The potential role of fatigue in difficult-to-treat rheumatoid arthritis

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Abstract

Objectives A subset of patients with rheumatoid arthritis (RA) who remains symptomatic after failing to multiple drugs are deemed to have "difficult-to-treat RA" (D2T RA). Fatigue is a burdensome symptom for RA patients, hindering their improvement. Our purpose was to evaluate the role of fatigue in D2T RA.

Methods This cross-sectional study included rheumatoid arthritis (RA) patients between 2018 and 2022, treated with biological agents or targeted synthetic disease-modifying antirheumatic drugs. D2T RA was defined attending EULAR criteria. Independent variable was fatigue (dimensions and impact) assessed by the Bristol Rheumatoid Arthritis Fatigue Multidimensional Questionnaire and Numerical Rating Scales. Covariables: sociodemographic, clinical and treatment. To identify factors independently associated to D2T RA, multivariable logistic regression was run.

Results The study included 145 patients and 38 (26.21%) developed D2T RA. D2T RA group were older, with more comorbidity and disability. D2T RA patients scored higher for global fatigue ($p = 0.003$), and almost for all their dimensions except for cognitive fatigue ($p = 0.06$) and fatigue coping ($p = 0.07$). Females with D2T RA showed more fatigue than those with non-D2T RA. In the adjusted models, all fatigue dimensions were associated with D2T RA: global fatigue RA (OR: 1.03; $p = 0.007$), physical (OR: 1.09; $p = 0.008$), living (OR: 1.09; $p = 0.016$), cognitive (OR: 1.1; $p = 0.046$) and emotional (OR: 1.18; $p = 0.012$).

Conclusions Despite the absence of an explicit mention of fatigue in the definition of D2T RA, it appears to be associated to this outcome. Fatigue should be evaluated in a multidimensional perspective, and gender-specific differences should be considered.

Keywords Fatigue, Rheumatoid arthritis, Biological Agents, Targeted Synthetic DMARDs

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Background

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterised by chronic synovial joint inflammation that causes disability and reduces the quality of life [1]. The prevalence of RA in Europe ranges from 0.20 to 0.40% [2] Fatigue is a common symptom rheumatoid arthritis (RA) [3], affecting approximately 40–80% of patients [4]. This variability is due to the different definitions and scales used to assess fatigue [5]. It is a burdensome symptom in rheumatoid arthritis (RA) patients, often perceived as overwhelming, uncontrollable, and different from normal tiredness in severity, quality, and unpredictability [6].

In the literature, there is still no consensus on a standard definition for RA-related fatigue, likely due to several knowledge gaps regarding its etiology [7, 8]. In published studies, fatigue is mostly described as a multi-causal, multidimensional and complex concept in which psychological, biochemical and physiological mechanisms play a role [2].

The phenomenon of RA fatigue is not well understood yet, being a complex construct with multiple components, such as pain, stress, depression, inflammation, and disability. All this likely contribute to varying degrees at different times [9]. Qualitative research has shown that patients perceive fatigue as a multidimensional experience. Recent proposals categorize it into various dimensions, affecting physical, daily living, cognitive, and emotional aspects in RA patients [10]. In this sense Hewlett et al. [11] propose a conceptual framework with three main components: inflammation (directly or through pain, sleep disruption, disability), personal factors (work, comorbidities) and cognitive behavioral elements (under/over activity, driven by thoughts/feelings).

The treatment and self-management of fatigue in RA patients are gaining more interest, requiring accurate measurement of fatigue. The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) have recognized fatigue as a crucial outcome in rheumatoid arthritis (RA) trials, recommending its inclusion in all trials involving RA patients [12]. This emphasis on evaluating fatigue in RA should be extended to clinical practice, where the routine use of patient-reported outcome measures (PROMs) is increasing. This approach not only enhances communication with patients but also promotes shared decision-making processes.

