# Challenges and insights in managing difficult-to-treat rheumatoid arthritis: real-world clinical perspectives

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## Abstract

### Objective

*The treatment options for rheumatoid arthritis (RA) have expanded with the availability of biological and targeted synthetic disease-modifying anti-rheumatic drugs. Despite all these developments and treatments, an important group of patients remain symptomatic and have not achieved clinical remission. The terminology "difficult-to-treat" (D2T) has been developed to describe this group. This study aimed to determine the frequency of D2T RA among our patients according to the EULAR 2021 definition of D2T RA and to identify the differences in demographic and disease characteristics, contributing factors, and disease burden.*

### Methods

*The study included 302 consecutive patients diagnosed with RA according to the 2010 ACR criteria. These patients were categorised into the D2T and non-D2T RA groups. Risk factors independently associated with D2T RA were identified using logistic regression analysis.*

### Results

*Of the 302 patients (mean age, 56.5 years, 80.1% female, 75% seropositive), 27 (8.9%) had D2T RA. Those with D2T RA had a lower age at diagnosis and longer disease duration and showed significantly higher rates of peripheral erosion, Sjögren's syndrome, extra-articular manifestations, and PtGA-PhGA discordance, together with high disease activity scores. Furthermore, the median number of comorbidities and concomitant fibromyalgia was significantly higher in the D2T RA group. In the multiple regression analysis, D2T RA was independently associated with higher HAQ-DI, RF levels, and concomitant fibromyalgia.*

### Conclusion

*D2T RA requires more intensive management, and patients with D2T RA have higher disease activity, poorer functional status, and quality of life than those without D2T RA.*

**Key words**

difficult-to-treat, fibromyalgia, rheumatoid factor, rheumatoid arthritis,

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## Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterised by chronic synovial joint inflammation that causes disability and reduces the quality of life (1). With the availability of current biological and targeted synthetic disease-modifying anti-rheumatic drugs (b/tsDMARDs), patients have both increased options and achieved remission or low disease target. Despite the availability of current b/tsDMARDs, a significant group of patients remains symptomatic and has not achieved clinical remission. These patients are considered to have difficult-to-treat RA (D2T RA), and the need for a separate definition came to the fore. For this purpose, the D2T RA terminology is used. As a result of evaluations using different definitions of various RA cohorts, 7.9–10.1% of the patient population was accepted as having D2T RA (2, 3).

A detailed definition of D2T RA has been made in EULAR 2021 (3). All three criteria must be present in D2TRA, including (a) treatment according to EULAR recommendations and failure of two or more b/tsDMARDs (with different mechanisms of action) after nonresponse to conventional synthetic DMARD (csDMARD) therapy (unless contraindicated); (b) signs suggestive of active/progressive disease defined as presenting with one or more of the following: moderate disease activity according to validation composite indexes, signs and/or symptoms suggestive of active disease, inability to taper glucocorticoid (GC) treatment below 7.5 mg/day of prednisone or equivalent, rapid radiographic progression or well-controlled disease according to standards but still presenting with RA symptoms, and (c) the management of signs and/or symptoms is perceived as problematic by the rheumatologist and/or the patient (4).

In the first study conducted according to this definition, 52 patients with D2T RA were cross-sectionally compared with 100 patients with non-D2T RA. A low socioeconomic status at disease onset was found to be an independent risk factor (2). The main difficulties in planning the treatment of patients with D2T RA are based on the low level of evidence (5). In the current approach, DMARD change is recommended only in the presence of inflammatory disease activity. However, explaining all signs and symptoms to the patients in this group is impossible because of inflammatory reasons. Mechanisms such as smoking, alcohol consumption, obesity, and multi-drug resistance can be added to this multifactorial situation (6-8). Diseases that may mimic symptoms such as osteoarthritis, depression, fibromyalgia (FM), or metabolic factors such as obesity often confuse the appropriate assessment of RA activity (9-11). Thus, defining the causes of this highly heterogeneous condition is essential, and an appropriate treatment strategy must be developed. For this purpose, a structured and individualised method that includes pharmacological and non-pharmacological treatments for patients with D2T RA will help with patient management.

Despite the increasing treatment options for RA, the low disease and remission rate still need improvement. D2T RA is referred to cases that have treatment difficulty for different reasons. In this group, we frequently encounter a D2T disease because of the limited choice of drugs due to ineffectiveness and comorbidities caused by non-inflammatory reasons, and the high rate of drug discontinuation is due to side effects. Limited treatment options are important in older patients (5).

Buch *et al*. reported that refractory RA could be stratified into two major categories; persistent inflammatory refractory RA, in which unabated inflammation is evident, and non-inflammatory refractory RA, which lacks discernible inflammation (12). Identifying the causes of this highly heterogeneous condition and developing an appropriate treatment strategy are essential. Thus, the burden of disease for individual patients and the socioeconomic effect on society can be reduced.

