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Evaluation of difficult-to-treat rheumatoid arthritis using EULAR definition: Prevalence and clinical determinants from a single-center cross-sectional study

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Abstract

In 2021, the European Alliance of Associations for Rheumatology (EULAR) introduced standardized criteria to define difficult-to-treat rheumatoid arthritis (D2T RA). This study aimed to examine the prevalence and clinical features of D2T RA within a real-world cohort. This study included 72 RA patients followed at Gazi University Rheumatology Clinic for a minimum of one year between May 2021 and August 2022. Data on sociodemographic parameters, disease activity, therapeutic history, and functional status were collected. All participants were assessed using validated instruments for fibromyalgia (2016 American College of Rheumatology criteria), neuropathic pain (DN4), mood symptoms (HADS), pain catastrophizing (PCS), and physical function (HAQ). The overall prevalence of D2T RA was found to be 6.9%. Compared to the non-D2T group, patients meeting D2T criteria exhibited longer disease duration, higher inflammatory activity, reduced functional capacity, and greater exposure to B-cell–targeted therapies. These findings underscore the critical role of individualized treatment strategies in managing D2T RA.

Keywords: Rheumatoid arthritis, treatment, disease-modifying antirheumatic drug, biologic drugs

Introduction

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory disorder that predominantly targets synovial joints, frequently resulting in progressive articular damage, functional decline, and impaired health-related quality of life. To enhance treatment outcomes, treat-to-target (T2T) strategies have been widely adopted, aiming to achieve remission or low disease activity. In this approach, disease activity is assessed regularly using validated tools, and if the predefined therapeutic target is not reached within a specified timeframe, the treatment is intensified either through dose escalation or by modifying the therapeutic regimen [1].

Although the availability of advanced therapies has expanded considerably, a clinically significant subset of patients continues to exhibit refractory disease despite multiple treatment attempts. Contributing factors may include poor adherence to medication, adverse drug effects, comorbid conditions, obesity, joint degeneration, structural damage from longstanding disease, depression, sleep disturbances, and coexisting fibromyalgia [2]. These confounding elements can give the false impression that RA is more active or treatment-resistant than it truly is, thereby complicating the accurate clinical assessment of disease activity.

To standardize identification of this complex disease phenotype, the European Alliance of Associations for Rheumatology (EULAR) established in 2021 a three-pronged definition for difficult-to-treat (D2T) RA [3]. The criteria necessitate: 1) previous exposure to ≥2 biologic or targeted Disease-Modifying Anti-Rheumatic Drugs (b/tsDMARDs) with divergent mechanisms of action post conventional synthetic DMARDs (csDMARDs) failure, 2) documented inflammatory activity (Disease Activity Score 28–C-Reactive Protein (DAS28-CRP)

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≥3.2, radiographic progression, or glucocorticoid dependence ≥7.5 mg/day prednisone equivalent), and 3) clinician- and/or patient-reported challenges in disease control.

Various studies based on the EULAR definition of D2T RA including real-world data have reported a wide range of prevalence rates. Female sex, long disease duration, seropositivity, high-titer autoantibodies, high baseline disease activity, and the presence of comorbidities have been identified as risk factors for the development of D2T RA [4].

Identifying patients who meet the D2T RA definition is critical for tailoring effective therapeutic strategies. For these patients, structured and personalized management may improve clinical outcomes. The present study aims to assess the prevalence of D2T RA in a real-world cohort using EULAR's definition, to explore associated clinical factors, and to investigate non-inflammatory contributors that may mimic persistent disease activity.

Material and Methods

Study Design

The study, designed as a cross-sectional analysis, was conducted at the Department of Rheumatology, Gazi University Faculty of Medicine. The study population consisted of patients diagnosed with RA who had been under regular follow-up for at least one year. Data were collected during routine outpatient visits between May 2021 and August 2022. Ethical approval was obtained from the Gazi University Ethics Committee for Scientific Research and Publication (Date: 12.04.2021, No: 355). All procedures were conducted in line with the ethical guidelines of the Declaration of Helsinki, with written informed consent secured from each participant before inclusion.

Patient Selection

The study included patients with a confirmed diagnosis of RA based on the 2010 American College of Rheumatology (ACR)/ EULAR classification criteria [5] who had been followed regularly for a minimum of 12 months. Patients were excluded if they had incomplete clinical records or were diagnosed with another inflammatory rheumatic disease that could confound the assessment.

