Arthritis & Rheumatology
Vol. 76, No. 4, April 2024, pp 510–521
DOI 10.1002/art.42767

American College of Rheumatology
Empowering Rheumatology Professionals

Poly-Refractory Rheumatoid Arthritis: An Uncommon Subset of Difficult to Treat Disease With Distinct Inflammatory and Noninflammatory Phenotypes

Paula David,[1,2] Andrea Di Matteo,[1,3] Or Hen,[1,2] Shouvik Dass,[3] Helena Marzo-Ortega,[1,3] Richard J. Wakefield,[1,3] Leslie-Anne Bissell,[3] Jacqueline Nam,[3] Kulveer Mankia,[1,3] Paul Emery,[1,3] Benazir Saleem,[3] and Dennis McGonagle[1,3]

Objective. To investigate the prevalence of poly-refractory rheumatoid arthritis (RA) defined as failure of all biological (b)/targeted synthetic (ts)-disease-modifying drugs (DMARDs). To further investigate whether patients with persistent inflammatory refractory RA (PIRRA) and noninflammatory refractory RA (NIRRA), determined by objective ultrasound (US) synovitis, have distinct clinical phenotypes in both EULAR difficult-to-treat RA (D2T-RA) and poly-refractory RA groups.

Methods. A cross-sectional study of 1,591 patients with RA on b/tsDMARDs that evaluated D2T-RA criteria and subclassified as poly-refractory if inefficacy/toxicity to at least one drug of all classes. PIRRA was defined if US synovitis in one or more swollen joint and NIRRA if absent. Univariate tests and multivariate logistic regression were conducted to investigate factors associated with poly-refractory, PIRRA, and NIRRA phenotypes.

Results. 122 of 1,591 were excluded due to missing data. 247 of 1,469 (16.8%) had D2T-RA and only 40 of 1,469 (2.7%) poly-refractory RA. This latter group had higher disease activity score 28 C-reactive protein (CRP) (median 5.4 vs 5.02, $P < 0.05$), CRP levels (median 13 vs 5 mg/l, $P < 0.01$), and smoking (ever) rates (20% vs 4%, $P < 0.01$) compared with other D2T patients. Smoking was associated with poly-refractory RA (odds ratio 5.067, 95% CI 1.774–14.472, $P = 0.002$). Of 107 patients with D2T-RA with recent US, 61 (57%) were PIRRA and 46 (43%), NIRRA. Patients with NIRRA had elevated body mass index (median 30 vs 26, $P < 0.001$) and higher fibromyalgia prevalence (15% vs 3%, $P < 0.05$), lower swollen joint count (median: 2 vs 5, $P < 0.001$), and lower CRP levels (5 vs 10, $P < 0.01$).

Conclusion. Only 2.7% of D2T-RA failed all classes of b/tsDMARDs. Among D2T-RA, less than 60% had objective signs of inflammation, representing a target for innovative strategies.

INTRODUCTION

In the last two decades, tremendous advancements in the management of rheumatoid arthritis (RA) have occurred. From the introduction of methotrexate and the combination of classical synthetic (cs) disease-modifying drug (DMARD) therapy and then biologic treatments, the long-term complications of chronic RA, including accelerated joint destruction, atherosclerosis, and extra-articular manifestations such as vasculitis, are now relatively uncommon.[1] A major advance in therapeutic management of RA was the introduction of tumor necrosis factor inhibitors (TNFi) drugs, and subsequently three other biological (b)-DMARDs classes and latterly target synthetics (ts) DMARDs; the janus-kinase inhibitors (JAKis)[2] resulted in better disease control, improved prognosis, and better long-term outcomes in many patients.[3–8] The success of b/tsDMARDS resulted in low disease activity or even remission as the ultimate goal in RA treatment.[9]

Despite the multiple therapeutic options, a group of patients remains with signs/symptoms of active disease. "Difficult-to-treat (D2T) RA" is defined as the failure of two or more different classes

[1]Paula David, MD, Andrea Di Matteo, PhD, Or Hen, MD, Helena Marzo-Ortega, PhD, Richard J. Wakefield, BM, Med, MD, Kulveer Mankia, MA, MD, Paul Emery, MA, MD, FRCP, FMedSci, Dennis McGonagle, FRCPI, PhD: Leeds Institute of Rheumatic and Musculoskeletal Medicine (LIRMM), University of Leeds, Leeds, United Kingdom; [2]Paula David, MD, Or Hen, MD: Sheba Medical Center- Tel Hashomer, Ramat Gan, Israel; [3]Andrea Di Matteo, PhD, Shouvik Dass, MD, FRCP, Helena Marzo-Ortega, PhD, Richard J. Wakefield, BM, Med, MD, Leslie-Anne Bissell, BMBCh, MA Cantab, PhD, Jacqueline Nam, PhD, Kulveer Mankia, MA, MD, Paul Emery, MA, MD, FRCP, FMedSci, Benazir Saleem, MRCP, MD, Dennis McGonagle, FRCPI, PhD: Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom.