In this study, we aimed to define the frequency of D2T RA among our patients with RA according to the EULAR 2021 definition and reveal the differences between demographic and disease characteristics, contributing factors, and

**Table I.** Demographic, clinical characteristics, extra-articular manifestation and comorbidities of overall patients.

| Variables | Overall n=302 | Variables | Overall n=302 |
|---|---|---|---|
| Age at last visit, years, mean (±SD) | 50.7 (9.5) | PtGA, (0-100) mm, median (IQR) | 40 (30) |
| Age of disease onset, years, mean (±SD) | 46 (13.3) | PhGA, (0-100) mm, median (IQR) | 20 (25) |
| Disease duration, years, median (IQR) | 10 (10) | Pain VAS, (0-100) mm, median (IQR) | 40 (20-50) |
| Gender, female, n (%) | 242 (80.1) | Morning stiffness, minutes, median (IQR) | 25 (75) |
| Smoking (ever), n (%) | 90 (29.8) | Fatique VAS (0-100) mm, median (IQR) | 65 (23) |
| Unemployment, n (%) | 155 (51.3) | DAS28-CRP, mean (±SD) | 3.4 (2.0) |
| Education >8 years, n (%) | 81 (26.8) | DAS28-ESR, mean (±SD) | 4.6 (1.6) |
| Body mass index, mean (±SD) | 27.8 (5.2) | CDAI, median (IOR) | 14.5 (18.2) |
| Seropositive, n (%) | 229 (75.7) | SDAI, median (IOR) | 26.1 (30.9) |
| RF-positive, n (%) | 183 (60.8) | Any lung disease, n (%) | 52 (17.3) |
| ACPA-positive, n (%) n:297 | 204 (68.7) | Extraarticular manifestation, n (%) | 47 (15.6) |
| RF, median (IQR), IU/ml | 56 (141) | İnterstitial lung disease, n (%) n=275 | 15 (5.5) |
| CCP, median (IQR), IU/ml | 75 (200) | Sjögren's syndrome, n (%) | 31 (10.3) |
| ANA positive, n (%) | 58 (15.9) | Secondary osteoarthritis, n (%) | 28 (9.3) |
| Erosion in hand radiographs, n (%) | 109 (39.6) | Osteoporosis, n (%) | 47 (15.6) |
| Erosion in foot radiographs, n (%) | 39 (17.8) | Diabetes mellitus, n (%) | 44 (14.6) |
| Joint deformity, n (%) | 29 (9.6) | Hypertension, n (%) | 111 (36.8) |
| ESR, median (IQR), mm/h | 32 (26) | FMS, n (%) | 18 (6) |
| CRP, median (IQR), mg/L | 4.9 (10.1) | At least one comorbidity, n (%) | 208 (68) |
| TJC (0-28), median (IQR) | 2.5 (14) | CCI (0-36), median (IQR) | 0 (1) |
| SJC (0-28), median (IQR) | 0 (2) | RDCI (0-9), median (IQR) | 1 (2) |

ACPA: anti-cyclic citrullinated peptide antibodies; BMI: Body Mass Index(kg/m$^2$); CDAI: Clinical Disease Activity Index; CCI: Charlson Comorbidity Index; CRP: C-reactive protein; DAS28-ESR: Disease Activity Score of 28-ESR; DAS28-CRP: Disease Activity Score of 28-CRP; ESR: erythrocyte sedimentation rate; EAM: extra-articular manifestation; FMS: fibromyalgia syndrome; IQR: interquartile range; PtGA: patient global assessment; PhGA: physician global assessment; RDCI: Rheumatic Disease Comorbidity Index; RF: rheumatoid factor; SDAI: Simplified Disease Activity Index; VAS: Visual Analogue Scale; n: number of patients.

disease burden in patients with and without D2T.

## Methods

The baseline characteristics of the 302 consecutive patients diagnosed with RA were evaluated according to the 2010 ACR RA criteria (13) and those with >6 months of follow-up in a cross-sectional study at the Department of Rheumatology of İzmir Katip Celebi University Medical Faculty Hospital.

The enrolment period for the study started from December 2021 to March 2022. Patients with RA were classified as having D2T RA if they fulfilled all criteria of the EULAR definition (3). The item of the existence of rapid radiographic progression was not applied because of the cross-sectional analysis.

The sociodemographic characteristics of the evaluated patients included age, age at diagnosis, sex, height, body weight, body mass index (BMI), disease duration, educational levels, smoking, extra-articular manifestation (EAM), joint deformity, and current and past medications for RA. The comorbidities evaluated included FM, osteoarthritis, and obesity. The number and types of comorbidities were calculated using the modified Charlson Comorbidity Index (CCI) (14) and the Rheumatic Diseases Comorbidity Index (RDCI) (15). The status and titres of the rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPAs) were also recorded. The tender and swollen joint counts (TJC and SJC, respectively) of all patients were evaluated by the same physician, and the physician's global assessment of RA activity (PhGA), patient's global assessment of RA activity (PtGA), serum C-reactive protein (CRP) level, and erythrocyte sedimentation rate (ESR) at the current visit were recorded. Pain [Visual Analogue Scale (VAS)], and morning stiffness duration were also evaluated. These data were used to calculate the DAS28-ESR, DAS28-CRP, clinical disease activity index (CDAI), and simplified disease activity index (SDAI). X-ray images of the hands and feet of the past 2 years were collected or performed, if not yet available, to assess the presence of joint erosions.