Data Collection

Sociodemographic information including age, sex, body mass index (BMI), marital status, educational attainment, and history of smoking or alcohol consumption was recorded for all participants. Clinical data included disease duration, presence of extra-articular manifestations, and treatment history encompassing both prior and ongoing RA therapies.

Physical Examination and Laboratory Assessment

During clinical evaluation, the number of tender and swollen joints was recorded, along with documentation of any residual joint deformities. Laboratory investigations included measurement of rheumatoid factor (RF), Anti-Citrullinated Protein Antibody (ACPA), CRP, and Erythrocyte Sedimentation Rate (ESR). RF and ACPA results were considered high-positive if their titres exceeded three times the upper limit of the reference range defined by the laboratory.

Conventional anteroposterior radiographs of the hands and feet were reviewed to assess structural joint damage. Particular attention was given to identifying the presence of bone erosions as an indicator of radiographic progression.

Assessment of Disease Activity

Disease activity was assessed through the DAS28. In addition, visual analogue scales (VAS) were employed to assess patient-reported outcomes, including global health (VAS-global), physician assessment (VAS-physician), pain intensity (VAS-pain), and fatigue levels (VAS-fatigue).

Assessment Tools and Case Definition

All participants were evaluated for D2T RA using the 2021 EULAR classification criteria during routine outpatient visits [3]. A diagnosis of D2T RA was assigned to patients who met all three mandatory criteria defined by EULAR.

To identify potential non-inflammatory contributors to persistent symptoms or treatment resistance, several validated instruments were administered:

- The Hospital Anxiety and Depression Scale (HADS), including subscales for anxiety (HADS-A) and depression (HADS-D),
- The 4-item DN4 (Douleur Neuropathique en 4 Questions) questionnaire to screen for neuropathic pain,
- The Pain Catastrophizing Scale (PCS) to assess cognitive-emotional aspects of pain,
- The 2016 ACR criteria for the diagnosis of fibromyalgia,
- The Health Assessment Questionnaire (HAQ) for evaluating physical function.

The validated Turkish versions of the HADS [6], DN4 questionnaire [7], PCS [8], 2016 ACR Fibromyalgia Criteria [9], and HAQ [10] were used in this study.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 27.0 (IBM Corp., Armonk, NY, USA). The Shapiro–Wilk test was used to assess the distribution of continuous variables. Variables following a normal distribution are reported as mean±standard deviation (SD), while those with skewed distributions are expressed as median and interquartile range (IQR). Categorical variables are reported as counts and percentages. Between-group comparisons (D2T vs. non-D2T RA) employed independent-samples t-tests for normally distributed continuous variables and Mann–Whitney U tests for non-normally distributed continuous variables. For categorical variables, Pearson's χ^2 test was used when expected cell counts were ≥5, and Fisher's exact test when counts were <5. Prevalence rates per 100 persons and corresponding 95% confidence intervals (CIs) for the overall EULAR D2T-RA

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definition and each sub criterion were calculated in R (version 4.2.0; R Foundation for Statistical Computing, Vienna, Austria). Prevalence estimates were obtained from Poisson regression models. Exact CIs for individual case counts were derived using the poisson.test function in R's stats package. The p-value of <0.05 was considered statistically significant.

Results

A total of 72 patients diagnosed with RA were enrolled in the analysis. Of these, 5 patients (6.9%) met the EULAR criteria for D2T RA. The mean age of the patients was 55.2±9.4 years, and the majority were female (81.9%). No statistically significant differences were observed between D2T and non-D2T RA patients regarding age, sex, BMI, smoking or alcohol use, educational background, or marital status (p>0.05 for all comparisons). Similarly, common comorbidities such as hypertension, diabetes mellitus, coronary artery disease, and chronic pulmonary disease were comparable between the groups. Although arrhythmia and heart failure were more frequently encountered in the D2T group, these differences did not reach statistical significance (p=0.069 and p=0.135, respectively). An overview of the demographic and clinical characteristics is provided in Table 1.