Additional supplementary information cited in this article can be found online in the Supporting Information section (http://onlinelibrary.wiley.com/doi/10.1002/art.42767).

Author disclosures and graphical abstract are available at https://onlinelibrary.wiley.com/doi/10.1002/art.42767.

Address correspondence via email to Dennis McGonagle, FRCPI, PhD, at meddgm@leeds.ac.uk.

Submitted for publication August 22, 2023; accepted in revised form November 27, 2023.

of b/tsDMARDs post csDMARDs, in the presence of active/progressive disease as defined by ≥1 of the following: (1) score activity of at least moderate disease (eg, disease activity score using C-reactive protein [DAS-CRP] ≥3.2), (2) the presence of extra-articular manifestations (eg, vasculitis, glomerulonephritis, scleritis, pleuritis), (3) difficulty to taper down steroids under 7.5 mg/day prednisone or equivalent, (4) rapid radiographic progression, and (5) well-controlled disease according to above standards, but still having RA symptoms that are causing a reduction in quality of life.[10] In addition, disease management must be perceived as problematic by either the rheumatologist or the patient.[10]

The prevalence of D2T-RA is estimated to be between 5% and 20%.[11–13] However, the rate of failure or intolerance to all available DMARD classes in the real-world setting, which is described herein as "poly-refractory RA," is not established. In clinical practice, failure or intolerance of two or more DMARD classes is less of a concern than having exhausted all available therapeutic options—ie, poly-refractory RA. In fact, a recent systematic literature review on D2T-RA and the possible mechanisms leading to it questioned whether "true refractory," what we call here poly-refractory RA, actually exists.[14]

Furthermore, patients with D2T-RA may have high DAS scores that are driven not only by persistent recalcitrant synovitis but also by noninflammatory pain mechanisms or sometimes a mixture of the two.[15] It was recently proposed that these groups could be defined as persistent inflammatory refractory RA (PIRRA) or noninflammatory refractory RA (NIRRA) and that this could have implications for management.[16] Identifying D2T and poly-refractory RA groups could be of major therapeutic relevance, for example, avoidance of futile therapy cycling in cases without objective inflammation, which is equally helpful even before that, on the first line of therapy. It is important to note that the EULAR D2T definition is broad and includes both patients with PIRRA and NIRRA, in which the latter may not benefit from medication change,[16] although further research in this regard is needed.

The aim of this work was to investigate the prevalence of poly-refractory RA, ie, subjects that had failed at least one option of all available classes of b/tsDMARDs, sometimes including failure of two or more DMARDs within the same class. We also aimed to determine whether patients with PIRRA/NIRRA, as determined by objective signs of synovitis in musculoskeletal ultrasound (US), have distinct clinical phenotypes in both D2T and poly-refractory RA groups, which could possibly influence management decisions.

METHODS

Study design. This was a cross-sectional observational study focused on the D2T-RA population and conducted as an approved retrospective service evaluation (audit) of the Leeds Teaching Hospitals Trust's specialist RA Biologics Clinic; therefore, a formal ethical approval was not required. The reporting of the study follows the Strengthening the Reporting of observational studies in Epidemiology (STROBE) guidelines.[17]

Population, variables, and data collection. All patients treated with b/tsDMARDs were identified and included if they had tried two or more classes of b/tsDMARD and either the DAS-28-CRP score was 3.2 or greater in the last consultation, or there were active RA extra-articular manifestations (eg, glomerulonephritis, pericarditis, scleritis, vasculitis) considered as D2T-RA. Patients who were less than 3 months under treatment of their second class of b/tsDMARD were not considered to have tried two classes, because there was not enough time to assess efficacy and thus were excluded from the initial analysis. Similarly, the classification according to the number of b/tsDMARDs classes that the patient was exposed to follow the same logic, and, for example, a patient that was in his fourth class, but for less than 3 months, was considered as failing three.