Reasons for failure of previous cs-DMARDs (side effects, comorbidities, and infections), previous and current use of csDMARDs, glucocorticoids (GCs), and duration of use (months) of previous b/ts DMARDs and reason for discontinuation were recorded. The time to first, second, and third biological discontinuation events (in months) and the total number of ineffective cs/b/tsDMARDs were recorded. The questionnaires addressed physical functioning [Health Assessment Questionnaire Disability Index (HAQ-DI)] (16), quality of life [Euro Quality of Life using 5 Dimensions (EQ5D)] (17), fatigue [Functional Assessment of Chronic Illness Therapy (FACIT)] (18), and anxiety and depression [Hospital Anxiety and Depression Scale (HADS)] (19) scores were evaluated at the same visit. The international physical activity questionnaire (IPAQ) (20) allows the calculation of metabolic equivalent (MET) by measuring the frequency, duration, and physical activity intensity level over the past 7 days and presents the amount of physical activity per week. It is calculated as weekly working hours (MET-hours/week). MET divides people into physical activity groups according to the frequency and intensity of physical activity. Calculated accordingly, MET can be classified as low, intermediate, and high.

The mismatch between the patient and rheumatologists in their wish to inten-

sify treatment strategies (the patient's wish to intensify and not rheumatologist) was recorded by asking the patient and physician. Discordance was defined as >30 mm differences between PtGA and PhGA.

They will be evaluated at the last control of the patients. D2T RA was defined as patients whose DAS28-ESR was 3.2 or higher at the last visit, and the disease was perceived as problematic by the physician or patient, despite using at least two b/tsDMARDs with different mechanisms of action. Patients with improved baseline data were assessed for factors predicting D2T RA, which can help identify patients at risk for treatment failure and guide treatment decisions.

*Statistical analysis*

Patient characteristics, disease burden, and contributing factors were summarised with descriptive statistics and compared between patients with D2T and non-D2T RA. The independent t-test or one-way analysis of variance was used for continuous parameters, and the Mann-Whitney U or Kruskal-Wallis test as alternatives. Fisher's exact or Pearson chi-square test was used to compare binary or categorical parameters.

Multivariate logistic regression was used to evaluate the factors associated with D2T RA as the dependent variable and disease-related factors at RA onset (baseline RF status). Relevant clinical or demographic factors were evaluated in the univariate analysis, and those with $p<0.10$ were included in the multiple models in logistic regression. $p<0.05$ was considered statistically significant in all results. Statistical analyses were performed using IBM SPSSS software v. 26.0 (IBM Corp., Armonk, NY, USA) ready package programme.

*Ethics*

The study protocol was approved by the Ethics Committee of the Izmir Katip Celebi University Faculty of Medicine (decision date: 10.11.2021, decision no: 187) and performed according to the Declaration of Helsinki. Written informed consent from all participants was obtained.

**Table II.** Demographic, clinical, disease activity characteristics, extra-articular manifestation, and comorbidities of comparison with D2T RA and with non-D2TRA

| Variables | D2T RA n=27 | Non-D2T RA n=275 | *p*-value |
|---|---|---|---|
| Age at last visit, years, mean (±SD) | 56.4 (10.7) | 56.5 (11.2) | 0.958 |
| Age of disease onset, years, mean (±SD) | 39.6 (11.8) | 46.8 (13.1) | **0.006** |
| Disease duration, y, median (IQR) | 14.5 (8) | 7 (9) | **<0.001** |
| Gender, female, n (%) | 25 (92.6) | 217 (78.9) | 0.089 |
| Unemployment, n (%) | 19 (70.4) | 136 (49.5) | **0.016** |
| Seropositive, n (%) | 19 (70.4) | 209 (76.3) | 0.494 |
| RF-positive, n (%) | 19 (70.4) | 164 (59.9) | 0.286 |
| ACPA-positive, n (%), n=297 | 17 (63) | 187 (69.3) | 0.501 |
| RF, median (IQR), IU/ml | 67 (104) | 56 (193) | 0.219 |
| RF titre >150 IU/ml, (0-30), n (%) | 145 (58) | 8 (34.8) | **0.032** |
| Erosion in hand radiographs, n (%) | 17 (68) | 92 (36.8) | **0.002** |
| Erosion in foot radiographs, n (%) | 8 (38.1) | 31 (15.7) | **0.017** |
| Joint deformity, n (%) | 9 (33.3) | 20 (7.3) | **<0.001** |
| Extra-articular manifestation, n (%) | 9 (33.3) | 38 (13.8) | **0.021** |
| Sjögren's syndrome, n (%) | 6 (22.2) | 25 (9.1) | **0.044** |
| PtGA, (0-100), median (IQR), mm | 50 (15) | 40 (30) | **0.005** |
| PhGA, (0-100), median (IQR), mm | 20 (25) | 20 (20) | **0.010** |
| PhGA-PtGA discordance, ≥30 mm, n (%) | 18 (69.2) | 102 (38.5) | **0.006** |
| Pain VAS, (0-100) mm, median (IQR) | 50 (33) | 40 (30) | **0.004** |
| Morning stiffness, min. median (IQR) | 10 (19) | 0 (30) | **0.008** |
| Fatique VAS (0-100 mm), median (IQR) | 50 (25) | 50 (50) | **0.018** |
| DAS28-CRP, mean(±SD) | 3.25 (1.21) | 2.80 (1.28) | 0.130 |
| DAS28-ESR, mean(±SD) | 4.37 (1.25) | 3.78 (1.13) | **0.034** |
| CDAI, median (IQR) | 16 (13) | 8 (8) | **0.014** |
| SDAI, median (IQR) | 17.8 (19.7) | 14.9 (15.6) | **0.042** |
| Fibromyalgia, n (%) | 5 (18.5) | 13 (4.7) | **0.015** |
| At least one comorbidity, n (%) | 22 (81.5) | 186 (67.6) | 0.138 |
| Comorbidity numbers ≥2, n (%) | 17 (63) | 117 (42.5) | **0.042** |
| Number of comorbidities, median (IQR) | 1 (2) | 1 (3) | **0.045** |

