Characteristics of difficult-to-treat rheumatoid arthritis: results of an international survey

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Word count: 1283

ABSTRACT

Objectives: Patients with difficult-to-treat rheumatoid arthritis (RA) remain symptomatic despite treatment according to current EULAR management recommendations. These focus on early phases of the disease and pharmacological management. We aimed to identify characteristics of difficult-to-treat RA and issues to be addressed in its workup and management that are not covered by current management recommendations.

Methods: An international survey was conducted among rheumatologists with multiple-choice questions on disease characteristics of difficult-to-treat RA. Using open questions, additional items to be addressed and items missing in current management recommendations were identified.

Results: 410 respondents completed the survey: 50% selected disease activity score assessing 28 joints (DAS28) >3.2 OR presence of signs suggestive of active disease as characteristics of difficult-to-treat RA; 42% selected fatigue; 48% selected failure to ≥2 conventional synthetic disease-modifying anti-rheumatic drugs (DMARDs) AND ≥2 biological/targeted synthetic DMARDs; 89% selected inability to taper glucocorticoids below 5 or 10 mg prednisone equivalent daily. Interfering comorbidities, extra-articular manifestations and polypharmacy were identified as important issues missing in current management recommendations.

Conclusions: There is wide variation in concepts of difficult-to-treat RA. Several important issues regarding these patients are not addressed by current EULAR recommendations.

Keywords: Rheumatoid Arthritis – Disease activity – Treatment

INTRODUCTION

The European League Against Rheumatism (EULAR) recommendations and the American College of Rheumatology (ACR) guidelines on management of rheumatoid arthritis (RA) focus on early phases of the disease and on pharmacological management.[1,2] These recommendations suggest intensifying the disease-modifying anti-rheumatic drug (DMARD) strategy, if improvement or the treatment target is not achieved within 3 or 6 months, respectively. Nevertheless, a significant proportion of patients remains symptomatic after several cycles of treatment, which makes them difficult-to-treat; this is a significant clinical problem in daily practice.[3]

A wide array of potential factors contributes to difficult-to-treat RA, such as DMARD resistance or intolerance, adverse reactions, treatment non-adherence and limited drug options due to comorbidities. Importantly, RA patients may also remain symptomatic due to non-inflammatory factors, such as secondary osteoarthritis, pain syndromes, social and occupational decline and coping difficulties. All these may (in different combinations) play a role in individual patients and require specific management approaches, which should be addressed in management recommendations.

Currently, different concepts exist on difficult-to-treat RA, such as refractory, multidrug resistant or persistent RA, or concepts based on number of failed DMARDs and failed treatment goals.[4–7] Depending on the criteria used, the estimated prevalence of difficult-to-treat RA ranges from 5 to 20%.[6]

We aimed to identify characteristics of the concept of difficult-to-treat RA and to explore issues to be addressed in its workup and management that are not covered by current EULAR management recommendations.

METHODS

Online survey among rheumatologists

An online survey (Supplementary File 1, set up by DvdH, GN, JWGJ, JMvL, MJHdH and PMJW) was conducted among rheumatologists (including rheumatologists-in-training). The survey was distributed by email in the network of the authors and by Emerging EULAR Network (EMEUNET), and it was asked to additionally forward it to other rheumatologists. The survey consisted of two questions regarding the background of the respondents (Where do you work? How many RA patients do you treat?).

Four multiple-choice questions addressed the necessity of incorporating the following items, and their cut-offs, into the concept of difficult-to-treat RA: disease activity level; presence of fatigue; number of DMARDs that failed; inability to taper glucocorticoid (GC) treatment. Only one response option could be selected at each multiple-choice item, which were selected as - according to expert opinion - among the most frequent and relevant characteristics in clinical practice. Fatigue was selected as one of the most relevant patient reported outcomes in RA.[8] Three open questions were: 'Please define any additional characteristics and suggested criteria for difficult-to-treat RA'; 'Please mention additional clinical issues or comorbidities to be addressed in the workup and management of these patients'; 'Please mention any clinically relevant situations which are not covered by the current RA EULAR recommendations'.