Table 1. Demographic and clinical profiles of patients with difficult-to-treat RA compared to matched non-D2T RA patients

Variable	Overall (n=72)	D2T+ (n=5)	D2T– (n=67)	p-value
Age, years	55.2±9.4	55.0±4.9	55.2±9.7	0.936*
Sex				0.627‡
Female	59 (81.94%)	5 (100.00%)	54 (80.60%)	
Male	13 (18.06%)	0 (0.00%)	13 (19.40%)	
BMI kg/m²	27.5±4.9	24.1±5.1	27.7±4.8	0.193*
Smoking status				0.680‡
Active smoker	26 (36.11%)	2 (40.00%)	24 (35.82%)	
Past smoker	9 (12.50%)	0 (0.00%)	9 (13.43%)	
Never skomed	37 (51.39%)	3 (60.00%)	34 (50.75%)	
Alcohol use				1.000‡
Current	4 (5.56%)	0 (0.00%)	4 (5.97%)	
Former	0 (0.00%)	0 (0.00%)	0 (0.00%)	
Never	68 (94.44%)	5 (100.00%)	63 (94.03%)	
Education level				0.774‡
Primary	39 (54.17%)	2 (40.00%)	37 (55.22%)	
Middle school	8 (11.11%)	1 (20.00%)	7 (10.45%)	
High school	17 (23.61%)	2 (40.00%)	15 (22.39%)	
University	7 (9.72%)	0 (0.00%)	7 (10.45%)	
Postgraduate	1 (1.39%)	0 (0.00%)	1 (1.49%)	
Marital status				0.056‡
Single	4 (5.56%)	0 (0.00%)	4 (5.97%)	
Married	61 (84.72%)	3 (60.00%)	58 (86.57%)	
Widowed	7 (9.72%)	2 (40.00%)	5 (7.46%)	
Comorbidities				
Hypertension	28 (38.89%)	1 (20.00%)	27 (40.30%)	0.642§
Chronic obstructive pulmonary disease/asthma	8 (11.11%)	1 (20.00%)	7 (10.45%)	0.455§
Coronary artery disease	6 (8.33%)	1 (20.00%)	5 (7.46%)	0.361§
Diabetes mellitus	9 (12.50%)	1 (20.00%)	8 (11.94%)	0.498§
Arrhythmia	1 (1.39%)	1 (20.00%)	0 (0.00%)	0.069§
Hepatitis	3 (4.17%)	0 (0.00%)	3 (4.48%)	1.000§
Hypothyroidism	2 (2.78%)	0 (0.00%)	2 (2.99%)	1.000§
Hyperlipidemia	1 (1.39%)	0 (0.00%)	1 (1.49%)	1.000§
Chronic kidney disease	1 (1.39%)	0 (0.00%)	1 (1.49%)	1.000§
Heart failure	2 (2.78%)	1 (20.00%)	1 (1.49%)	0.135§
Cardiomyopathy	1 (1.39%)	0 (0.00%)	1 (1.49%)	1.000§

*Independent samples t-test; † Mann–Whitney U test; ‡ Chi-square test; § Fisher's exact test (cell count <5)

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Patients with D2T RA had a significantly longer disease duration compared to the non-D2T group (median 20.0 vs. 10.0 years, p=0.020). While CRP levels were numerically higher among D2T patients, this difference did not reach statistical significance (p=0.124). Similarly, the proportion of patients with high-titre RF positivity was greater in the D2T group (80.0% vs. 41.8%), though not statistically significant (p=0.208). Indicators of active disease were more prominent in the D2T subgroup. The number of swollen joints was higher (median 3.0 vs. 0.0, p=0.005), and DAS28-CRP scores were also significantly elevated (3.6 vs. 2.7, p=0.033). In terms of functional capacity, HAQ scores indicated greater impairment in the D2T group (median 0.6 vs. 0.1, p=0.038). Radiographic findings revealed more advanced joint damage among D2T RA patients, as reflected by a higher frequency of hand erosions (p=0.010) and presence of joint deformities (p=0.008). Extra-articular features and patient-reported outcomes related to fatigue, fibromyalgia, anxiety, and depression were similar across both groups. Details of clinical, serological, functional, and radiographic comparisons are provided in Table 2.

Table 2. Clinical, radiological, disease activity characteristics, and EAMs of comparison with D2T RA and with non-D2T RA