ACPA: anti-cyclic citrullinated peptide antibodies; CDAI: Clinical Disease Activity Index; CRP: C-reactive protein; DAS28-ESR: Disease Activity Score of 28-ESR; DAS28-CRP: Disease Activity Score of 28-CRP; ESR: erythrocyte sedimentation rate; EAM: extra-articular manifestation; IQR: interquartile range; PtGA: patient global assessment; PhGA: physician global assessment; RDCI: Rheumatic Disease Comorbidity Index; RF: rheumatoid factor; SDAI: Simplified Disease Activity Index; VAS: Visual Analogue Scale.

## Results

Considering the baseline characteristics of the 302 patients, patients with D2T RA accounted for 8.9 % of the overall patients. The mean disease age, mean age at onset, and median disease duration were 50.7±9.5 years, 46.4±13.3 years, and 11 years, respectively. More than half (75.7%) of the patients were seropositive (RF and/or ACPA); as expected, the vast majority (80.1%) were female, with a mean BMI of 27.8±5.2 kg/m$^2$. As EAM, scleritis in 2 patients, rheumatoid vasculitis in 3, Sjögren's syndrome in 31, and interstitial lung disease in 15 were observed (Table I).

Patients' ages (including >65 and <65 years) were comparable; however, the age at disease onset was statistically significantly lower in patients with D2T. D2TRA was higher in the unemployed group, and although it was higher in women, the difference was not statistically significant ($p$=0.089). BMI, smoking, education levels, marital status, seropositivity, RF, ACPA positivity rates, and median RF/ACPA titre were comparable between the groups. Patients with higher RF titres (≥5 times; range 0–30, ≥150 IU) were significantly more likely to have D2T ($p$=0.032). The D2T group had significantly higher erosion rates in hand and foot x-ray images and joint deformity.

All composite disease activity scores, except DAS28CRP, were higher in the D2T RA group. ESR, CRP, TJC, and SJC were comparable between the groups. The D2T RA group had a higher rate of accompanying FM, EAM, and Sjögren's syndrome. The rates of secondary osteoarthritis and osteoporosis, diabetes mellitus, hypertension, and any lung disease were comparable between the groups, and no significant differences in CCI and RDCI

were found. However, a higher median number of comorbidities was found in the D2T group, and the presence of ≥2 comorbidities was significantly higher in the D2T RA group. These findings are consistent with the table of results (Table II).

Patients with D2T RA have worse scores on measures of physical function (HAQ-DI), health-related quality of life (EQ5D), fatigue (FACIT), and pain (VAS). In addition, higher anxiety levels were more commonly found in the D2T RA group. No difference was noted in depression, IPAQ physical activity, and total weekly sitting time (Table III). This information suggests that the D2T-RA group may have a lower quality of life, more fatigue, and higher anxiety levels than the -D2TRA group.

While the median number of total current DMARDs and non-steroidal anti-inflammatory drugs (NSAIDs) did not differ statistically significantly, the use of leflunomide (LEF) and salazopyrin at any time was significantly higher in the D2T RA group than in the non-D2T RA group. Moreover, 12 of the 27 patients with D2T RA and 164 of 275 patients without D2T RA received an average of 15 mg/week of methotrexate (MTX) at the last visit. Regarding the use of GCs, 20 of the 27 patients in the D2T RA group and 181 of 275 patients in the non-D2T RA group received a median of 4 mg/day of methylprednisolone at the last observation. The current use of MTX, NSAIDs, GCs, and MTX initiation dosage was comparable between the groups. However, the rate of biological therapy was higher in the D2T RA group, with a preference for tocilizumab, tofacitinib, and abatacept. The number of failed cs- and b/tsDMARDs was higher in the D2T group than in the non-D2T RA group, suggesting a more refractory disease course in the former (Table IV).