Data were collected by reviewing electronic medical records (EMRs) from the most recent clinical visit. Data encompassed routine clinical and demographic data, including date of birth, sex, height, weight, body mass index (BMI), date of diagnosis, current treatment, use of steroids, use of each drug, and reason for discontinuation, main joint involvement, extra-articular manifestation (active or past), tender joint count (TJC), swollen joint count (SJC), visual analog scale (VAS), CRP levels, rheumatoid factor and anti-CCP, and antinuclear antibodies. We also looked into other diagnoses according to EMR (osteoarthritis [OA] [as diagnosed by clinical or radiographic features], fibromyalgia [clinically diagnosed], depression, osteoporosis, hypertension, diabetes, ischemic heart disease, cerebral vascular accident, dyslipidemia, asthma, chronic obstructive pulmonary disease, interstitial lung disease, liver disease, kidney disease, inflammatory bowel syndrome, and others), history of osteoporotic fractures (number), joint replacement surgeries (number), and smoking status. We collected data of all patients that had their most recent consultation between January 2018 and March 2023.

Within the D2T-RA group, poly-refractory RA was defined as failure (either inefficacy or intolerance) of one or more medication of all available classes of b/tsDMARDs (ie, TNFi, interleukin 6 receptor inhibitors, anti-CD20 [ie, Rituximab]), T cell receptors costimulatory blockade with anti-CTLA4-Ig (ie, abatacept), and JAKi. Other than drug inefficacy (primary or secondary), we also looked at discontinuation for any major toxicity (eg, severe infections or patient intolerance). We appreciate that intolerance/toxicity and actual drug failure are biologically distinct. However, we decided to include intolerance and toxicity, as in this "real-world" setting, the same drug would not be used after an unacceptable side effect again. Moreover, Roodenrijs et al[14] recently suggested that side effects could also be shaped by immune mechanisms, including epigenetics and clinical characteristics.

US assessment and objective definition of PIRRA or NIRRA. Of all the patients included (D2T-RA), the ones with a recent US (performed within the last year) were divided into the following two groups: PIRRA and NIRRA, defined as the presence/absence of US synovitis and/or tenosynovitis, respectively, in one or more joint that was deemed to be clinically inflamed (ie, tender and swollen) on physical examinatio[18,19] (Figure 1). The US scans were performed by one of three rheumatologists experienced in the use of US, using a GE Logiq E9 machine with a linear ML 15-6 MHz transducer. Pulse repletion frequency was set at 700–1,000 Hz, and Doppler frequency at 10 MHz.

The sonographers were blinded to all clinical data except for the physical examination findings. The US protocol consisted of scanning all joints that were deemed to be clinically swollen by a rheumatologist assessing the patients with RA independently of the sonographer. Clinically swollen joints alone were scanned and tender joints without swelling were not scanned because it is well known that clinically swollen joints are the best predictors of future damage and poor outcomes.[20] Tenderness without swelling is less likely to be associated with damage.[21] US synovitis was defined as a combination of greyscale changes and power Doppler signal (greyscale ≥1 + power Doppler ≥1) as described by EULAR/Outcome Measures in Rheumatology.[22]

Statistical analysis. Data were first tested for their normality graphically and with the Kolmogorov-Smirnov test. Continuous variables were presented as mean ± SD for parametric data and median with interquartile range for nonparametric data. Parametric data were compared using the independent samples Student's *t*-test and the Mann–Whitney U test used for nonparametric data. Categorical variables were presented using numbers and percentages. Associations between categorical variables were tested using the chi-square test, and Fisher's exact test was used when cells count less than five was expected. The cutoff for significance was an α of 0.05. Analyses assessed the two dependent variables: poly-refractory RA versus nonpoly-refractory RA groups (ie, D2T patients that failed 2, 3 or 4 classes). Secondly, within the entire D2T-RA group, we employed US synovitis to sample and define features of the PIRRA versus NIRRA groups. A Multivariate (MV) Logistic regression model was performed to investigate factors associated with poly-refractory RA, testing independent variables that were found to be significant in univariate tests in an effort to neutralize possible confounders and/or were of clinical interest. The final MV model included just the variables remaining statistically significant in age- and sex-adjusted logistic regression analysis and where we felt there was a clinical rationale to investigate an association with the outcome (ie, poly-refractory status). The cutoff for significance was an α of 0.05. Statistical analysis was performed by IBM SPSS Statistics 28 version software.

Missing data. All variables analyzed had less than 10% of missing data and thus were considered with no need for imputation, and listwise deletion was used. Missing variables were not included in the final analysis but are shown in the supplemental material (Supplementary Tables 1–4).

