EXTENDED REPORT

Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force

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ABSTRACT

Background Reaching the therapeutic target of remission or low-disease activity has improved outcomes in patients with rheumatoid arthritis (RA) significantly. The treat-to-target recommendations, formulated in 2010, have provided a basis for implementation of a strategic approach towards this therapeutic goal in routine clinical practice, but these recommendations need to be re-evaluated for appropriateness and practicability in the light of new insights.

Objective To update the 2010 treat-to-target recommendations based on systematic literature reviews (SLR) and expert opinion.

Methods A task force of rheumatologists, patients and a nurse specialist assessed the SLR results and evaluated the individual items of the 2010 recommendations accordingly, reformulating many of the items. These were subsequently discussed, amended and voted upon by >40 experts, including 5 patients, from various regions of the world. Levels of evidence, strengths of recommendations and levels of agreement were derived.

Results The update resulted in 4 overarching principles and 10 recommendations. The previous recommendations were partly adapted and their order changed as deemed appropriate in terms of importance in the view of the experts. The SLR had now provided also data for the effectiveness of targeting low-disease activity or remission in established rather than only early disease. The role of comorbidities, including their potential to preclude treatment intensification, was highlighted more strongly than before. The treatment aim was again defined as remission with low-disease activity being an alternative goal especially in patients with long-standing disease. Regular follow-up (every 1–3 months during active disease) with according therapeutic adaptations to reach the desired state was recommended. Follow-up examinations ought to employ composite measures of disease activity that include joint counts. Additional items provide further details for particular aspects of the disease, especially comorbidity and shared decision-making with the patient. Levels of evidence had increased for many items compared with the 2010 recommendations, and levels of agreement were very high for most of the individual recommendations (≥9/10).

Conclusions The 4 overarching principles and 10 recommendations are based on stronger evidence than before and are supposed to inform patients, rheumatologists and other stakeholders about strategies to reach optimal outcomes of RA.

The treatment of rheumatoid arthritis (RA) has undergone dramatic changes over the past 20 years, which may be subsumed under five captions: (i) availability of reliable assessment tools for clinical trials and practice;[1–5] (ii) appreciation of the importance of early diagnosis and concomitant start of conventional synthetic disease-modifying antirheumatic drug (csDMARD) therapy, including their combination with low-dose glucocorticoids;[6–10] (iii) recognition of the potential to halt or at least minimise damage progression upon attainment of good clinical states;[11 12] (iv) appreciation that methotrexate, if applied in accordance with relevant insights on dose and folate use, is a powerful agent and the anchor drug in RA;[13–15] and (v) development and approval of new biologic DMARDs (bDMARDs). In recent years, this knowledge has been further consolidated, not least by virtue of defining a treatment target and applying tight control and respective therapeutic adaptations to reach this target.[16–18] This paradigm has been incorporated into the 'treat-to-target' recommendations.[19] Indeed, this principle is also advocated by recommendations for the management of RA.[20–24]

In line with all these developments, the main pillars of the 2010 treat-to-target recommendations were the definition of a treatment target, namely remission or at least low-disease activity (LDA); the

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assessment of disease activity using composite measures that include joint counts; the regular adaptation of therapy if the target is not achieved within a particular timeframe; the accounting for individual patient aspects including risks when pursuing the therapeutic goals; and the shared decision-making with the patient. The treat-to-target (T2T) recommendations are generic as they do not advocate any particular type of intervention, but just the principle that should be adhered to, irrespective of the availability of particular drugs. They were based on the rationale of first defining the aim and then considering how one may generally approach reaching that goal, before defining means to arrive there. Attaining (or not attaining) this target can serve as a benchmark for an individual practice, centre or country. The target was defined as clinical remission or at least low-disease activity since these states convey the best and second best outcomes in RA.[25–27] At the time of the formulation of the recommendations, a task force of the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) was still engaged in elaborating new remission criteria that has meanwhile been accomplished;[28] therefore, in the treat-to-target and related recommendations, remission originally had been defined in general terms, but reference was made to this activity as an ultimate definition of clinical remission.[19 21]

There are several reasons to reconsider the treat-to-target recommendations. When they were developed, several of the items were based on expert opinion or indirect support rather than stringent, direct evidence and, therefore, it was deemed advisable to look out for new pieces of evidence for or against one or more of the items, as also stated as research agenda at that time. Beyond this aspect, some criticism had arisen.[29 30] While most points of this critique had actually been already quite clearly accounted for in the recommendations or the accompanying text, it indicated that the verbalisation and/or the positioning of some of the recommendations might have not been sufficiently clear. Also, the adherence to the treat-to-target recommendations in clinical practice may be low,[31] despite all the evidence regarding the importance of this approach. Therefore, revisiting the formulation of individual recommendations in line with available evidence and/or reassessment of expert opinion seemed desirable. Finally, all recommendations should be revisited every few years for their timeliness, appropriateness and accuracy, especially in the light of new developments in the field. Such reshaping of the recommendations may also help improving adherence of health professionals to the recommendations[32] and adherence of patients to therapies they have agreed upon with their physicians.

For all these reasons, a Task Force was convened to re-evaluate the treat-to-target recommendations with the objective of addressing all overarching principles and recommendations individually for their content and contextual positioning as well as evaluating the newest evidence accrued since the development of the 2010 treat-to-target recommendations based on a systematic literature review (SLR).[33]

METHODS

This endeavour consisted of several stages. Initially, a Steering Committee comprised of rheumatologists from several areas of the world and a patient was brought together in 2012 to discuss the potential need for updating the recommendations. During these deliberations, questions related to the practicability of some of the items; aspects of risks on the way to attain the treatment target; the issue of comorbidities both from the viewpoint of their association with active RA and as potential contraindications for intensifying therapy; the role of work productivity; and reduction or withdrawal of therapy upon achievement of the target were distilled in an iterative discussion process as important themes that had not, or not sufficiently, been addressed in 2010. Also, in the SLR performed for the 2010 recommendations,[34] only very few publications had focused on differences between treatment strategies as primary endpoint, namely comparing a treatment strategy towards a particular target with other therapeutic approaches, and these almost exclusively dealt with early but not established RA. As a consequence of these discussions, details for an SLR of studies published between 2008 and 2012 were elaborated and an initial search performed by MSch. When the Steering Committee reconvened at the end of 2012 and discussed these SLR results, it was disappointing to see that evidence for many of the questions addressed was still scarce. Therefore, it was decided to wait for additional information and the re-evaluation of the recommendations was postponed. A new SLR that accounted for the literature accumulated between 2012 and April 2014 was performed in the middle of 2014 by MSt and TS. These results were presented to the Steering Committee.[33] Indeed, novel evidence related to the questions posed was found, expanding the data obtained by the initial SLR[34] and the SLR performed in 2012.[33] At a new meeting, the Steering Committee was informed on the results of the SLRs and subsequently revisited the individual recommendations and performed a preliminary reformulation, where necessary. The committee also evaluated the sequence of the recommendations for logical coherence or risk of being overlooked. Aspects to be discussed in the text accompanying the individual points were documented.