Fatigue impairs quality of life, adding to disease burden in RA patients, and it is evaluated through PROMs. The use of multidimensional instruments seems to be a suitable proposal [13], such as the Bristol Rheumatoid Arthritis Fatigue Multidimensional Questionnaire (BRAF-MDQ) and the Bristol Rheumatoid Arthritis Numerical Rating Scales (BRAF-NRS). Both are developed to measure broader impacts of RA, not captured by existing single item PROMs for pain, disability and function [14]. Besides, these scales have shown a strong factor structure, a robust internal consistency and a moderate-good construct validity across different European countries [15]. The BRAF-MDQ had four dimension or subscales assessing physical, living, cognitive and emotional fatigue in RA patients, which could be understood as different dimensions of fatigue.

Biologic therapies and small-molecule inhibitors have significantly advanced the treatment of rheumatoid arthritis (RA) by targeting key inflammatory factors involved in the disease process, leading to the achievable goal of clinical remission [16]. While these treatments have shown high selectivity and therapeutic efficacy, there is scarce evidence regarding their potential impact on fatigue in RA. Fatigue in RA is complex, influenced by various factors beyond joint disease activity, both inflammatory and non-inflammatory [17]. This multifactorial nature of fatigue suggests that its association with biologic therapies and small-molecule inhibitors requires further investigation.

Difficult-to-treat RA (D2T-RA) is an umbrella concept aimed to characterize RA individuals where disease activity persists despite the use of several drugs. Clinically, D2T-RA is a relevant issue, with an estimated prevalence to range between 3% and 20% depending on the series reviewed [18–21] A EULAR task force has endorsed a definition of D2T-RA as: resistance to multiple biological or targeted synthetic disease-modifying antirheumatic drugs (DMARDs) with different mechanisms of action along with the persistence of physical symptoms or high disease activity [22].

D2T RA encompasses not only uncontrolled inflammatory disease, but also wider contextual factors such as chronic pain and fatigue, as well as comorbidities, recurrent infections, and treatment-limiting adverse events [18, 23–26]. Moreover, the economic burden of D2T RA is significantly higher than that of non-D2T RA [27]. Fatigue reflects other aspects of RA disease activity rather than inflammation, in the same way that D2T-RA definition does it, so there is likely to be a relationship between fatigue scores and D2T-RA outcome. Although the definition with respect to the D2T-RA criteria does not explicitly include fatigue, the impact of the fatigue on patients with D2T-RA has barely been assessed, so our purpose was to evaluate the role of fatigue on D2T-RA outcome.

Methods

Setting

The study was performed at a hospital of the National Health System of the Community of Madrid, Spain, namely, Hospital Clínico San Carlos (HCSC), with a

catchment population of approximately 400,000. The Rheumatology Service provides care to its catchment population. Medication and healthcare costs in RA are covered by Spain's national health system, and RA patients are follow-up by their rheumatologist.

Study design

We performed an observational, cross-sectional study. Since we have been treating RA according to the EULAR/ACR classification criteria under a treat-to-target strategy since 2010, patients diagnosed before 2009 were proposed for inclusion. The inclusion period was from June 2018 to June 2022.

Population, patients, and data sources

Patients ≥18 years with confirmed diagnosis of RA according to the 2010 (ACR/EULAR) classification criteria [28], and on current treatment with biological or targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs), were invited to participate and a specific patient visit were schedule for data collection.

Inability to access the selected patient's medical data, to have only one visit in the rheumatology consultation and inability to complete the study questionnaires were exclusion criteria.

The study was conducted in accordance with the Declaration of Helsinki and national regulations, was approved by the Hospital Clinico San Carlos Institutional Ethics Committee (nº 18/295-E) and all patients provided written informed consent. According to the compliance of the law, in order to ensure the confidentiality of data, the database may not include the name and surname of the patient, and instead a patient code was assigned. Anonymous questionnaires were returned for data entry and analysis.