Variables	Overall (n=72)	D2T+ (n=5)	D2T– (n=67)	p value
Disease duration, year	10.0 (5.8–17.2)	20.0 (20.0–29.0)	10.0 (5.0–16.0)	**0.020**†
Erythrocyte sedimentation rate, mm/h	23.5 (13.8–36.0)	23.0 (20.0–32.0)	24.0 (13.0–36.0)	0.602†
C-reactive protein, mg/l	4.3 (2.9–9.9)	10.2 (4.1–23.0)	4.2 (2.8–8.7)	0.124†
Rheumatoid factor				0.208‡
Negative	20 (27.78%)	1 (20.00%)	19 (28.36%)	
Low titre	20 (27.78%)	0 (0.00%)	20 (29.85%)	
High titre	32 (44.44%)	4 (80.00%)	28 (41.79%)	
Anti-citrullinated protein antibody		4.0 (2.0–6.0)	3.0 (2.0–5.0)	0.814‡
Negative	14 (19.44%)	1 (20.00%)	13 (19.40%)	
Low titre	5 (6.94%)	0 (0.00%)	5 (7.46%)	
High titre	52 (72.22%)	4 (80.00%)	48 (71.64%)	
Swollen joint	0.0 (0.0–1.2)	3.0 (1.0–3.0)	0.0 (0.0–1.0)	0.005†
Tender joint	1.0 (0.0–4.0)	3.0 (3.0–4.0)	1.0 (0.0–3.5)	0.169†
Disease activity score-28-CRP	2.8 (2.1–3.5)	3.6 (3.2–4.3)	2.7 (2.0–3.4)	**0.033**†
Patient's global assessment (0-10)	3.0 (2.0–5.0)	4.0 (2.0–6.0)	3.0 (2.0–5.0)	0.831†
Physician's global assessment (0-10)	3.0 (2.0–4.0)	5.0 (3.0–6.0)	3.0 (2.0–4.0)	0.076†
Pain visual analogue scale (0-10)	3.0 (2.0–5.2)	4.0 (2.0–7.0)	3.0 (2.0–5.0)	0.704†
Fatique visual analogue scale (0-10)	4.0 (2.0–5.0)	4.0 (0.0–4.0)	4.0 (2.0–5.0)	0.235†
Health assessment questionnaire	0.1 (0.1–0.5)	0.6 (0.4–0.7)	0.1 (0.1–0.5)	**0.038**†
Pain catastrophizing scale	10.5 (2.0–20.5)	12.0 (1.0–12.0)	10.0 (2.0–21.0)	0.764†
Hospital anxiety and depression scale, depression	3.0 (1.0–6.0)	5.0 (4.0–7.0)	3.0 (1.0–6.0)	0.366†
Hospital anxiety and depression scale, anxiety	3.0 (1.0–6.0)	3.0 (0.0–7.0)	3.0 (1.5–6.0)	0.789†
Douleur neuropathique 4 questions	2.0 (0.0–3.0)	0.0 (0.0–2.0)	2.0 (0.5–3.0)	0.353†
Neuropathic pain	7 (9.72%)	1 (20.00%)	6 (8.96%)	0.410§
Functional assessment of chronic illness therapy –fatigue	13.0 (7.0–20.0)	10.0 (3.0–19.0)	13.0 (7.0–20.0)	0.579†
Fibromyalgia syndrome	9 (12.50%)	0 (0.00%)	9 (13.43%)	1.000§
Widespread pain index	3.0 (1.0–4.2)	4.0 (1.0–5.0)	3.0 (1.0–4.0)	0.858†
Symptom severity scale	2.0 (1.0–4.0)	0.0 (0.0–0.0)	2.0 (1.0–4.0)	0.059†
Extra-articular manifestations				0.877‡
Sjögren's syndrome	10 (13.89%)	0 (0.00%)	10 (14.93%)	
Pulmonary nodule	5 (6.94%)	0 (0.00%)	5 (7.46%)	
Interstitial lung disease	2 (2.78%)	0 (0.00%)	2 (2.99%)	
Rheumatoid nodule	1 (1.39%)	0 (0.00%)	1 (1.49%)	
Hand erosion on X-ray	30 (41.67%)	5 (100.00%)	25 (37.31%)	**0.010§**
Foot erosion on X-ray	16 (22.22%)	3 (60.00%)	13 (19.40%)	0.069§
Joint deformity	16 (22.22%)	4 (80.00%)	12 (17.91%)	**0.008§**

† Mann–Whitney U test (applied when Shapiro–Wilk test $p < 0.05$ in one or both groups); ‡ Pearson's chi-square test; § Fisher's exact test (used when any cell count < 5)

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All patients with D2T RA had been exposed to at least two advanced therapies, most commonly biological agents. Rituximab use was significantly more frequent in the D2T group (80.0% vs. 11.94%, p=0.002), suggesting a treatment shift toward B-cell–targeted approaches following previous treatment failures. Although tocilizumab was used more often among non D2T patients (0% vs. 2.99%), this difference was not statistically significant (p=1.0). Current use of csDMARDs, particularly methotrexate, was comparable between groups. However, D2T patients had significantly greater exposure to corticosteroids both in duration (80.0% vs. 70.15%). Despite similar levels of fibromyalgia, anxiety, and depression, the PCS scores were notably higher in the D2T group (median 12.0 vs. 10.0, p=0.764). Detailed treatment data for both groups are summarized in Table 3.

