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EULAR definition of difficult-to-treat rheumatoid arthritis

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ABSTRACT

Background Despite treatment according to the current management recommendations, a significant proportion of patients with rheumatoid arthritis (RA) remain symptomatic. These patients can be considered to have 'difficult-to-treat RA'. However, uniform terminology and an appropriate definition are lacking.

Objective The Task Force in charge of the "Development of EULAR recommendations for the comprehensive management of difficult-to-treat rheumatoid arthritis" aims to create recommendations for this underserved patient group. Herein, we present the definition of difficult-to-treat RA, as the first step.

Methods The Steering Committee drafted a definition with suggested terminology based on an international survey among rheumatologists. This was discussed and amended by the Task Force, including rheumatologists, nurses, health professionals and patients, at a face-to-face meeting until sufficient agreement was reached (assessed through voting).

Results The following three criteria were agreed by all Task Force members as mandatory elements of the definition of difficult-to-treat RA: (1) Treatment according to European League Against Rheumatism (EULAR) recommendation and failure of ≥2 biological disease-modifying antirheumatic drugs (DMARDs)/targeted synthetic DMARDs (with different mechanisms of action) after failing conventional synthetic DMARD therapy (unless contraindicated); (2) presence of at least one of the following: at least moderate disease activity; signs and/or symptoms suggestive of active disease; inability to taper glucocorticoid treatment; rapid radiographic progression; RA symptoms that are causing a reduction in quality of life; and (3) the management of signs and/or symptoms is perceived as problematic by the rheumatologist and/or the patient.

Conclusions The proposed EULAR definition for difficult-to-treat RA can be used in clinical practice, clinical trials and can form a basis for future research.

INTRODUCTION

European League Against Rheumatism (EULAR) recommendations provide valuable guidance to direct the management of rheumatoid arthritis (RA). The treat-to-target (T2T) strategy advises an agreed disease activity target, remission or at least low disease activity, that can in turn inform responsive treatment escalation.[1–3] However, a number of patients remain symptomatic despite recommended treatment changes reflecting the complex interplay of disease and wider patient and clinical factors that leads to the increasingly recognised term of 'difficult-to-treat RA'.[4–7]

A recent international survey of rheumatologists highlighted the perceived management problems and features in this patient category; the results of which confirmed the unmet need of this subpopulation of RA patients.[8] The survey indicated that in addition to new drugs, new management approaches are also needed for the optimal treatment of these patients. Consequently, a EULAR Task Force was established to derive comprehensive recommendations addressing unmet needs in the management of difficult-to-treat (D2T) RA. Uniform terminology and a clear definition for this patient group are lacking. In the current literature, different terms are used to describe this subpopulation of RA patients, for example, severe, refractory, resistant to multiple drugs or treatments, established and difficult-to-treat.[4–7] As an initial step in the development of the management recommendations for D2T RA, terminology and a definition of this complicated RA patient group was established by the Task Force, guided by the results of the survey.[8]

METHODS

Steering committee and task force

The Steering Committee of the Task Force included a convenor (GN), co-convenor (JMvL), two methodologists (PMJW and DvdH) a rheumatology postdoctoral fellow (MJHdH) and three fellows (NMTR, MK and AH). The Task Force comprises 32 individuals (including the Steering Committee members) of which 25 members were present at the first Task Force meeting, which took place in August 2018. Among the Task Force members, there were 26 rheumatologists (including two EMerging EUlar

Network (EMEUNET) representatives), two patient partners, one health professional, one psychologist, one pharmacist and one occupational therapist. All rheumatologists are experienced in the treatment of RA, the majority with significant experience in clinical trials and a proportion in outcomes research. Numerous Task Force members have a leading role in organising and evaluating patient registries. All Task Force members declared their potential conflicts of interest before the start of the project.

