of csDMARDs and those who had an IR to bDMARDs. There is currently no evidence for differential responses solely based on disease duration, when leaving differences in baseline damage due to delayed treatment initiation aside. Indeed, trials on MTX-naïve RA patients used different disease durations for inclusion, which ranged from a few months to several years, without appreciable differences in outcomes upon indirect comparison.[65-68] However, the Task Force distinguished between early and established RA in terms of the targeted outcome (see recommendation 2). The Task Force also took prognostic factors (Table 1) into account,

which have similar predictive power irrespective of disease duration.[69] Of note, recommendations for the management of early arthritis, including undifferentiated arthritis, have been recently updated.[70] The present recommendations address the management of patients with RA from the time of its diagnosis and not pre-RA or undifferentiated arthritis.

Overarching principles

As in previous versions, the Task Force endorsed the presentation of general principles for the treatment of patients with RA as overarching (Table 2). Their nature is so generic that there was no requirement to base them on specific searches or levels of evidence, but at the same time the group believed it is crucial to communicate them as a foundation on which the actual recommendations were based. However, while all three former overarching principles were maintained as formulated in 2010, the Task Force added a 4th one as overarching principle B.

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 both in its textual details and in its place as item A, a prominent position within the recommendations. Shared decision-making between patient and rheumatologist involves all aspects of the disease: information on the disease and its risks, the modalities of disease assessment, decisions on the therapeutic target and the potential means to reach the target, the development of a management plan and discussions on the benefits and risks of individual therapies. These aspects have also been detailed in recommendations on standards of care.[71] Naturally, “best care” refers to the recommendations presented here and inherently “shared decision”

relates to all individual recommendations. To this end also quality indicators have been developed more recently.[72]

B. *Treatment decisions are based on disease activity and other patient factors, such as progression of structural damage, comorbidities and safety issues.* This is a new principle. It derives from previous recommendation 14, the last item of the 2013 version, which was deemed by the current Task Force to represent such a central and self-evident rule to any therapeutic approach that it should constitute an overarching principle rather than a recommendation. Indeed, in line with these considerations, the level of evidence of this recommendation had been rather low in 2013. Withdrawing this item from the recommendations elicited some discussions. Especially the patients brought forward that ending the list of recommendations with an item on patient-related factors would convey prominence to patient preferences and patient aspects in the management of RA. However, the reasoning that this item would even benefit more from being a general principle than a recommendation, which was unlikely to ever be studied in all its subtleties, prevailed to an extent that principle B was unanimously accepted (Table 2).

C. *Rheumatologists are the specialists who should primarily care for RA patients.* Originally presented as item B, the wording of this principle was not changed. Of interest, in 2010 this was even presented as overarching principle A. However, over the last years it was recognized, that shared decision-making and considerations of patient factors should receive the most prominent recognition. Whether positioned as A, B or C, this item addresses the importance of specialty care for a complex

disease like RA. There is compelling evidence that being cared for by a rheumatologist is advantageous for the patients in terms of early initiation of therapy, prevention of damage and reduction in surgical procedures.[73-77] Moreover, rheumatologists have the most profound experience regarding the use of csDMARDs and bDMARDs. This includes the adverse event profiles of these drugs, as well as awareness of and experience with comorbidities in RA. Therefore, rheumatologists can provide the "best care" in accordance with item A, in the sense of a holistic approach. The reasoning behind the term "primarily" has been discussed amply in previous versions of the recommendations and relates to considerations of multidisciplinary care, including specialty nurses, and to the fact that in certain areas of the world Rheumatology training is not sufficiently provided and other experts may have experience in the management of RA. Moreover, some comorbidities, such as chronic hepatitis or interstitial lung disease, may require consultation of, and treatment by, other specialists.

D. *RA incurs high individual, medical and societal costs, all of which should be considered in its management by the treating rheumatologist.* Again, this principle is worded exactly as last time, except that it was item C, but also last.[16] It is meant to remind all stakeholders that effective RA therapy – in spite of its direct costs – will reduce the economic burden on the individual patients, their families and society, which not only includes direct medical costs, but also indirect costs such as work disability and premature retirement. In this context it must be borne in mind that direct medical costs accrue beyond those attributed to directly treating the overt manifestations of RA and include costs ensuing from comorbidities related to the

inflammatory process. This point, however, is also meant to echo that cost-effective treatment approaches must be preferred as long as safety and outcomes are similar compared with more costly ones and in line with the therapeutic paradigms.[46] In some countries, the high cost of treatment is an important factor limiting the availability of modern therapies (inequity) , and this factor has to be considered when choosing a treatment strategy.[78] In this respect, the advent of biosimilars provides potential for reduction of pressure on health care budgets.[48] At this point it also must be considered that many patients still do not attain the therapeutic targets, despite all of our modern therapies and therapeutic strategies. Furthermore, any of the bDMARDs, if applied after at least one csDMARD and a bDMARD has failed, leads to only about 10% good treatment responses in terms of ACR70 rates.[79] These aspects impose the need to continue the search for new therapies or strategies.

Recommendations

General aspects

The Task Force's deliberative process resulted in 12 recommendations. The reduction by 2 recommendations compared with the past EULAR document may be somewhat surprising given the allegedly increasing intricacy of therapeutic modalities and strategies. However, the content of recommendation 14 was shifted into the overarching principles as discussed above. Moreover, item 11 of the 2013 version, which addressed the use of tofacitinib, was deleted as a separate item, because Janus kinase inhibitors as tsDMARDs have now entered into and expanded other recommendations; this will be discussed in more detail in the

context of items 8, 9 and 10. Also former recommendation 6, which addressed the use of csDMARD combinations, was deleted by the Task Force; combination therapy with csDMARDs and the reasons to remove it from its previous prominence within the list of recommendations and the algorithm will be addressed in the discussion on recommendations 4 and 5. While 3 of the 2013 recommendations were deleted via either complete omission or incorporation into other items, former recommendation 8 which addressed the absence or presence of prognostic risk factors was split into new recommendations 7 and 8; a detailed rationale for this decision is discussed below.

The 12 recommendations form a logical sequence. They start with the need to initiate effective therapy immediately after diagnosis and the requirement to set a treatment target and to assess the disease on the way toward that target, employing a treat-to-target strategy. Such strategy has been strongly embedded into the recommendations since their first version in 2010. With these prerequisites in mind, different drugs or combinations of agents are recommended in the course of the therapeutic procedures, with suggested sequential increments, taking prognostic factors and all approved agents into account. They also mention some agents of potential future interest, even though not yet approved by international regulatory authorities. Thus, the recommendations also include a prospective view on drugs that have undergone phase 3 trials and were available for evidence assessment; obviously their actual prescription will depend on the regulatory approval status in individual countries. The set of recommendations concludes with suggestions toward reduction of therapy and even withdrawal of some drugs when the desired target has been attained and is sustained.