RESULTS

Of 1,591 patients with RA receiving b/tsDMARDs, 848 (53.2%) had only received one class and were excluded from the initial evaluation. Of the 743 (46.7%) exposed to at least two b/tsDMARDs with different mechanisms of action, half (374 of 743) were in remission or low disease activity and 122 of 743 (16.4%) were excluded due to missing clinical data to define disease activity (Figure 1). The remaining 247 of 743 cases fulfilled the criteria for D2T-RA as previously described and represented 16.8% of all 1,469 patients that tried at least two b/tsDMARDs and had available data on disease activity (Figure 1). All D2T-RA of our patients had DAS-CRP-28 greater than 3.2. Only 40 of 1,469 patients fulfilled the poly-refractory RA definition (2.7%), representing 16.2% of the D2T RA (40 of 247). Just 42 patients were tested for Human Leukocyte Antigen -B27, all seronegative, and 16.7% (7 of 42) were positive.

Baseline characteristics. The mean age was 60, and most were females (n = 197 of 247, 80%) with a higher-than-average BMI (median = 27.7). The median disease duration was 17 years,[13–17] and the median DAS28 was 5.11 (Table 1). Therapeutic details are also shown in Table 1, including the number of cases failing three and four classes and the poly-refractory RA having failed all five classes of b/tsDMARDs. Regarding previous DMARD history (ie, all b/tsDMARDs since disease onset), most patients were exposed to TNFis (94%). The second most used therapy was rituximab with 73% of patients' exposure followed by interleukin 6 receptor inhibitors (60%), abatacept (49%), and JAKis (44%).

It is notable that across the bDMARDs, the most common reason for interrupting a drug was inefficacy (primary and secondary together), whereas for csDMARDs it was intolerance. In the JAKi era, most of the patients that tried this class are currently still under this treatment. The reasons for discontinuation and proportions for each drug separately are detailed in Figure 2.

Poly-refractory RA (failed 5 b/tsDMARD classes) versus nonpoly-refractory RA (failed 2–4 classes). Within the 247 patients with D2T-RA, 40 (16%) were defined as poly-refractory RA, representing 2.7% of all patients treated with b/tsDMARDs (40 of 1,469). The baseline characteristics of patients with poly-refractory were generally similar to the nonpoly-refractory group (n = 207). However, more patients in the poly-refractory group had a current or past smoking history (n = 8 of 40 [20%] vs n = 9 of 207 [4%] $P = 0.002$) (Table 1).