Qualification and quantification of the responses to the open questions

NMTR and MJHdH independently classified the responses to the open questions into categories (Supplementary File 1). This enabled summarising and quantifying. Categories were defined based on the responses that were given to the open questions. One response could fit multiple categories. 'Other' was used to classify characteristics that did not fit into one of the categories. Discrepancies in classification between NMTR and MJHdH were resolved by consensus.

Statistical analyses

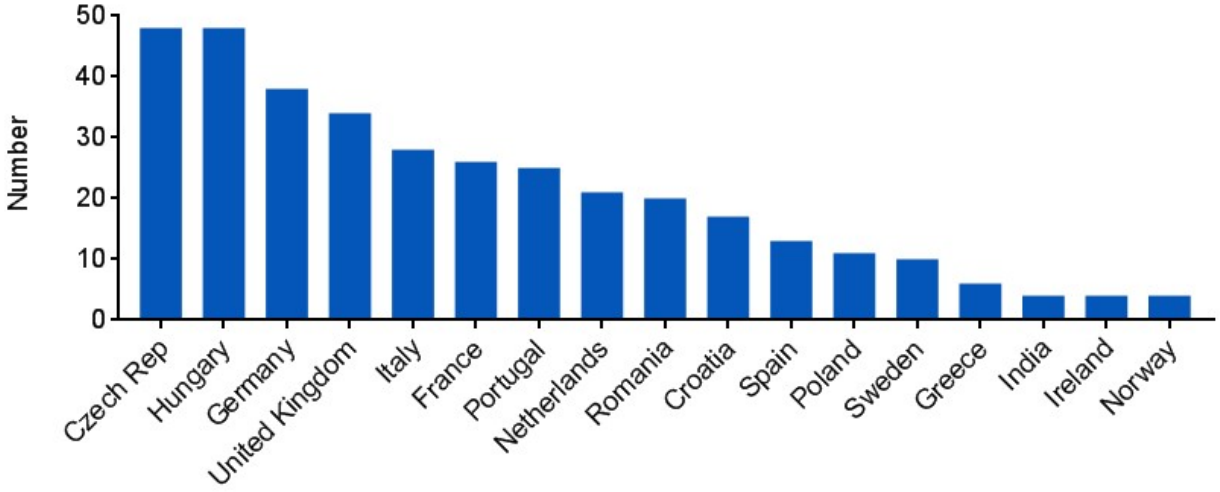
All responses were evaluated using descriptive statistics, performed using IBM SPSS Statistics 21 software.

RESULTS

Respondents

410 respondents from 33 countries completed the survey between July 2017 and March 2018. Of the 385 respondents who filled out the name of their country, 96% was European (Figure 1); 25% of respondents treated <100 unique patients with RA, 42% 100-300 patients, and 32% >300 patients (n=7 missing).

Figure 1. Number of respondents per country



Less than 4: Austria, Belarus, Bulgaria, Denmark, Egypt, Estonia, Iceland, Israel, Kenya, Pakistan, Russia, Serbia, Slovakia, Slovenia, Tunisia, Turkey

Selected difficult-to-treat RA disease characteristics

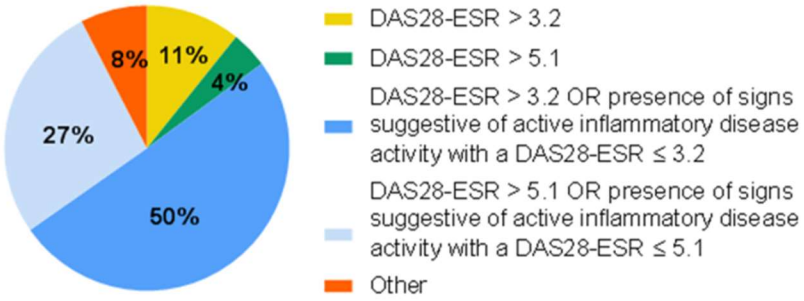
50% of respondents selected 'DAS28-ESR>3.2 OR presence of signs suggestive of active inflammatory disease activity with a DAS28-ESR≤3.2' as characteristics (Figure 2a). 42% included fatigue (Figure 2b). 48% selected '≥2 conventional synthetic (cs)DMARDs AND ≥2 biological (b)DMARDs or targeted synthetic (ts)DMARDs with different mode of action' for how many insufficiently effective anti-rheumatic drugs should at least have been applied (Figure 2c). 89% selected inability to taper GCs <5 (43%) or 10 (46%) mg prednisone or equivalent daily for more than 1 year, irrespective of DMARD treatment (Figure 2d), as difficult-to-treat RA characteristic.

