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EULAR points to consider for the management of difficult-to-treat rheumatoid arthritis

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ABSTRACT

Objective To develop evidence-based European Alliance of Associations for Rheumatology (EULAR) points to consider (PtCs) for the management of difficult-to-treat rheumatoid arthritis (D2T RA).

Methods An EULAR Task Force was established comprising 34 individuals: 26 rheumatologists, patient partners and rheumatology experienced health professionals. Two systematic literature reviews addressed clinical questions around diagnostic challenges, and pharmacological and non-pharmacological therapeutic strategies in D2T RA. PtCs were formulated based on the identified evidence and expert opinion. Strength of recommendations (SoR, scale A–D: A typically consistent level 1 studies and D level 5 evidence or inconsistent studies) and level of agreement (LoA, scale 0–10: 0 completely disagree and 10 completely agree) of the PtCs were determined by the Task Force members.

Results Two overarching principles and 11 PtCs were defined concerning diagnostic confirmation of RA, evaluation of inflammatory disease activity, pharmacological and non-pharmacological interventions, treatment adherence, functional disability, pain, fatigue, goal setting and self-efficacy and the impact of comorbidities. The SoR varied from level C to level D. The mean LoA with the overarching principles and PtCs was generally high (8.4–9.6).

Conclusions These PtCs for D2T RA can serve as a clinical roadmap to support healthcare professionals and patients to deliver holistic management and more personalised pharmacological and non-pharmacological therapeutic strategies. High-quality evidence was scarce. A research agenda was created to guide future research.

INTRODUCTION

Treatment options for rheumatoid arthritis (RA) have expanded with availability of biological and targeted synthetic disease-modifying anti-rheumatic drugs (b/tsDMARDs).[1] The updated European League Against Rheumatism (EULAR, from 2021, European Alliance of Associations for Rheumatology) recommendations for the management of RA[2] focusing on pharmacological therapy are similar to those developed by other international organisations.[3–5] Other recommendations and points to consider (PtCs) provide specific management support on cardiovascular disease (CVD) risk,[6] comorbidities,[7] imaging,[8] pain[9] and patient education.[10] Together with implementation of treat-to-target and tight control strategies,[2 11] specifically in the early phase of the disease, these have contributed to improved outcomes for the majority of patients with RA.

However, some patients with RA do not reach low disease activity or remission and/or remain symptomatic after several cycles of conventional synthetic (cs) DMARDs, bDMARDs and/or tsDMARDs.[12–14] Such patients may be referred to as having 'difficult-to-treat (D2T)' disease. Optimal management of these patients poses a significant challenge in clinical practice.[15] Hitherto, no specific guidance has been developed for the management of this complex patient population. Therefore, an EULAR Task Force was convened to develop PtCs for the management of D2T RA.

METHODS

Steering Committee and Task Force

The convenor (GN) and co-convenor (JMvL) formed the Steering Committee and Task Force that followed the EULAR standardised operating procedures (SOPs).[16] The Steering Committee included the (co-)convenors, a methodologist (DvdH), a co-methodologist (PMJW), a rheumatology post-doctoral fellow (Maria J H de Hair) and three fellows (NMTR, MK and AH). The Task Force comprised the Steering Committee members and another 18 rheumatologists (including 2 EMerging EUlar Network representatives), 3 patient partners, 1 rheumatology nurse, 1 rheumatology occupational therapist, 1 psychologist and 2 pharmacists. All rheumatologists were experienced in the treatment of RA, the majority with significant experience in clinical trials and some also in outcomes

Box 1 Definition of D2T RA[17]

All three criteria need to be present in D2T RA:

1. Treatment according to EULAR recommendations and failure of ≥two b/tsDMARDs (with different mechanisms of action)† after failing csDMARD therapy (unless contraindicated).†
2. Signs suggestive of active/progressive disease, defined as ≥one of:
   a. At least moderate disease activity (according to validated composite measures including joint counts, for example, DAS28-ESR >3.2 or CDAI >10).
   b. Signs (including acute phase reactants and imaging) and/or symptoms suggestive of active disease (joint related or other).
   c. Inability to taper glucocorticoid treatment (below 7.5 mg/day prednisone or equivalent).
   d. Rapid radiographic progression (with or without signs of active disease).‡
   e. Well-controlled disease according to above standards, but still having RA symptoms that are causing a reduction in quality of life.
3. The management of signs and/or symptoms is perceived as problematic by the rheumatologist and/or the patient.

b/tsDMARDs, biological and targeted synthetic disease-modifying antirheumatic drugs; CDAI, Clinical Disease Activity Index; csDMARD, conventional synthetic disease-modifying antirheumatic drug; D2T, difficult-to-treat; DAS28-ESR, Disease Activity Score assessing 28 joints using erythrocyte sedimentation rate; RA, rheumatoid arthritis.
†Unless restricted by access to treatment due to socioeconomic factors.
†If csDMARD treatment is contraindicated, failure of ≥two b/tsDMARDs with different mechanisms of action is sufficient.
‡Rapid radiographic progression: change in van der Heijde-Modified Sharp Score ≥5 points in 1 year[184] or a similar progression in another validated scoring method.

research and patient registries. All 34 Task Force members declared their potential conflicts of interest before the start of the project. Two of the Task Force members (Maria J H de Hair and Loriane Gutermann (pharmacist)) left the Task Force during the process, due to new positions, and did not attend the second and third Task Force meetings.

Target audience

In accordance with the EULAR SOP, the primary target audience of these PtCs is healthcare professionals (HCPs) and patients (and their carers).[16] In addition, these PtCs may serve to highlight unmet needs in D2T RA and, therefore, also target policy-makers, pharmaceutical and health insurance companies.