Survey

An online survey was conducted among rheumatologists to identify characteristics of D2T RA; the survey was distributed by email via the authors' networks and by EMEUNET. The survey consisted of nine questions, including two general questions 'Where do you work? How many RA patients do you treat?', and four multiple-choice and three open questions regarding the definition of D2T RA. Four hundred and ten respondents from 33 countries completed the survey between July 2017 and March 2018, 96% of the respondents were European.[8]

Development of terminology and definition for D2T RA

The Steering Committee created the first draft of the definition based on the results of the survey and on a scoping literature search that was performed to explore different definitions that currently have been used (by NMTR, MJHdH and PMJW, see, online supplemental material 1). The results of the survey, the proposed terminology and the draft definition were presented to the Task Force at the first Task Force meeting. The definition was divided into three parts: treatment failure history, characterisation of active/symptomatic disease and clinical perception.

Agreement process

After the presentation of the draft terminology and definition, the general concepts were discussed and amended. Thereafter, the detailed wording was discussed and amended until consensus was reached. A voting process was conducted for each item of the terminology and definition. In case no consensus was reached among the present Task Force members, the preferred version was selected by voting. Twenty-one Task Force members were present during this discussion and voting process. After the meeting, two versions of the definition were distributed among all Task Force members to select the final version.

RESULTS

Terminology

At the first Task Force meeting, based on a scoping literature search and the suggestions of the Task Force members a variety of potential terms to describe this patient population were presented, including severe, refractory, multidrug/treatment resistant and complex RA. None of these terms was deemed to cover the wide range of possible clinical scenarios which may be relevant for this patient population. Since 'difficult-to-treat' is a widely accepted term in several fields including pulmonology, psychiatry and cardiology[9–11] this terminology was finally proposed by the Steering Committee and unanimously endorsed by the Task Force (21/21 agreed by voting).

Definition

Thereafter, we sought to create a definition of D2T RA based on the results of the previously mentioned international survey[8] and expert opinions. The Task Force agreed that both articular and extra-articular components should be considered and agreed to include the following criteria in the definition: (1) treatment failure history; (2) characterisation of active/symptomatic disease; and (3) clinical perception. All three criteria need to be present to confirm the state of D2T RA.

Criterion #1: treatment failure history

In the survey, 48% of the respondents selected '≥2 conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) AND ≥2 biological (b)DMARDs or targeted synthetic (ts) DMARDs with different mode of action' for the number and type of antirheumatic drugs that should have failed before a patient can be considered to have D2T RA. The Steering Committee initially proposed to include treatment duration in the definition 'Treatment according to the current standard of care/EULAR recommendations for ≥1 year'. This was chosen so that D2T RA patients are in phase III of the current RA management recommendations, in which no recommendation is given other than to switch to another b/tsDMARD.[1] However, inclusion of a certain time period in the definition was not supported by all Task Force members (primarily in order to provide flexibility) and the Task Force voted against referral to a treatment duration period for the definition of D2T RA (19/21 agreed, 2 abstained).

All Task Force members agreed to include the number of DMARDs previously failed in the definition and to create the definition consistent with the current EULAR RA management recommendations. 'Failure of at least two b/tsDMARDs with different mode of action' was selected by the majority of the respondents of the survey.[8] Although according to the current EULAR recommendations[1] no prioritisation for switching mechanism of action versus cycling is stated, it was decided that before being classified as D2T RA, a patient should at least have failed two b/tsDMARDs with different mechanisms of action. Consequently, it was decided to select this cut-off by the Task Force. With this cut-off, patients had to have completed phase III of the recommendations at least once (ie, they may also have been treated with multiple bDMARDs of a single class (eg, several tumour necrosis factor inhibitors) and also have failed another b/tsDMARD). Finally, all members agreed to select the following proposal: 'Treatment according to EULAR recommendation and failure of ≥2 b/tsDMARDs with different mechanisms of action after failing csDMARD therapy (unless contraindicated)' (21/21 agreed). This also indicates that if csDMARD treatment is contraindicated, failure of ≥2 b/tsDMARDs with different mechanisms of action is sufficient.

Socioeconomic factors may limit the access to expensive DMARDS (eg, in low income countries), therefore (with the agreement of all Task Force members) we have added to the first criterion: 'unless restricted by access to treatment due to socioeconomic factors'.