Individual recommendations

1. *Therapy with DMARDs should be started as soon as the diagnosis of RA is made.* This recommendation remained unchanged compared with 2013 and is one of the mainstays of any treatment approach to RA. It implies (i) the necessity to establish a diagnosis as early as possible, as has been reflected also in the 2010 ACR-EULAR classification criteria;[14 80;81] and (ii) the advantage of early initiation of DMARD treatment ("as soon as possible"), which enables prevention of damage in a large proportion of patients.[76;82-84] Because of the generic nature of this bullet point, the Task Force did not specify the type of DMARD here. Indeed, all DMARDs enable a better long-term outcome upon early, compared with delayed institution, and the sequence of the types of DMARD therapies is addressed in subsequent recommendations. The Task Force did not deal with pre-RA or undifferentiated arthritis and thus assumed that a diagnosis of RA had already been made. However, it should be borne in mind that any chronic arthritis, even if undifferentiated, requires appropriate treatment, including consideration of DMARD therapy, because it usually does not subside spontaneously,[85;86] and an update of the recommendations for management of early arthritis has just been presented by EULAR.[70] With a level of agreement of 9.9, this recommendation achieved the highest agreement of all items (Table 2). LoE 1a; LoA 9.9

2. *Treatment should be aimed at reaching a target of sustained remission or low disease activity in every patient.* This recommendation addresses two treatment targets: remission, especially in DMARD-naïve patients, and low disease activity, primarily in patients who failed previous therapies. Since clinical remission or low

disease activity are mentioned as the sole therapeutic targets, any higher disease activity state has to be regarded as inadequate disease control, thus mandating a therapeutic change, obviously unless patient factors preclude this.[15] Communication with the patient to clarify and agree on the treatment goal and the means to attain this goal is of utmost importance. It allows alignment of the patient's and provider's considerations and aims and enhances adherence. In 2010, the notion "as soon as possible" was also part of this item[87] and in the current discussion it was specifically decided to mention that the treatment target should be rapidly attained rather than aiming to achieve it in a more distant future. Indeed, there is sufficient evidence that most patients who do not attain significant improvement within 3 months, or do not achieve the treatment target within 6 months, will not reach the desired state subsequently;[31;88-90] exceptions pertain to those patients whose disease activity has been reduced to a level close to the treatment target.

Regarding remission, EULAR and ACR have agreed on Boolean and index-based definitions, the latter based on the simplified or clinical disease activity index (SDAI, CDAI).[22] Both correlate highly with the absence of subclinical synovitis by magnetic resonance imaging and sonography[91;92] and absence of progression of joint damage.[23] They can even be reliably used when drugs that interfere directly with the acute phase response are employed.[93-96] Moreover, recent strategic clinical trials that compared targeting sonographic remission with targeting clinical remission or low disease activity resulted in the conclusions that aiming at imaging remission had no advantages over the clinical target, but economic disadvantages.[97;98] Low disease activity also needs to be properly defined and measured. Measures that highly weigh CRP or ESR (e.g. the DAS28) may not convey sufficiently reliable results when used

with agents that interfere with the acute phase response, such as anti-cytokine agents (especially IL-6 inhibitors) or Jak inhibitors.[93;96;99]

It is important that the target-state should be sustained. The term "sustained" is still not defined precisely, and different studies have used different definitions, but some voices in the Task Force suggested at least 6 months as a minimal time frame. This requires follow-up and a strategy to adapt therapy intensity up- or downward, aspects that are dealt with in subsequent recommendations. However, treatment intensification must take patient factors into consideration, especially risks and comorbidities (overarching principle B). LoE 1a; LoA 9.6

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.* This recommendation on treat-to-target is unchanged in position and formulation from the 2013 version. The frequencies of follow-up examinations should be adjusted in accordance with the level of disease activity, namely more frequently, such as monthly, when patients have high disease activity, and less frequently, such as every 6 to 12 months when the treatment target has been attained and sustained. EULAR generally recommends the use of a composite measure of disease activity that includes joint counts and the ACR-EULAR definitions for remission.[22;100] Improvement by 3 months refers to the fact that if a minimal change is not achieved, there is only a low likelihood of reaching the treatment target. Thus, a change to a better disease activity state should be seen at 3 months or a relative improvement, pertaining to at least 50% improvement in activity by a composite score, at that point in time, in order to have

a considerable chance of reaching the target.[31;89;101;102] Of note, adjustment of therapy includes the optimization of MTX (or other csDMARD) dose or route of administration,[4] or intraarticular injections of glucocorticoids in the presence of one or few residual active joints, and refers to a change of drugs only if these measures have not been successful or are not appropriate. Further, in an individual patient the treatment target may not have been fully achieved yet at 6 months. But if disease activity is close to the target, one may think about continuing the effective therapy for a few more weeks to make a final judgment, especially since a considerable proportion of patients may attain the target at a slightly later time point than at 6 months.[103;104] Consequently, the change in disease activity from baseline, and its slope should be considered when making treatment decisions. LoE 2b; LoA 9.5

4. *MTX should be part of the first treatment strategy.* Compared with 2013, when this item read "MTX should be part of the first treatment strategy in patients with active RA", the recommendation was slightly shortened. The Task Force felt that pointing to active disease was not necessary, since the EULAR recommendations primarily address patients with active disease. Based on its efficacy, safety (especially in the presence of folic acid), the possibility to individualize dose and method of administration as well as relatively low costs, MTX continues to be the anchor ("first") drug for patients with RA both as monotherapy as well as in combination with other drugs ("treatment strategy"; see below). Moreover, MTX appears to reduce comorbidities and mortality in RA.[105;106] In clinical trials of bDMARDs in early arthritis patients, MTX-monotherapy has been associated with 25% ACR70 response rates (which brings patients into the range of low disease activity) within 6 months,

even though it had not been combined with *de novo* glucocorticoids in these trials.[79] MTX should be rapidly escalated, usually to 25-30mg/week, orally or subcutaneously administered, with folic acid supplementation,[4] and the maximal MTX dose, if tolerated, should be sustained for about 8-12 weeks to judge the MTX treatment response. Indeed, when MTX is rapidly escalated to 25mg per week, the response rate may even be higher (~40% low disease activity).[107] Of course, contraindications and the potential of early toxicity have to be taken into account; this is addressed in item 5. The doses mentioned here do not pertain to Asian patients. In China, it is not recommended to exceed 20mg/week[104] and in Japan the maximum recommended dose for MTX is 16mg/week.[108]

Of note, at this point in time the Task Force decided to delete previous recommendation 6 ("In DMARD-naïve patients, irrespective of the addition of glucocorticoids, csDMARD monotherapy or combination therapy of csDMARDs should be used"). The inclusion or exclusion of combinations of csDMARDs within the bullet points elicited long debates within the respective breakout group and the whole Task Force (and the withdrawal of one Task Force member).

The first ballot of the Task Force involved a choice of the following two wordings: (a) "MTX should be part of the first treatment strategy" and (b) "In DMARD-naïve patients, irrespective of the addition of glucocorticoids, csDMARD monotherapy or combination therapy of csDMARDs should be used" (identical with the respective 2013 recommendation), with 23 votes favoring (a), 22 votes favoring (b) and 1 abstention. Therefore further discussions took place. Advocates in favor of including combination therapy referred to publications suggesting its superior efficacy compared with csDMARD monotherapy and similar efficacy compared with

biological agents;[109-113] moreover, in some countries csDMARD combination therapy is recommended by the national societies as preferred initial therapy.