Additional difficult-to-treat RA characteristics

243 additional characteristics for difficult-to-treat RA were given by 169 respondents (Figure 2e), most frequently categorised into 'interfering comorbidities' and 'extra-articular manifestations'. Examples are cardiovascular risk, malignancies, interstitial lung disease and vasculitis. A diversity of 'other' responses was given, e.g. inflammation on magnetic resonance imaging, morning stiffness and patient dissatisfaction.

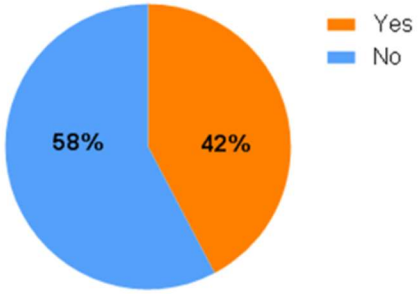
Figure 2. Difficult-to-treat RA characteristics

a. What should be the definition for not well-controlled disease in the definition of difficult-to-treat RA?



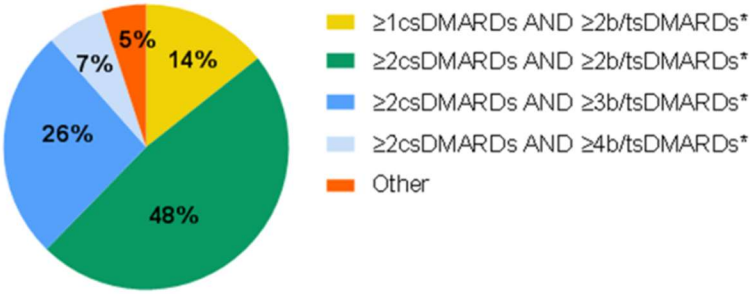
Total responses = 409

b. Would you include fatigue in the definition of not well-controlled disease?



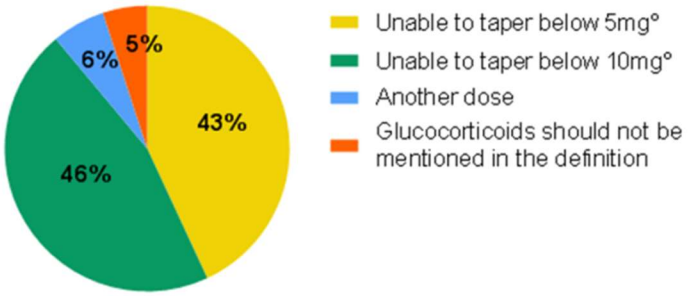
Total responses = 396

c. Which and how many anti-rheumatic drugs should at least be tried with insufficient effect for the definition of difficult-to-treat RA?