Criterion #2: characterisation of active/symptomatic disease

Fifty per cent of the respondents of the international survey selected 'disease activity score assessing 28 joints using erythrocyte sedimentation rate (DAS28-ESR)>3.2 OR presence of signs suggestive of active inflammatory disease activity with a DAS28-ESR≤3.2' as a characteristic of D2T RA. Additionally, 95% of the respondents of the international survey suggested to include the inability to taper glucocorticoids (GCs) in the criteria of D2T.[8] Therefore, the Steering Committee proposed the following characterisation of active/symptomatic disease: 'Presence of active disease defined as ≥1 of: (1) DAS28-ESR>3.2; (2) Presence of signs suggestive of active RA; and/or (3) Inability to taper oral glucocorticoids (below 7.5 mg/day prednisone or

equivalent)'. At the Task Force meeting, it was decided to include not only DAS28, which was the only composite disease activity measure offered in the survey, but to rather use a more generic definition: 'at least moderate disease activity (according to validated composite measures including joint counts, for example, DAS28-ESR>3.2 or clinical disease activity index (CDAI)>10)' (21/21 agreed). In addition to clinical signs and symptoms, it was agreed that this clarification should also include imaging and biochemical markers suggestive of active disease.

Furthermore, all Task Force members agreed that not only patients with joint-related problems should qualify to be defined as being D2T. Extra-articular manifestations, such as vasculitis, pericarditis, scleritis or glomerulonephritis may complicate the management of RA, and were therefore decided to be included in the definition. This resulted in the following wording: 'Signs (including acute phase reactants and imaging) and/or symptoms suggestive of active disease (joint related or other)' (21/21 agreed).

In the survey, 43% of the respondents selected to include 'unable to taper glucocorticoids below 5 mg prednisone or equivalent daily' and 46% selected 'unable to taper glucocorticoids below 10 mg prednisone or equivalent daily' (in addition, another 6% chose to include inability to taper GCs, although with a different, unspecified dose).[8] At the Task Force meeting, it was decided to include the following definition as a compromise: 'Inability to taper oral glucocorticoids (below 7.5 mg/day prednisone or equivalent)'. The Task Force voted to keep this item in the definition (19/21 agreed).

During the Task Force meeting, additional possible signs of active disease were explicitly suggested for inclusion in the definition. First, the Task Force agreed to include rapid radiographic progression in the definition as a possible feature of D2T RA, as this might be occasionally observed even in case of clinically inactive disease. The following was proposed: 'Rapid radiographic progression (with or without signs of active disease)' (21/21 agreed). Second, non-inflammatory disease was considered, since these complaints, for example, concomitant fibromyalgia, might mimic inflammatory activity. Non-inflammatory disease may lead to several aforementioned characteristics of active/symptomatic disease. Furthermore, non-inflammatory disease might also lead to other clinically important complaints. Therefore, to ensure that patients with non-inflammatory complaints could be classified as having difficult-to-treat RA, it was suggested and unanimously agreed to add 'Well-controlled disease according to above standards, but still having RA symptoms that are causing a reduction in quality of life' (21/21 agreed).

The Task Force discussed whether to add fatigue to the definition, as this is one of the most common problems.[12 13] Since fatigue can diminish quality of life, it was suggested to be already included in the definition. In accordance with the survey (58% of respondents suggested not to include fatigue),[8] all Task Force members agreed to leave out the explicit mentioning of fatigue from the definition of D2T RA (21/21 agreed).

Criterion #3: clinical perception

As a final criterion, the Steering Committee suggested to include 'The disease is perceived as problematic by the rheumatologist and/or the patient'. This suggests that only clinical scenarios which are judged as problematic (eg, apparently ineffective treatment) are referred to as D2T RA. Since the definition is only applicable to patients in which a management problem is present, it was agreed to adapt the definition accordingly: 'The management of signs and/or symptoms is perceived as problematic by the rheumatologist and/or the patient'. There were some concerns that this criterion might be too subjective, especially for research. However, the focus of the recommendations should be on the clinical implications, which supports to include this criterion. All Task Force members agreed unanimously on this (21/21 agreed).

Box 1 EULAR definition of difficult-to-treat RA

1. Treatment according to European League Against Rheumatism recommendation and failure of ≥2 b/tsDMARDs (with different mechanisms of action)* after failing csDMARD therapy (unless contraindicated).†
2. Signs suggestive of active/progressive disease, defined as ≥1 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.