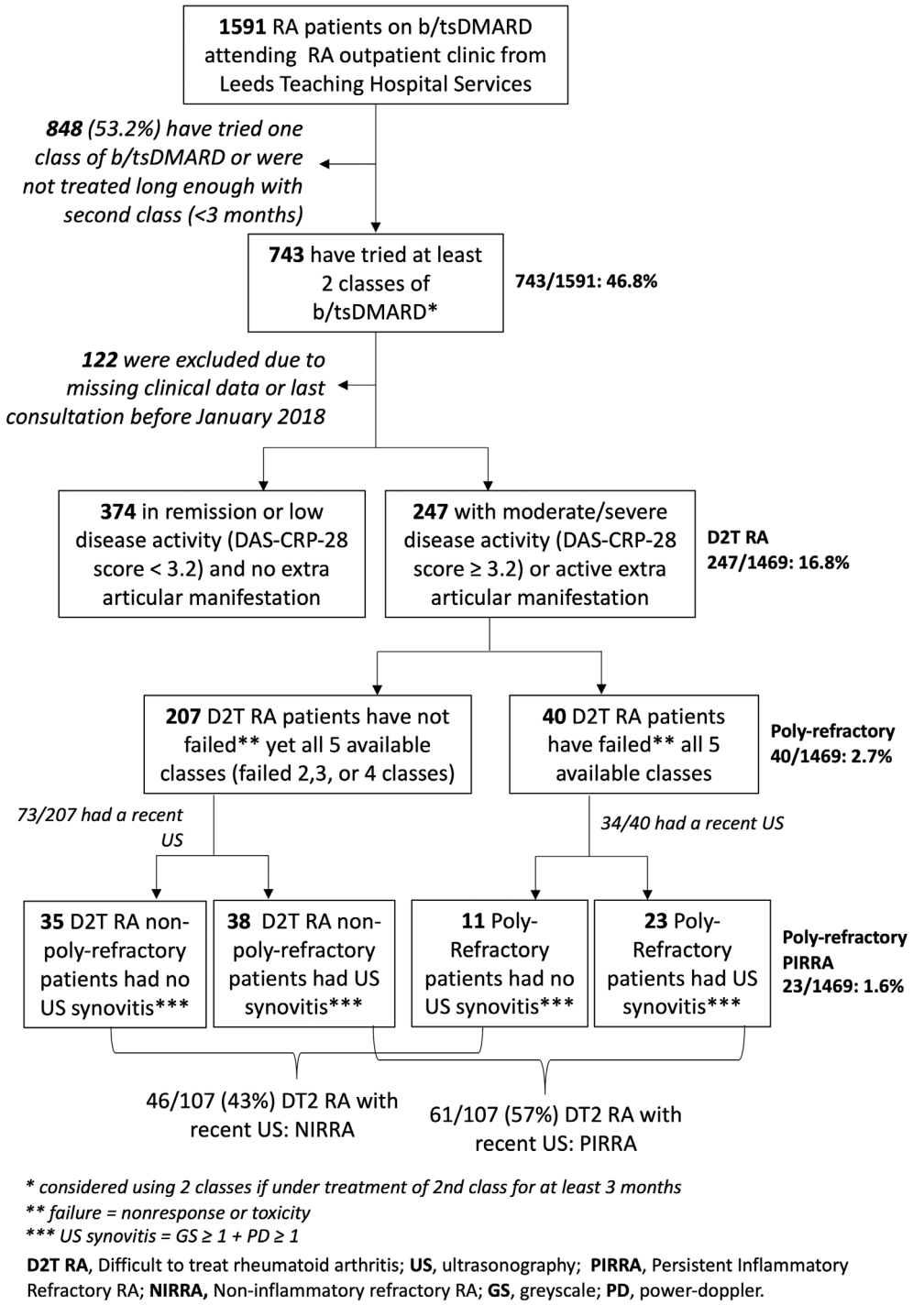

Figure 1. Flow diagram of patients included in the study and proportions of poly-refractory RA, PIRRA, and NIRRA. b/tsDMARD, biological/targeted synthetic-disease-modifying drug; D2T, difficult-to-treat; DAS-CRP-28, disease activity score C-reactive protein 28; GS, greyscale; NIRRA, noninflammatory refractory rheumatoid arthritis; PD, powder-doppler; PIRRA, persistent inflammatory refractory rheumatoid arthritis; RA, rheumatoid arthritis; US, ultrasonography.

In addition, poly-refractory cases had a slightly longer disease duration (median, 18 vs 16 years, $P < 0.01$). Current steroid use was higher in the poly-refractory group (19 of 40, 48% vs 41 of 207, 20%, $P < 0.001$) as well as a higher DAS28 score (median, 5.4 vs 5.02, $P < 0.05$) and a higher CRP (median, 13 vs 5 mg/l $P < 0.01$). Of note, the TJC, SJC, and VAS were not significantly different from the rest of the D2T-RA defined group, suggesting that the higher DAS was driven by CRP (Table 1).

Factors associated with poly-refractory RA. Age- and sex-adjusted multiple logistic regression analysis was used to

Table 1. Total D2T and poly-refractory vs non-pookly-refractory RA characteristics*