Outcomes measures

The primary outcome was D2T RA as defined by the EULAR criteria which are set out below [18]. In order to collect the variables, we based on the Task Force agreements [29–31] and the clinical criteria of the research team. All three criteria (EULAR's definition of D2T) need to be present 1. Treatment according to EULAR recommendations and failure of ≥2 b/tsDMARDs (with different mechanisms of action) after failure of conventional synthetic DMARDs (unless contraindicated); 2a Presence of at least one of the following: At least moderate disease activity (according to validated composite measures including joint counts, for example, DAS28-ESR > 3.2 or CDAI > 10)), 2b) signs and/or symptoms suggestive of active disease, inability to taper glucocorticoids (below 7.5 mg/day), 2c) rapid radiographic progression; 3) The management of signs and/or symptoms is perceived as problematic by the rheumatologist and/or the patient.

Fatigue was measured using the Spanish version of Bristol Rheumatoid Arthritis Fatigue Multidimensional Questionnaire (BRAF-MDQ) including physical (e.g. lacked psychical energy), living (e.g. Difficult to dress, shower, work or restrict social life), cognitive (e.g. lacked mental energy, concentration, forgotten things) and emotional (e.g. embarrassment, down mood) dimensions. The BRAF-MDQ comprises 20 items (yielding a total score of 0–70) and four subscales of physical fatigue (0–22), living with fatigue (0–21), cognitive fatigue (0–15) and emotional fatigue (0–12), with high scores representing worse fatigue [14, 15, 32, 33].

We also assessed fatigue applying the Bristol Rheumatoid Arthritis Fatigue Numerical Rating Scale (BRAF-NRS). The BRAF-NRS contains three items (fatigue, effect on life and coping ability) measured from 0 to 10 on numeric rating scales: (i) fatigue severity describing the average level of fatigue (no fatigue–totally exhausted), (ii) effect of fatigue on your life (no effect–a great deal of effect) (items are measured from 0 to 10, with 0 being no problems) and (iii) coping with fatigue (not coping at all well–coping very well) (items are measured from 0 to 10, with 10 indicating no problems in coping with fatigue) [15].

In addition, we collected sociodemographic variables (age and sex), disease duration and laboratory parameters such as rheumatoid factor (RF) and anti-citrullinated peptide antibodies (Anti-CCP antibodies). Comorbidities included were cardiovascular disease (comprising cerebrovascular disease, ischemic heart disease, peripheral vascular disease and other risk factors such as hypertension, diabetes, obesity or dyslipidemia), and depression. We also collected pain (VAS) and disability (Health Assessment Questionnaire). Furthermore, amongst others C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were measured for disease activity scores (DAS28).

Treatment included glucocorticoid use, prednisone dose (defined as average dosage in the previous two months after collection), number of conventional synthetic – csDMARDs and use of biological agents [anti-TNF agents (infliximab, adalimumab, certolizumab, golimumab, etanercept), other therapies with non anti-TNF agents (abatacept, tocilizumab and rituximab), or use of Janus kinase inhibitors (JAKi) [tofacitinib, baricitinib, upadicitibib].

Statistical analyses

Descriptive statistics of patients' sociodemographic and clinical characteristics, as well as their disease activity and treatment, are presented as frequency distributions for qualitative variables and as the mean and standard deviation or median and percentiles for quantitative variables.

In order to compare D2T RA and non D2T RA, continuous variables were analyzed using the Mann-Whitney or t test, and discrete variables were analyzed using the chi-square or Fisher exact testFurthermore, in order to assess the possible influence of each dimension of fatigue on the main outcome, D2T RA, fitting for potential confounders, logistic multivariate regression models were run. All were also adjusted for age, sex, disease duration, concomitant treatments, and the presence of comorbidities.

Analyses were performed using STATA 13 statistical software. A two-tailed *p* value under 0.05 was considered to indicate statistical significance.