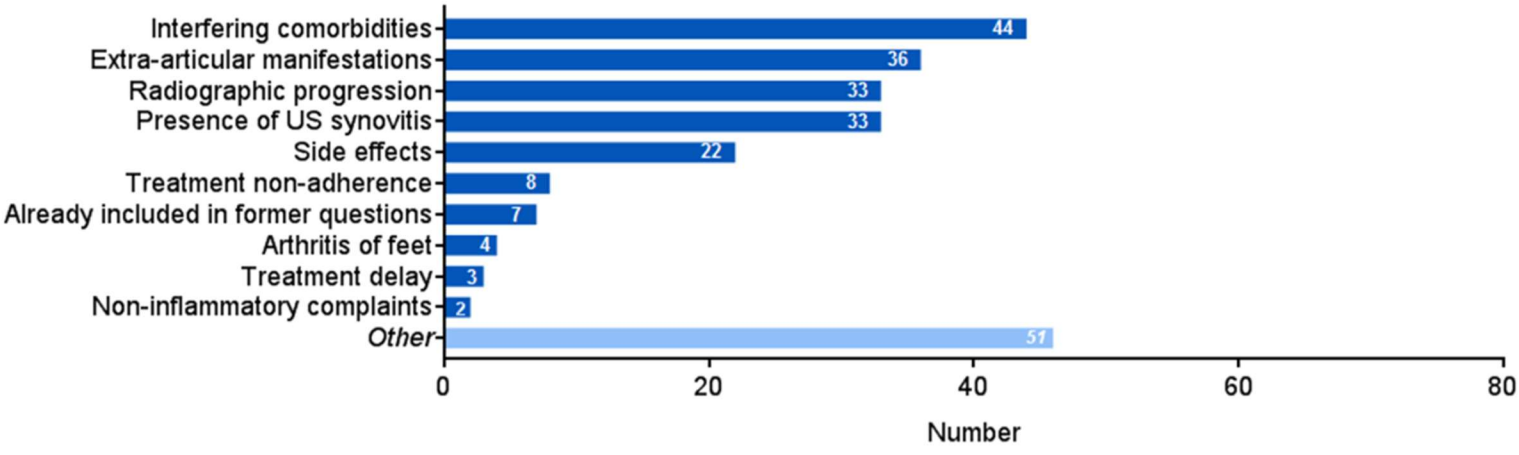
Total responses = 398

d. Treatment with glucocorticoids should be mentioned in the criteria for difficult-to-treat RA as follows:



Total responses = 397

e. Additional characteristics for difficult-to-treat RA



b/tsDMARDs: biological/targeted synthetic disease-modifying anti-rheumatic drugs; csDMARDs: conventional synthetic disease-modifying anti-rheumatic drugs; DAS28-ESR: disease activity score assessing 28 joints using erythrocyte sedimentation rate; RA: rheumatoid arthritis; US: ultrasonography.

** with different mode of action*

° or equivalent daily for more than 1 year, irrespective of DMARD treatment

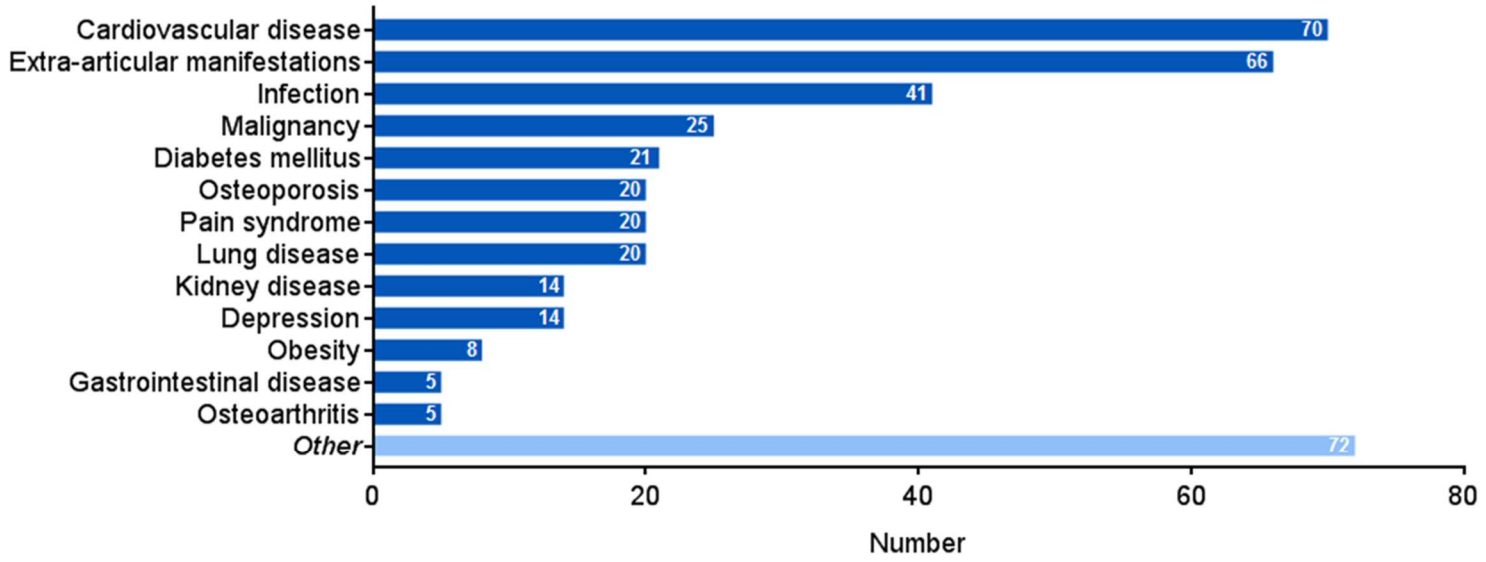
Interfering clinical issues and items missing in current EULAR recommendations, important to manage difficult-to-treat RA