All three criteria need to be present in D2T RA.
b, biological; CDAI, clinical disease activity index; cs, conventional synthetic; DAS28-ESR, disease activity score assessing 28 joints using erythrocyte sedimentation rate; DMARD, disease-modifying antirheumatic drug; mg, milligram; RA, rheumatoid arthritis; ts, targeted synthetic.
*Unless restricted by access to treatment due to socioeconomic factors.
†If csDMARD treatment is contraindicated, failure of ≥2 b/tsDMARDs with different mechanisms of action is sufficient.
‡Rapid radiographic progression: change in van der Heijde-modified Sharp score ≥5 points at 1 year.[16]

Order

Most Task Force members agreed to start the definition with the treatment failure history criterion instead of the characterisation of active/symptomatic disease. However, the group noted that starting with signs of active disease might be better focussed on the patients' needs. Therefore, with the agreement of all Task Force members, it was decided to vote on the order of the two criteria, by which all Task Force members supported the first version of the definition (agreed 31/31 (AH, who joined the Task Force later, did not vote), box 1).

DISCUSSION

The treatment of the heterogeneous patient population that comprises D2T RA is often a clinical challenge for which practical management recommendations are needed. Several factors may complicate the management of these patients. Such factors include persistent inflammatory activity due to resistance of disease to DMARDs, limited drug options due to adverse drug reactions and/or comorbidities that preclude the use of DMARDs or treatment non-adherence. On the other hand, concomitant

syndromes or diseases, such as fibromyalgia, osteoarthritis and psychosocial factors associated with poor coping, can result in non-inflammatory symptoms (eg, pain) that can mimic inflammatory activity and therewith contribute to D2T RA. Currently, D2T RA EULAR management recommendations are under development, aiming to cover all inflammatory and non-inflammatory factors underlying D2T RA. These will include both pharmacological and non-pharmacological treatment options and will be complementary to the existing RA recommendations.[1–3] As an essential initial step in the development of recommendations for D2T RA, the Task Force provided terminology and a definition of D2T RA.

The term 'difficult-to-treat' was selected because it was deemed to best capture the possible clinical scenarios. A definition of D2T RA, consisting of three criteria was agreed on by consensus by a multidisciplinary group of experts including patient representatives: (1) treatment failure history; (2) characterisation of active/symptomatic disease; and (3) clinical perception. These elements were selected based on the results of the survey.

The second criterion has five subelements, reflecting all potential clinically meaningful indicators of active/symptomatic disease. In this definition, in accordance with recent recommendations, the term 'moderate disease activity according to validated composite measures including joint counts' was used.[1 3] However, these indices might not always include the affected joints (eg, feet) or other signs of disease activity.[14] The 'Signs (including acute phase reactants and imaging) and/or symptoms suggestive of active disease (joint related or other)' item covers all potentially affected joints, as well as extra-articular manifestations.

The acceptable GC dose for chronic use remains a matter of discussion, although there is a significant group of RA patients that is treated with GCs long-term. Current EULAR RA recommendations suggest to consider using GCs, when initiating or changing csDMARDs, but GCs should be tapered as rapidly as clinically feasible.[1] The EULAR Task Force in charge of evaluating the risk of long-term GC therapy suggested that the risk of harm is generally low at long-term doses of ≤5 mg prednisone equivalent per day.[15] In the currently proposed definition of D2T RA, in accordance with the result of the survey,[8] 'Inability to taper glucocorticoid treatment (below 7.5 mg/day prednisone or equivalent)' is listed as a criterion. We realise that lower GC doses were suggested by other EULAR Task Forces, on the other hand, we believe that less stringent criteria will be more realistic to define the D2T patients, as inability to follow these criteria can indicate a management problem.

The Task Force felt that not only patients fulfilling criterion 1 and 3 with inflammatory activity should be able to be classified as having D2T RA, but also those patients with non-inflammatory complaints. Coexisting non-inflammatory conditions may lead to a high clinical burden. These may mimic inflammatory activity by hampering proper grading of disease activity and 'falsely' elevating disease activity scores through rather subjective measures.[5] Additionally, these symptoms (such as fatigue or pain) could reduce quality of life. Therefore, the second criterion 'Signs suggestive of active/progressive disease' was deemed to cover the wide variety of patients with inflammatory activity and/or non-inflammatory complaints.