Results

A total of 145 patients with RA treated with b/tsDMARDs were included, and 38 (26.21%%) developed D2T RA. Table 1 shows the sociodemographic and clinical characteristics of the patients.

Most of them were women, with similar percentage between D2T RA group (63.16%) and non D2T RA group (67.29%) with a mean (SD) age of 56.7 (11.78) years. They were long-term RA patients with a median (p25-p75) disease duration of 14 (10-19) years, with slightly more duration in those patients with D2T-RA. We did not found differences in comorbidities like depression or cardiovascular disease. Disease markers as ESR, CRP, RF positive or Positive Anti-CCP antibodies were similar between groups, however, D2T RA group showed higher disability level (*p*=0.001).

In relation to concomitant treatment, 78 (53.8%) patients were on glucocorticoids and as expected glucocorticoid use was most frequent in D2T RA group (65.79% vs. 48.60%, *p*=0.03). In those patients on glucocorticoids 47.37% of D2T RA vs. 12.5% of non-D2T RA were using doses of at least 7.5 mg (*p*=0.003). Regarding csDMARDs, the distribution was similar between

Table 1 Characteristics and fatigue measures of RA patients

Variable	D2T RA (n = 38)	Non-D2T RA (n = 107)	p
Age, mean (SD), years	60 (13.02)	56 (12.2)	0.13
Female, n (%)	24 (63.16)	72 (67.29)	0.69
Disease duration, median [p25-p75], years	16 [11–21]	13 [6–18]	0.02
ESR, mean (SD) (mm/h)	12.34(10.78)	9.75 (9.25)	0.22
CRP, mean (SD) (mg/dL))	0.47 (0.43)	0.48 (0.71)	0.79
RF positive, n (%)	20 (58.82)	69 (67.65)	0.26
Positive Anti-CCP antibodies, n (%)	21 (70)	61 (67.78)	0.75
DAS28, mean (SD)	3.52 (1.08)	2.47(1.06)	0.01
Pain (VAS) mean (SD)	53.55(26.96)	30.42(24.03)	0.01
HAQ, mean (SD)	1.36 (0.63)	0.71 (0.57)	0.01
Comorbidities, n (%)			
Cardiovascular disease	19 (63.3)	52 (65.82)	0.8
Depression	5 (16.13)	10 (12.5)	0.59
Glucocorticoid use, n (%)	26 (68.42)	52 (48.60)	0.03
Prednisone dose, median [p25-p75],mg (n = 126)	5 [5-7.5]	0 [0–5]	0.01
Prednisone dose, intervals n(%) (n = 126)			
None	12 (38.7)	55 (57.9)	0.01
1.25-2.5mg	3 (9.7)	8 (8.4)	
5mg	7 (22.6)	27 (28.4)	
>=7.5mg	9 (29.0)	5 (5.3)	
Treatment			
Conventional DMARDs, n (%):			
None	12 (11.22)	2 (5.26)	0.58
1	42 (39.25)	15 (39.47)	
2 or more	53 (49.53)	21 (55.27)	
b/tsDMARDs, n (%):			
Anti TNF	10 (26.32)	69 (64.49)	0.01
Non-Anti TNF	19 (50)	35 (32.71)	
JAKi	9 (23.68)	3 (2.8)	
Treatment ≥ 4 b/tsDMARDs, n (%)	11 (28.95)	5 (4.67)	0.01

Abbreviations: RA: rheumatoid arthritis; D2T: difficult to treat; SD: standard deviation; ESR: erythrocyte sedimentation rate; CPR: C-reactive protein; RF: rheumatoid factor; DAS28: disease activity score 28-joint counts; VAS: visual analogue scale; TNF: tumor necrosis factor; HAQ: Health Assessment Questionnaire, DMARDs: Disease modifying anti-rheumatic drugs, JAKi: small molecule Janus kinasa inhibitors. Prednisone dose, intervals referred to average dosage in the two previous months to specific visit scheduled for data collection