Definition

As an initial step, a definition and a uniform term for the patient population had to be established. The Steering Committee proposed terminology and created a first draft of a definition, guided by the results of the international survey and a scoping literature review.[15] These were discussed with the whole Task Force and amended during the first Task Force meeting (held in August 2018). The final terminology and definition were agreed by a voting process. All Task Force members agreed with 'D2T RA' as the term and the final definition (box 1).[17]

Clinical questions and systematic literature reviews

The Steering Committee formulated the clinical questions for the systematic literature reviews (SLRs). Clinical questions focused on techniques for the confirmation of the diagnosis of RA and/or a relevant differential diagnosis (either as alternative (ie, misdiagnosis) or coexisting disease mimics). Additional questions centred around the assessment of inflammatory activity in patients with RA in general and in those with specific comorbidities, which may influence this assessment, adherence, pharmacological and non-pharmacological therapeutic strategies for different aspects of D2T RA: patients with limited DMARD choices because of adverse events, comorbidities or other contraindications; patients in whom at least two b/tsDMARD with different mechanisms of action (MOA) failed; and patients with predominantly non-inflammatory complaints (not directly related to inflammation). In addition, the therapeutic role of lifestyle interventions, of goal setting between patients and HCPs and of self-management was assessed. All questions were discussed and finalised during the first Task Force meeting.

SLRs on these questions were performed by the fellows (NMTR, MK and AH) under supervision of the co-methodologist (PMJW) in accordance with the EULAR SOP.[16] As other ongoing EULAR projects were already focusing on adherence and lifestyle factors, it was decided not to perform separate SLRs on these topics, but to refer to the respective SLRs and PtCs.[18 19] For the other questions, PubMed, Embase and Cochrane bibliographic databases were searched for relevant papers until December 2019, as well as EULAR and American College of Rheumatology (ACR) conference abstracts from 2017 up to and including 2019. Relevant papers were selected and critically appraised. Results were summarised, including assessment of risk of bias (RoB).[16] Further details on the methodology and results of the SLRs are published separately.[20 21]

Consensus finding

Based on the results of the SLRs, draft of overarching principles and PtCs were proposed. The results of the SLRs as well as the proposed overarching principles and PtCs were considered, then presented by the Steering Group and discussed at three consecutive online meetings (the second Task Force meeting was split into three different online meetings) of the Task Force in September 2020 and October 2020. Twenty-five, 30 and 27 Task Force members, respectively, participated in these online meetings. Thereafter, overarching principles and PtCs were discussed and amended.

A voting process was applied per PtC. In round 1, a majority of at least 75% was required to accept the PtC. If this was not achieved, the PtC was discussed and amended and subjected to the second ballot. In round 2, a majority of at least 66% was required to accept the rephrased PtC. If this was not achieved, the PtC was discussed and amended again and subjected to the third ballot. In round 3, a majority of at least 50% was required to accept the rephrased PtC. If this was not achieved, the PtC was rejected.

After the meeting, the level of evidence (LoE) and strength of recommendations (SoR) according to the Oxford Centre for Evidence-Based Medicine system were determined.[22] The agreed overarching principles and PtCs were distributed among all Task Force members via email to assess their level of agreement (LoA) for each PtC. LoA was anonymously scored on a scale from 0 to 10 (0: completely disagree and 10: completely agree). LoA is shown as mean (SD) and as the proportion of Task

Force members with an LoA of at least 8. Additionally, a research agenda was created.

All Task Force members reviewed the draft of the manuscript. Thereafter, the manuscript was submitted to the EULAR Quality of Care Committee and the EULAR Council for review and approval. A third virtual meeting was held in April 2021 to discuss the comments by the EULAR Council, with 30 Task Force members in attendance. The manuscript was revised and the final version was submitted to EULAR and subsequently to the journal.

RESULTS

General aspects

Due to the scarcity of high-quality evidence (table 1), we prepared 'PtCs' for the management of D2T RA. Our PtCs complement current EULAR recommendations that also address elements of management of D2T RA.[2] The SLRs and the formulation of the PtCs predominantly focused on topics not addressed previously and refer to several published[2 6–10 23–25] and ongoing EULAR projects where appropriate.[19]

The discussion of the Task Force resulted in 2 overarching principles and 11 PtCs (table 1). The LoE ranged from 3 to 5 and the SoR ranged from C to D, predominantly, because high-quality evidence derived in the population of interest was scarce. The LoA was generally high and ranged from 8.4 to 9.6. The order of PtCs was presented in what was considered as logical sequence—in particular the first two PtCs, which serve as a basis for all subsequent items. The PtCs as presented can be used as a clinical roadmap (figure 1). Below, a point-by-point discussion is presented, explaining the reasoning behind the different topics and the supporting evidence.

Overarching principles

The Task Force formulated the following overarching principles.

(A) These PtCs pertain to patients who fulfil the definition of D2T RA and are underpinned by the EULAR recommendations for the management of RA including the overarching principles (LoA: 9.6 (1.0)).[2 17]

This principle emphasises the relationship between these PtCs and the EULAR definition of D2T RA.[17] All overarching principles and EULAR recommendations for the management of RA also apply to D2T RA.[2] Patients who fail at least two b/tsDMARDs with different MOA, and are, therefore, potentially classified as having D2T RA, fall in phase III of the management algorithm of the 2019 EULAR RA management recommendations. These D2T RA PtCs, therefore, provide further guidance on factors contributing to the D2T RA state. The Task Force unanimously agreed with this overarching principle (100% agreed, first round, n=27).

(B) The presence or absence of inflammation should be established to guide pharmacological and non-pharmacological interventions (LoA: 9.5 (1.3)).

The Task Force emphasised that confirming the presence of inflammatory RA disease activity is essential and should be done prior to adjustment of DMARD therapy. If the persistence of signs and/or symptoms is not caused by RA disease activity, DMARD therapy would in all probability be ineffective and may lead to apparent failure of multiple (b/ts)DMARDs. Concomitant fibromyalgia, osteoarthritis and/or psychological conditions, non-adherence, and comorbidities (eg, infections and malignancies) may contribute to the D2T state.[13 26] Moreover, when the presence of inflammatory activity has been ascertained, the coexistence and role of these factors should be considered. It was agreed that in the absence of inflammatory activity, DMARD therapy should not be escalated (figure 1), and careful tapering might be considered. This overarching principle was accepted in the second round of the voting process (78% agreed, second round, n=24).

Points to consider

(1) If a patient has a presumed D2T RA, the possibility of misdiagnosis and/or the presence of a coexistent mimicking disease should be considered as a first step (LoE: 5, SoR: D, LoA: 9.3 (1.2)).

An accurate RA diagnosis is the cornerstone of appropriate management. In the SLR, very few studies could be identified on this clinically relevant item.[20 27–31] Consequently, this PtC is based on expert opinion, reinforced by indirect evidence.