Other Task Force members pointed to trials that did not show a real benefit of combination therapy (especially when csDMARD monotherapy was combined with glucocorticoids in the comparator arms);[114-116] differences in glucocorticoid co-intervention between combination- and monotherapy arms in previous trials;[117] issues concerning the design of some investigator initiated trials suggesting superiority of csDMARD combinations;[118] the significantly higher rate of profound responses upon combination with bDMARDs compared with the combination with csDMARD therapy after insufficient response to MTX;[112] and the higher level of toxicity of csDMARD combinations versus monotherapy.[115;119]

It was also argued that a higher prevalence of adverse events when using combination therapy, even though often mild, may preclude escalation of therapy and result in not reaching a full dose of some of the drugs. Also, the SLR on csDMARDs did not show evidence for superiority of csDMARD combinations compared with csDMARD monotherapy.[52] Moreover, the ACR Committee on the 2015 update of the ACR management guideline, in contrast to previous versions,[120] did not longer recommend csDMARD combination as initial therapy, but prioritized MTX monotherapy.[17] In line, the updated EULAR recommendations for the management of early arthritis do not advocate the use of csDMARD combination therapy.[70] It was also pointed out that choice (a) included the term “treatment strategy” and thus comprised the option to use csDMARD combinations. These discussions resulted in a new ballot between two versions for recommendation 4: (a) “MTX should be part of the first treatment strategy” (as above); and (b) “MTX should

be the first csDMARD, either as monotherapy or in combination with other csDMARDs". In this 2nd ballot a 71% majority voted for version (a). Thus, csDMARD combination therapy is no longer presented explicitly as initial treatment suggestion within the abbreviated list of recommendations. It should be mentioned, though, that the simple fact that csDMARD combination therapy is not included in the bullet point anymore, does not preclude using it. This is obviously at the discretion of the physician and the patient in light of all pros and cons that had been discussed ('shared decision').

This recommendation ultimately attained a very high level of agreement (9.8). The Task Force was well aware that in some countries, such as in the UK or Canada, rheumatologists are required to use at least two csDMARDs before the application of bDMARDs is approved by the payers and that combinations of two or three csDMARDs are accepted in lieu of two csDMARD courses. However, for the reasons just mentioned, the Task Force was not in favour of the practice to define an insufficient response to a combination of csDMARDs as a failure of two or more csDMARDs (when in reality it constitutes only one therapeutic strategy) nor to preclude the approval of bDMARD use when a first csDMARD has failed and the patient has bad prognostic markers (see below item 8 and Table 1). LoE 1a; LoA 9.8

5. *In patients with a contraindication to MTX (or early intolerance), leflunomide or sulfasalazine should be considered as part of the (first) treatment strategy.* The contents of this recommendation were maintained; however, compared with the previous version of item 5, the wording "in cases of MTX contraindications" was slightly amended, because it is patients who have contraindications, rather than

'cases'. The Task Force reiterated the relative safety of MTX and it was also discussed that the frequent fears of patients after reading the package insert should be addressed by providing appropriate information (overarching principle A). Nevertheless, there are occasional contraindications (e.g. kidney or liver disease) or intolerances. Under these circumstances, leflunomide (dosed at 20mg per day without loading dose)[121] or sulfasalazine (escalated to 3g per day) are regarded the best alternatives. Older trials have suggested similar efficacy for both these drugs compared with MTX, although MTX was used at much lower doses than recommended today.[122;123] However, no new trials have been performed to disprove the previous conclusions. Among all the above agents, only sulfasalazine has an acceptable safety profile during pregnancy.[124] In some countries, parenteral gold is still utilized and, while clinical efficacy is undisputed, there are controversies regarding its safety;[125;126] in other countries gold salts are not available any more. In contrast, the use of antimalarials, such as hydroxychloroquine and chloroquine, is still substantial, especially in combination therapy[111] or as monotherapy in patients with very mild disease,[127] particularly in China. Interestingly, antimalarials may have significant positive effects on lipid and glucose metabolism[128] and may reduce cardiovascular risk in RA.[129] However, joint damage is not retarded to a similar extent as with other csDMARDs.[130] This recommendation also uses the term "treatment strategy" implying, as with MTX, that leflunomide and sulfasalazine can be used as monotherapy or in combination with other csDMARDs or biologic agents.[131-134] Indeed, step-up combination therapy is frequently employed, even though comparing step-up combination with switching of csDMARD did not reveal significant differences in outcomes.[135] LoE 1a; LoA 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.* The added efficacy of glucocorticoids when combined with csDMARDs is well established. Indeed, hitherto all trials comparing glucocorticoids plus csDMARD with bDMARDs plus csDMARD revealed similar efficacy.[135;136] In 2013, glucocorticoids were dealt with in recommendation 7, but the wording was different: "Low-dose glucocorticoids should be considered as part of the initial treatment strategy (in combination with one or more csDMARDs) for up to 6 months, but should be tapered as rapidly as clinically feasible". The current wording constitutes a compromise attempting to accommodate most of the concerns and suggestions raised during the Task Force's debate.

   The term "low-dose" was critically discussed. While all members of the Task Force agreed that high doses of glucocorticoids should not be used for prolonged periods, it also became clear that the label "low-dose" (which means a daily dose of 7.5mg or less prednisone per day),[137;138] while preferred by some Task Force members, does not capture several current ways of glucocorticoid application. Indeed, recent clinical trials have revealed the efficacy of short-term glucocorticoids, but at doses >7.5mg per day, namely orally at 30mg starting dose,[115] as a single intramuscular injection of 120mg methylprednisolone[114] or as a single 250mg intravenous pulse therapy of methylprednisolone.[136] Therefore, the term "low-dose" was deleted and replaced by "short-term", leaving the choice about "dose regimens and routes of administration" (another new piece of wording in this item) to the individual rheumatologist and patient. Indeed, it was argued that a single intramuscular or intravenous application

entails a much lower cumulative dose than a few weeks of oral low-dose therapy, but this view was not shared by all Task Force members.

Yet another change involved the replacement of the phrase “part of the initial treatment strategy” by “when initiating or changing csDMARDs”. This change clarifies the intention of the Task Force, in that glucocorticoids should be considered with all csDMARD starts, either as part of a first csDMARD therapy at the time of diagnosis or subsequently if an initial strategy has failed. Finally, the fact that csDMARDs are mentioned specifically implies that glucocorticoids are typically not needed as a bridging therapy when bDMARDs or tsDMARDs are used, as these usually have a rapid onset of action and the infection risks may be potentiated[139;140] Thus, it is important to reiterate that the Task Force recommends using glucocorticoids in combination with csDMARDs primarily as bridging therapy until the csDMARD reaches its maximum effect, and this should be done using one of the dosing and tapering approaches mentioned above, for which respective evidence exists. To reflect the position of the Task Force, the algorithm depicted in Figure 1 was modified to show a “+” for the use of glucocorticoids in the new version rather than a “±” as previously.

By stating “…tapered as rapidly as clinically feasible” the Task Force underlines that glucocorticoids should be gradually reduced and ultimately stopped, usually within 3 months from treatment start and only exceptionally by 6 months. Long-term use of glucocorticoids, especially at doses above 5mg per day, should be avoided because of the many potential risks presented in the SLR.[50;52;57] While some of these risk associations may be due to confounding by indication in patients with high disease

activity,[141] the evidence for increased overall and cardiovascular mortality at a dose above a threshold of 7.5mg/day or a cumulative dose of 40g is considerable.[142] Of note, applying glucocorticoids as a sole therapeutic change in patients with insufficient response to csDMARD therapy does not convey good efficacy and is associated with significant adverse events.[143] Moreover, if glucocorticoids cannot be withdrawn within the time frame mentioned above, the DMARD therapy may have to be considered a failure. Finally, intra-articular glucocorticoid application may have to be considered in certain instances, such as a residually inflamed or a reactivated joint.