Table 2 Fatigue measures of RA patients

Variable	D2T RA (n = 38)	Non-D2T RA (n = 107)	p
Global fatigue (0–70), median [p25-p75]	28 [21–37]	19[6–32]	0.003
Physical (0–22)	13 [10–17]	10 [4–15]	0.008
Living (0–21)	7[3–11]	4 [0–7]	0.003
Cognitive (0–15)	5 [1–7]	3 [0–6]	0.06
Emotional (0–12)	3.5 [2–7]	2 [0–4]	0.006
BRAF-NRS, median [p25-p75]			
Fatigue severity (0–10)	7 [5–8]	5 [2–7]	0.009
Effect of fatigue (0–10)	5 [3–7]	4 [2–6]	0.03
Fatigue coping* (0–10)	4 [2–6]	3 [1–5]	0.08

Abbreviations: RA: rheumatoid arthritis; D2T: difficult to treat; BRAF-NRS Bristol Rheumatoid Arthritis Fatigue Numerical Rating Scales. *Higher score=better outcome

groups (*p*=0.58), being methotrexate the most frequent (39.31%).

About the use of b/tsDMARDs, the D2T RA group used less anti-TNF, and a greater number of other biologics non anti-TNF and JAKi, compared to non D2T RA. A 68.75% of patients with D2T RA used more than 4 b/tsD-MARDs, compared with a 31.25% in non D2T RA group.

Assessing RA fatigue, the median (p25-p75) for the BRAF-MDQ was 22 (11-33) with higher scores in D2T RA group regarding physical (*p*=0.008), living (*p*=0.003) and emotional dimensions (*p*=0.006). In the BRAF-NRS scale, the D2T RA group had more fatigue severity (*p*=0.009) and more effect of fatigue in daily living (*p*=0.03) (Table 2).

Interestingly, in a sex-disaggregated analysis, higher fatigue scores were observed in women with D2T RA compared to non-D2T RA, for global fatigue(*p*=0.002), physical (*p*=0.003), living (*p*=0.002) and emotional dimensions (*p*=0.002). However, this effect was not found for men across any of the fatigue dimensions. (Fig. 1).