In a next step, the proposal of the Steering Committee was presented to a large Task Force of 33 expert individuals, which comprised rheumatologists from many regions of the world (Australia, Europe, Japan, Latin America and North America), 5 patient representatives who had either been already involved in the development of the original recommendations or were identified as having particular interest in this area of research, and a rheumatology nurse. After presentation of the steering group's proposal and the background for it, three breakout groups were formed to address (a) the overarching principles, (b) recommendations 1–5 and (c) recommendations 6–10. Chaired by a patient representative (group dealing with the overarching principles) and rheumatologists (the other two groups), further discussions took place during these breakout sessions and the proposed wordings reformulated as deemed appropriate, with majority votes where controversy existed. It was agreed that individual items of the 2010 recommendations should only be changed based on new evidence, expansion of knowledge or if the wording appeared not being sufficiently clear. The results obtained by the breakout groups were reported to the whole Task Force, which then discussed these proposals, amended them and arrived at final wordings that were subjected to an anonymous voting process using voting cards. Items that achieved at least a two-third majority (≥67%) were taken as final recommendation in the exact way as they had been worded. Items that did not attain such majority approval straight away were re-discussed, re-formulated and re-voted on, until the majority was achieved.

In a final exercise, the bullet points were sent to each participant and additional members who could not be present at the face-to-face meeting by email to determine the level of agreement using an 11-point numerical rating scale (0=I do not agree at all, 10=I completely agree). At this stage, no changes to the wording could be made unless a mistake had been detected.

Also, the final text of the manuscript was sent to all participants for their comments and ultimate approval.

RESULTS

The new evidence base

The two SLRs revealed a total of 176 T2T-related publications, of which 6 were found to provide new evidence that was useful for the update of the recommendations.[33] A few randomised controlled approaches or cohort studies offered direct support, while others supplied indirect evidence found useful to expand the recommendations. Two studies of patients with early RA targeted 'remission' by the disease activity score (DAS) or DAS28 compared with usual care;[35 36] another study in early RA focused at low-disease activity;[37] a further investigation compared two cohorts of patients with early RA, one with a targeted and the other one with a conventional approach;[38] and one comparative cohort study addressed treatment to target of DAS28 <2.6 versus conventional therapy in late RA;[39] all these studies confirmed that a targeted therapy is superior to conventional therapeutic approaches, now even including a study on late RA.[40] Two studies compared treatment approaches targeting good clinical outcomes versus sonographic remission, showing similar outcomes.[41 42] One study compared the presence of comorbidities in relation to different definitions of remission and found that with ACR–EULAR remission criteria comorbidities such as osteoporosis were significantly less frequent than with less stringent criteria, and there was even a similar trend for cardiovascular disease,[43] in line with data showing that cardiovascular risk is significantly lower with stringent remission than active disease and similar to that of the healthy population.[44] Two studies compared different definitions of remission for residual sonographic activity and showed significantly lower power Doppler scores with ACR–EULAR than less stringent definitions.[45 46]

With this database at hand, the steering committee discussed the limitations of the treat-to-target recommendations and potential means to adapt them. Many themes were addressed: clinical versus 'imaging' or 'laboratory' remission (the latter meaning remission by non-clinical means); minimisation of comorbidities, especially cardiovascular, but also the risk that LDA or remission may not be targeted by rheumatologists because comorbidities preclude intensifying therapy; individualised therapy; work productivity and work-force maintenance aspects; and factors confounding the treatment target.

After the discussions on the SLR, its consequences for the recommendations and the rewording and repositioning proposals in relation to the 2010 recommendations as suggested by the steering committee and in the breakout groups all items underwent voting and the resulting recommendations are shown in table 1; for comparative purposes, the old version is presented in small font. Table 2 reveals the results of the ballots, the levels of evidence and grades of recommendation and the levels of agreement.

Overarching principles

A. *The treatment of RA must be based on a shared decision between patient and rheumatologist*. While this principle remained unchanged, it was discussed that the follow-up of patients with RA and therapeutic dialogues are increasingly also involving other healthcare professionals (HCPs) than physicians, particularly specialist nurses. In healthcare systems where this is already established, the shared decision-making also has to include these HCPs, thus involving the whole team in the care of RA. All 33 participants voted in favour of the statement.

B. *The primary goal of treating patients with RA is to maximise long-term health-related quality of life through control of symptoms, prevention of structural damage, normalisation of function and participation in social and work-related activities*. Two changes were made to the previous item B: a minor one, where 'the patient' was replaced by 'patients'; but more importantly, the previous item B ended with '… social participation' which was changed to 'participation in social and work related activities'. It was deemed particularly important to include aspects of work productivity and employment, especially since work participation has been associated with a better quality of life,[47] which is also implied by using the term 'through'. Moreover, participation in work is an important part among the categories of the WHO's International Classification of Functioning, Disability and Health.[48] Other aspects mentioned while discussing this item were comorbidities, including osteoporosis and cardiovascular risk, and systemic features of RA, but also the role of comorbidities as contraindication to amend therapy. However, it was decided by majority vote to only mention this in the text accompanying this item as an important consideration when treating RA but not to include it in the current wording of the point, especially also because comorbidity is mentioned specifically in one of the current recommendations (recommendation no. 7).