Some Task Force members advocated the chronic use of glucocorticoids as a possibility for some patients, however, this proposal was not endorsed by the majority. While the bullet point on glucocorticoids was, as in previous years, most heavily debated, the final wording received a 98% majority vote. The level of agreement, though, was much lower (8.7), in line with previous versions of the recommendations. This relatively low level of agreement is presumably due to the fact that many task force members felt that this point was too liberal and the use of glucocorticoids should be more restricted, while others were of the opinion that it was too restrictive. LoE 1a; LoA 8.7

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.* This sentence constitutes the first part of previous recommendation 8. It is essentially worded in an identical way, except that the last portion, “change to another csDMARD strategy should be considered”, was reworded as “other csDMARDs

should be considered", in light of the fact that combination with glucocorticoids has now been recommended clearly also for this step of the treatment algorithm (item 6) and combinations of csDMARDs are not specifically recommended as initial treatment strategy anymore. The poor prognostic factors are presented in Table 1. The Task Force also discussed that early intolerance for a csDMARD should not be considered as a treatment failure, which would imply moving immediately to the next phase of the algorithm, but rather require re-institution of another first csDMARD (replacement). LoE 5; LoA 8.5

8. *If the treatment target is not achieved with the first csDMARD strategy, when poor prognostic factors are present, addition of a bDMARD* or a tsDMARD* should be considered; current practice would be to start a bDMARD[§].* The separation of the 2nd part of previous recommendation 8 ("when poor prognostic factors are present, addition of a bDMARD should be considered") and the new item 7 reflects the Task Force's desire to give stratification by prognostic factors more prominence. The bDMARDs currently available include a series of TNF-inhibitors (adalimumab, certolizumab, etanercept, golimumab and infliximab); abatacept (a costimulation inhibitor); tocilizumab (an IL-6 receptor blocker, but in the future also possibly another IL-6 receptor inhibitor, sarilumab, and IL-6 inhibitors, such as clazakizumab or sirukumab); rituximab (an anti-B-cell agent); both as biological originator (bo) DMARDs and as EMA- or FDA- approved biosimilar (bs) DMARDs.

   This recommendation was also expanded to include tsDMARDs, namely the Jak inhibitor tofacitinib and possibly further Jak inhibitors, such as baricitinib. In the

2013 update, tsDMARDs (bullet point 11) were recommended for use after a bDMARD had failed. Since then, more data on tofacitinib, especially regarding long-term safety aspects, and new data for baricitinib have been published. The data suggest that baricitinib may be more efficacious than a TNF-inhibitor.[144] Currently, the term tsDMARDs refers only to Janus kinase (Jak) inhibition. Tofacitinib is approved in many countries, such as in the USA, Latin America and Asia as well as some European countries, but still not in the European Union; baricitinib has completed phase 3 trials and is currently under regulatory review; and filgotinib and other Jak inhibitors are undergoing evaluation in clinical trials. However, similar to the 2010 recommendations, in which TNF-inhibitors had been given a slight preference over other biologics due to availability of long-term registry data for the former but not the latter, preference is given here to bDMARDs over Jak inhibitors for the same reason. This notion on current practice is an expert opinion and not based on solid evidence. This bullet point still received a very high vote at the meeting and a high level of agreement.

The recommendation to use these agents in patients who have bad prognostic factors (rather than those who have not) is also not based on solid evidence in the literature. However, in most trials of bDMARDs and tsDMARDs the existing inclusion criteria, such as high disease activity, presence of autoantibodies and pre-existing joint damage, assured that patients with bad prognostic factors were included. Nevertheless, formal trials comparing the use of any of these agents in patients with and without bad prognostic markers do not exist. On the other hand, several post-hoc analyses revealed the value of using TNF-inhibitors in patients with bad prognostic markers (Table 1) relative to those without.[69;145]

The footnote to bDMARDs mentions that all approved bDMARDs may be used without hierarchical positioning, and that EMA- or FDA-approved biosimilars (bsDMARDs) have similar efficacy and safety as the respective biological originator (bo) DMARDs, and should be preferred if they are indeed appreciably cheaper than originator or other bDMARDs or tsDMARDs. Since the 2013 update, several bsDMARDs targeting TNF have been approved in Europe and some in the USA.[146-148] Among the bDMARDs there is no difference in outcomes, irrespective of their target. This conclusion rests on head-to-head trials, meta-analyses, the results of the SLRs, [50-52;149] and indirect comparison (the latter being less reliable and therefore least informative)[13;150;151] Of note, the SLR also included data from clinical trials of sarilumab, a human anti-IL-6 receptor antibody, and sirukumab, a human anti-IL-6 antibody, both of which are not approved at the present time; based on the SLR, the Task Force regarded these two antibodies and tocilizumab as having overall similar efficacy and safety[51].

While rituximab is approved for use after TNF-inhibitors have failed, there is ample evidence for its efficacy in bDMARD-naïve patients and early RA.[60;150] It is, therefore, frequently used after insufficient response to csDMARDs, especially when there are specific contraindications to other biologic agents, such as past lymphoma or demyelinating disorders, given its efficacy in these diseases.[152;153]

The separation of points 7 and 8 was also based on the reason that the previous bullet point comprised of two recommendations and that separating them would give the stratification by prognostic factors better visibility. The poor prognostic factors are presented in Table 1 and now also include failure of two csDMARDs; if

patients have insufficient efficacy to two csDMARD courses, either consecutively or as combination, a further csDMARD may have only little additional impact.[116;154]

The Task Force also discussed whether the use of a bDMARD as first-line therapy should be reconsidered, as had been the case in the original 2010 recommendations. Such use has been tested in a large number of randomized trials and has consistently been found to be statistically superior to MTX monotherapy. Importantly, however, none of the respective phase 3 trials used a combination with de novo glucocorticoids in the MTX monotherapy arm and the few investigator-initiated studies that compared first-line bDMARDs plus MTX with glucocorticoids plus MTX (or with a combination of csDMARDs) did not show a clear clinical or structural advantage of early bDMARD therapy.[116;136] Also, embedded within responders to initial treatment with bDMARDs+MTX are 20-25% good responders to MTX alone, leading to overtreatment of these patients.[155] Finally, it was shown that patients who had an insufficient response to MTX but then rapidly received bDMARD responded to a similar extent as those who had started with the bDMARD plus MTX.[68] Thus, this proposal did not find a majority vote.

Nevertheless, it is still conceivable that an induction regimen followed by the subsequent cessation of the bDMARD and continuation of the csDMARD may become a valuable option in the future; there is some support in the literature for such an approach.[68;156-159] However, this would need further confirmation by additional trials before it could be put into place, especially also because the number of initial responders in whom tapering could be considered does not comprise a majority of the patients. The recommendation, as worded above, received 94% of the Task Force members' votes. LoE *1b, §5; LoA 9.0

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.* This recommendation replaces former no. 9 ("In patients responding insufficiently to MTX and/or other csDMARD strategies, with or without glucocorticoids, bDMARDs [TNF inhibitors, abatacept or tocilizumab, and, under certain circumstances, rituximab] should be commenced with MTX"). While the individual bDMARDs and tsDMARDs have been already discussed above, item 9 now refers to the fact that all bDMARDs have superior efficacy when combined with MTX than as monotherapy. Compared with the 2013 update, more evidence has now accrued in favor of combination, even for tocilizumab.[160-162] Also for baricitinib, combination therapy conveys better structural, though not clinical or functional efficacy than monotherapy.[163] However, regarding signs and symptoms, physical function and joint damage, there are indications for a somewhat better efficacy of tocilizumab monotherapy, and more strongly so for Jak-inhibitors compared with MTX.[163-165] Monotherapy of the other biologic agents has not been found clinically superior to methotrexate monotherapy.[66;67;166] MTX can be used at 7.5 to 10mg to provide added efficacy to TNF-inhibitors[167;168] and intolerance at these low doses leading to discontinuation is very rare. Moreover, biologics can also be effectively combined with other csDMARDs.[131;133]