More disagreements were found between patients and rheumatologists with D2T RA (non-D2T RA (2.2%) *vs*. D2T RA (25.9%), $p<0.001$). The discordance between PtGA-PhGA was 85.2% when it was considered ≥20 mm, and 69.2% when it was considered as ≥30 mm in D2T RA patients (Fig. 1). When categorised groups PtGA-PhGA ≥30 mm, corelation between PtGA and PhGA was higher in non D2T patients than in the D2TRA patients (R2 respectively 0.501 and 0.400) (Fig. 2). In our study, a difference of between PtGA-PhGA was found to be significantly higher in patients with and without D2TRA ($p=0.006$) (Table II).

In these groups, drug discontinuation due to similar side effects and with primary and secondary ineffectiveness rates were reported. The time from the first biological onset to the first biological failure and from the second biological onset to the second biological failure was comparable between the groups.

Univariate and multivariate analyses were performed to identify factors associated with D2T RA. Variables were selected based on the clinical significance and comparison of patients with D2T RA with those with non-D2T RA. Then, multivariate analysis showed that high RF levels, accompanying FM, and HAQ-DI were identified as independent factors related to D2T RA (Table V).

**Table III.** Comparison of physical function, quality of life, fatigue, depression, and physical activity characteristics of patients with D2T RA and with non-D2TRA.

| Variables | Overall n=302 | D2T RA n=27 | Non-D2T RA n=275 | *p*-value |
|---|---|---|---|---|
| HAQ-DI (1-3), median (IQR) | 47 (15.6) | 1.62 (1) | 0.75 (1) | **<0.001** |
| Quality of Life EQ5D, median (IQR) | 31 (10.3) | 0.643 (0.76) | 0.737 (0.29) | 0.118 |
| EQ5D-VAS (0-100), median (IQR) | 15 (5.5) | 55 (10) | 60 (30) | 0.081 |
| FACIT-F (0-52), median (IQR) | 52 (17.3) | 23 (21) | 19 (18) | **0.019** |
| HADS, Anxiety, probable, n (%), n=298 | 72 (24.2) | 12 (44.4) | 60 (22.1) | **0.010** |
| HADS, Depression, probable n (%), n=298 | 48 (16.1) | 4 (14.8) | 44 (16.2) | 1 |
| IPAQ, total, median (IQR) | 47 (15.6) | 49.5 (330) | 438 (964) | 0.311 |
| High activity, median (IQR) | 208 (68) | 1 (4.8) | 16 (6.5) | 0.201 |
| Moderate activity, median (IQR) | 134 (44.4) | 5 (23.8) | 64 (26.0) | 0.340 |
| Low activity, median (IQR) | 2 (2) | 49.5 (330) | 297 (693) | 0.476 |
| Total hours of sitting per week, median (IQR) | 0 (1) | 38.5 (37) | 35 (49) | 0.297 |

EQ-5D: Euro Quality of Life using 5 Dimensions; FACIT-F: Functional Assessment of Chronic Illness Therapy Fatigue; HAQ-DI: Health Assessment Questionnaire Disability Index; VAS: Visual Analogue Scale; HADS: Hospital Anxiety and Depression Scale; IQR: interquartile range; n: number of patients.

**Table IV.** Comparison of current and past treatments of patients with D2T RA and with non-D2TRA.

| Variables | D2T RA n=27 | non-D2T RA n=275 | *p*-value |
|---|---|---|---|
| MTX current, n (%) | 12 (44.4) | 164 (59.6) | 0.127 |
| MTX ever, n (%) | 26 (96.3) | 258 (93.8) | 0.604 |
| HCQ current, n (%) | 3 (11.1) | 74 (26.9) | 0.072 |
| HCQ ever, n (%) | 19 (70.4) | 145 (52.7) | 0.079 |
| LEF current, n (%) | 14 (51.9) | 129 (46.9) | 0.624 |
| LEF ever, n (%) | 24 (88.9) | 170 (61.8) | **0.005** |
| SSZ current, n (%) | 0 | 24 (8.7) | 0.146 |
| SSZ ever, n (%) | 20 (74.1) | 111 (40.4) | **0.001** |
| Steroid current, n (%) | 20 (74.1) | 181 (65.8) | 0.386 |
| csDMARD, median (IQR) | 2.5 (1) | 2 (1) | 0.896 |
| 2 or more csDMARDs, n (%) | 11 (45.8) | 29 (10.7) | **<0.001** |
| Failed csDMARDs, median (IQR) | 1.5 (1) | 0 (1) | **<0.001** |
| 2 failed csDMARD, n (%) | 11 (45.8) | 29 (10.7) | **<0.001** |
| Biological therapy, n (%) | 27 (100) | 73 (26.5) | **<0.001** |
| Anti TNF, current, n (%) | 4 (14.8) | 39 (14.2) | 1 |
| Rituximab, current, n (%) | 3 (12.5) | 13 (4.7) | 0.162 |
| Abatacept, current, n (%) | 3 (11.1) | 5 (1.8) | **0.026** |
| Tocilizumab, current, n (%) | 9 (33.3) | 8 (2.9) | **<0.001** |
| Tofasitinib, current, n (%) | 6 (22.2) | 9 (3.3) | **0.001** |
| Barisitinib, current, n (%) | 2 (7.4) | 5 (1.8) | 0.122 |
| Failed b/tsDMARDs numbers, median (IQR) | 4 (1) | 0 (0) | **<0.001** |
| 3 or more, b/tDMARD, median (IQR) | 15 (62.5) | 10 (3.8) | **<0.001** |

b-: biological; cs-: conventional synthetic; DMARD: disease-modifying anti-rheumatic drug; HCQ: hydroxychloroquine; LEF: leflunomide; MTX: methotrexate; ts-: targeted synthetic; SSZ: salazopyrin; TNF: tumour necrosis factor; IQR: interquartile range.