Misdiagnosis (ie, an alternative disease mimic) may be more common in seronegative disease,[32 33] but should be considered in all patients with D2T RA. Several diseases may mimic ongoing RA disease activity, such as: crystal arthropathies, polymyalgia rheumatica, psoriatic arthritis, spondyloarthritis, Still's disease, systemic lupus erythematosus, Rhupus (RA–lupus) syndrome, idiopathic inflammatory myopathies, vasculitis, remitting symmetric seronegative synovitis and pitting oedema, reactive arthritis (eg, parvo B19, rubella, Whipple's disease and hepatitis B virus (HBV) and hepatitis C virus (HCV) infections), paraneoplastic syndromes, osteoarthritis and fibromyalgia.[1 34] Furthermore, such other conditions may coexist and underlie signs and/or symptoms suggestive of active RA.

Current RA management approaches may also lead to misdiagnosis. Based on the 'window of opportunity',[35] EULAR and other international guidelines emphasise the importance of early diagnosis and immediate DMARD initiation to achieve optimal and sustained benefit.[2 3] However, this raises the possibility of misdiagnosis.[36] In this context, an RA treatment approach would inevitably lead to apparent inefficacy and unnecessary risk of toxicity.

The Task Force unanimously agreed with this PtC (100% agreed, first round, n=24).

(2) Where there is doubt on the presence of inflammatory activity based on clinical assessment and composite indices, ultrasonography (US) may be considered for this evaluation (LoE: 4, SoR: C, LoA: 9.2 (1.4)).

This PtC is linked closely to overarching principle B. In daily practice, composite indices (at patient level) and the clinical evaluation of a joint being swollen (at joint level) are most frequently used to assess the presence of inflammatory disease activity.[2] However, in patients with D2T RA in whom there is a doubt about the presence of inflammation[37] (see also PtC #1), these traditional measures may be difficult to interpret.

Limited (high-quality) evidence was found on diagnostics that can be used to assess the presence or absence of inflammatory disease activity in this patient group.[20] When traditional measures are challenging, US appears to be the most feasible measure to detect inflammatory activity both in patients with D2T RA in general and in those with conditions that might compound assessment, such as obesity or concomitant fibromyalgia. In the general population of RA (where composite indices can be considered reliable), moderate-to-strong correlations were reported between US sum scores and composite indices on a group level.[38–45] In a study in established patients with RA in whom there was explicit doubt about the presence of inflammation, only weak and non-statistically significant correlations between US sum scores and composite indices were found.[46]

Table 1 EULAR PtCs for the management of D2T RA

		LoE[22]	SoR[22]	LoA mean (SD)	≥8/10 (%)
	Overarching principles				
A	These PtCs pertain to patients who fulfil the definition of D2T RA and are underpinned by the EULAR recommendations for the management of RA, including the overarching principles.[2 17]	NA	NA	9.6 (1.0)	97
B	The presence or absence of inflammation should be established to guide pharmacological and non-pharmacological interventions.	NA	NA	9.5 (1.3)	91
	PtCs				
1	If a patient has a presumed D2T RA, the possibility of misdiagnosis and/or the presence of a coexistent mimicking disease* should be considered as a first step.	5	D	9.3 (1.2)	91
2	Where there is a doubt on the presence of inflammatory activity based on clinical assessment and composite indices, US may be considered for this evaluation.	4	C	9.2 (1.4)	91
3	Composite indices and clinical evaluation should be interpreted with caution in the presence of comorbidities‡ in particular obesity and fibromyalgia§ as these may directly heighten inflammatory activity and/or overestimate disease activity.	‡5 §4	‡D §C	9.2 (1.3)	88
4	Treatment adherence should be discussed and optimised within the process of shared decision-making.	5	D	9.5 (1.0)	97
5	After failure of a second or subsequent b/tsDMARD‡ and particularly after two TNFi failures§ treatment with a b/tsDMARD with a different target should be considered.	‡4 §3	‡C §C	9.2 (1.3)	94
6	If a third or subsequent b/tsDMARD is being considered, the maximum dose, as found effective and safe in appropriate testing, should be used.	3	C	8.4 (1.8)	75
7	Comorbidities† that impact quality of life either independently or by limiting RA treatment options should be carefully considered and managed.	5	D	9.3 (0.8)	97
8	In patients with concomitant HBV/HCV infection, b/tsDMARDs can be used‡ and concomitant antiviral prophylaxis or treatment should be considered in close collaboration with the hepatologist§.	‡4 §5	‡C §D	8.9 (1.4)	88
9	In addition to pharmacological treatment, non-pharmacological interventions (ie, exercise‡, psychological§, educational‡ and self-management interventions‡) should be considered to optimise management of functional disability, pain and fatigue.	‡3 §4	‡C §C	9.4 (1.2)	97
10	Appropriate education and support should be offered to patients to directly inform their choices of treatment goals and management.	4	C	9.4 (1.2)	97
11	Consider offering self-management programmes, relevant education and psychological interventions to optimise patient's ability to manage their disease confidently (ie, self-efficacy).	3	C	9.1 (1.7)	91

Continued

Table 1 Continued

	LoE[22]	SoR[22]	LoA mean (SD)	≥8/10 (%)

In case the LoE and SoR differed for different items within a PtC, differences in LoE and SoR are shown using the symbols‡ and §.
*Relevant mimicking diseases, for instance, crystal arthropathies, polymyalgia rheumatica, psoriatic arthritis, spondyloarthritis, Still's disease, SLE, Rhupus syndrome, vasculitis, idiopathic inflammatory myopathies, RS3PE, reactive arthritis (eg, parvo B19, Rubella, Whipple's disease, HBV and HCV infections), paraneoplastic syndromes, osteoarthritis and fibromyalgia.
†Relevant comorbidities: for instance, infections, malignancies, polymyalgia rheumatica and osteoarthritis, and consequences of longstanding destructive disease such as subluxations and joint dislocations.
b/tsDMARD, biological and targeted synthetic disease-modifying antirheumatic drugs; D2T, difficult-to-treat; EULAR, European Alliance of Associations for Rheumatology; HBV, hepatitis B virus; HCV, hepatitis C virus; LoA, levels of agreement; LoE, level of evidence (according to the standards of the Oxford Centre for Evidence-Based Medicine); NA, not applicable; PtCs, points to consider; RA, rheumatoid arthritis; RS3PE, remitting symmetric seronegative synovitis and pitting oedema; SLE, systemic lupus erythematosus; SoR, strengths of recommendations (according to the standards of the Oxford Centre for Evidence-Based Medicine); TNFi, tumour necrosis factor inhibitor; US, ultrasonography.