There are some limitations of this work. The definition of D2T RA needs to be validated. Rheumatologists' and patients' acceptance can, as a first step, be used as a sign of face validity. Furthermore, not all aspects of D2T RA may have been adequately captured by the currently proposed definition, although the criteria mentioned are agreed on by a large group of experts based on a survey involving >400 rheumatologists. A further complicating factor might be that, as also apparent from the definition, this patient group is rather heterogeneous and hence difficult to capture in one definition.

In conclusion, the principal goal of RA management is to achieve sustained remission or at least low disease activity following steps of the current EULAR recommendations.[1] A new management approach is necessary for D2T RA patients, in which this treatment goal is not achieved. Hopefully, the definition presented here will provide a robust and consistent identification of patients with D2T RA. In addition, this definition can provide a platform to define a group of similar patients for research. Further work is underway to provide detailed recommendations for the management of D2T RA.

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REFERENCES

1 Smolen JS, Landewé RBM, Bijlsma JWJ, *et al*. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann Rheum Dis* 2020;79:685–99.
2 Singh JA, Saag KG, Bridges SL, *et al*. 2015 American College of rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Rheumatol* 2016;68:1–26.
3 Smolen JS, Breedveld FC, Burmester GR, *et al*. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international Task force. *Ann Rheum Dis* 2016;75:3–15.
4 Kearsley-Fleet L, Davies R, De Cock D, *et al*. Biologic refractory disease in rheumatoid arthritis: results from the British Society for rheumatology biologics register for rheumatoid arthritis. *Ann Rheum Dis* 2018;77:1405–12.
5 de Hair MJH, Jacobs JWG, Schoneveld JLM, *et al*. Difficult-To-Treat rheumatoid arthritis: an area of unmet clinical need. *Rheumatology* 2018;57:1135–44.
6 Bécède M, Alasti F, Gessl I, *et al*. Risk profiling for a refractory course of rheumatoid arthritis. *Semin Arthritis Rheum* 2019;49:30553–5.
7 Buch MH. Defining refractory rheumatoid arthritis. *Ann Rheum Dis* 2018;77:966–9.
8 Roodenrijs NMT, de Hair MJH, van der Goes MC, *et al*. Characteristics of difficult-to-treat rheumatoid arthritis: results of an international survey. *Ann Rheum Dis* 2018;77:1705–9.
9 Robinson DS, Campbell DA, Durham SR, *et al*. Systematic assessment of difficult-to-treat asthma. *Eur Respir J* 2003;22:478–83.
10 Thase ME. Therapeutic alternatives for difficult-to-treat depression: a narrative review of the state of the evidence. *CNS Spectr* 2004;9:808–21.
11 Papademetriou V, Tsioufis C, Gradman A, *et al*. Difficult-To-Treat or resistant hypertension: etiology, pathophysiology, and innovative therapies. *Int J Hypertens* 2011;2011:1–4.
12 Almeida C, Choy EHS, Hewlett S, *et al*. Biologic interventions for fatigue in rheumatoid arthritis. *Cochrane Database Syst Rev* 2016;6:CD008334.
13 Katz P, Margaretten M, Trupin L, *et al*. Role of sleep disturbance, depression, obesity, and physical inactivity in fatigue in rheumatoid arthritis. *Arthritis Care Res* 2016;68:81–90.
14 Landewé R, van der Heijde D, van der Linden S, *et al*. Twenty-eight-joint counts invalidate the DAS28 remission definition owing to the omission of the lower extremity joints: a comparison with the original DAS remission. *Ann Rheum Dis* 2006;65:637–41.
15 Strehl C, Bijlsma JWJ, de Wit M, *et al*. Defining conditions where long-term glucocorticoid treatment has an acceptably low level of harm to facilitate implementation of existing recommendations: viewpoints from an EULAR Task force. *Ann Rheum Dis* 2016;75:952–7.
16 Fautrel B, Granger B, Combe B, *et al*. Matrix to predict rapid radiographic progression of early rheumatoid arthritis patients from the community treated with methotrexate or leflunomide: results from the ESPOIR cohort. *Arthritis Res Ther* 2012;14:R249.