Table 3. Comparison of previous and ongoing RA treatments between D2T and non-D2T groups

Variables	Overall (n=72)	D2T+ (n=5)	D2T– (n=67)	p value
total ts/bDMARD	0.0 (0.0–1.0)	2.0 (2.0–3.0)	0.0 (0.0–1.0)	0.000†
TNFi	0.0 (0.0–1.0)	1.0 (1.0–2.0)	0.0 (0.0–0.0)	0.000†
b/tsDMARD*				**0.023‡**
Naive	47 (65.3%)	0 (0.00%)	47 (70.1%)	0.209¶
Rituximab	12 (16.9%)	4 (80.00%)	8 (11.94%)	**0.002§**
Tocilizumab	2 (2.78%)	0 (0.00%)	2 (2.99%)	1.000¶
Baricitinib	1 (1.39%)	0 (0.00%)	1 (1.49%)	1.000¶
Abatacept	2 (2.78%)	0 (0.00%)	2 (2.99%)	1.000¶
Golimumab	2 (2.78%)	1 (20.00%)	1 (1.49%)	1.000¶
Infliximab	2 (2.78%)	0 (0.00%)	2 (2.99%)	1.000¶
Tofacitinib	2 (2.78%)	0 (0.00%)	2 (2.99%)	1.000¶
Adalimumab	2 (2.78%)	0 (0.00%)	2 (2.99%)	1.000¶
Etanercept	1 (1.39%)	0 (0.00%)	1 (1.49%)	1.000¶
csDMARD and steroid				
Methotrexate experienced	63 (88.73%)	5 (100.00%)	58 (86.57%)	1.000§
Methotrexate current	33 (46.48%)	2 (40.00%)	31 (46.27%)	1.000§
Leflunomid experienced	53 (74.65%)	5 (100.00%)	48 (71.64%)	0.316§
Leflunomid current	38 (53.52%)	3 (60.00%)	35 (52.24%)	1.000§
Sulfasalazine experienced	36 (50.70%)	4 (80.00%)	32 (47.76%)	0.357§
Sulfasalazine current	7 (9.86%)	0 (0.00%)	7 (10.45%)	1.000§
Hydroxychloroquine experienced	54 (76.06%)	5 (100.00%)	49 (73.13%)	0.322§
Hydroxychloroquine current	25 (35.21%)	0 (0.00%)	25 (37.31%)	0.156§
Steroid current	51 (71.83%)	4 (80.00%)	47 (70.15%)	1.000§
Steroid dose current				0.772‡
None	21 (29.58%)	1 (20.00%)	20 (29.85%)	
<5 mg	7 (9.86%)	0 (0.00%)	7 (10.45%)	
5–10 mg	43 (60.56%)	4 (80.00%)	39 (58.21%)	
>10 mg	1 (1.41%)	0 (0.00%)	1 (1.49%)	

† Mann–Whitney U test (Shapiro–Wilk p<0.05); ‡ Pearson's χ^2 test; § Fisher's exact test (cell count <5); ¶ Bonferroni-adjusted post hoc Fisher's exact test (9 comparisons); *at any time during the study period; b/tsDMARD: biological or targeted synthetic disease-modifying antirheumatic drug, TNFi: tumor necrosis factor inhibitor, csDMARD: conventional sDMARD

According to the EULAR classification, the overall prevalence of D2T RA in our cohort was 6.9% (95% CI: 2.3–16.2). Among patients who had received at least one b/tsDMARD), the prevalence increased to 19.0% (95% CI: 5.2–48.8). Evaluation of individual EULAR components revealed that 18.1% (95% CI: 9.6–30.9) of the total cohort and 52.4% (95% CI: 26.1–93.7) of those exposed to b/tsDMARDs met the first criterion (EC1), which requires failure of at least two different advanced therapies. The combination of EC1 and evidence of active disease (EC2) was present in 8.3% of all patients and 23.8% of the b/tsDMARD subgroup. Less frequent but clinically relevant combinations included EC1 with radiographic progression (6.9%), elevated composite disease activity scores (6.9%), or patient-perceived management difficulty (6.9%). Dependence on glucocorticoids alongside EC1 was the least common pattern, observed in only one patient (1.4) Table 4 presents the prevalence rates of overall D2T RA and its EULAR-defined sub-criteria among all RA patients and those treated with b/tsDMARDs.