For interfering issues to be addressed in the workup and management of difficult-to-treat RA, 396 suggestions were given by 170 respondents (Figure 3a), most frequently cardiovascular disease and extra-articular manifestations. Other interfering clinical issues were drug intolerance, smoking and chronic liver disease.

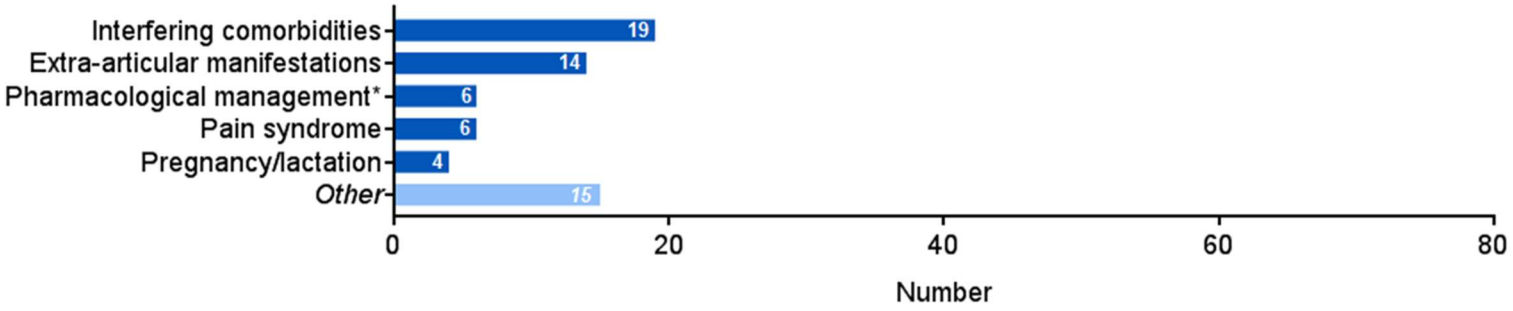
For issues not covered by the current EULAR recommendations, 64 were mentioned by 54 respondents (Figure 3b). These were most frequently classified as interfering comorbidities and extra-articular manifestations. Also issues regarding pharmacological management (e.g. tapering regimen, adverse events and polypharmacy), pain syndromes and pregnancy and lactation were mentioned. Other items were ongoing joint destruction, coping problems and persistent single joint involvement.

Figure 3. Interfering clinical issues and items missing in the current EULAR recommendations, important to manage difficult-to-treat RA

a. Interfering clinical issues or comorbidities to be addressed in the workup and management of these patients



b. Clinically relevant situations which are not covered by the current RA EULAR recommendations



EULAR: European League Against Rheumatism; RA: rheumatoid arthritis.
** e.g. tapering strategies, adverse events, polypharmacy*

DISCUSSION

Our results show a wide variety in concepts of difficult-to-treat RA; active disease, failure to DMARDs treatment and inability to taper GCs are considered main characteristics. Additional difficult-to-treat RA characteristics were mostly related to extra-articular manifestations and interfering comorbidities that may hamper assessment of disease activity or limit treatment possibilities. As items missing in current RA EULAR management recommendations, interfering comorbidities (especially cardiovascular disease, infection and malignancy), extra-articular

manifestations, pharmacological management (e.g. tapering strategies, adverse events and polypharmacy) and pain syndromes were mentioned most frequently.

Of the factors mentioned as contributing to difficult-to-treat RA in this survey, e.g. treatment non-adherence, adverse events and coping strategies, exact prevalences are unknown. These should be determined in future research for an indication of their need to be included in management recommendations.