C. *Abrogation of inflammation is the most important way to achieve these goals*. This item remained unchanged compared with the 2010 version. As during the deliberations 4 years ago, the term 'abrogation' was discussed and also the question raised if the most important aspect was really inflammation, but at the end of these discussions everyone was convinced that this point should remain as it was since there were no data available allowing to make any other conclusion than that interfering with the inflammatory response was of utmost importance for optimal outcomes.

D. *Treatment to target by measuring disease activity and adjusting therapy accordingly optimises outcomes in RA*. Also, this item remained unchanged compared with 2010; there was no further discussion and full agreement within the Task Force (33 positive votes).

Final set of 10 recommendations on treating RA to target based on both evidence and expert opinion*

Before addressing the recommendations individually, it was decided to add a footnote (asterisk) to the heading of the table to ensure the recognition that the text accompanying each item is an integral part of the recommendations and that any interpretation that does not account for the information provided in the text should be seen as wrong.

1. *The primary target for treatment of RA should be a state of clinical remission*. This first item was not changed at all versus 2010 and seen as the cardinal point of the recommendations. Clinical remission has consistently been shown to convey better outcomes than other disease activity states, even low-disease activity.[11 25 26 49] Meanwhile, also two studies targeting DAS28<2.6 compared with conventional not DAS28-steered therapy, one in early RA and one in established RA, showed a significant advantage in favour of targeting this activity state.[36 39] While the Task Force discussed in depth whether the term 'clinical remission' should be changed or expanded to include 'imaging remission' or 'laboratory remission', there was final agreement on the term clinical remission, especially as defined by the

Table 1 The updated recommendations (2014), including a comparison with the 2010 version

Overarching principles*	
2014	**2010†**
A. The treatment of rheumatoid arthritis must be based on a shared decision between patient and rheumatologist	A. The treatment of rheumatoid arthritis must be based on a shared decision between patient and rheumatologist
B. The primary goal of treating patients with rheumatoid arthritis is to maximise long-term health-related quality of life through control of symptoms, prevention of structural damage, normalisation of function and participation in social and work-related activities	B. The primary goal of treating the patient with rheumatoid arthritis is to maximise long-term health-related quality of life through control of symptoms, prevention of structural damage, normalisation of function and social participation
C. Abrogation of inflammation is the most important way to achieve these goals	C. Abrogation of inflammation is the most important way to achieve these goals
D. Treatment to target by measuring disease activity and adjusting therapy accordingly optimises outcomes in rheumatoid arthritis	D. Treatment to target by measuring disease activity and adjusting therapy accordingly optimises outcomes in rheumatoid arthritis
Final set of 10 recommendations on treating rheumatoid arthritis to target based on both evidence and expert opinion*	
2014	**2010**
1. The primary target for treatment of rheumatoid arthritis should be a state of clinical remission	1. The primary target for treatment of rheumatoid arthritis should be a state of clinical remission
2. Clinical remission is defined as the absence of signs and symptoms of significant inflammatory disease activity	2. Clinical remission is defined as the absence of signs and symptoms of significant inflammatory disease activity
3. While remission should be a clear target, low-disease activity may be an acceptable alternative therapeutic goal, particularly in long-standing disease	3. While remission should be a clear target, based on available evidence low-disease activity may be an acceptable alternative therapeutic goal, particularly in established long-standing disease
4 The use of validated composite measures of disease activity, which include joint assessments, is needed in routine clinical practice to guide treatment decisions	6. The use of validated composite measures of disease activity, which include joint assessments, is needed in routine clinical practice to guide treatment decisions
5 The choice of the (composite) measure of disease activity and the target value should be influenced by comorbidities, patient factors and drug-related risks	9. The choice of the (composite) measure of disease activity and the level of the target value may be influenced by consideration of comorbidities, patient factors and drug-related risks
6. Measures of disease activity must be obtained and documented regularly, as frequently as monthly for patients with high/moderate disease activity or less frequently (such as every six months) for patients in sustained low-disease activity or remission	5. Measures of disease activity must be obtained and documented regularly, as frequently as monthly for patients with high/moderate disease activity or less frequently (such as every 3–6 months) for patients in sustained low-disease activity or remission
7. Structural changes, functional impairment and comorbidity should be considered when making clinical decisions, in addition to assessing composite measures of disease activity	7. Structural changes and functional impairment should be considered when making clinical decisions, in addition to assessing composite measures of disease activity
8. Until the desired treatment target is reached, drug therapy should be adjusted at least every three months*	4. Until the desired treatment target is reached, drug therapy should be adjusted at least every three months
9. The desired treatment target should be maintained throughout the remaining course of the disease	8. The desired treatment target should be maintained throughout the remaining course of the disease
10. The rheumatologist should involve the patient in setting the treatment target and the strategy to reach this target	10. The patient has to be appropriately informed about the treatment target and the strategy planned to reach this target under the supervision of the rheumatologist

The actual changes are highlighted in the online supplementary table.
*As worded, these recommendations constitute solely a brief summary of the discussions on individual aspects of the Task Force's activity. The Task Force specifies that these recommendations must not be interpreted without taking the respective text accompanying each item into account.
†The numbers at the left of the 2010 recommendations refer to the original numbering at that time.

ACR–EULAR remission criteria for clinical trials and practice,[28] since the vast majority of the literature, if not the entire inflammatory rheumatology literature addressing 'hard outcomes' of RA, like radiographic changes, disability and quality of life, has been based on clinical observations, not on observations using imaging techniques. Upon fulfilment of clinical remission according to the ACR–EULAR definition, functional and structural outcomes are maximised and only minimal abnormalities can be detected by imaging such as sonography.[45 46 50] Also, a first study targeting a clinical low-disease activity state compared with targeting sonographic remission revealed no major differences in clinical or functional outcomes despite the use of low-disease activity rather than ACR–EULAR defined remission as the clinical target.[42] On the other hand, some data indicate that there may still be residual active synovitis by sonographic examinations in patients in clinical remission[51] and, therefore, further studies on sonography and MRI, especially in relation to important long-term outcomes, need to be awaited. Given all these data,[52] imaging remission was not included into the current update of the recommendations, leaving clinical remission as the therapeutic target.