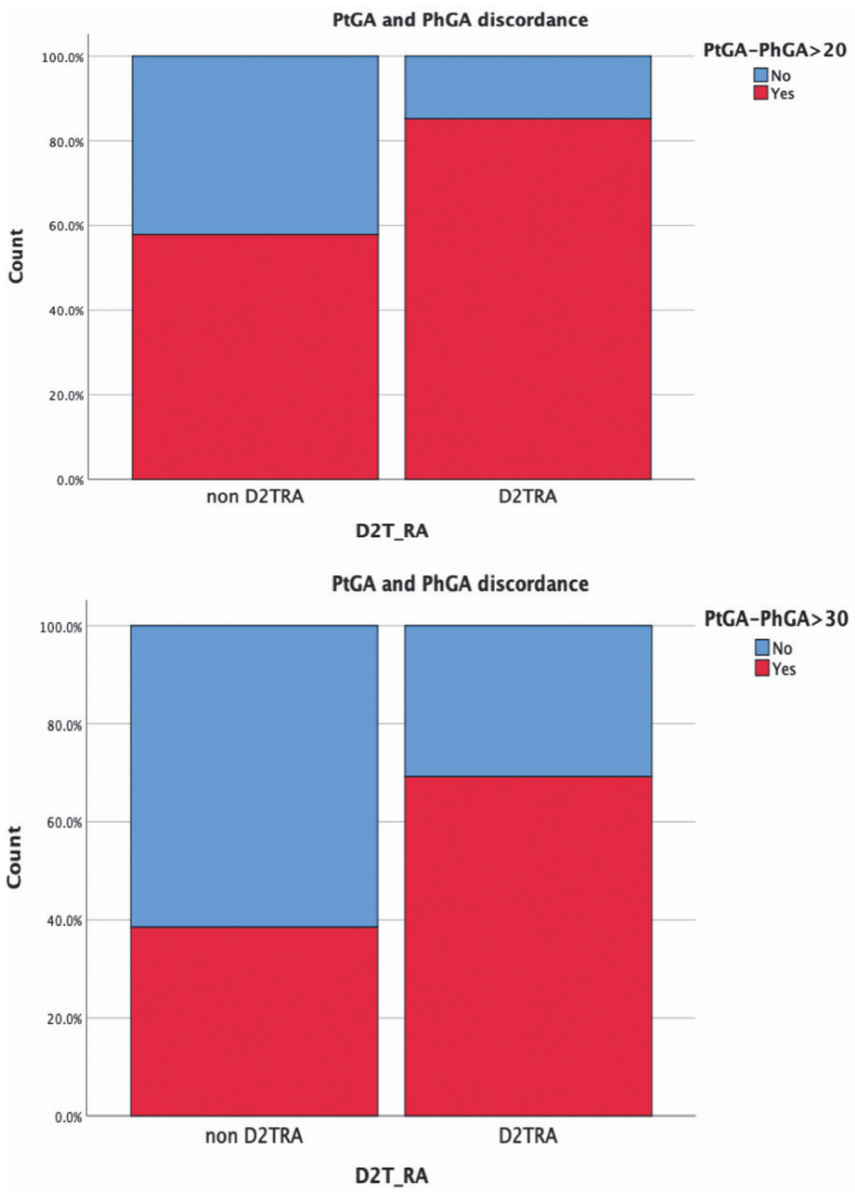


**Fig. 1.** Discordance between patient global assessment and physician global assessment.

**Table V.** Evaluation of related parameters D2T RA in logistic regression analysis.

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | OR | %95 CI | *p*-value | OR | %95 CI | *p*-value |
| Fibromyalgia, (present *vs*. absent) | 4.580 | 1.495-14.030 | 0.008 | 4.074 | 1.243-13.352 | **0.020** |
| High RF levels, >5 times ULN | 2.365 | 1.014-5.518 | 0.037 | 2.337 | 1.007-5.428 | **0.048** |
| HAQ-DI | 2.750 | 1.641-4.609 | <0.001 | 2.730 | 1.602-4.652 | **<0.001** |

HAQ-DI: Health Assessment Questionnaire Disability Index; ULN: upper limits of normal; RF: rheumatoid factor.