This suggests that US may be better related to 'true' inflammatory activity in these patients and may have additional value in patients with D2T RA in whom a doubt about the presence of inflammatory activity exists. However, the minimal number of joints that should be included in an US assessment remains unclear,[41] which hampers the use of a sum score to determine the overall level of disease activity in daily practice. Of note, no studies were found on tests in patients with comorbidities that may influence the assessment of disease activity.

The evidence for biomarkers (eg, miR-146, fibrinogen, resistin, matrix metallopeptidase 3, interleukin 6 and multibiomarker disease activity score) and other imaging measures (eg, MRI or optical spectral transmission measures) is currently less convincing.[20 40 47–61] The quality of this evidence was low to moderate and no evidence could be identified on their role in patients in whom there was explicit doubt about the presence of inflammatory activity resulting in indirectness. These limitations hamper the current use of these biomarkers and imaging modalities in daily practice.

The Task Force unanimously agreed with this PtC (100% agreed, first round, n=24).

(3) Composite indices and clinical evaluation should be interpreted with caution in the presence of comorbidities‡, in particular obesity and fibromyalgia§, as these may directly heighten

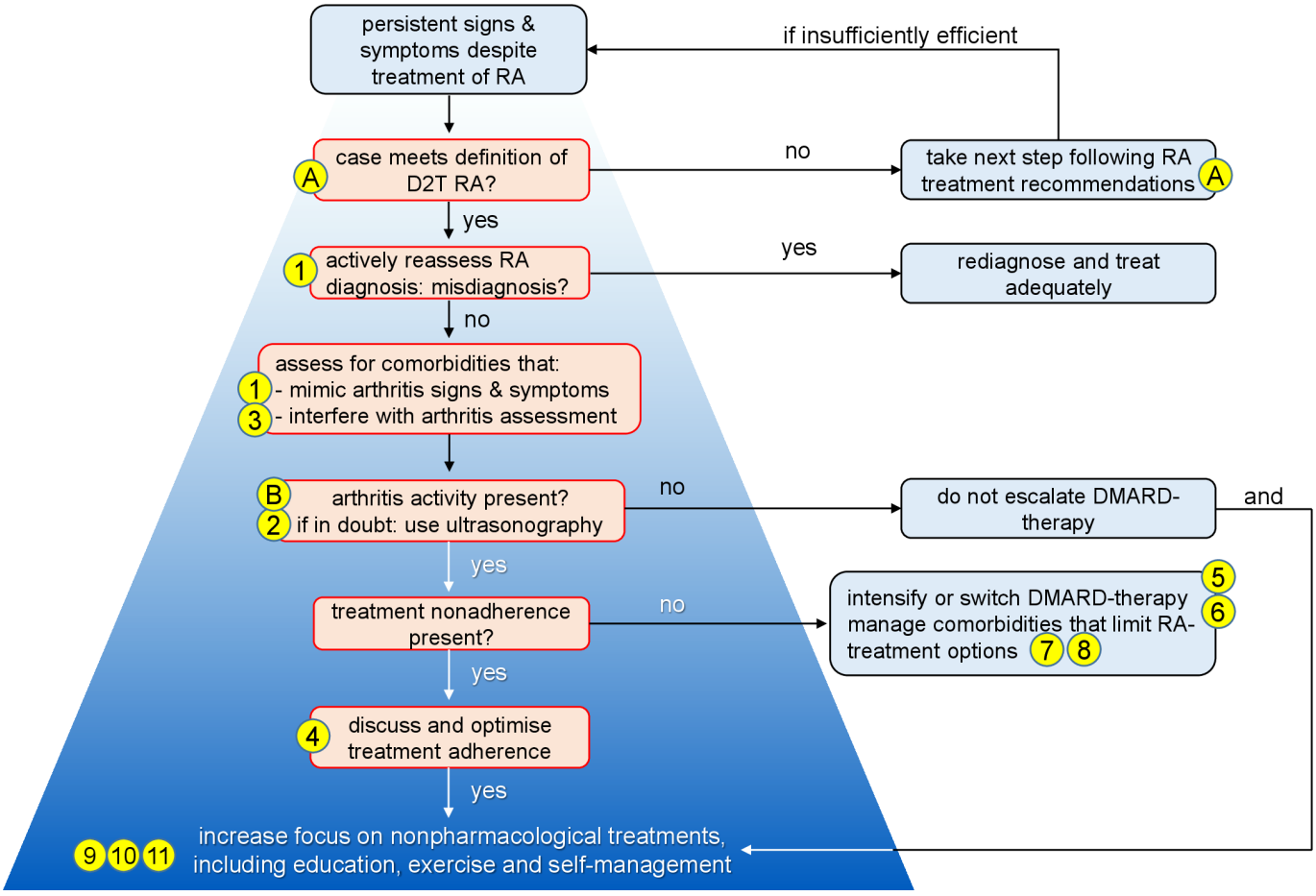

Figure 1 Algorithm based on the EULAR PtCs for the management of D2T RA. The pyramid background with increasing intensity of blue colour indicates non-pharmacological approaches and treatments, which are important throughout all phases of RA, but especially so if pharmacological treatment options are limited. The letters and numbers indicate the corresponding overarching principles and PtCs, respectively; see table 1. D2T, difficult-to-treat; DMARD, disease-modifying antirheumatic drug; EULAR, European Alliance of Associations for Rheumatology; PtCs, points to consider; RA, rheumatoid arthritis.

inflammatory activity and/or overestimate disease activity (‡LoE: 5, SoR: D; §LoE: 4, SoR: C; LoA: 9.2 (1.3)).