In the multivariate final model including global fatigue as independent variable and adjusted for age, sex, disease duration, concomitant therapy (glucocorticoids and csD-MARDs) and comorbidities, global fatigue was associated with D2T RA regardless the rest of the factors (OR:
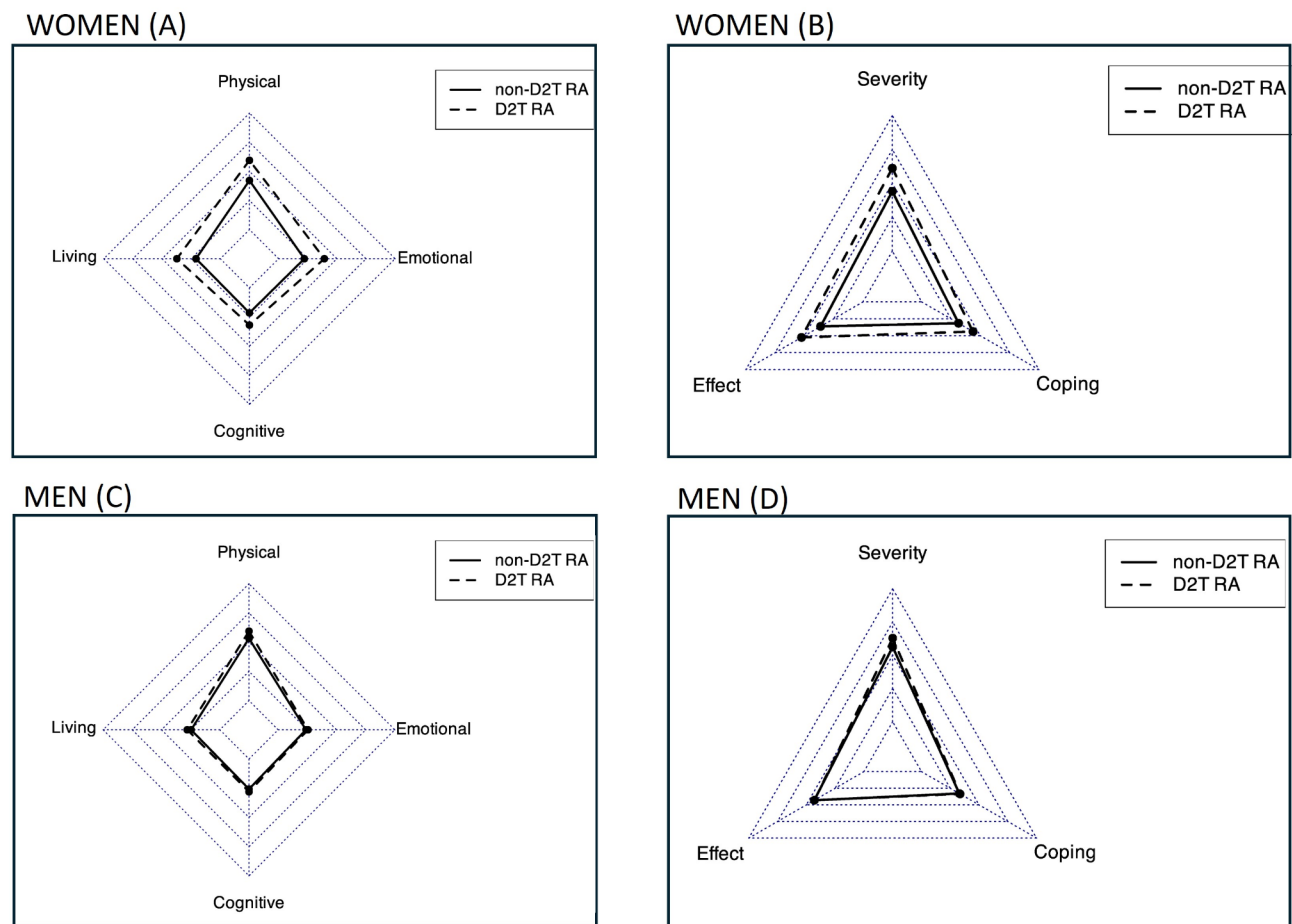
Fig. 1 Mean scores in fatigue dimensions (**A**) and numerical rating scale (**B**) in RA women. Mean scores in fatigue dimensions (**C**) and numerical rating scale (**D**) in RA men. D2T RA: difficult to treat rheumatoid arthritis, non-D2T RA: non difficult to treat rheumatoid arthritis

1.04; $p=0.007$). Comorbidities and concomitant therapy did not influence in any way and could be dropped from the model ($p>0.4$). In the other multivariate models, regarding to the different fatigue dimensions, our results showed that physical fatigue (OR: 1.10; $p=0.01$), living fatigue (OR: 1.09; $p=0.06$), cognitive fatigue (OR: 1.11; $p=0.04$) and emotional fatigue (OR: 1.18; $p=0.01$) were associated with D2T RA (Table 3). In all models, adjusted by sex, age and disease duration, the treatment variables and comorbidities dropped from the models.

Discussion

Our findings confirm that fatigue appears to be a significant factor influencing the outcomes for patients with difficult-to-treat RA, despite its current exclusion from the D2T RA definition.

One of the most interesting results is that the significant differences between D2T RA and non-D2T RA groups were mainly in the subjective component variables (pain, disability and fatigue), rather than the more objective markers of disease activity. The weak association between objective disease activity markers and fatigue perception aligns with current evidence. Berman et al. concluded that inflammatory components of the DAS28 contribute minimally to fatigue [34]. Another study found that all fatigue subscales, except the emotional subscale, were correlated with disease activity, but this was measured using DAS28, SDAI, or CDAI, which include subjective assessments [35]. A recent study in RA patients on bDMARDs showed significant cross-sectional correlations between fatigue and patient-reported outcome measures (PROMs) but not with objective inflammatory assessments [36]. Despite low reported disease activity due to updated RA management guidelines emphasizing a treat-to-target strategy, fatigue perception remains prevalent in daily clinical practice.