## Discussion

This study evaluated the clinical characteristics and factors associated with D2T RA in real-world clinical practice, according to the latest EULAR definition. In recent years, although novel insights into RA management have emerged, a pragmatic approach is still lacking (21, 22). This study found that D2T RA accounted for 8.9% of overall patients with RA, and these patients had higher disease activity, worse functional status, and worse quality of life than in the non-D2T RA group. The study also identified several factors independently associated with the progression to D2T RA, high RF levels, accompanying FM, and HAQ-DI. These data may be useful in identifying patients who are at higher risk of D2T RA development.

In a study conducted according to the latest EULAR definition, low socioeconomic status at RA onset was an independent risk factor for D2T RA development (23). Our study did not find a relationship between education level, a surrogate for socioeconomic status, and D2T RA; however, unemployment groups have a higher rate of D2T RA. This suggests the role of socioeconomic factors in developing D2T RA and may need to be considered in managing patients with RA.

In this study, high RF levels were independently associated with D2T RA when the RF titre was categorised as five times or more (≥150, IU). The KURAMA cohort study found that despite using two b/tsDMARDs, the active disease rate was 7.9% in the cohort of 672 patients, and in the multivariate analysis, high RF levels, high disease activity at baseline, and coexisting pulmonary disease were associated with D2T RA (2). This finding may have implications for managing patients with RA being treated with b/tsDMARDs. Patients with high RF levels may require more intensive monitoring and treatment to achieve disease control. A similar rate of D2T RA was found as in the previous study; however, no difference was observed between the groups regarding concomitant interstitial and any lung disease.

Similar to our study, Takanashi *et al*. reported Japanese D2T RA according to the EULAR definition of patients with RA; 10.1% were still D2T, and the study showed that patients with D2T RA were more likely to be female, seropositive, receiving GCs, and have lung disease than non-D2T RA patients (3). In our study, female patients had higher D2T rates but it was not statistically significant.

The age of disease onset was statistically significantly lower in the D2T group, and high HAQ-DI scores were independently associated with D2T RA. Similar to our results, Leon *et al*. did find that at

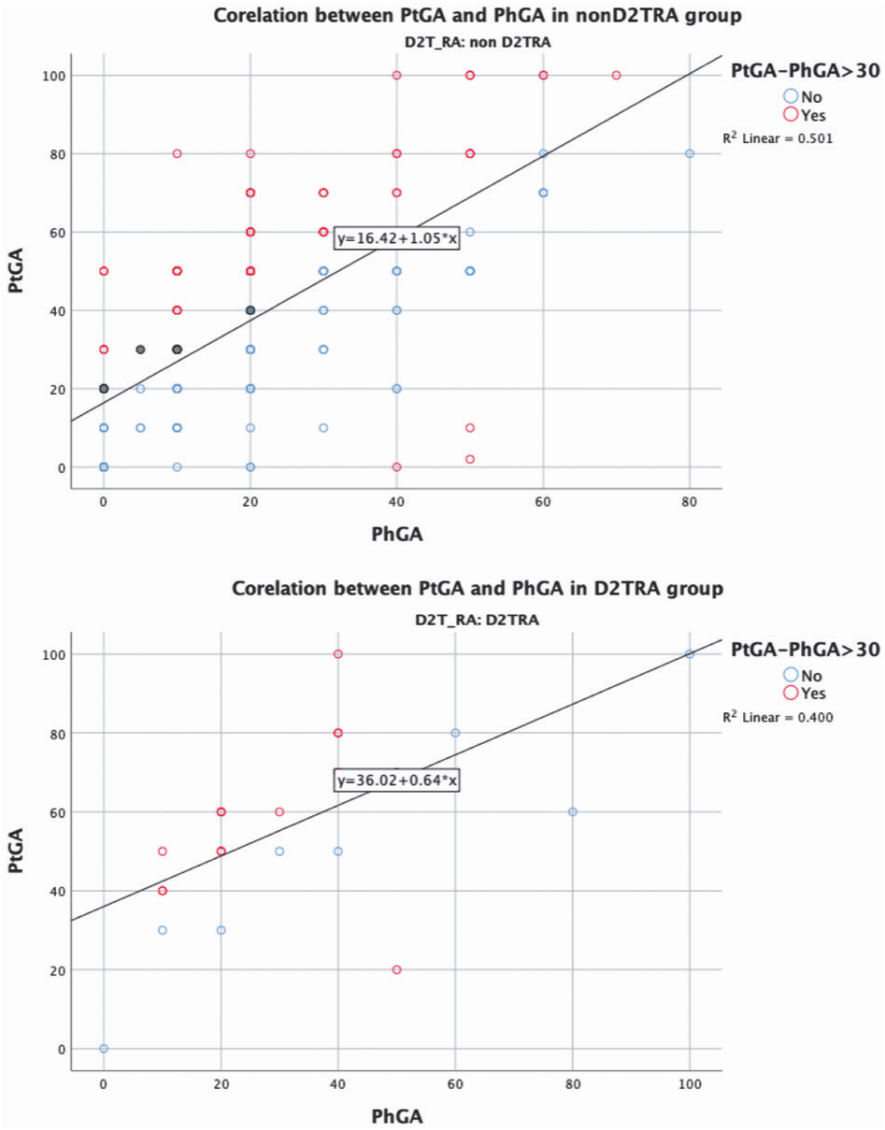


**Fig. 2.** Correlation between patient global assessment and physician global assessment.

the time of diagnosis, the D2T RA group were younger and had higher disability, DAS28 score, TJC, and pain scores. In this study, younger patients and those with high initial disability scores are more likely to develop D2T RA regardless of other factors (24).