2. *Clinical remission is defined as the absence of signs and symptoms of significant inflammatory disease activity.* Also, this point was not changed. There was a major discussion ongoing as to which remission criteria should be used. Whereas with few exceptions everyone agreed that composite measures, in particular Clinical Disease Activity Index (CDAI), DAS, DAS28 or Simplified Disease Activity Index (SDAI),[53] should be generally used to assess disease activity (see also item 4), several participants felt that, despite the existence of the new preliminary ACR–EULAR remission definition,[28] one should not dismiss DAS and DAS28 remission, while others were of the opinion that the new definition of remission (Boolean or SDAI-based) should be used, to which the 2010 Task Force had already referred to, in particular given even considerations of its sonographic

Table 2 Evidence, grade of recommendation, agreement and votes for each of the recommendations (as pertinent)

Item	Category of evidence	Grade of recommendation	Level of agreement	Percentage of votes at last ballot*
1	1b	A	9.53±0.80	100
2	2c	B	9.50±0.69	100
3	1b, 4†	A, D	9.68±0.57	97
4	1b, 4V‡	A, D	9.26±1.13	97
5	4	D	9.18±1.09	67
6	1b, 4§	A, D	9.21±1.09	94
7	4	D	9.47±1.06	67
8	1b, 4¶	A, D	9.08±1.08	67
9	2c	B	9.61±0.75	67
10	4	D	9.73±0.77	67

*Most items required just one ballot and none underwent more than two votings.
†1b for the evidence that low-disease activity is a good treatment target, but 4 because it is expert opinion that it is an alternative goal for remission.
‡1b for the evidence that the use of composite measures is important compared with routine care, but no large study has compared measures that included joint counts with some that did not; therefore 4 for the joint count part.
§1b for the necessity to use composite measures, 4 for some of the time components mentioned.
¶1b for regular adjustment that was mostly done every three months, but 4 for the timelines mentioned, since no comparisons between adjustments at different time points were done.

correlates (see above). It was then argued that the ACR–EULAR remission criteria had been developed for clinical trials, but this view was contended by the fact that also remission definitions for clinical practice (Boolean criteria without C-reactive protein (CRP) and CDAI remission criteria) had been presented in the ACR–EULAR publication.[28] Moreover, evidence that the residual disease activity in the presence of DAS28 scores <2.6 is associated with progression of joint damage and some functional impairment has accumulated since the time of formulating the 2010 recommendations. Indeed, patients in DAS28 remission not fulfilling ACR–EULAR remission criteria compared with those achieving ACR–EULAR remission (Boolean- or index-based) may have a large number of residually swollen joints,[54–56] show more damage progression, worse physical function, worse quality of life and increased rates of comorbidities. DAS28 remission is thus not easily compatible with the term remission.[27 46 57–59] Some fears were raised that using stringent remission criteria would allow for achievement by only few patients and might lead to overtreatment, but this view was opposed by pointing to the relatively large frequency of attaining these criteria in clinical practice and trials of patients with early RA.[60 61] The significant residual disease activity that can be observed with DAS28<2.6 has been debated for long[28 45 46 54 55 62 63] and is associated with progression of joint damage.[57 64] Also, a recent publication evaluating several clinical trials addressed the underestimation of disease activity by the DAS28 remission criteria.[65] Important in this context is further that the US Food and Drug Administration classifies DAS28<2.6 as reflection of low-disease activity,[66] which is in line with all of the above notions. It was further mentioned that clinical remission was mainly a treatment goal for early disease and that there is an alternative target of low-disease activity, especially for established disease (see item 3), while in early disease one would aim for stringent remission with a minimum of residual disease activity. Moreover, since some of the discussions focused on imaging (sonographic) remission that is even more difficult to achieve, stringent clinical remission as defined by ACR–EULAR may currently be the definition best reflecting the wording of item 2, leaving other definitions reflecting low-disease activity as alternative targets (see item 3).

Another aspect of debate around this recommendation was the term 'significant'. Some participants suggested to delete the term 'significant' and thus just define clinical remission as the 'absence of signs and symptoms of disease activity'; however, that would have made even the ACR–EULAR remission criteria look insufficiently stringent, as they allow for a single residual swollen and tender joint (Boolean-based and index-based criteria) or possibly two of either plus none of the other joint count (index-based criteria). Thus, it was decided in the course of the deliberations to first vote on the sentence maintaining the term 'significant' that indeed received a unanimous result (33 'yes'). Notwithstanding all these discussions, maintaining the definition of remission as the 'absence of signs and symptoms of significant inflammatory disease activity' has been further supported by the evidence mentioned above since residual joint swelling beyond one or two, as an obvious sign of significant inflammatory activity, is associated with damage progression.[57]

3. *While remission should be a clear target, low-disease activity may be an acceptable alternative therapeutic goal, particularly in long-standing disease.* The meaning of this recommendation remained unchanged, but it was shortened by deleting the insert 'based on available evidence' because that evidence had further increased over the last four years, making obsolete to specifically point it out. It was further discussed that comorbidities may be present that might preclude the intensification of therapy to target remission, especially in long-standing disease. However, this aspect was not included here since it was felt that 'long-standing' disease in itself inferred not only RA with significant damage but also the potential presence of comorbidities and that this would be dealt with in a subsequent recommendation anyway (no. 5). Moreover, the word 'particularly' implied that low-disease activity could also be a target in early disease, although—as the item is worded—low-disease activity is not a preferred state for early disease but may be so more in established RA. Importantly, defining the alternative to remission as being low-disease activity in the context of treatment targets precludes any other state, such as moderate disease activity, as a therapeutic goal, although even this viewpoint is to some extent counterbalanced for exceptional situations by recommendation 7. It was also regarded important to recommend documentation of the chosen treatment target in the files and to share this decision with the patient, in line with overarching principle A (shared decision). Importantly and to reiterate, the Task Force does not insinuate to replace the target of remission by the alternative target of low-disease activity but rather implies that if remission cannot be achieved for any reason (such as in patients with long-standing disease), low-disease activity is an alternative and valid target, but any other state than low-disease activity would usually not be acceptable. However, patient factors, such as comorbidities, have to be taken into account in the course of a shared decision with the patient when defining the treatment target and the way to arrive there.