Although the Task Force was unanimous in its opinion that numerous comorbidities might influence the assessment of inflammatory disease activity, substantial evidence was only found for obesity and fibromyalgia.[20 62–65] These two conditions may also frequently coexist, further complicating the precise assessment of inflammatory disease activity. Other comorbidities (especially those increasing acute phase reactants: eg, infections, malignancies or polymyalgia rheumatica) may lead to misclassification of inflammatory RA activity, although no substantial evidence was identified to support this. In addition, no evidence was identified regarding the impact of osteoarthritis, subluxation or joint dislocations on clinical evaluation of joints.[20] It should be noted that the identification of synovitis and tenderness due to inflammation is generally more difficult in joints with destruction, since, for example, tenderness could be due to destruction rather than synovitis. The Task Force agreed that this PtC should refer to all potential comorbidities that may influence the evaluation of inflammatory disease activity. The Task Force unanimously agreed with this PtC (100% agreed, first round, n=24).

(4) Treatment adherence should be discussed and optimised within the process of shared decision-making (LoE: 5, SoR: D, LoA: 9.5 (1.0)).

In RA, drug non-adherence rates reportedly vary between 30% and 80%[18 66–68] and these rates are indicated to be substantially higher in patients with D2T RA compared with patients with non-D2T RA.[26] Suboptimal adherence is associated with higher disease activity levels, which may result in inappropriate treatment switches and reduced quality of life.[69–73] In a patient with D2T RA, this could exhaust all currently available (b/ts) DMARDs. Therefore, the Task Force unanimously agreed that adherence should be addressed as a standalone PtC. Another EULAR project has recently provided detailed PtCs for the detection, assessment and management of non-adherence in people with rheumatic and musculoskeletal diseases (RMDs). We, therefore, refer to their SLR and PtCs.[18 19]

The Task Force agreed to concur with WHO definitions[74] and especially considered ‘treatment adherence’ instead of ‘drug adherence’, as the PtC also applies to non-pharmacological strategies. There is no gold standard for identifying non-adherence. Questionnaires or serum and/or urine drug level measurements may be used.[18 75 76] If suboptimal adherence is present, this might be explained by various factors; both unintentional (eg, forgetting to take the prescribed drugs) and intentional non-adherence (driven by a decision not to take the prescribed drugs, eg, due to fear of side effects) are common in RA.[66 76 77] The patient’s evaluation of the risk–benefit ratio of the selected drug(s) is also of paramount importance. Therefore, discussions on adherence remain highly important. In addition to physicians, other HCPs, such as nurses experienced with patients with RA, psychologists and pharmacists, may also be involved in these discussions.

Shared decision-making is clearly vital to optimise adherence.[18 76] In this context, the quality of the relationship between the patient and the HCP is important.[78 79] As non-adherence is a vulnerable topic, the patient should be made to feel safe and supported to discuss all aspects. In addition, appropriate education, especially in case of intentional non-adherence, would be useful and could strengthen the process of shared decision-making (see also PtCs ‡9 and 10).[18 76] This PtC was accepted in the first round of the voting process (96% agreed, first round, n=28).

(5) After failure of a second or subsequent b/tsDMARD‡ and particularly after two tumour necrosis factor inhibitor (TNFi) failures§ treatment with a b/tsDMARD with a different target should be considered (‡LoE: 4, SoR: C; §LoE: 3, SoR: C; LoA: 9.2 (1.3)).

Increasing numbers of b/tsDMARDs (with different MOA) are available for the treatment of RA.[80] Switching within class as well as switching to a drug with a different MOA can be effective.[2 20 80] However, a considerable proportion of patients with RA fail at least two b/tsDMARDs with different MOA, which may result in reaching criteria for D2T RA.[12 13 81] In routine practice, a trial-and-error approach to DMARD cycling predominates when signs and/or symptoms suggestive active disease are present.[13] In the SLR, only limited evidence was identified on pharmacological therapeutic strategies in patients with RA in whom at least two b/tsDMARDs (specifically with different MOA) failed.[21] Several identified trials in patients with RA in whom multiple b/tsDMARDs failed did not clearly state reasons for previous DMARD failure (eg, toxicity, lack of efficacy or other factors). This resulted in the inclusion of heterogeneous patient populations, complicating interpretation of outcomes.

After failure of at least two b/tsDMARDs, some evidence was identified regarding the beneficial effect of treatment with a b/tsDMARD with a different target.[21] This evidence indicated that a third or fourth b/tsDMARD (ie, tocilizumab, tofacitinib, baricitinib, upadacitinib and filgotinib) is more effective than placebo.[82–87] However, no preference can be given to any of these DMARDs. In patients with failure of at least one prior bDMARD, TNFi, abatacept and rituximab were more effective than placebo,[80 88–92] although direct evidence was lacking about the efficacy as third and fourth bDMARD compared with placebo.[21] Where a higher number of prior bDMARDs had been ineffective, the extent of the beneficial effect of several b/tsDMARDs (TNFi and the lower doses of tocilizumab, tofacitinib and baricitinib) was less.[82 83 93–97] Furthermore, a tendency was identified for non-TNFis to be more efficacious than TNFis in patients in whom at least one bDMARD failed (predominantly if TNFi was failed).[88 89 95 98–115] Our current PtC proposes to switch to a b/tsDMARD of different MOA, after failure of a second or subsequent b/tsDMARD and, particularly, after failure of two TNFis. This PtC was accepted in the first round of the voting process (96% agreed, first round, n=24).

The Task Force emphasised that the current PtC is in line with the 2019 EULAR RA recommendation on b/tsDMARD switches. Our PtC adds the following: first, there is value in prescribing another b/tsDMARD after failure of a second or subsequent b/tsDMARD; and second, a b/tsDMARD with a different MOA is preferred after failure of a second or subsequent b/tsDMARD.[2] Concerning DMARD combination therapy, we refer to the 2019 RA EULAR recommendations, as no additional evidence was identified for D2T RA.[2]

(6) If a third or subsequent b/tsDMARD is being considered, the maximum dose, as found effective and safe in appropriate testing, should be used (LoE: 3, SoR: C, LoA: 8.4 (1.8)).