	Total D2T-RA (n = 247)	Nonpoly-refractory RA (n = 207), ie, failed 2, 3, or 4 classes	Poly-refractory RA (n = 40), ie, failed all 5 classes	*P* value
Age, mean ± SD	60 ± 14	59 ± 14	61 ± 13	0.318
Female, n (%)	197/247 (80)	168/207 (81)	29/40 (73)	0.281
BMI, median (IQR)	27.7 (24–32)	27.7 (24–33)	27.2 (23–32)	0.579
Cardiovascular risk factors, n (%)				
Obese	83/247 (33.6)	68/188 (36)	15/39 (39)	0.856
Smoking (past or current)	17/247 (6.8)	9/207 (4)	8/40 (20)	0.002
Hypertension	46/247 (6.5)	37/207 (18)	9/40 (23)	0.508
Diabetes	23/247 (9.3)	19/207 (9)	4/40 (10)	0.773
Ischemic heart disease	19/247 (7.7)	15/207 (7)	4/40 (10)	0.522
CVA/TIA	11/247 (4.6)	8/207 (4)	3/40 (8)	0.393
Dyslipidaemia	14/247 (5.7)	12/207 (6)	2/40 (5)	1.000
OSA	10/247 (4)	8/207 (4)	2/40 (5)	0.667
Patients with autoimmune diseases, n (%)				
Coeliac	5/247 (2)	4/207 (2)	1/40 (3)	0.590
CTD overlap	0/247 (0)	0/207 (0)	1/40 (3)	0.162
Sjogren syndrome	6/247 (2.4)	4/207 (2)	2/40 (5)	0.251
Discoid lupus	1/247 (0.4)	0/207 (0)	1/40 (3)	0.162
SLE	1/247 (0.4)	1/207 (1)	0/40 (0)	1.000
IBD	7/247 (2.8)	6/207 (3)	1/40 (3)	0.751
Hypothyroidism, n (%)	21/247 (8.5)	16/207 (8)	5/40 (13)	0.351
Osteoarthritis, n (%)	153/247 (61.9)	123/207 (59)	30/40 (75)	0.076
Fibromyalgia, n (%)	13/247 (5.2)	12/207 (6)	1/40 (3)	0.699
Depression, n (%)	10/247 (4)	9/207 (4)	1/40 (3)	1.000
Chronic widespread pain, n (%)	12/247 (4.9)	9/207 (4)	3/40 (8)	0.418
Osteoporosis, n (%)	42/247 (9.7)	33/207 (16)	9/40 (23)	0.357
Osteoporotic fractures, median (IQR)	0 (0–0)	0 (0–0)	0 (0–0)	0.869
Joint replacements, median (IQR)	0 (0–1)	0 (0–1)	0 (0–2)	0.003
Disease duration in years, median (IQR)	—	16 (12–19)	18 (15–19)	0.008
TJC28, median (IQR)	10 (6–16)	10 (6–15)	11 (8–18)	0.160
SJC28, median (IQR)	4 (2–8)	4 (2–8)	5 (2–8)	0.503
Main joint involvement, n (%)				
Small[a]	175/247 (71)	146/207 (71)	29/40 (73)	0.852
Large[b]	9/247 (4)	7/207 (3)	2/40 (5)	0.642
Both	63/247 (25)	54/207 (26)	9/40 (23)	0.697
VAS in mm, median (IQR)	70 (60–80)	70 (60–80)	70 (60–80)	0.821
DAS28-CRP, median (IQR)	5.10 (4.4–5.7)	5.02 (4.4–5.7)	5.4 (4.7–6.1)	0.041
Patients with extra-articular manifestations, n (%)				
Vasculitis	4/247 (1.6)	3/207 (1)	1/40 (3)	0.509
Glomerulonephritis	0/247 (0)	0/207 (0)	0/40 (0)	CNC
Scleritis	6/247 (2.4)	3/207 (1)	3/40 (8)	0.056
Pericarditis	6/247 (2.4)	4/207 (2)	2/40 (5)	0.251
CRP, median (IQR)	5 (5–15)	5 (5–11)	13 (5–28)	0.006
CRP elevated >10, n (%)	79/247 (32)	58/207 (28)	21/40 (53)	0.005
RF positive, n (%)	185/247 (74.9)	153/207 (74)	32/40 (80)	0.550
Anti-CCP positive, n (%)	189/247 (76.5)	154/207 (74)	35/40 (88)	0.102
Number of patients on current class, n (%)				
csDMARDs only	10/245 (4)	8/207 (4)	2/40 (5)	0.669
TNFi	38/245 (15.4)	29/207 (14)	9/40 (22.5)	0.230
Anti CD20	68/245 (27.5)	66/207 (32)	2/40 (5)	<0.001
Anti IL-6	26/245 (10.6)	23/207 (11)	3/40 (7.5)	0.587
JAKi	57/245 (23.0)	40/207 (19.5)	17/40 (42.5)	<0.001
Abatacept	38/245 (15.5)	36/207 (17)	2/40 (5)	0.054
Other	1/245 (0.4)	1/207 (0.5)	0/40 (0)	1.000
None	9/245 (3.6)	4/207 (2)	5/40 (12.5)	0.001
Use of glucocorticoid therapy in the last year, n (%)	74/247 (29.9)	49/207 (24)	25/40 (62)	<0.001
Current e of glucocorticoid therapy, n (%)	60/247 (24.2)	41/207 (20)	19/40 (48)	<0.001
Number of patients exposed to a specific class, n (%)				
TNFi	223/247 (94.3)	193/207 (93)	40/40 (100)	0.135
Anti CD20	180/247 (72.9)	140/207 (68)	40/40 (100)	<0.001
Anti IL-6	147/247 (59.5)	107/207 (52)	40/40 (100)	<0.001

(Continued)

Table 1. (*Cont'd*)