4. *The use of validated composite measures of disease activity, which include joint assessments, is needed in routine*

clinical practice to guide treatment decisions. The wording of this recommendation has not been changed, but it was shifted upward from its previous position as no. 6. This change in order had two reasons: first, it appeared to be more rational to refer to the means to measure disease activity immediately after having defined the therapeutic targets, namely clinical remission or low-disease activity; second, making this item more visible in the order of recommendations reflects the Task Force's conviction on the importance of regular disease activity assessment by appropriate methods. As before, the vast majority of the Task Force members felt that the measures used should comprise joint counts, and mentioning 'joint assessments' (plural) refers to the evaluation of both swollen and tender joint counts. It has been known for long that swollen joint counts correlate with progression of joint damage,[67–70] while tender joint counts relate to physical function.[68] The respective instruments have been discussed in a EULAR–ACR publication,[71] and the choice of the instrument should be recorded in the files. There was a discussion whether one should also recommend using an instrument purely based on patient-reported outcomes, such as the RAPID3,[72] plus a swollen joint count, but this would require the rheumatologist to consider two scores rather than just one and thus would not be in line with the term 'composite measures…which include joint assessments'. On the other hand, a recent study that compared a score comprising joint counts with one that did not, revealed higher frequencies of low-disease activity with the former, indicating that by using the measure not containing joint counts, patients are at risk of being overtreated when aiming for low-disease activity,[73] because a larger number of patients would appear to have moderate or high disease activity than is truly the case according to the composite measure that includes joint counts. At this point, it is noteworthy that it is mostly expert view to use composite measures that include joint counts, since no head-to-head study comparing such measures has been performed. However, this expert view is based on the consistently shown relationship between swollen joint counts and damage progression.[74]

5. *The choice of the (composite) measure of disease activity and the target value should be influenced by comorbidities, patient factors and drug-related risks.* This recommendation, previously comprised in no. 9, underwent a change in wording in two respects: first, the prior word 'may' was replaced by 'should', making a stronger point on the choice of other treatment targets than remission (or even low-disease activity) under certain circumstances (see below); second, old no. 9 stated "…influenced by consideration of co-morbidities,…" while the 'consideration' has now been removed and the recommendation calls for adaptation of treatment targets according to the presence of comorbidities, patient factors and drug-related risks. Moreover, this recommendation was shifted from its previous position as no. 9 of 10 to no. 5. Again, logic and the desire to give more prominence and thus attention to this recommendation were driving this decision. Logic, since this item now follows immediately after the recommendation on the importance to apply composite measures of disease activity and brings some respective caveats forward. Since in particular the presence of some comorbidities, such as severe cardiovascular disease, uncontrolled diabetes, or impaired renal or hepatic function, may preclude attempts to change treatment geared at reaching the main treatment target, the therapeutic goal may have to be different in such patients. Similar thoughts pertain to contraindications or safety aspects; if a patient suffers from recurrent infections, one will likely refrain from intensification of therapy to avoid risky overtreatment. Regarding the choice of the composite measure and the potential need to employ other instruments, such as comorbidities that increase or decrease acute phase reactants (which will confound scores that comprise erythrocyte sedimentation rate or CRP), some of our traditional composite measures may not be useful tools and other means may have to be the focus of disease activity assessment in such patients. On the other hand, with some particular aspects accompanying RA, such as pain hypersensitivity, patient-reported outcomes may not reflect the inflammatory events correctly but will likely be overshadowed by the comorbidity; this relates to the patient global assessment, but also to function and quality-of-life questionnaires as well as tender joint counts. Importantly, and in line with what was stated above, the instrument used to assess disease activity and the treatment target should be documented. The discussion partly focused around combining this point with the previous one, but it was felt that they address different issues and that this cautionary recommendation might be 'diluted' if it became an appendix of the previous one. Moreover, some criticism had arisen around this particular aspect[29] despite its prior existence and, therefore, its presentation as a distinct recommendation was deemed important. It is now less likely to be overlooked. In the course of the discussion, another important point emerged: while comorbidities may preclude intensification of therapy due to perceived risks, some comorbid conditions (such as amyloidosis or cardiovascular disease) are a consequence of active inflammation and, therefore, they may even require to aim for a target of remission without tolerance of low-disease activity; indeed, there has been a significant survival advantage in recent years with modern treatment approaches.[75–79] Also, in elderly patients with RA intensive therapy is frequently avoided out of the perception that they may not require it,[80] although there is evidence against such contention.[81 82] Another 'patient factor' to be considered is work capacity and its impairment. Moreover, it needs to be borne in mind that comorbidities and other patient factors may change in the course of the disease and its treatment, which may impact the maintenance of the treatment target as requested in recommendation 9. Thus, overall, this recommendation relates to a personalised approach of the treatment strategy, considering all factors related to the individual patient.

6. *Measures of disease activity must be obtained and documented regularly, as frequently as monthly for patients with high/moderate disease activity or less frequently (such as every six months) for patients in sustained low-disease activity or remission.* There was only a small change regarding this item, which was previously no. 5. It had stated 'such as every 3–6 months' for control examinations in patients who sustain the therapeutic target of low-disease activity or remission, maintenance of remission being an important goal. However, 3-month intervals were felt undue for this population of patients, and some rheumatologists may even consider less frequent control examinations than every six months to be appropriate. Nevertheless, assessments at different time points have not been compared and therefore most of these time-related aspects have a low level of evidence, but strong expert opinion with good agreement, as

indicated by the 94% positive vote. This recommendation also explicitly calls for documentation of the measure of disease activity chosen in the patient's chart. On the other hand, since with very active disease frequent adaptation of therapy may be needed, the Task Force reiterated the potential need for monthly controls in such situations. Moreover, as will be also stated in a subsequent recommendation (no. 9), the necessity for maintenance of remission (or low-disease activity) is already mentioned at this point in time. However, even patients in sustained remission must be assessed at certain intervals to ensure maintenance of the good outcome and lack of adverse events. In the course of sharing decisions with the patient, it is also important to advise the patient to reach out for the rheumatologist earlier than at the predetermined time point if the condition changes unexpectedly. In many countries, follow-up assessments are undertaken by health professionals other than physicians in the setting of a multidisciplinary care. Irrespective of the assessing person, numerous practice trials have revealed the importance of regular disease activity assessments. Without such regular evaluations using respective instruments, patients will be undertreated and therefore may encounter worse structural and functional outcomes, but also more comorbidities. It was also discussed if longer intervals should not be suggested for patients who have reached remission. However, the majority of participants felt that a first achievement of remission may still be a vulnerable situation and longer intervals should only be considered for patients in sustained remission; also the duration to which the term 'sustained' would pertain was not clear—3 months or 6 months might be considered as the absolute minimum requirement in this respect.