The extent of the beneficial effect of b/tsDMARDs was generally less in patients in whom a higher number of previous bDMARDs failed.[21] This tendency was not so apparent for upadacitinib and filgotinib, and for the higher doses of tocilizumab (intravenously administered, 8 mg/kg), baricitinib (4 mg once daily) and tofacitinib (10 mg two times per day, although tofacitinib is not licensed at higher doses than 5 mg two times per day because of safety concerns).[82 83 85 87 96 97] It should be noted, however, that baricitinib (4 mg once daily) should not be used in patients older than 75 years or those with reduced creatinine clearance (30–60 mL/min).

This suggests that the higher doses of intravenous tocilizumab, and tofacitinib and baricitinib may be preferred in patients in whom previously a higher number of bDMARDs failed.[82 83 96 97] The evidence supports the use of higher doses from the beginning, excepting patients in whom contraindications for this higher dose are present.

In addition, it was argued that this PtC might be more informative by including the names of the specific b/tsDMARD (baricitinib and tocilizumab, and not tofacitinib, as tofacitinib is not licensed at higher doses than 5 mg two times per day). The following wording was accepted (95% agreed, first round, n=22): 'If a second or subsequent b/tsDMARD has failed, and baricitinib or iv tocilizumab are being considered, the higher licensed dose should be used if appropriate'. However, it was also discussed that explicitly mentioning drug names (ie, baricitinib and tocilizumab) should be avoided in management PtCs as novel evidence may emerge for other drugs. Therefore, the Steering Committee initiated a new voting after the Task Force meeting regarding this PtC without explicit drug names. The Task Force members agreed to change the wording of the PtC and to exclude the drug names resulting in the current recommendation (94% agreed, second round, n=32).

(7) Comorbidities that impact quality of life either independently or by limiting RA treatment options, should be carefully considered and managed (LoE: 5, SoR: D, LoA: 9.3 (0.8)).

In clinical practice, comorbidities may significantly limit treatment options, potentially contributing to the D2T state.[7 13 15 116] The Task Force agreed to formulate a PtC on the importance of comorbidities (100% agreed, first round, n=28).

We sought evidence about safe and efficacious therapies in patients with such contraindications.[21] No studies were identified for patients with RA with HIV, gastrointestinal disease, latent tuberculosis and malignancies; only limited evidence was identified for patients with RA with extra-articular manifestations, hepatic disease, osteoporosis, psychological distress, pulmonary disease and renal disease. More than one study per intervention was identified only for patients with RA with HBV, HCV (see also PtC #8), CVD, before and during pregnancy and lactation, and obesity.

Concerning venous thromboembolisms (VTEs), higher frequencies of VTEs were reported in patients with RA using tsDMARDs at high doses, and in whom risk factors for VTE are present.[117] The Task Force unanimously agreed that in patients at risk for VTEs, tsDMARDs, specifically at high doses, should be used with caution and per drug label recommendations. As this item is covered in the 2019 EULAR RA management recommendations[2] and as the increased risk of VTEs is not specific for patients with D2T RA, the Task Force unanimously decided not to include this item as a standalone PtC (no formal voting). Nevertheless, the increased risk of VTEs should be considered as factor limiting treatment options, particularly for patients with D2T RA with VTE risk factors.

Recommendations about safe DMARDs use before and during pregnancy and lactation are published as 2016 EULAR PtCs and as a 2020 ACR guideline.[118 119] Few additional studies were identified, subsequently on these papers[21 120–122]; therefore, we refer to the existing guidance.[118 119]

Although obesity does not limit drug options per se, treatment efficacy might be different in obese patients.[13 123] Intravenously administered infliximab may be less effective in patients with a body mass index (BMI) above 30 kg/m^2 compared with those with a BMI below 30 kg/m^2.[124 125] The Task Force voted whether this issue should be a standalone PtC. The first vote did not clearly indicate the preference of the Task Force (formulate a separate PtC on this item 58%, n=24). Further discussion noted that evidence for several other comorbidities was lacking or very limited. Two studies of relevance had a high RoB.[124 125] The repeat vote indicated not to formulate a separate PtC on this item (formulate a separate PtC on this item: 12%, n=24).

Clinically meaningful contraindications of some therapies may result in limited treatment options, for example, tocilizumab in case of diverticulitis or janus kinase (JAK) inhibitors in case of repeated herpes zoster infections.[117] However, no substantial clinical evidence was identified about safe and/or efficacious therapies for patients with these conditions[21] and, therefore, no specific PtCs were formulated. A broad range of comorbidities and coexisting conditions were discussed at the Task Force meeting but are not explicitly part of the PtCs due to the lack of evidence.[21]

(8) In patients with concomitant HBV/HCV infection, b/tsDMARDs can be used‡ and concomitant antiviral prophylaxis or treatment should be considered in close collaboration with the hepatologist§ (‡LoE: 4, SoR: C, §LoA: 5; SoR: D, LoA: 8.9 (1.4)).

Substantial evidence was identified related to HBV and HCV infections prompting a standalone PtC.[21] TNFi, abatacept and tocilizumab may be considered in patients with HBV,[126–128] and TNFi in patients with HCV.[129 130] Furthermore, no evidence was identified regarding other b/tsDMARDs, but this does not indicate that these b/tsDMARDs are unsafe to use. Therefore, the Task Force voted not to include specific b/tsDMARDs in the PtC (83% agreed, n=24). Furthermore, the Task Force agreed that concomitant antiviral prophylaxis should be considered,[126] and that the treatment should be conducted in close collaboration with the hepatologist. The Task Force unanimously agreed with this PtC (100% agreed, first round, n=24). It should be noted that concomitant antiviral prophylaxis is appropriate for HBV infection in case of HCV infection, antiviral treatment is necessary.

(9) In addition to pharmacological treatment, non-pharmacological interventions (ie, exercise‡, psychological§, educational‡ and self-management interventions†) should be considered to optimise management of functional disability, pain and fatigue (‡LoE: 3, SoR: C; §LoE: 4, SoR: C; LoA: 9.4 (1.2)).

A wide spectrum of factors may contribute to the persistence of signs and/or symptoms, although these are not always directly related to inflammation (eg, functional disability, pain and fatigue).[13 26] Individually tailored non-pharmacological interventions are also important components of the management of D2T RA.[13 21 26] The SLR focused on non-DMARD interventions to improve non-inflammatory complaints in patients with RA who do not clearly have active inflammatory disease.[21] It is not always possible to disentangle inflammatory and non-inflammatory symptoms in clinical practice. Non-pharmacological interventions should also be considered in all patients with D2T RA[26] and not only in those patients without inflammatory RA activity.