A notable finding from the study was the differential impact of fatigue on women with and without D2T RA. In the sample, males with both D2T RA and non-D2T RA exhibited similar fatigue scores, both overall and across various dimensions. However, females with D2T RA reported significantly higher fatigue scores compared to females with non-D2T RA. This suggests that fatigue could be a more relevant factor in the D2T RA outcome for female patients compared to male patientsAs far as we know, there are no studies assessing differences in fatigue between both sexes among patients with and without D2T RA, although there are some publications related to fatigue and sex differences in RA patients. Although stronger fatigue in women has been associated to gonadal hormones, the QUEST-RA study suggested that (especially at low levels of disease activity) it is needed to be cautious about interpretations of differences since disease measures themselves may be influenced by sex [37].

Findings highlight the need to evaluate and manage fatigue in a multidimensional perspective, as the different dimensions of fatigue may be modulated by various factors, including desegregated sex data and intra-sex differences. Another study showed a metabolic profile related to fatigue severity in RA patients, suggesting that metabolic pathways could be important in their fatigue modulation, adding information about the biological origin of chronic fatigue [38].

Focusing on our findings, another possible explanation for the significant differences between women with D2T RA and those without could be that the fatigue dimensions assessed may have more sensitivity to detect relevant changes in women compared to men.

The predominance of female patients in RA might have influenced the design and development of various PROMs outcomes, including those related to fatigue, making them more sensitive to women's experiences, particularly in the emotional and living with fatigue dimensions. This suggests that female RA patients may be more vulnerable to fatigue compared to their male counterparts. Additionally, it implies that the clinical measures used in rheumatology might be more attuned to the challenges faced by women, highlighting the need for gender-specific considerations in the assessment and management of RA-related fatigue.

This study was able to show that global fatigue, all its dimensions, fatigue severity and effect of fatigue were raised as independent factors of D2T RA regardless age, sex, and disease duration. Nevertheless, fatigue coping did not influence, maybe because this fatigue variable represents the patient's resources to deal with fatigue rather than the components of fatigue itself. These findings, although relevant, are still exploratory, due to the sample size and further research may be needed to fully elucidate the relationship between the various fatigue dimensions and D2T RA.

With this study it was not possible to determine whether biologic therapy modifies fatigue or not. It is

Table 3 Logistic regression analyses for D2T RA

Variables	OR (95% CI)	*p*
Global fatigue	1.04 (1.01–1.06)	0.006
Physical fatigue	1.10 (1.02–1.18)	0.007
Living fatigue	1.09 (1.02–1.18)	0.01
Cognitive fatigue	1.11 (1.01–1.24)	0.04
Emotional fatigue	1.18 (1.04–1.35)	0.01
Fatigue severity	1.24 (1.06–1.45)	0.008
Effect of fatigue	1.17 (1.01–1.37)	0.03
Fatigue coping	1.12 (0.97–1.31)	0.18

Abbreviations: RA: rheumatoid arthritis; D2T: difficult to treat; CI: Confidence Interval

All models adjusted by age, sex, duration of RA, comorbidities (dropped), treatments (dropped)

an important issue analyzed in other publications, but our aim was focused on fatigue and D2T RA. In other publications it is shown that treatment with bDMARDs, has led to some improvements in fatigue in RA patients being similar for both anti-TNF and non-anti-TNF biologics [39, 40]. Nevertheless, it is uncertain whether the improvement is directly due to the biologics or indirectly through other outcomes.