Our results mainly reflect how difficult-to-treat RA is experienced in European countries. Additional contributing factors to difficult-to-treat RA in countries outside Europe might be limited access to diagnostic tests, rheumatologists and DMARDs. These should be addressed in management recommendations as well.

Our study has limitations. The survey was distributed via email and it was asked to forward it to other rheumatologists to increase the number of respondents. As a drawback, the total number of rheumatologists who received it is unknown.

The four multiple-choice questions had pre-specified response options, limiting input to these questions, but enabling the responses to be easily summarised and quantified. The open questions required a classification system for the responses; some responses were classified in two categories and there was a number of responses that was classified as ‘other’. Additionally, the pre-specified multiple-choice questions may have biased the results of the open questions. However, by these open questions, we received a large inventory of issues that may need to be addressed in clinical practice.

The strengths of this study are the large number of respondents and of European countries represented by the respondents; the many suggestions of items which are not covered by the current EULAR RA management recommendations underline the unmet clinical need for this subpopulation of RA patients.

Recently a EULAR Task Force has been initiated on the development of recommendations for the comprehensive management of difficult-to-treat RA. The results of this survey will fuel discussions on items to include in the management recommendations of difficult-to-treat RA.

In conclusion, the results of this survey underscore the difficulty in establishing an unambiguous concept of difficult-to-treat RA, which is seen as a heterogeneous condition not fully covered by current EULAR recommendations. The recently established EULAR Task Force will explore the management of difficult-to-treat RA further.

ACKNOWLEDGEMENTS AND AFFILIATIONS

Not applicable.

REFERENCES

1 Smolen JS, Landewé R, Bijlsma J, *et al.* EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. *Ann Rheum Dis* 2017;76:960–77.

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 de Hair MJH, Jacobs JWG, Schoneveld JLM, *et al.* Difficult-to-treat rheumatoid arthritis: an area of unmet clinical need. *Rheumatology (Oxford)* 2017. doi: 10.1093/rheumatology/kex349 [Epub ahead of print 4 Oct 2017]

4 Unger M, Alasti F, Supp G, *et al.* The good, the bad and the ugly – refractory rheumatoid arthritis in 2016. *Arthritis Rheumatol* 2016;68(suppl 10).

5 Miossec P. Introduction: Why is there persistent disease despite aggressive therapy of rheumatoid arthritis? *Arthritis Res Ther* 2014;16:113.

6 Kearsley-Fleet L, De Cock D, Watson K, *et al.* Refractory disease in rheumatoid arthritis: results from the British society of rheumatology biologics register for rheumatoid arthritis. *Ann Rheum Dis* 2017;76:960–77.

7 Buch MH. Defining refractory rheumatoid arthritis. *Ann Rheum Dis* 2018. doi:10.1136/annrheumdis-2017-212862 [Epub ahead of print 27 Mar 2018]

8 Taylor PC, Moore A, Vasilescu R, et al. A structured literature review of the burden of illness and unmet needs in patients with rheumatoid arthritis: a current perspective. Rheumatol Int 2016;36:685–95.

FOOTNOTES

Contributors

NMTR contributed to the data analysis, interpretation of data and manuscript preparation. MJHdH and JWGJ contributed to the design of the study, data analysis, interpretation of data and manuscript preparation. PMJW, DvdH, and JMvL contributed to the design of the study, interpretation of data and manuscript preparation. MvdG, DA, MD, KLH, IBM, UM, LS and ZS contributed to the acquisition of data and manuscript preparation. GN contributed to the design of the study, acquisition of data, interpretation of data and manuscript preparation. All authors read and approved the final manuscript.

Funding

Not applicable.

Disclaimer

Not applicable.