Evidence emerged regarding the beneficial effect of exercise, education, psychological and self-management interventions to improve pain, fatigue and functional disability in RA, while substantial evidence regarding the role of non-pharmacological interventions to improve quality of life was lacking.[21] Benefit of exercise in RA is well established[131] and was specifically found to improve physical functioning. A wide range of physical activities might be advised in accordance with the patients' status, for example, aerobic exercises, water-based dynamic exercises, muscle strengthening or hand exercises.[132–144] Psychological interventions could be applied, specifically to reduce pain and fatigue, for example, cognitive behavioural therapy and interventions focusing on stress management.[142 145–149] Furthermore,

patient education can assist patients in learning about their disease and management options (see also PtCs #4, 9 and 10)[10] and was specifically found to improve physical functioning.[139] Education can be provided one on one, but also in group sessions promoting patients to learn from each other. Lastly, self-management programmes can be applied. These programmes are typically a combination of different non-pharmacological interventions (eg, exercise and education) and were found to optimise the management of pain, fatigue and functional disability (see also PtCs #9 and 10).[136 150–159]

Ideally, a package of care (ie, multimodal treatment) should be considered in accordance with the patient's needs and preferences. This individually tailored multimodal treatment can be provided by different members of the rheumatology team (eg, rheumatologists, rehabilitation physicians, nurses experienced with patients with RA, physiotherapists, occupational therapists, psychologists, pharmacists and podiatrists). The Task Force unanimously agreed with this PtC (100% agreed, first round, n=29).

(10) Appropriate education and support should be offered to patients to directly inform their choices of treatment goals and management (LoE: 4, SoR: C, LoA: 9.4 (1.2)).

Setting treatment goals is central in the management of RA. In the current EULAR RA management recommendations, clinical remission or at least low disease activity is the ideal target with adjustment of therapeutic strategies if there is no improvement at 3 months or if the treatment target is not achieved at 6 months (recommendation #3).[2] These treatment targets may be unrealistic to achieve for patients with D2T RA, considering their disease history, accrued joint damage and other factors that may contribute to the D2T RA state,[13] and lead to unnecessary DMARD switches. Accordingly, in D2T RA, treatment goals should be tailored to the individual patient.

Discordance in a given set target between the patient and HCP could negatively impact disease outcomes.[13] The SLR did not find a diagnostic method to identify a mismatch in treatment goals (between HCP and patient with RA).[21] Treatment goals should be discussed to be able to identify a mismatch in treatment goals and to optimise goal setting in shared decision-making.

Web-based education tools improve patients' knowledge and certainty in treatment decisions.[21 160–163] Such tools could be used in addition to providing information via usual discussions. As perceptions on treatment goals and management may change over time continuous education between patients and HCPs remains important. This PtC was accepted in the first round of the voting process (89% agreed, first round, n=28).

(11) Consider offering self-management programmes, relevant education and psychological interventions to optimise patient's ability to manage their disease confidently (ie, self-efficacy; LoE: 3, SoR: C, LoA: 9.1 (1.7)).

Self-efficacy refers to patients' ability to control or manage various aspects of their disease and has a major role in the well-being of patients.[164] Self-efficacy beliefs determine how individuals think, feel and act, and are an important aspect of self-management. People with low self-efficacy quickly give up their goals when faced with difficulties and are at higher risk of worse levels of pain, fatigue, depression, anxiety and stress.[164–166] All this may contribute to the D2T RA state.[13 26] In contrast, a strong sense of self-efficacy improves human performance and well-being in several ways, promotes the accomplishment of challenging goals and supports commitment to them.[164] Improved self-efficacy may not only improve disease outcomes such as mental well-being but may also improve many aspects of health behaviour, including treatment adherence and willingness to change lifestyle factors. Therefore, strengthening self-efficacy is specifically important in D2T RA.

The Arthritis Self-Efficacy Scale (ASES), a tool to measure perceived self-efficacy to cope with the disease,[167] was found as the most reliable measure of self-efficacy.[21 168] However, the ASES is perhaps too general to evaluate self-efficacy[168] and cut-offs for suboptimal self-management are not well-validated, so a standalone PtC regarding its application was not pursued (89% agreed, n=27). There was consensus that the ASES may be used as a screening instrument and to assess the change in self-efficacy over time. The Task Force considered it challenging to clearly define what constituted a suboptimal level of self-efficacy and agreed that offering interventions to improve self-efficacy could be beneficial for all patients with D2T RA.

The SLR identified self-management programmes, educational interventions and psychological interventions to have a beneficial effect on self-efficacy.[21] Some evidence suggested patients would like more education on disease processes.[21 169 170] Educational interventions, for example, individual education, a group education programme or education through a mobile app, specifically improved self-efficacy and RA knowledge.[154 155 171–175] Psychological interventions, for example, cognitive behavioural therapy or relaxation therapy, not only improve self-efficacy, but may also reduce symptoms related to anxiety and depression.[148 151 176] Self-management programmes (ie, typically a combination of different non-pharmacological interventions) were also found to be effective in improving self-efficacy.[136 143 151–153 155–158 177–181] In addition, mobile health applications may improve self-management.[182]

The Task Force thoroughly debated if these interventions should be offered to every patient (mandatory) or should be considered only (optional). The Task Force agreed that self-management programmes should be optional (agreed 82%, n=28). If a patient wishes to improve their self-efficacy, a shared decision-making that captures the patient's status and preferences should decide the type of intervention. This PtC was accepted in the first round of the voting process (96% agreed, first round, n=28).

Research agenda

The Task Force created a research agenda containing research questions that are considered most relevant to address (table 2).

DISCUSSION

The term 'D2T RA' has recently been defined to characterise a heterogeneous group of patients with RA with persistent signs and symptoms.[8 10 12 26] While the typical patient with D2T RA is characterised by longstanding disease and structural damage in whom (b/ts)DMARDs have been ineffective (multidrug resistant or 'true refractory' RA), this only represents a subgroup of this heterogeneous patient population. Identification of all factors potentially contributing to D2T RA warrants a holistic management approach and is essential in order to tailor management strategies to the individual patient. D2T RA constitutes an area of unmet need, which motivated our Task Force to develop a roadmap for clinical decision-making by HCPs and patients laid out in the current PtCs on diagnostic challenges and pharmacological and non-pharmacological therapeutic strategies (summarised in figure 1).