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Table 4. Prevalence rates (with 95% CI) of overall and sub-criteria according to the EULAR definition of D2T RA

EULAR D2T-RA suc-criteria	Prevalant case	Participants with RA (n=72) prevalans/100 persons (95% CI)	Participants with RA treated with a b/tsDMARD (n=21) patients/100 persons (95% CI)
D2T EULAR (EC1, 2, and 3)	5	6.9 (2.3–16.2)	19.0 (5.2–48.8)
DMARD citeria only (EC1)	13	18.1 (9.6–30.9)	52.4 (26.1–93.7)
DMARD + persistant disease activity (EC1 and 2)	6	8.3 (3.1–18.1)	23.8 (7.7–55.6)
DMARD + DAS 28 (EC1 and 2a)	5	6.9 (2.3–16.2)	19.0 (5.2–48.8)
DMARD + EAM (EC1 and 2b)	4	5.6 (1.5–14.2)	14.3 (2.9–41.7)
DMARD + glucocorticoid (EC1 and 2c)	1	1.4 (0.0–7.7)	4.8 (0.1–26.5)
DMARD + radiologic progression (EC1 and 2d)	5	6.9 (2.3–16.2)	19.0 (5.2–48.8)
DMARD + RA symptoms (EC1 and 2e)	3	4.2 (0.9–12.2)	14.3 (2.9–41.7)
DMARD + preception of a problem (EC1 and 3)	5	6.9 (2.3–16.2)	19.0 (5.2–48.8)

Prevalence rates and 95% confidence intervals were calculated using exact Poisson confidence intervals (n=72 and n=21); CI: confidence interval, EC: EULAR criterion, D2T: difficult-to-treat, DAS28: Disease Activity Score in 28 joints, EAM: Extra-Articular Manifestation

Discussion

In our findings 6.9% of RA patients fulfilled the EULAR definition of D2T-RA, representing a clinically distinct subgroup with prolonged disease duration, higher disease activity scores, more functional impairment, and increased exposure to advanced therapies. Following the introduction of the EULAR definition for D2T RA, multiple real-world studies have investigated its prevalence, reporting a wide range between 5.9-27.5% [4]. A recent study from Türkiye by Alp et al. reported a prevalence of 8.9% for D2T RA among patients with rheumatoid arthritis [11]. The variability in reported prevalence across these real-world studies may be attributed to the heterogeneity of patient populations, differences in healthcare systems, access to advanced therapies, and inconsistencies in the application of EULAR criteria. Additionally, the way patients and physicians perceive refractory disease may also influence classification.

Comorbidities notably affect RA treatment outcomes, especially in patients with fibromyalgia or obesity [12]. However, this association could not be demonstrated in our study, potentially due to the relatively small sample size. Contrary to the findings of Paudel et al., who reported significant differences in demographic and comorbidity profiles including younger age at diagnosis, female predominance, lower educational status, and higher prevalence of hypertension, cardiovascular disease, and depression in D2T RA patients our study did not reveal any statistically significant differences in baseline demographic characteristics or comorbidity burden between D2T and non-D2T groups [13]. This discrepancy may be attributed to differences in sample size, study design, or regional variations in disease expression and healthcare access. Nevertheless, we observed a numerical trend toward increased rates of arrhythmia and heart failure in D2T RA patients, supporting the notion that cumulative disease burden and chronic inflammation may predispose these individuals to cardiovascular risk [14]. This study did not find statistically significant differences in fatigue, pain or anxiety/depression scores. However, patient-reported outcomes including pain perception, and functional impairment tended to be worse in the D2T RA group. Leon et al. emphasized the prominent role of fatigue in patients with D2T RA, noting its association with increased disease burden and dissatisfaction with treatment despite adequate control of inflammation [15].

Our findings indicated that patients with D2T RA had a significantly longer disease duration, more swollen joints, higher DAS28-CRP scores, and greater functional impairment as assessed by HAQ. These features are consistent with the clinical phenotype described in the EULAR definition of D2T RA [3]. Moreover, the higher frequency of joint erosions and deformities observed in D2T RA patients reflects the progressive joint damage associated with persistent disease activity. Importantly, a high burden of irreversible damage may lead to the misinterpretation of ongoing disease activity, potentially resulting in the inappropriate use of advanced and costly treatment options. Hence, it is essential to differentiate between damage-related symptoms and true disease activity to guide appropriate treatment decisions.