Competing interests

NMTR, MJHdH, MvdG, JWGJ, PMJW, DA, MD, KLH, IBMI, UML and ZS declare to have no competing interests. DvdH received consulting fees AbbVie, Amgen, Astellas, AstraZeneca, BMS, Boehringer Ingelheim, Celgene, Daiichi, Eli-Lilly, Galapagos, Gilead, Glaxo-Smith-Kline, Janssen, Merck, Novartis, Pfizer, Regeneron, Roche, Sanofi, Takeda, UCB. LS received fees from AbbVie, BMS, Celgene Corporation, Eli Lilly, Merck Sharp and Dohme, Novartis, Pfizer, Roche, Takeda, UCB. JMvL received fees from Arthrogene, MSD, Pfizer, Eli Lilly, and BMS and research grants from Astra Zeneca, Roche-Genentech. GN received fees from Amgen, AbbVie, BMS, KRKA, MSD, Pfizer, Roche, UCB and research grants from Pfizer and AbbVie.

Patient consent

Not applicable.

Ethics approval

Not applicable.

Provenance and peer review

Not commissioned; externally peer reviewed.

Author note

Not applicable.

SUPPLEMENTARY FILE 1

Questionnaire

Q1: Where do you work? (city, country)

_____

Q2: How many RA patients do you treat?

a. Less than 100

b. Between 100 and 300

c. More than 300

d. I'm not a physician

Q3: What should be the definition for not well-controlled disease in the definition of difficult-to-treat RA?

a. DAS28-ESR > 3.2

b. DAS28-ESR > 5.1

c. DAS28-ESR > 3.2 OR presence of signs suggestive of active inflammatory disease activity with a DAS28-ESR ≤ 3.2

d. DAS28-ESR > 5.1 OR presence of signs suggestive of active inflammatory disease activity with a DAS28-ESR ≤ 5.1

e. Other (please specify) _____

Q4: Would you include fatigue in the definition of not well-controlled disease?

a. Yes

b. No

c. Please elaborate (if applicable) _____

d. Other (please specify) _____

Q5: Which and how many anti-rheumatic drugs should at least be tried with insufficient effect (failed) for the definition of difficult-to-treat RA:

a. ≥1 csDMARD AND ≥2 b/tsDMARDs with different mode of action

b. ≥2 csDMARDs AND ≥2 b/tsDMARDs with different mode of action

c. ≥2 csDMARDs AND ≥3 b/tsDMARDs with different mode of action

d. ≥2 csDMARDs AND ≥4 b/tsDMARDs with different mode of action
e. Further suggestions (please specify) _____

Q6: Treatment with glucocorticoids should be mentioned in the criteria for difficult-to-treat RA as follows:
a. Unable to taper glucocorticoids below 5 mg prednisone or equivalent daily for more than 1 year, irrespective of DMARD treatment
b. Unable to taper glucocorticoids below 10 mg prednisone or equivalent daily for more than 1 year, irrespective of DMARD treatment
c. Glucocorticoids should not be included in the criteria
d. Suggested glucocorticoid dose/duration of treatment (if other than above) _____

Q7: Please define any additional characteristics and suggested criteria for difficult-to-treat RA

_____

Q8: Please mention additional clinical issues or comorbidities to be addressed in the workup and management of these patients

_____

Q9: Please mention any clinically relevant situations which are not covered by the current RA EULAR recommendations

_____

Categories per question

We have created this categories to categorise the responses to the open questions. If not clearly stated if a disease/problem was meant as ‘extra-articular manifestation’ or as ‘interfering comorbidity’ it was classified according to both categories

Q7: Please define any additional characteristics and suggested criteria for difficult-to-treat RA

- Interfering comorbidities
- Extra-articular manifestations
- Radiographic progression

- Persistence of US synovitis
- Side effects
- Treatment non-adherence
- Already included in former questions
- Arthritis of the feet
- Treatment delay
- Non-inflammatory complaints
- Other

Q8: Please mention additional clinical issues or comorbidities to be addressed in the workup and management of these patients

- Cardiovascular disease
- Extra-articular manifestations
- Infection
- Malignancy
- Diabetes Mellitus
- Osteoporosis
- Pain syndrome
- Lung disease
- Kidney disease
- Depression
- Obesity
- Gastrointestinal disease
- Osteoarthritis
- Other

Q9: Please mention any clinically relevant situations which are not covered by the current RA EULAR recommendations

- Interfering comorbidities
- Extra-articular manifestations
- Pharmacological management
- Pain syndrome
- Pregnancy/lactation
- Other