Response to: 'Correspondence on 'EULAR definition of difficult-to-treat rheumatoid arthritis'' by Novella-Navarro et al

Roodenrijs, N.M.T.; Welsing, P.M.J.; Goes, M.C. van der; Jacobs, J.W.; Heijde, D. van der; Laar, J.M. van; Nagy, G.

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We read with great interest the correspondence of Novella-Navarro *et al* on our paper regarding the European League Against Rheumatism (EULAR) definition of difficult-to-treat rheumatoid arthritis (D2T RA).[1 2] We appreciate their acknowledgement of the need for uniform terminology and a uniform definition to describe the concept of D2T RA. Previously, this need had also been underlined by rheumatologists participating in an international survey.[3] The use of heterogeneous terminology and definitions might hamper research and management of these patients.[4–9]

Novella-Navarro *et al* compared their definition of multirefractory RA in their recently conducted retrospective study with the three criteria of the EULAR definition of D2T RA (box 1).[2 10] They classified patients with RA as having 'multirefractory' disease after failing ≥2 biological and/or targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) with different mechanisms of action or ≥3 b/tsDMARDs with the same target, and as having 'non-refractory' disease if achieving low disease activity or remission on the first bDMARD. Noteworthy, 96% of their multirefractory patients met the EULAR definition of D2T RA (box 1),[2] which supports the clinical usefulness of our definition.[1]

Box 1 EULAR definition of difficult-to-treat rheumatoid arthritis[1]

1. Treatment according to EULAR recommendations 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, eg, 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 the 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; D2T, difficult-to-treat; DAS28-ESR, Disease Activity Score assessing 28 joints using erythrocyte sedimentation rate; DMARD, disease-modifying antirheumatic drug; EULAR, European League Against Rheumatism; 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.[15]

As some members of our Task Force also conducted a study in D2T RA patients,[11] we feel it would be interesting to compare our results with those of Novella-Navarro *et al*, applying their slightly different criteria.[10] In our cross-sectional study, consecutive patients with RA, treated for at least 1 year, were prospectively enrolled and classified as having D2T RA if they fulfilled the EULAR definition (box 1).[1] Patients with RA who did not fulfil all three criteria served as a control group.

Regarding the first criterion of the EULAR definition (box 1),[1] it should be noted that a specific number of failed csDMARDs is not included in the definition. Novella-Navarro *et al* showed that 95% of the multirefractory patients (39 of 41) had been treated with ≥2 csDMARDs.[10] In our study, 89% of the D2T RA patients (46 of 52) failed ≥2 csDMARDs.[11] As csDMARDs may be contraindicated and socioeconomic factors—including differences in the availability of (b/ts)DMARDs—may result in different treatment schedules between countries, the Task Force added two exceptions to the first criterion (box 1),[1] enabling that the patients who it would concern could still fulfil the D2T RA definition.

As second criterion of the EULAR definition, patients should have 'signs suggestive of active/progressive disease (defined as ≥1 of 5 prespecified items, box 1)'.[1] One of the prespecified items is having 'at least moderate disease activity'. This was reflected in our study with D2T RA patients having a significantly higher DAS28-ESR (Disease Activity Score assessing 28 joints using erythrocyte sedimentation rate) compared with non-D2T RA patients (median (IQR) 4.1 (3.5–6.1) vs 2.5 (1.8–3.3), p<0.001).[11] In the paper of Novella-Navarro *et al*, disease activity scores when meeting the criteria of multirefractory RA are not described, prohibiting comparison of these results.[10]

The third criterion of the EULAR definition (box 1)[1] was added to emphasise that the definition is only applicable to patients in whom a management problem is acknowledged. Novella-Navarro *et al* did not apply a similar criterion, although they found at the start of the first bDMARD statistically significantly worse levels of global patient assessment and functional disability in multirefractory compared with in non-refractory RA patients, potentially also indicating a management problem.[10] In our study, the patients' burden of D2T RA was substantial too, indicated by statistically significantly worse levels of functional disability, quality of life, pain and fatigue compared with that of non-D2T RA.[11] The Task Force discussed that this criterion might be too subjective and, therefore, might also be too complicated to integrate in research (specifically in retrospective studies). However, as the definition and management recommendations for D2T RA are primarily developed for clinical practice, eventually, the Task Force unanimously decided to add this criterion.

We agree with Novella-Navarro *et al* that identifying risk factors for developing D2T RA may be helpful to identify D2T RA patients.[10] Identifying risk factors at RA onset may even help preventing development of D2T RA. D2T RA is a heterogeneous condition, in which various contributing factors can be present (eg, concomitant fibromyalgia, treatment non-adherence, as described in our study).[4 11] By adequate management of these contributing factors, the risk of developing D2T RA may be diminished. In addition to the risk factors identified by Novella-Navarro *et al*, we identified lower socioeconomic status at RA onset as risk factor for developing D2T RA.[11] Although potentially helpful, all identified risk and contributing factors should be validated in other cohorts of D2T RA patients before they can be implemented in management strategies in clinical practice.[10 11]

In summary, the EULAR definition of D2T RA, based on international consensus, has been established to unify terminology and the definition. Preferably, this definition will be used in future studies to classify patients with D2T RA uniformly. However, we welcome studies such as that of Novella-Navarro *et al* to gain further insights into the intricate D2T RA state. Hopefully, all these initiatives, together with the EULAR recommendations for the management of D2T RA that are currently being developed,[12–14] will eventually improve outcomes of patients with D2T RA because that is what it is all about in the end.

Nadia M T Roodenrijs ,[1] **Paco M J Welsing,**[1] **Marlies C van der Goes,**[1,2] **Johannes WG Jacobs** ,[1] **Désirée van der Heijde** ,[3] **Jacob M van Laar,**[1] **György Nagy** [4]

[1]Rheumatology & Clinical Immunology, University Medical Center Utrecht, Utrecht, The Netherlands
[2]Rheumatology, Meander Medical Center, Amersfoort, The Netherlands
[3]Rheumatology, Leiden University Medical Center, Leiden, The Netherlands
[4]Genetics, Cell- and Immunobiology & Rheumatology and Clinical Immunology, Semmelweis University, Budapest, Hungary

Correspondence to Nadia M T Roodenrijs, Rheumatology & Clinical Immunology, University Medical Center Utrecht, 3508 GA Utrecht, The Netherlands; N.M.T.Roodenrijs@umcutrecht.nl

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ORCID iDs
Nadia M T Roodenrijs http://orcid.org/0000-0002-4364-3183
Johannes WG Jacobs http://orcid.org/0000-0002-7438-3468
Désirée van der Heijde http://orcid.org/0000-0002-5781-158X
György Nagy http://orcid.org/0000-0003-1198-3228

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