The higher proportion of high-titre RF positivity (80%) in the D2T RA group, although not statistically significant, supports previous findings linking seropositivity with refractory disease and radiographic progression [16]. This is further supported by the findings of Alp et al., who highlighted the potential predictive value of RF monitoring in identifying patients at risk for developing D2T RA [11]. In this study, four patients in the D2T-RA group were ACPA high-titre positive, while one patient was ACPA negative. Although ACPA positivity is known to be associated with a worse prognosis, no significant difference was observed between the D2T and non-D2T groups in this regard. This discrepancy may be attributed to several factors, such as variations in ACPA measurement techniques or threshold definitions across laboratories, which may have influenced the classification. Moreover, the development of a D2T phenotype may be driven not only by immunological mechanisms but also by non-immunological factors such as pain perception, comorbidities, and treatment adherence. Therefore, ACPA alone may not be sufficient to predict treatment refractoriness in routine clinical practice.

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In our cohort, the preferential use of rituximab in patients with D2T RA likely reflects a strategic shift toward B-cell depletion after multiple treatment failures, particularly TNF inhibitors. This trend is supported by findings from a recent network meta-analysis, which confirmed rituximab as an effective and relatively safe therapeutic option in the management of D2T RA, especially among seropositive patients [17]. Moreover, the same analysis also highlighted the high efficacy and tolerability of tocilizumab in this population, suggesting it as a strong candidate for earlier use in the treatment algorithm [17]. However, in our study, the use of tocilizumab was limited, which may be attributable to national reimbursement constraints, or institutional prescribing patterns in our country. These findings underscore the need to align local treatment strategies with emerging international evidence to optimize outcomes in this challenging patient population. Additionally, recent evidence indicates that Janus kinase inhibitors are effective both in patients refractory to csDMARDs and those unresponsive to bDMARDs, their uptake in our cohort remained modest [18].

In the context of our clinical cohort, the most commonly met EULAR criterion was EC1, indicating failure of at least two b/tsDMARDs with different mechanisms of action. This finding is consistent with a recent registry-based study by Paudel et al., which also identified EC1 as the most frequently observed criterion among patients with D2T RA [13]. On the other hand, EC3 reflecting the perception of the disease as problematic by either the physician or the patient was fulfilled less frequently in our study. This may be due to variability in clinical documentation or the absence of systematic tools to capture patient-reported outcomes in routine care. While Paudel et al. reported a higher frequency of persistent disease activity (EC2), our findings showed lower rates, possibly related to differences in sample size, patient population, or local monitoring practices [13]. Taken together, these results highlight the role of healthcare context and clinical assessment practices in influencing how the D2T RA definition is applied in real-world settings.

This study offers several important strengths. First, it applies the EULAR definition of DT2 RA in a structured and standardised manner, enabling comparability with other real-world cohorts. The inclusion of multidimensional assessments including not only disease activity but also functional disability, mood symptoms, pain perception, features of neuropathic pain, and the presence of fibromyalgia provides a more comprehensive understanding of disease burden. Additionally, the study reflects routine clinical practice in a tertiary care setting, thereby enhancing its external validity.

This study has several limitations, one of which is the relatively small sample size in the D2T RA subgroup, which may have reduced the ability to detect subtle differences and limited the generalizability of the findings. The cross-sectional design precludes evaluation of temporal changes and causal relationships. Furthermore, although validated instruments were used, certain measures such as radiographic damage or treatment response may be subject to inter-observer variability. The study was also limited by the lack of access to an objective parameter to assess medication adherence before labelling patients as having treatment-resistant disease. Finally, as the study population was derived from a single tertiary rheumatology center, the possibility of selection bias should be acknowledged.

Conclusion

This study highlights that a notable proportion of patients with in routine clinical settings meet the EULAR definition of D2T disease. These patients tend to exhibit higher disease activity, greater functional impairment, and more extensive radiographic damage. Moreover, advanced therapies particularly B-cell targeted agents are more frequently utilized in this subgroup. By incorporating a comprehensive assessment beyond conventional disease activity indices, our findings underscore the multifaceted nature of the D2T RA phenotype. These observations point to the need for more individualized and multidisciplinary treatment approaches. Future prospective, multicentre studies are warranted to validate these findings and inform effective management strategies for this challenging patient population.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
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Ethical Approval
This study was conducted with the approval of the Gazi University Scientific Research Ethics Committee (Date: 12.04.2021, No: 355).