   Another aspect, namely the occurrence of anti-drug antibodies (immunogenicity), was discussed, especially regarding secondary non-response. In this context the lack of knowledge about the role of non-adherence and non-persistence was also addressed. The Task Force then discussed routine testing of anti-drug-antibodies

and drug levels and felt that there was little place for these in clinical practice, since a good clinical response would not lead to cessation of therapy even in the presence of anti-drug antibodies, or low drug levels, and vice versa. Of note, the use of MTX at the doses mentioned above reduces the incidence of anti-drug antibodies.[167;168] For all these reasons the Task Force felt strongly (96% majority) that bDMARDs (and tsDMARDs) should primarily be added to, i.e. combined with csDMARDs, such as MTX or leflunomide, leaving the option of monotherapy, with a preference for certain drugs, as an exception in case of intolerance or contraindication to all csDMARDs. LoE *1a, #1b; LOA 9.2

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 another TNF inhibitor or an agent with another mode of action.* A similar recommendation was presented in 2013: "If a first bDMARD has failed, patients should be treated with another bDMARD; if a first TNF inhibitor therapy has failed, patients may receive another TNF inhibitor or a biological agent with another mode of action." Indeed, in a trial published after the elaboration of these recommendations, even primary non-responders to a TNF-inhibitor were shown to have some response to another anti-TNF, making ti difficult to draw different conclusions for subsequent therapy for primary compared with secondary failures to TNF-blockers.[169] The addition in the first part ("or tsDMARD") was partly needed because tsDMARDs (Jak inhibition) are now included in the earlier recommendations 8 and 9; "first" was deleted, because the Task Force did not decide to distinguish between failure of one or more bDMARDs. However, it must be noted that it is

currently neither known if a Jak inhibitor is effective once another one has failed nor established that a second IL-6 receptor inhibitor or inhibitors of the IL-6 ligand are effective if tocilizumab has failed – this is still part of the research agenda. We also lack studies exploring if TNF-inhibitors are efficacious and safe after bDMARDs with other modes of action have failed, and also studies investigating switching between these other modes of action. A few members raised the question if the use of csDMARDs should also be considered when bDMARDs had failed, but this suggestion did not find a majority.

The Task Force was also clear about its recommendations that any bDMARD, including another TNF-inhibitor, could be used if a TNF-inhibitor has previously failed. Thus, drugs with the same or with another mode of action are recommended in this situation. This was based on the data of clinical trials including meta-analyses[149] and on the fact that in contrast to registry data, which may be affected by a variety of confounders, several new prospective studies suggest that there is no difference between these two approaches.[170;171] If a second TNFi fails, patients should receive an agent with another mode of action. However, it is self-evident (and supported by the vast majority of the Task Force members) that a bsDMARD of any of the reference boDMARDs should not be used if the respective boDMARD (or another bsDMARD of the same molecule) has failed to induce sufficient efficacy or vice versa. LoE *1a, §5; LoA 9.2

11. *If a patient is in persistent remission after having tapered glucocorticoids, one can consider tapering bDMARDs, especially if this treatment is combined with a csDMARD.* This item remained unchanged compared to the 2013 publication. No

new data have been published that contest this conclusion. Tapering here means reduction of dose or extension of interval between applications ('spacing'). It does not necessarily imply discontinuation of a bDMARD, which may lead to a recurrence of disease in a majority of patients.[172;173] However, even if treatment is stopped and patients flare, the majority of them (>80%) will recover their previous good outcome upon reinstitution of therapy (but some do not),[173;174] and patients should be informed accordingly. There exist certain predictors in whom tapering will be likely successful and these relate primarily to early RA, depth of improvement and duration of remission;[175] prospective trials taking these aspects into consideration are needed in the future. This item also indirectly bolsters recommendation no. 9 on combination therapy of bDMARDs with MTX or another csDMARD, since it implies that bDMARDs should primarily, if not only, be tapered and possibly discontinued when combined with a csDMARD, while tapering and stopping of bDMARD monotherapy was not yet sufficiently studied. LoE 2b; LoA 9.0

12. *If a patient is in persistent remission, tapering the csDMARD could be considered.* The 2013 version of the respective point 13 reads: "In cases of sustained long-term remission, cautious reduction of the csDMARD dose could be considered, as a shared decision between patient and physician". This item elicited significant discussions, since it would mean leaving patients with RA either without any or with a low dose of a csDMARD. But in general, no new evidence for or against this view has been found over the last years. In the discussion, controversies emerged. It was mentioned that here tapering means primarily reducing the dose and that discontinuing csDMARDs may be possible only in exceptional cases. Many

rheumatologists on the Task Force panel, though, expressed a view stating that csDMARDs should never be stopped. Consequently, this item received the lowest level of agreement (8.5) of all, although still quite high on the scale of 0 to 10. Of note, the portion worded “as a shared decision between patient and physician” was now deleted. It was felt by the Task Force that mentioning the shared decision for this item among all 12 would imply that the other recommendations may not need to involve the patient, or single out this specific recommendation in comparison with all other ones and thus offset overarching principle A. Obviously, the removal of this phrase does not mean that shared decision making with the patients is not important, on the contrary: in line with principle A it is of utmost importance for this and for all other recommendations. LoE 4; LoA 8.5

The updated recommendations are depicted in an abbreviated way in Figure 1. Part and parcel of this figure are the respective footnotes as well as the full text as presented here.

DISCUSSION

The 2016 update of the EULAR RA management recommendations was developed by 50 experts, including patients, rheumatologists and other health care professionals. This was

the largest Task Force ever convened for the development of EULAR recommendations, both with respect to the overall number of members and the number of European countries involved, and it is also the first EULAR Task Force with a broad international representation, since rheumatologists from several other continents participated in this activity. This allowed us to also include some views from Asia, and Latin- and North America in the development of the recommendations, an input desired given the information provided in the recent publications of the updated ACR and the APLAR recommendations.[17;39]

The 2016 update presents the hitherto "leanest" EULAR recommendations for RA management. While in 2010 the document comprised of 3 overarching principles and 15 recommendations and in 2013 it contained 3 overarching principles and 14 recommendations, the 2016 update arrived with 4 principles and 12 recommendations. Despite this reduction, in light of a continuously increasing spectrum of therapeutic options and new information on existing agents and therapeutic strategies, this update covers more treatment aspects and is built on a better evidence base than ever before. This is due to the availability of at least partial answers to several of the research questions posed in 2013, such as items 4, 6, 9 and 21,[16] and of many new data on established and novel drugs as well as therapeutic strategies.

The Task Force adhered to several principles established in the course of the development of the 2013 update and even in 2010. For example, aside from evidence on efficacy and safety, economic aspects were generally considered in line with respective general specifications.[45;46] Also, agents that have not yet been approved by regulatory authorities but for which data from phase III trials were available, were considered with the caveat that their use would be only possible upon such approval. This pertains to bsDMARDs, for which

the Task Force relies on the stringency of the regulatory processes of EMA and FDA, for new IL-6 inhibitors and for Jak inhibitors, the first of which is currently only licensed in some parts of the world with increasing availability of data on others. Finally, the Task Force reiterated its previous conclusions on the importance of stratification according to risk factors of adverse RA outcome, [69;145] once an initial therapy has failed.