7. *Structural changes and functional impairment and comorbidity should be considered when making clinical decisions, in addition to assessing composite measures of disease activity.* '…and comorbidity' was now added to this recommendation to reiterate the importance of considering comorbidities in the context of making clinical decisions. Otherwise, this item points again to the importance of using composite activity measures. However, it also addresses the issue of structural changes since the presence of early joint damage is a risk factor for further damage.[22 67 69] In this context, estimation (not scoring) of damage progression may be done upon regular (such as annual) performance of radiographs. On the other hand, no specific imaging method is mentioned in this bullet point and some rheumatologist may wish to assess progression of damage using MRI or sonography, although joint space narrowing that has a particular impact on physical function[83] may be more easily discernible on radiographs. Further, impairment of physical function and work performance may sometimes be associated with a residual activity of a functionally important joint (eg, wrist or ankle) despite improvement in (most) other joints; thus, while the overall status may appear good, this impairment may have to direct particular treatment decisions. Importantly, it has also to be borne in mind that functional impairment in patients with RA may not only be due to the joint disease but also a consequence of comorbidities; indeed, even patients in stringent remission may experience high disability scores as a consequence of such concomitant diseases.[84–86]
8. *Until the desired treatment target is reached, drug therapy should be adjusted at least every three months.* The wording of this recommendation (originally no. 4) was not changed. Of particular importance, almost all practice trials have shown that patients under routine care that is not informed by a composite measure of disease activity have much worse outcomes than patients in whom treatment decisions are based on the disease activity assessment by such instruments.[16] This is an important concept since the observations that routine care that does not apply clinical scoring and a targeted therapeutic approach suggest that patients with RA have been significantly undertreated. The shift to its new positioning, therefore, does not imply that the Task Force did not appreciate this point as sufficiently important to be among the initial items; on the contrary, the Task Force felt, just as before, that this is a key recommendation. However, appropriate adjustments of therapy have already been implied in items 4 and 6, where we advocate guidance of treatment decisions by the use of composite measures and a high frequency of taking these measures in the presence of active disease. 'Adjust' is then an expansion of the term 'guide', but it does not primarily, let alone exclusively, imply a change of a drug regimen, but also comprises aspects such as dose increases of ongoing therapy (where pertinent) or intra-articular glucocorticoid injections, for example, in the presence of residual joint swelling. The recommendation regarding the frequency of treatment adjustments (the verbalisation 'at least every three months' includes a higher frequency) is based on the results of strategic clinical trials that showed that adapting therapy every month leads to good outcomes compared with conventional care.[16 17 36 39] Recommending adjustments in active disease 'at least' every three months, implying that this should not be later, is also based on evidence, since the treatment response at 3 months allows to predict if patients are highly likely or highly unlikely to achieve the treatment target at subsequent points in time.[38 87–89] Therefore, adjustments, potentially also a change of the drug regimen, may have to be performed. Importantly, by recommending to see these patients every three months, this item indirectly will also serve the purpose of treatment monitoring and prevention of overtreatment, yet another important aspect in the context of treatment to target. The term adjustment also comprises reduction or even withdrawal of some therapies, when stability of the overall response allows such decision to be made (see also item 9). In any case, if medication is reduced or intervals prolonged, the patients should be carefully watched by composite measures of disease activity to be sure that they do not experience a deterioration of their clinical status.
9. *The desired treatment target should be maintained throughout the remaining course of the disease.* Unchanged compared with 2010 (then no. 8), this item refers to observations that complete halt of joint damage and further improvement of physical function depend on the maintenance of the clinical remission state.[11 58 90] Moreover, loss of the targeted good outcome can reignite the process leading to joint damage.[91 92] Maintenance of the treatment target does not in itself imply maintenance of treatment; indeed, a number of studies on tapering of therapy, especially dose reduction, interval increases and even withdrawal of biologicals, have been performed since 2010.[92–101] These studies indicate that in established RA stopping biologicals leads to very frequent loss of low-disease activity or remission, while dose reduction or spacing of intervals of applications carries less risk of return of active disease. In early disease, the

question of successful withdrawal is not yet resolved. Stopping conventional synthetic DMARDs[102] is followed by flares more frequently compared with their continuation.[103] In this context, the aspect of adherence to therapy has also to be considered since non-adherent patients flare up to four times more frequently than adherent patients,[104] pointing to the significant importance of information and shared decision-making with the patients (items A and 10). Safety aspects and drug costs may also have to be taken into consideration in this respect.

10. *The rheumatologist should involve the patient in setting the treatment target and the strategy to reach this target*. The involvement of the patient in making decisions and the type of information provided should be recorded, along with the treatment target and the measures to be used during follow-up. The agreed and documented target should be visible in the patient records to every HCP involved in the monitoring of the disease evolution of the individual patient. Compared with previous no. 10, this recommendation has not only been simplified, but a proactive role is now assigned to the rheumatologist (previously: 'under the supervision of the rheumatologist'). Rheumatologists, but also all other health professionals caring for patients with RA, are reminded that the reasons to propose a particular treatment target and the means to achieve this ought to be not only properly communicated to the patient, but also agreed upon with the patient, in line with respective information on the disease and the benefits and risks of various therapies. Indeed, patients have a wide range of beliefs related to DMARD therapy[105] and appropriate communication allows patients to make informed decisions.[106] Moreover, adherence to treatment has been clearly shown to depend on the level of information and on a good interaction with the rheumatologist.[107] In this context, it also must be reiterated that patients with RA require a multidisciplinary care and that in many countries nurse practitioners/specialists or other health professionals take a very important role in informing, following and managing patients (see also overarching principle A). Offering such care where available, or attempting to establish it, is also part of the overall role of the rheumatologist. This item inherently comprises all aspects of the present recommendations, such as the setting of the treatment target, the means of disease evaluation, the chosen drug and non-medical therapy including their risks, the focus on comorbidities and other patient factors, the follow-up process—all this has to be taken into consideration when the rheumatologist 'involves' the patient. Indeed, it may be challenging to explain to a patient whose disease activity has significantly improved that therapy should be intensified—and these recommendations and especially their patient version[108] may be helpful to this end. Educational programmes supporting this process need to be expanded.