References

1. Messelink MA, den Broeder AA, Marinelli FE, et al. What is the best target in a treat-to-target strategy in rheumatoid arthritis? Results from a systematic review and meta-regression analysis. RMD Open. 2023;9:e003196.
2. de Hair MJH, Jacobs JWG, Schoneveld JLM, van Laar JM. Difficult-to-treat rheumatoid arthritis: an area of unmet clinical need. Rheumatology (Oxford). 2018;57:1135-44.
3. Nagy G, Roodenrijs NMT, Welsing PM, et al. EULAR definition of difficult-to-treat rheumatoid arthritis. Ann Rheum Dis. 2021;80:31-5.
4. Takanashi S, Kaneko Y. Unmet needs and current challenges of rheumatoid arthritis: difficult-to-treat rheumatoid arthritis and late-onset rheumatoid arthritis. J Clin Med. 2024;13:7594.
5. Kay J, Upchurch KS. ACR/EULAR 2010 rheumatoid arthritis classification criteria. Rheumatology (Oxford). 2012;51:vi5-9.
6. Aydemir Ö, Güvenir T, Küey L, Kultur S. Validity and reliability of the Turkish version of the Hospital Anxiety and Depression Scale. Turk Psikiyatri Dergisi. 1997;8:280-7.
7. Unal-Cevik I, Sarıoglu-Ay S, Evcik D. A comparison of the DN4 and LANSS questionnaires in the assessment of neuropathic pain: validity and reliability of the Turkish version of DN4. The Journal of Pain. 2010;11:1129-35.

DOI: 10.5455/medscience.2025.07.204

8. Ugurlu, M, Karakas-Ugurlu G, Erten S, Caykoylu A. Validity of Turkish form of Pain Catastrophizing Scale and modeling of the relationship between pain-related disability with pain intensity, cognitive, and emotional factors. Psychiatry and Clinical Psychopharmacology. 2017;27:189-96.

9. Hauser W, Brahler E, Ablin J, Wolfe F. Modified 2016 American College of Rheumatology Fibromyalgia Criteria, the Analgesic, Anesthetic, and Addiction Clinical Trial Translations Innovations Opportunities and Networks-American Pain Society Pain Taxonomy, and the Prevalence of Fibromyalgia. Arthritis Care Res (Hoboken). 2021;73:617-25.

10. Küçükdeveci AA, Sahin H, Ataman S, et al. Issues in cross-cultural validity: example from the adaptation, reliability, and validity testing of a Turkish version of the Stanford Health Assessment Questionnaire. Arthritis Rheum. 2004;51:14-9.

11. Alp G, Cinakli H, Kurut Aysin İ, et al. Challenges and insights in managing difficult-to-treat rheumatoid arthritis: real-world clinical perspectives. Clin Exp Rheumatol. 2024;42:1398-406.

12. Luciano N, Barone E, Brunetta E, et al. Obesity and fibromyalgia are associated with difficult-to-treat rheumatoid arthritis (D2T-RA) independent of age and gender. Arthritis Res Ther. 2025;27:2.

13. Paudel ML, Li R, Naik C, Shadick N, et al. Prevalence and characteristics of adults with difficult-to-treat rheumatoid arthritis in a large patient registry. Rheumatology (Oxford). 2025;64:1102-10.

14. Tekeoglu S. Prevalence and risk factors of cardiovascular disease in rheumatoid arthritis patients: a comparative analysis of real-world data. Int J Gen Med. 2024;17:5859-68.

15. Leon L, Freites-Núñez D, Madrid A, el al. The potential role of fatigue in difficult-to-treat rheumatoid arthritis. BMC Rheumatol. 2024;8:49.

16. Smolen JS. Poor prognostic factors and unmet needs in rheumatoid arthritis. Rheumatology (Oxford). 2025;64:ii3-8. Erratum in: Rheumatology (Oxford). 2025;64:ii25.

17. Su QY, Luo J, Zhang Y, et al. Efficacy and safety of current therapies for difficult-to-treat rheumatoid arthritis: a systematic review and network meta-analysis. J Transl Med. 2024;22:795.

18. Watanabe R, Okano T, Gon T, et al. Difficult-to-treat rheumatoid arthritis: Current concept and unsolved problems. Front Med (Lausanne). 2022;9:1049875.