The individual recommendations are not numbered by importance, but rather by a logical sequence: what is the treatment target and how should the patient be followed? What is the most prudent treatment approach once the diagnosis has been made? How can therapeutic success be maximized? Which therapies should follow a first treatment failure (phase I) and under which circumstances? Which agent or type of drug should be preferred in the course of the development of the treatment strategies?

Consequently, the first three items, which were either left fully unchanged or were only minimally changed, deal with the time point of starting effective therapy (as soon as the diagnosis is made and thus without any loss of time); with the definition of the treatment target (sustained remission or low disease activity); and with monitoring and the need to reach a significant improvement of disease activity within 3 months and attainment of the targeted state within 6 months. The preferred instruments to be used when following patients have been defined in previous EULAR activities[22;100] and comprise composite measures that include joint counts, such as the DAS28, CDAI and SDAI as well as the ACR/EULAR remission definitions. Of note, instruments weighing acute phase reactants highly, may exaggerate response, especially with IL-6 or Jak inhibitors.

The treatment target (stringent remission or low disease activity) continues to be clinically defined, since focusing at ultrasonographic remission has not shown better outcomes

compared with targeting clinical low disease activity or stringent remission, but rather induced overtreatment and thus inefficient use of healthcare resources.[97;98] Moreover, no strategy trial is available comparing the use of the serologic multi-biomarker disease activity (MBDA) test with targeting remission using clinical disease activity assessment by a clinical composite measure (with which MBDA correlates anyway); of note, the MBDA test has been reported to improve to a larger extent upon using a bDMARD that directly targets a cytokine compared with one that targets T-cell co-stimulation, despite similar clinical, functional and radiographic outcomes.[176] Moreover, it must be assumed that such test would falsely indicate high disease activity when an infection occurs. For all these reasons, the Task Force recommends to follow patients in clinical practice using a composite measure which comprises joint counts and may include an acute phase reactant. This clinical assessment is pertinent for every therapeutic phase (Figure 1).

Subsequent recommendations, however, have undergone some significant changes compared with the 2013 update. While MTX (or in the presence of intolerance another csDMARD) continues to be considered the pivotal drug once the RA diagnosis has been made (item 4), it is recommended more strongly than before to escalate MTX to a dose of 25-30mg weekly (with folate supplementation), given further recent insights on the high response rate with such strategy. [4;107] Moreover, the combination of csDMARDs, as monotherapy, with glucocorticoids (GC) is more strongly suggested than before in light of increasing evidence that this combination is not surpassed by csDMARD combinations, even if they are applied with glucocorticoids, or bDMARDs plus MTX in terms of efficacy and safety.[115;136] In the treatment algorithm (Figure 1, phase I), this is reflected by the respective change from "±" to "+" for the addition of glucocorticoids to csDMARDs. The term "low dose" GC has now been replaced by "short-term" GC, given that various modes of

application at different doses have shown to be efficacious. Moreover, the most important factors to reduce the risk of adverse event, such as cardiovascular events, infections, diabetes, or hypertension,[141;142;177] was deemed to be rapid tapering to discontinuation and a low cumulative dose of GC. This is, indeed, the case with these alternative glucocorticoid treatment modalities.

In contrast to the 2013 update, csDMARD combination therapy, with or without glucocorticoids, is no longer an explicit part of the recommendations. This conclusion was based on the accruing evidence that this csDMARD combination therapy may not be superior to MTX monotherapy plus GC, but may be associated with an increase in adverse events.[115;119] A recent indirect-comparison meta-analysis has suggested a superiority of csDMARD combination vs MTX monotherapy.[178] Not only was this study at odds with a previous direct-comparison meta-analysis[35;179] and with our own SLRs,[35;35;52;180] but indirect comparisons should also be considered with reservation since their rigor and value is insufficiently understood to date. Interestingly, using a somewhat different approach and based on an independent SLR, the ACR guideline has arrived at a similar conclusion as presented here and recommends MTX monotherapy as the first DMARD in early or established RA.[17] However, the use of csDMARD combination therapy is not precluded by the new recommendations, rather it is at the discretion of the rheumatologist to apply it in the context of the recommendation on the use of MTX as a (first) treatment “strategy”.

Once phase I has failed to reach the treatment target, either in the presence of bad prognostic markers or in the absence of bad prognostic markers after a second csDMARD strategy has failed, the Task Force recommends to add any bDMARD or, less preferably, a tsDMARD. If phase II as depicted in the algorithm fails to arrive at the treatment target,

another bDMARD or a tsDMARD should be used. The Task Force reiterated its position that if a TNF inhibitor fails, another TNF inhibitor – but not a biosimilar of the same molecule! – can be as effective as changing the mode of action. Vice versa, an effective biologic agent should not be switched to a biosimilar of another bDMARD for non-medical reasons. However, important data are missing for some of the drugs; for example, clinical trials did not address the efficacy of a TNF-inhibitor after bDMARDs with other modes of action or a Jak inhibitor have failed. Similar questions arise for the other agents and also for the use of IL-6 inhibitors, such as sarilumab or sirukumab, after tocilizumab has failed (see also research agenda).

Early bDMARD treatment, including an induction regimen with subsequent withdrawal of bDMARDs as supported by some strategy trials, was discussed but did not find a majority among the Task Force members. This decision was based on the lack of evidence for superiority of such therapy compared with the use of MTX plus glucocorticoids. Moreover, when placed in the context of a treat-to-target strategy, the initial use of csDMARDs yields equal results in the long-term. Finally the cost-effectiveness of first-line bDMARD therapy, especially in light of the reasons just mentioned, is very poor.

The 2016 update of the EULAR recommendations is based on the most recent evidence in the area of RA management and on discussions by a large and broadly international Task Force. The recommendations synthesize the current thinking on approaching RA treatment in a set of overarching principles and recommendations. These have been informed by SLRs on the efficacy and safety of the drugs. The Task Force is convinced that adhering to these recommendations, including shared decision making, defining the treatment target, assessing disease activity regularly with appropriate instruments and applying the sequence

of drugs as proposed and in a treat-to-target strategy, will maximize the overall outcome in a vast majority of RA patients. Still, a considerable proportion of patients will not reach the target despite all efforts, and for these patients new drugs will be needed. Also, new information from research activities on treatment strategies, predictive markers, and other aspects will become available in the near future and will likely necessitate yet another update of the recommendations in about 3 years; maybe we will then have new data on the research agenda, including precision medicine approaches in RA which allow predicting who will best respond to which drug at which stage of the disease. Until then we hope that the 2016 update will be broadly applied in clinical practice and/or serve as a template for national societies to develop local recommendations.