	Total D2T-RA (n = 247)	Nonpoly-refractory RA (n = 207), ie, failed 2, 3, or 4 classes	Poly-refractory RA (n = 40), ie, failed all 5 classes	*P* value
Abatacept	122/247 (49.4)	82/207 (40)	40/40 (100)	<0.001
JAKi	109/247 (44.1)	69/207 (34)	40/40 (100)	<0.001
Number of drugs tried in-class, median (IQR)				
csDMARDs	—	2 (2–3)	3 (2–4)	0.007
bDMARDs	—	3 (2–4)	5 (5–7)	<0.001
TNFi	—	2 (1–2)	2 (2–3)	<0.001
Anti-IL6	—	1 (0–1)	1 (1–1)	<0.001
JAKi	—	0 (0–1)	1 (1–2)	<0.001
tsDMARDs	—	0 (0–1)	1 (1–2)	<0.001
Number of patients tried X classes, n (%)				
2	88/247 (35.6)	88 (43)	—	
3	61/247 (24.7)	61 (30)	—	
4	58/247 (23.5)	58 (28)	—	
5	40/247 (16.2)	0 (0)	40 (100)	

* Anti-CCP, anti-cyclic-citrullinated peptide; bDMARD, biological DMARD; BMI, body mass index; CNC, cannot be calculated; csDMARD, conventional synthetic DMARD; CTD, connective tissue disease; CVA, cerebral vascular accident; D2T, difficulty-to-treat; DAS-28-CRP, disease activity score C-reactive protein; DMARD, disease-modifying antirheumatic drug; IBD, inflammatory bowel disease; IL, interleukin; IQR, interquartile range; JAKi, Janus-kinase inhibitors; OSA, obstructive sleep apnea; RA, rheumatoid arthritis; RF, rheumatoid factor; SD, standard deviation; SJC, swollen joint count; SLE, systemic lupus erythematosus; TIA, transient ischemic accident; TJC, tender joint count; TNFi, tumour necrosis factor inhibitor; tsDMARD, target synthetic DMARD; US, ultrasound; VAS, visual analogue scale.
[a] Small joints were considered: metacarpophalangeal, proximal interphalangeal, and metatarsophalangeal joints and wrists.
[b] Large joints were shoulders, elbows, hips, knees, and ankles.

identify factors associated with poly-refractory RA. The logistic regression model was adjusted for sex and age and included variables that we felt there was a clinical rationale to investigate an association and remained statistically significant in the adjusted MV model. In this model, smoking (current or past) was positively associated with poly-refractory RA (odds ratio 5.067, 95% CI 1.774–14.472, $P = 0.002$). Other variables were tested in the model and dropped out, such as disease duration, DAS-28, CRP, TJC, and SJC, independently. The fitness of the model and the model itself are found in Table 2. Other variables were tested in the model and dropped out, such as disease duration, DAS-28, CRP, TJC, and SJC independently. The fitness of the model and the model itself are found in Table 2.

PIRRA versus NIRRA in D2T-RA including Poly-refractory RA. US data were available for almost half of all patients with D2T-RA and 85% of the poly-refractory group to evaluate the relevance of clinically determined joint swelling thought to represent synovitis. Out of 247, 107 patients were US scanned recently, and up to a maximum of 12 months, 61 (57%) patients showed US synovitis in one or more clinically swollen joint (designated PIRRA group), and 46 (43%) did not have US synovitis in clinically swollen joints (NIRRA). The patient characteristics were generally similar between PIRRA and NIRRA groups, but the NIRRA group had significantly higher BMI values (median 30 vs 26, $P < 0.001$). Patients with NIRRA had higher rates of obesity (n = 24, 55% vs n = 15, 26%, $P = 0.004$) and fibromyalgia (n = 7, 15% vs n = 2, 3%, $P = 0.037$) (Table 3). On the other hand, the PIRRA group had significantly elevated DAS-28-CRP disease activity scores (median 5.3 vs 4.3, $P < 0.05$), SJC (median 5 vs 2, $P < 0.001$), and the CRP (median 10 vs 5 mg/l, $P < 0.01$). The patients with PIRRA also had a higher rate of steroid use contemporaneously with the US assessment (n = 25, 41% vs n = 7, 15%, $P < 0.01$). Other factors, such as age, sex, time of disease, and time on biologics, did not differ between the two groups (Table 3).