This study displays limitations. Due to its cross-sectional study design, it is difficult to assess temporality and causality, thus the study is not able to discern whether fatigue is underlying the disease state, worsen because of having RA D2T, or both. Long-term observational studies, starting at disease onset, will be needed to resolve all these issues. Another weakness is the small number of D2T RA found in the sample, which has limited the multivariate analysis. However, we were able to adjust for the main confounding factors. As this is a single center, it may not be representative at the national level. Finally, concomitant syndromes or diseases, such as fibromyalgia, osteoarthritis and psychosocial factors associated with fatigue could contribute to D2T RA, but in these types of designs, the prevalence might be underestimated.

On the other hand, our current study adds additional information to the understanding of RA fatigue with the following strengths. First, this study represents a real-life picture of unselected patients with RA, collecting sociodemographic, clinical data including conventional and biologic DMARDs, and information gained on PROMs. This study explores the relationship of a very important symptom for patients, such as fatigue, and a very important outcome for clinicians, such as the development of D2T RA. Besides, data are based on the implementation of outcome measures recommended by guidelines from the EULAR and ACR [12]. Moreover, the BRAF-MDQ is a validated questionnaire which has been developed by patients and should thus be relevant for exploring fatigue.

In summary, fatigue is a common symptom, even in patients with stable and well-controlled disease, but fatigue high scores may be important for the development of D2T RA. Considering that fatigue is a complex and subjective symptom in patients with RA, the comprehensive management of fatigue should involve identifying all dimensions of fatigue, to facilitate the development of individually tailored fatigue management programs. In addition to standard RA treatment, other non-pharmacological interventions, like educational programs incorporating self-management techniques targeting mood regulation and sleep improvement, could improve fatigue in these patients.

Studies addressing this symptom are much crucial, as fatigue is a very common symptom in all types of chronic diseases, and across comorbidities.

A broader approach covering all aspects of this burdensome symptom is needed. Each patient should be assessed individually, using the validated multidimensional questionnaires. For female RA patients, the evaluation and management of fatigue, should be an important target in the treatment of RA patients to prevent its potential contribution to the development of D2T RA.

Conclusions
A subset of patients with rheumatoid arthritis (RA) who remains symptomatic after failing to multiple therapies are deemed to have "difficult-to-treat" (D2T RA). Fatigue is a multidimensional and burdensome symptom for RA patients, hindering their improvement. The aim of our study was to evaluate the role of fatigue on D2T-RA outcome under real-life conditions.

This study highlights that fatigue seem to be far more important than other factors for D2T RA development. Clinicians treating PsA patients' need to be aware of the fatigue impact when aiming to prevent D2T RA development, and gender-specific differences should be considered. Thus, questionnaires addressing fatigue dimensions should be implemented as part of standard clinical care.

Abbreviations

ACR	American College of Rheumatology
b/tsDMARDs	Biological or targeted synthetic disease-modifying antirheumatic drugs
BRAF-MDQ	Bristol Rheumatoid Arthritis Fatigue Multidimensional Questionnaire
BRAF-NRS	Bristol Rheumatoid Arthritis Fatigue Numerical Rating Scales
CPR	C-reactive protein
D2T	Difficult to treat
DAS28	Disease activity score 28-joint counts
ESR	Erythrocyte sedimentation rate
EULAR	European Alliance of Associations for Rheumatology
HAQ	Health Assessment Questionnaire
JAKi	Small molecule Janus kinasa inhibitors
PROM	Patient-reported outcome measure
RA	Rheumatoid arthritis
RF	Rheumatoid factor
SD	Standard deviation
TNF	Tumor necrosis factor
VAS	Visual analogue scale

Declarations

Ethics approval and consent to participate
The study was conducted in accordance with the Declaration of Helsinki and national regulations. The study was approved by the Research Ethic Committee of the Hospital Clínico San Carlos, Madrid, Spain (nº 18/295-E). All patients provided written informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Clinical trial number
Not applicable.

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