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Table 1. Glossary and definitions

TERM	DEFINITION	
Poor prognostic factors	• Moderate (after csDMARD therapy) to high disease activity according to composite measures[181] • High acute phase reactant levels[182;183] • High swollen joint counts[182-184] • Presence of RF and/or ACPA, especially at high levels[182;185] • Combinations of the above[69;145] • Presence of early erosions[182] • Failure of 2 or more csDMARDs[154]	
Low dose glucocorticoid	• ≤7.5mg/day (prednisone equivalent)[57;137]	
Meanings of treatment reduction	•	
Tapering	• Usually reduction of drug dose or increase of application interval ('spacing') • May include discontinuation (tapering to 0), but then only after slow reduction	
Cessation, discontinuation	Stopping of a particular drug	
Disease activity states		
Remission	ACR-EULAR Boolean or index-based remission definition[22]	
Low disease activity	Low disease activity state according to any of the validated composite disease activity measures that include joint counts[186-188]	
Moderate, high disease activity	Respective disease activity state according to any of the validated composite disease activity measures that include joint counts[186-188]	
DMARD nomenclature[12]		
Synthetic DMARDs (sDMARDs)	• Conventional synthetic DMARDs (csDMARDs)	E.g. methotrexate, leflunomide, sulfasalazine, hydroxychloroquine
	• Targeted synthetic DMARDs (tsDMARDs)	E.g. tofacitinib
Biological DMARDs (bDMARDs)	• Biological originator DMARDs (boDMARDs)	
	• Biosimilar DMARDs (bsDMARDs)	

Table 2. The 2016 EULAR Updated Recommendations

	Overarching Principles
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.
B	Treatment decisions are based on disease activity and other patient factors, such as progression of structural damage, comorbidities and safety issues.
C	Rheumatologists are the specialists who should primarily care for RA patients.
D	RA incurs high individual, medical and societal costs, all of which should be considered in its management by the treating rheumatologist.
	Recommendations
1.	Therapy with DMARDs should be started as soon as the diagnosis of RA is made.
2.	Treatment should be aimed at reaching a target of sustained remission or low disease activity in every patient.
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.
4.	MTX should be part of the first treatment strategy.
5.	In patients with a contraindication to MTX (or early intolerance), leflunomide or sulfasalazine should be considered as part of the (first) treatment strategy.
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.
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.
8.	If the treatment target is not achieved with the first csDMARD strategy, when poor prognostic factors are present, addition of a bDMARD*[1,2] or a tsDMARD*[3] should be considered; current practice would be to start a bDMARD[§].
9.	bDMARDs*[1,2] and tsDMARDs[#3] 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.
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 another TNF inhibitor or an agent with another mode of action.
11.	If a patient is in persistent remission after having tapered glucocorticoids, one can consider tapering bDMARDs, especially if this treatment is combined with a csDMARD.
12.	If a patient is in persistent remission, tapering the csDMARD could be considered.

DMARDs, disease modifying antirheumatic drugs; boDMARDs, biological originator DMARDs; bsDMARD, biosimilar DMARDs; csDMARDs, conventional synthetic DMARDs; tsDMARDs, targeted synthetic DMARDs

[1]TNF-inhibitors: adalimumab, certolizumab pegol, etanercept, golimumb, infliximab boDMARDs or the respective EMA/FDA approved biosimilars; [2]abatacept, rituximab (as first bDMARD under special circumstances – see text), or tocilizumab or respective FDA/EMA approved biosimilars, as well as other IL-6 pathway inhibitors, sarilumab and/or sirukumab, once approved. [3]Jak-inhibitors (where approved)

*,§,#These symbols indicate different levels of evidence which are correspondingly provided together with voting results and levels of agreement in Table3.

Table 3. Evidence levels, voting results and agreement

	LoE	SoR	Final vote (%)	Level of Agree-ment (0-10)
A	n.a.	n.a.	100	9.9
B	n.a.	n.a.	100	9.9
C	n.a.	n.a.	100	9.8
D	n.a.	n.a.	98	9.7
1.	1a	A	96	9.9
2.	1a	A	91	9.6
3.	2b		100	9.5
4.	1a	A	71	9.8
5.	1a	A	85	9.0
6.	1a	A	98	8.7
7.	5	D	94	8.5
8.	*1b §5	*A §D	96	9.0
9.	*1a #1b	*A #A	96	9.2
10.	*1a §5	A* §D	71	9.1
11.	2b	B	86	9.0
12.	4	C	86	8.5

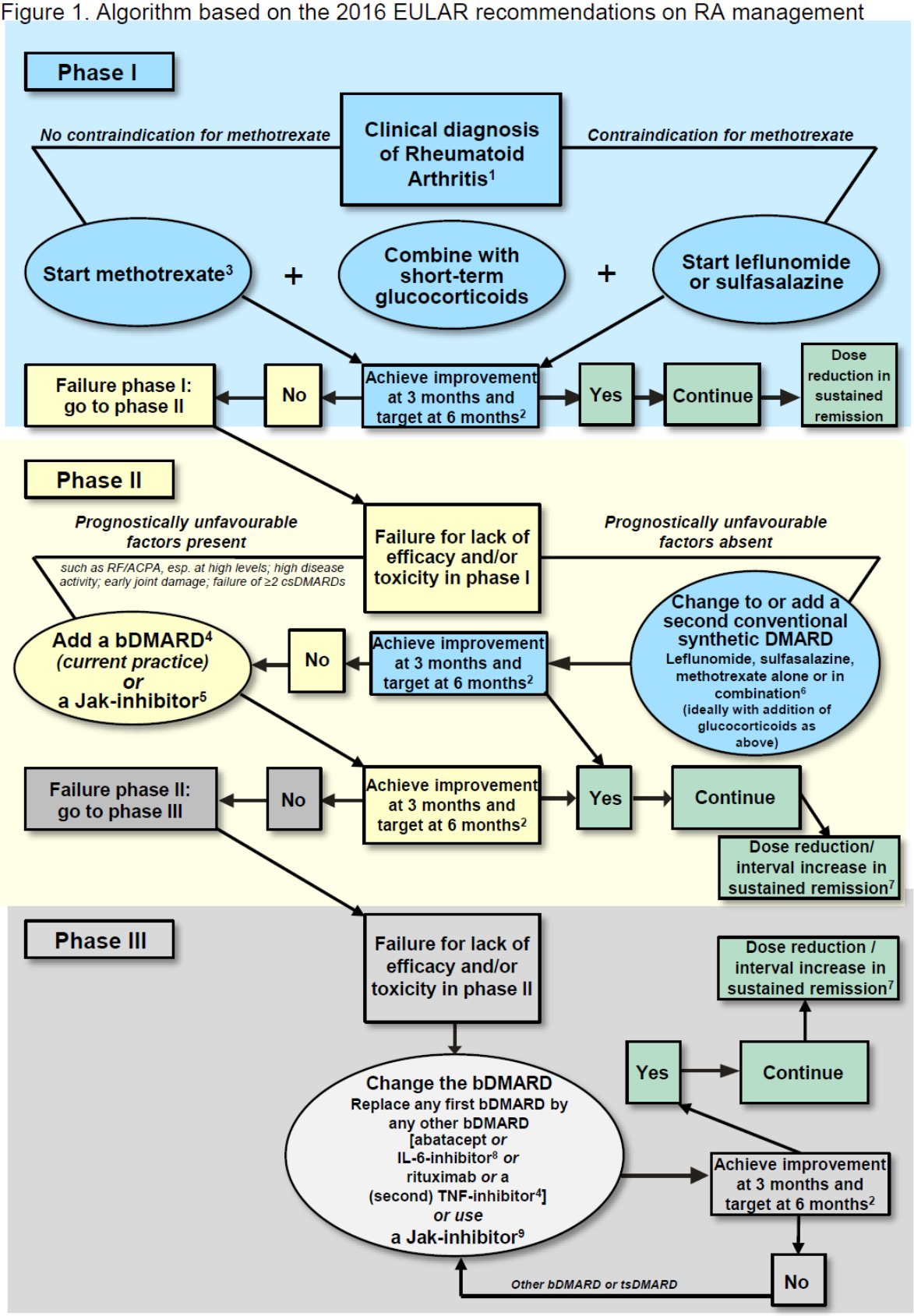
*,§,#These symbols relate to the corresponding symbols in the recommendations (Table 2), showing the respective levels of evidence.