DISCUSSION

Like the 2010 'treat-to-target' recommendations, the updated version is aimed at practising rheumatologists and other health professionals caring for patients with RA; official bodies such as governments or payers who may have an interest to assess clinical practice in their environment; but also clinical trialists and regulators, given that strategic trials have meanwhile become a focus of industry-initiated studies after having had a sole investigator initiated nature for long. Patients are another important audience for whom a separate version is planned in line with the 2010 recommendations.[108]

The procedures were initiated by a Steering Committee that adhered to the EULAR operating procedures.[109] The Steering Committee solicited the SLRs.[33] Based on this new evidence, a large Task Force was convened comprising 43 individuals, of whom 5 were patient representatives and 37 rheumatologists from around the world. Contrasting the previous Task Force, the current one also obtained input from a nurse specialist.

As before, the recommendations focused on a treatment target that would allow for an optimal outcome of RA for the individual patient. In contrast to guidance documents on the management of RA with drugs,[20 22] the present recommendations are of generic nature and do not address particular agents or classes of drugs. The Task Force was aware that with different accessibilities to certain medications overall outcomes may differ between countries and regions,[110 111] but a good outcome can also be attained in a large proportion of patients with easily accessible and affordable therapies, as long as a strategic treatment approach is adhered to.[16 112]

The Task Force revisited the overarching principles and the 10 itemised recommendations and reiterated that a pivotal aspect in the care of RA is the shared decision-making with the patient. The whole set presented is framed by this aspect, with overarching principle A introducing it and item 10 calling again for the involvement of the patient in setting the goals and the strategy. Overarching principle B has been amended to now include work participation since this is not only an important aspect related to overall quality of life,[47] but an important outcome that can be increasingly achieved with modern therapeutic strategies.

All Task Force members agreed unanimously that abrogation of inflammation (overarching principle C) and thus reaching a state of clinical remission (recommendation 1) is the most important goal in the treatment of RA, at least in its early stages, meaning 'the absence of signs and symptoms of significant inflammatory disease activity' (recommendation 2). The new ACR–EULAR remission definitions provide the assessment tools that account for this principle. Less stringent criteria comprise patients who have significant residual inflammation, less functional improvement and more damage progression, while potentially more stringent targets, such as remission by sonography, while having been discussed, have to await conclusive evidence of better outcomes compared with the stringent ACR–EULAR clinical criteria. Indeed, recommendations 1 and 2 remained unchanged from the 2010 version, but are now supported by more direct and indirect evidence.[28 33 39 46 49 57 64 65]

Also, recommendation 3, namely that low-disease activity constitutes the alternative for remission, has not been changed and was regarded equally important as item 1 by the Task Force. This is particularly true for patients with long-standing disease who will mostly not be able to achieve clinical remission. Indeed, low-disease activity is the second best state, leading to much better functional and structural as well as work-related outcomes than moderate let alone high-disease activity.[11 25 26] Indeed, most evidence for the benefit of targeting a good therapeutic outcome compared with conventional care exists for the low-disease activity state target. Having defined low-disease activity as the alternative target to remission implies that any higher disease activity state would not be an acceptable outcome. However, this conclusion is pertinent to the care of uncomplicated RA and may have to be adjusted in line with recommendation 5, when comorbidity, drug-related risks or other patient factors mandate to refrain from intensifying therapy to reach the most desired target.

Likewise, while usually composite measures of disease activity that include joint counts, such as DAS, DAS28, CDAI or SDAI, should be employed to assess disease activity during follow-up (recommendation 4); other instruments may be a better choice to evaluate disease activity if one or more components of the composite measures are confounded by non-RA-related factors, especially comorbidities such as exaggerated pain sensitivity (fibromyalgia); this aspect is encompassed in item 5. On the other hand, in the course of caring for our patients we need to bear in mind that drugs are not the only therapeutic approach, and sometimes interventions, such as physiotherapy, surgical procedures to prevent tendon rupture or a particular focus on foot-care,[113] may be helpful and important.

Recommendation 6 addresses the need for regular assessment of disease activity and its documentation. The major change here is the deletion of a 3-month assessment if the treatment target is maintained; the Task Force felt that once the desired state is achieved for prolonged periods of time, less frequent assessments, such as every six -months (or less), is sufficient. The term 'sustained' is important in this respect since if the targeted status is achieved for the first time additional control examinations to ensure maintenance of the therapeutic success are usually needed. Recommendation 7 now refers to comorbidity in addition to structural damage progression and functional impairment. Usually, joint damage will not progress in sustained clinical remission but may increase slightly in low-disease activity. Thus, addressing destruction may be particularly pertinent to a state of low-disease activity that, should damage be rapidly progressing or functional impairment increase, may require intensification of therapy. However, comorbidity may also require adaptation of treatment, such as withdrawal or dose reduction of certain agents. On the other hand, it should be borne in mind that some comorbidities may be a consequence of inflammation and their prevention may require more intensive therapy.

As recommended in item 8, the adjustment of therapy in accordance with disease activity under the provisos discussed above is a pivotal item in the treatment strategy. It was shifted from position 4 to 8 for two reasons: first, it is only logical that before making treatment decisions disease activity has to be assessed and all factors pertaining to the treatment decision, starting with the target and ending with thoughtfulness regarding disease activity assessment, that is, recommendations 1–7, have to be accounted for; second, the need to control disease by therapeutic adaptations is implicitly included in several of the prior recommendations, namely items 4–6 (disease activity assessment), but also in items 1–3 (treatment target): how else than by treatment adaptation would one usually reach the treatment target? All the evidence currently available relates to such therapeutic adjustments at 1-to-3-month intervals—this is the foundation of treatment success, based on regular disease activity assessment and definition of a treatment target.[33] The subsequent recommendation relates to the maintenance of the treatment target and implicitly includes the possibility to taper therapy by reducing dose or expanding intervals between applications, whether csDMARDs or bDMARDs.