The PtCs promote individually tailored treatment interventions by addressing specific aspects of b/tsDMARD selection (including in patients with comorbidities and coexisting conditions) and non-pharmacological interventions to improve

Table 2 Research agenda

1	How can we optimally confirm a diagnosis of RA in patients with D2T RA?
2	Which reference standard should be used to assess the presence or absence of inflammation in patients with D2T RA, in whom there is a doubt after assessment by traditional measures?
3	What is the role of synovial biopsies in the assessment of the presence or absence of inflammation in D2T RA?
4	Could synovial tissue analyses be used to stratify b/tsDMARD treatment in D2T RA?
5	Could treatment history be used to stratify b/tsDMARD treatment in D2T RA?
6	Are any of the b/tsDMARDs superior to treat inflammatory disease activity in D2T RA?
7	Which DMARD is preferred in patients with D2T RA with specific adverse events, comorbidities (including extra-articular manifestations), other coexisting conditions and other contraindications that limit DMARD options?*
8	Could the development of the D2T RA state be prevented by adequate management of the potentially contributing factors in an earlier phase of RA?
9	Could the D2T RA state be ameliorated if potentially contributing factors are adequately addressed?
10	Does 'true' refractory RA (patients in whom (b/ts)DMARDs are truly ineffective) really exist?
11	Which immunological mechanisms and/or pathways underlie inefficacy to multiple b/tsDMARDs in D2T RA?
12	How does smoking impact D2T RA?
13	How does obesity impact D2T RA? And which treatment is preferred in patients with D2T RA with obesity?
14	What is the role of therapeutic drug monitoring to in the management of DT RA?

*For example, infections (HIV and TB); malignancies; lung disease (fibrosis, asthma and COPD); CVD (hypertension and cardiomyopathy); hyperlipidaemia; chronic kidney dysfunction; chronic liver dysfunction; liver enzyme elevation; osteoporosis; diabetes mellitus; thrombosis; depression and anxiety.
b/tsDMARDs, biological or targeted synthetic disease-modifying antirheumatic drugs; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; D2T, difficult-to-treat; RA, rheumatoid arthritis; TB, tuberculosis.

adherence, functional disability, pain, fatigue, goal setting and self-efficacy. Although some of these PtCs may seem self-evident, our purpose in offering this PtC is to promote the need to address each of them in D2T RA management strategies. This approach mitigates against both overtreatment as well as undertreatment.

Although the Task Force aimed to cover all potential aspects of D2T RA, not all relevant topics were addressed in the SLRs because of overlap with previous or ongoing EULAR projects (eg, treatment non-adherence, lifestyle factors, pain syndromes and osteoarthritis, see below). Joint replacement and reconstructive surgery, both of which may have relevance in D2T RA, were not included in the systemic literature search, as these were considered out of scope. There was no substantial evidence identified regarding non-steroidal-anti-inflammatory drugs and analgesics in the context of D2T RA.[21] For a few topics, the Task Force members considered a theme particularly relevant in the context of D2T RA as to merit highlighting herein. For instance, education is already addressed in separate EULAR recommendations[10] but is crucial in the management of D2T RA (§4 and 9–11). Additionally, treatment non-adherence is common in patients with RMDs and may also contribute to the D2T RA state[13 26 74 76]; therefore, it has also been addressed in the D2T RA PtCs (#4). Additional guidance on treatment non-adherence can be found in the recently published EULAR PtCs for the detection, assessment and management of non-adherence in people with RMDs.[19]

Furthermore, lifestyle factors, including diet, lack of exercise, smoking and alcohol consumption, might also be associated with D2T disease.[13 183] Therefore, the management of lifestyle factors in patients with D2T RA was raised as a clinically relevant issue at our first Task Force meeting and resulted in the formulation of a research question on this topic. However, an ongoing EULAR project is focusing on lifestyle behaviour PtCs to prevent progression of RMDs and will be published soon. The Task Force, therefore, decided to refer to these PtCs for the management of these factors, as evidence in patients with D2T RA specifically was expected to be lacking.

Concomitant fibromyalgia and other pain syndromes as well as osteoarthritis may coexist in patients with D2T RA and may (partly) explain the persistence of signs and/or symptoms suggestive of active disease.[13 26] Because previous EULAR projects focused on these conditions, it was decided to refer to their recommendations. Guidance on the management of these coexisting conditions can be found in the 'EULAR revised recommendations for the management of fibromyalgia',[23] 'EULAR recommendations for the health professional's approach to pain management in inflammatory arthritis and osteoarthritis',[9] '2018 update of the EULAR recommendations for the management of hand osteoarthritis'[24] and 'EULAR recommendations for the non-pharmacological core management of hip and knee osteoarthritis'.[25]

One of the main conclusions of the SLRs was the scarcity of high-quality direct evidence regarding D2T RA.[20 21] This is not surprising, considering the recent establishment of the EULAR definition of D2T RA.[17] However, indirect evidence (ie, in patients with RA in whom at least two b/tsDMARDs failed, especially with different MOA) was also scarce and the quality was generally low to moderate.[20 21] This lack of (high-quality) direct evidence can be seen as a limitation of these PtCs, but also as a stimulus for future studies to address patients with D2T RA specifically. Importantly, the heterogeneity of D2T RA should be considered when conducting such studies, as not all management strategies will be helpful in all patients with D2T RA. Selecting the appropriate patient population will, therefore, be crucial in order to obtain relevant results (see also table 2). As new evidence regarding D2T RA emerges, the PtCs on the management of D2T RA will need to be updated.

In summary, the evidence as identified in the SLRs together with expert opinion have resulted in a comprehensive set of overarching principles and PtCs for the management of D2T RA, promoting a holistic management approach and individually tailored pharmacological and non-pharmacological therapeutic strategies. Although high-quality evidence was scarce, these PtCs can be seen as a clinical roadmap and will provide assistance to HCPs and patients in the management of D2T RA. A research agenda was created to support future research in this emerging field.

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