BOX: Research Agenda

1. How does MTX monotherapy in combination with glucocorticoids compare to monotherapies of sulfasalazine or leflunomide in combination with glucocorticoids, at the doses of csDMARDs as used today?
2. In what proportion of patients is an induction therapy with a bDMARD+MTX with subsequent cessation of the bDMARD effective in inducing sustained remission?
3. Is the application of a TNF-inhibitor after abatacept, tocilizumab, rituximab or a Jak inhibitor has failed, safe and efficacious?
4. How safe and efficacious are abatacept, tocilizumab and rituximab after any of the other non-TNFi-bDMARDs or a tsDMARD has failed? H
5. How safe and efficacious is the use of an IL-6 pathway inhibitor if another another IL-6 pathway inhibitor/another Jak-inhibitor has failed?
6. How safe and efficacious is the use of a Jak-inhibitor after another another IL-6 pathway inhibitor/another Jak-inhibitor has failed?

7. Is the risk stratification as recommended by EULAR after failure of MTX improving outcome in those with risk factors and not harming those without bad prognostic markers? Do patients who lack bad prognostic factors benefit as much from a switch or addition of a csDMARD as from the addition of a bDMARD?
8. Can we find predictors of differential response to the different bDMARDs and tsDMARDs?
9. When starting a DMARD, how can we best predict who will attain the treatment target (remission or low disease activity) and who not?
10. Can we predict who will maintain remission after withdrawal a bDMARD?
11. Will we be able to develop precision (personalized, stratified) medicine approaches in RA?
12. Is tapering of bDMARD monotherapy, where potentially indicated, comparable with bDMARD tapering in the presence of csDMARDs?
13. Will RCTs on tapering of bDMARDs following the deducted predictors for successful withdrawal of bDMARDs show success?
14. How good is patient adherence to a bDMARD or tsDMARD and can non-adherence explain secondary loss of efficacy?
15. Is measurement of serum drug or anti-drug antibody levels useful in clinical practice?
16. Which biomarkers will help to find better predictors of bad outcome or response and which have failed in the numerous clinical trials that evaluated gene-expression and other biomarkers?
17. What is the effect of csDMARD, tsDMARD and bDMARD therapies on cardiovascular outcomes and to which extent is a potential effect dependent on a clinical response?
18. Is the use of telemedicine or e-medicine approaches as effective as direct contact in the clinic for treat-to-target strategies?

Figure 1. Algorithm based on the 2016 EULAR recommendations on RA management



[1]2010 ACR-EULAR classification criteria can support early diagnosis. [2]The treatment target is clinical remission according to ACR-EULAR definition or, if remission is unlikely to be achievable, at least low disease activity; the target should be reached after 6 months, but therapy should be adapted or changed if no sufficient improvement is seen after 3 months. [3] "Methotrexate should be part of the first treatment strategy"; while combination therapy of csDMARDs is not preferred by the Task Force, starting with methotrexate does not exclude its use in combination with other csDMARDs. [4]TNF-inhibitors (adalimumab, certolizumab, etanercept, golimumab, infliximab, including EMA/FDA approved bsDMARDs), abatacept, IL-6-inhibitors, or rituximab (under certain conditions); in patients who cannot use csDMARDs as comedication, IL6-inhibitors and tsDMARDs have some advantages. [5]Current practice would be to start with a bDMARD (in combination with MTX or another csDMARD) because of the long-term experience compared with tsDMARDs (Jak-inhibitors). [6]The most frequently used combination comprises methotrexate, sulfasalazine and hydroxychloroquine. [7]Dose reduction or interval increase can be safely done with all bDMARDs with little risk of flares; stopping is associated with high flare rates; most but not all patients can recapture their good state upon re-institution of the same bDMARD. [8]Efficacy and safety of bDMARDs after Jak-inhibitor failure is unknown; also, efficacy and safety of an IL-6 pathway inhibitor after another one has failed is currently unknown. [9]Efficacy and safety of a Jak-inhibitor after insufficient response to a previous Jak-inhibitor is unknown

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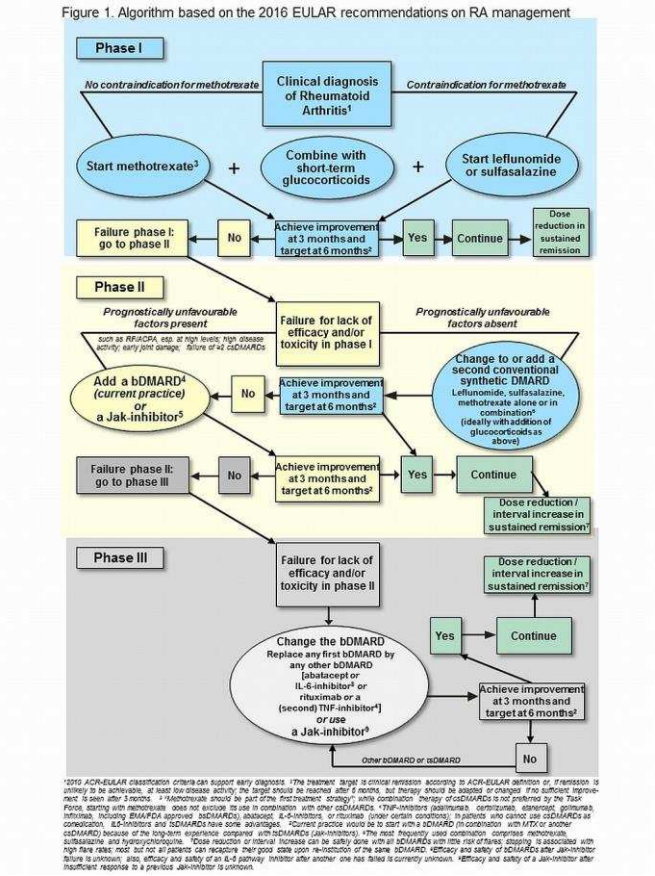
Figure 1. Algorithm based on the 2016 EULAR recommendations on RA management



*2010 ACR-EULAR classification criteria can support early diagnosis. [1]The treatment target is clinical remission according to ACR-EULAR definition or, if remission is unlikely to be achievable, at least low disease activity; the target should be reached after 6 months, but therapy should be adapted or changed if no sufficient improvement is seen after 3 months. [2] [3]Methotrexate should be part of the first treatment strategy[3]; while combination therapy of csDMARDs is not preferred by the Task Force, starting with methotrexate does not exclude its use in combination with other csDMARDs. [4]TNF-inhibitors (adalimumab, certolizumab, etanercept, golimumab, infliximab, including EMA/FDA approved biosimilars), abatacept, IL-6-inhibitors, or rituximab (under certain conditions); in patients who cannot use csDMARDs as comedication, IL6-inhibitors and bDMARDs have some advantages. [5]Current practice would be to start with a bDMARD (in combination with MTX or another csDMARD) because of the long-term experience compared with tsDMARDs (Jak-inhibitors). [6]The most frequently used combination comprises methotrexate, sulfasalazine and hydroxychloroquine. [7]Dose reduction or interval increase can be safely done with all bDMARDs with little risk of flares; stopping is associated with high flare rates; most but not all patients can recapture their good state upon re-institution of the same bDMARD. [8]Efficacy and safety of bDMARDs after Jak-inhibitor failure is unknown; also, efficacy and safety of an IL-6 pathway inhibitor after another one has failed is currently unknown. [9]Efficacy and safety of a Jak-inhibitor after insufficient response to a previous Jak-inhibitor is unknown.