During the 5 years since the first formulation of the recommendations, we have witnessed an increasing proportion of patients in low-disease activity or remission, both in clinical trials and observational studies, especially when the treat-to-target strategy is employed.[92 99 100 114–117] The amended set of recommendations may allow for even further improvement as we have addressed aspects of work productivity and comorbidities more clearly and have strengthened the advice to not only evaluate disease activity but also record it in conjunction with recording the treatment target and strategy as well as the information given to the patient. This documentation is of particular importance in settings where patients are seen by different rheumatologists in the course of their disease, but are also a good prompt in all situations of interactions between patients with RA and health professionals.

The updated recommendations constitute a major advancement when compared with the 2010 version because several of the items are now based on much better evidence. In particular, the SLR has now revealed evidence for the validity and effectiveness of the T2T approach also in patients with established RA (before evidence existed only for early RA); for remission as a

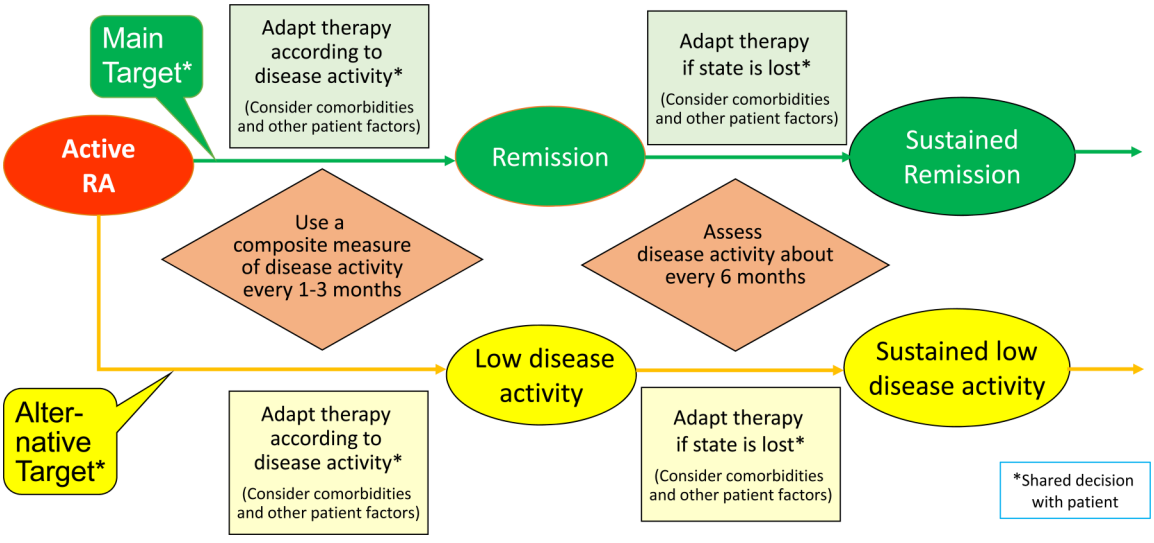

Figure 1 Algorithm of treating rheumatoid arthritis (RA) to target based on the updated recommendations provided in the table 1 and discussed in detail in the 'Results' section. Indicated as separate threads are the main target (remission and sustained remission) and the alternative target (low-disease activity in patients with long-term disease and sustained low-disease activity), but the approaches to attain the targets and sustain them are essentially identical. Adaptation of therapy should be usually done by performing control examinations with appropriate frequency and using composite disease activity measures that comprise joint counts, but should take comorbidities and other patient factors into account. Setting the target as well start and adaptation of therapy should be done as a shared decision with the patient.

treatment target (rather than only low-disease activity as before); and for the effect of a T2T approach on working ability. In addition, several items were strengthened by the new evidence. Overall, this also led to a dramatic change in the level of evidence: while originally only two recommendations had an evidence level of 1 or 2, now 7 of them are based on such high levels. Moreover, four recommendations in 2010 had levels of agreement of <9.0, while now all recommendations achieved agreement levels of ≥9.0, indicating that the members of the Task Force felt much more confident with the 2014 recommendations than was the case a few years ago. Moreover, the updated recommendations focus more strongly than the original version on the individual patient level since they more clearly address aspects of daily life that patients are rooted in, such as return to work, as well as comorbidity. They continue to emphasise the importance of shared decision-making with the patient. All this is also reflected in the algorithm depicting the recommendations in a graphic way (figure 1).

The research agenda for a potential next revision of these recommendations is inherent in the open question discussed before. To name a few: (i) Is attaining imaging remission superior to stringent clinical remission (ACR–EULAR) regarding structural and functional outcomes? (ii) If imaging remission provides statistically superior radiographic and functional outcomes compared with stringent clinical remission, is it of clinical significance that makes it worth the effort and risk of controlling patients regularly by sonography and intensifying therapy? (iii) Which measures of disease activity could be reliably used to evaluate patients with RA with particular pain sensitivity? (iv) Is monthly adaptation of therapy[16] superior to adaptations done every three months?[118] (v) How much improvement in outcomes do well informed patients experience compared with less informed patients? Finally, another important research item relates to (vi) adherence of T2T strategies in clinical practice.

While recommendations like the ones presented here may be able to summarise the current state of evidence and provide the respective target audience with some guidance, their implementation is difficult to follow. Evaluating the implementation of the T2T strategy is clearly an additional important research aspect of the future. To this end, it must be borne in mind that the success of T2T implementation, even if it constitutes a generic concept, may be different in different areas of the world. However, despite such differences the T2T concept is helpful for all societies, as so nicely summarised in a recent reflection on the situation in Russia.[119]

In summary, the updated version of the treat-to-target recommendations have brought this guidance document to a new level regarding evidence and agreement and will hopefully be adopted by the community of rheumatologists, patients and the other stakeholders.

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