In this study, we showed that FM is independently associated with D2T RA, similar to the results of our systematic review showing that FM is common in inflammatory arthritis and is associated with higher disease activity scores due to inflated TJC and PtGA (25). Although TJC and SJC, the ESR and CRP were comparable between the two subgroups in our study, higher disease activity composite indices of D2T RA including PtGA were detected. FM may affect PtGA and thus the global indices of disease activity, resulting in higher composite disease activity scales.

Consequently, many patients with RA and concomitant FM may fail to reach the treatment target and switch to alternate DMARDs frequently. According to EULAR, concomitant FM is an important consideration in assessing D2T RA (5). In another study, patients exposed to three bDMARDs with different mechanisms of action were studied, resembling the D2T RA definition (26). For inflammatory disease activity in the general established population of patients with RA, ultrasonography has an additional value and, therefore, could also be an additional tool in patients with D2T RA (5). Non-inflammatory conditions such as FM, neuropathic pain, and central sensitisation may be considered a separate group, such as difficult to manage, rather than D2T RA.

PtGA and PhGA, together with DAS-28CRP, are important in accurately distinguishing patients who will have multiple drug failure because of ineffectiveness from those who will have good responders, while being ineffective in predicting patients who will have D2T RA for reasons other than ineffectiveness (27). In this study, the evaluation of disease activity along with patient and physician perceptions is an important element in correctly distinguishing patients who will develop D2T RA ineffectiveness. However, in this study, patients and rheumatologists often disagreed about the need to intensify treatment, highlighting the need for clear communication and shared decision-making between patients and their healthcare providers. In this study, we found more disagreement with D2T RA.

Navarro *et al*. showed that patients categorised as D2 TRA-other had less EAM than D2 TRA-inefficacy, as well as lower values of DAS28 at the start of the b/tsDMARD (28). Similarly, in our study, the presence of EAM was higher with D2T RA. Thus, EAM may be important in managing patients with RA, particularly those with D2T disease.

In our study, the comorbidity index (RDCI and CCI) was comparable between the RA groups. While the overall comorbidity index scores were comparable between the RA group, significant differences were found in the median number of comorbidities and two or more comorbidities, with higher rates observed in the D2T RA groups. Batko *et al*. found that patients with RA who were difficult to control despite previous use of at least two csDMARDs had a higher burden of comorbidities such as hypertension, cardiovascular diseases, respiratory system diseases, and gastroduodenal ulcers than the adequate control group. In addition, the RDCI was independently associated with patients with D2T RA (14). It may be necessary to consider and manage comorbidities in addition to the primary treatment of RA to achieve better disease control and outcomes. The

management of an older RA population requires special care. Age-related conditions can lead to patients being classified as D2T because of comorbidities and risk of adverse events. The study also found that patients with D2T RA were more likely to experience adverse events and have comorbidities that limited their treatment options (29). When we compared patients aged >65 years and <65 years, no difference was detected when compared with D2T RA.

Hecquet *et al*. show that low socioeconomic status, diabetes, interstitial lung disease, and absence of combination with MTX allow the identification of D2T RA (30). In another study conducted on the management of diseases with DMARDs, failure to start MTX within 3 months and not being off GCs within 6 months are early predictive features of D2T RA (31). Both prolonged use of GCs and poor optimisation of MTX were associated with D2T RA. These factors may help clinicians recognise patients at risk of developing or having D2T RA.

This study had several limitations. The study has a cross-sectional design, consecutive patients have been enrolled, and participants were selected consecutively without any matching. It was conducted in a single centre in Turkey, which could hamper its generalisability. In addition, the factors predicting the development of a D2T disease could not be evaluated because the initial activity and clinical findings of the patients were not available. Our cross-sectional investigation did not evaluate longitudinal radiological and functional progressions, and we did not evaluate the patients' drug adherence in our study.

The findings suggest that patients with D2T RA may require more intensive and personalised treatment approaches to achieve disease control and improve their quality of life.

## Conclusions

The accurate identification of the factors contributing to the disease state, disease burden, and heterogeneity in patients with D2T RA is crucial for developing appropriate treatment strategies for this highly heterogeneous condition. A structured and individualised approach that includes pharmacological and non-pharmacological treatments can help manage the disease burden for each patient and reduce the socioeconomic effect on society. The complexity of RA requires personalised management strategies that consider each patient factor.

## Key messages

- D2T-RA affects 8.9% of patients, requiring more intensive management because of higher disease activity.
- Monitoring of RF levels may be predictive of D2T-RA.
- The presence of concomitant fibromyalgia is independently associated with D2T-RA, affecting the overall disease burden of the patients.

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