PIRRA and NIRRA among the poly-refractory patients with RA only. Out of 40 patients with poly-refractory, 34 (85%) patients had US scans available, of those 23 of 34 (67.6%) were classified as PIRRA, and 11 of 34 (32.4%) were classified as NIRRA (Figure 1). As per the aforementioned D2T-RA results, the patients classified as PIRRA had more indicators of disease activity than patients with NIRRA, such as a significantly higher SJC (median, 7 vs 1, $P < 0.001$), a higher DAS28 (median, 5.42 vs 4.75, $P = 0.05$), and higher steroids use in the past year (17% vs 3%, $P < 0.05$). Both BMI and CRP were numerically higher but not statistically different between the two groups, (15 mg/l patients with PIRRA vs 5 mg/l in NIRRA) and BMI higher was in NIRRA (27 in PIRRA vs 30 in NIRRA). As expected, the patients with NIRRA had a numerically higher prevalence of OA (82%) against 70% in PIRRA group (Table 4).

DISCUSSION

In this retrospective observational study using real-world data in the contemporary JAKi therapy era, only 2.7% of cases of RA treated with b/tsDMARDs had poly-refractory disease.

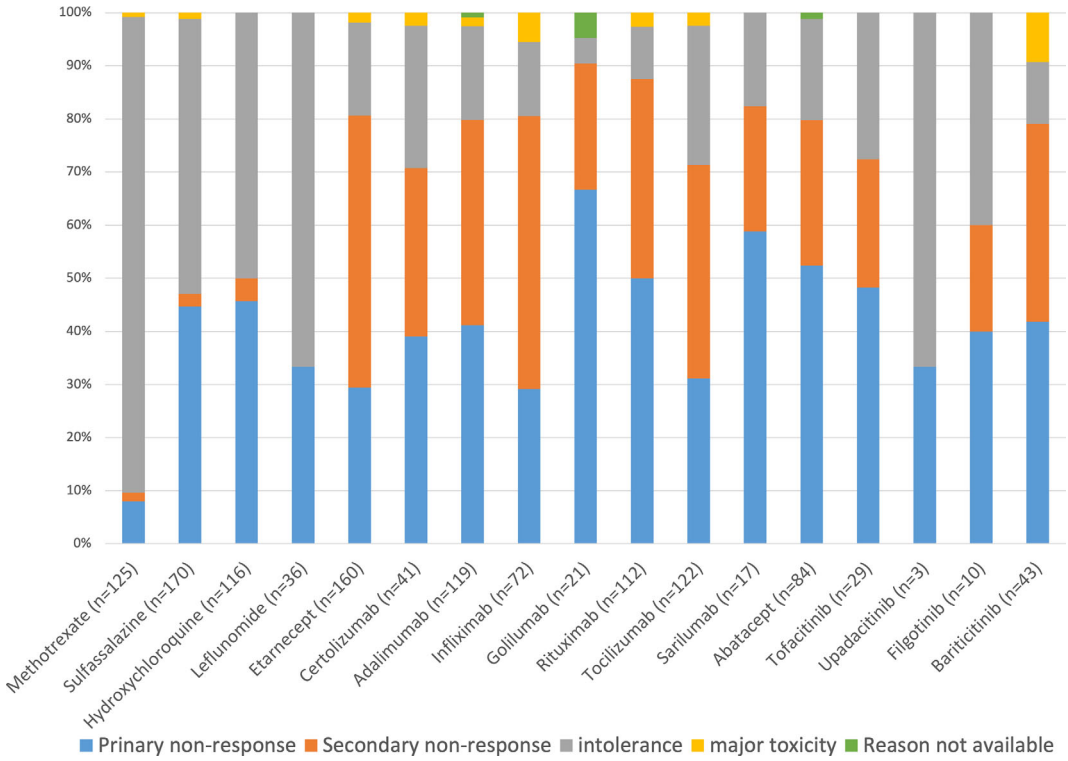

Figure 2. Most common reasons for interrupting each DMARD in percentage. Figure showing the reasons for interrupting each DMARD. N points to the number of patients exposed to this specific drug who have stopped taking it at any point of their disease course. csDMARDs were mainly stopped due to intolerance or are still in use in combination with other b/tsDMARD. Apart from Upadacitinib, more than 50% of patients stopped the b/tsDMARDs because of primary or secondary nonresponse. The drugs being used at the moment of the data collection were not included in this graph (current use). b/tsDMARD, biological/targeted synthetic disease-modifying drug; csDMARD, classical synthetic disease modifying drug.

Furthermore, DT2-RA encompassing poly-refractory RA could be split into two distinct subgroups (PIRRA and NIRRA), with more than 40% having the NIRRA phenotype. Of particular note, the sonographically defined NIRRA phenotype was identified within all D2T-RA groups and appears clinically relevant because it was strongly linked to both obesity and clinically diagnosed fibromyalgia. In the smaller poly-refractory RA group, the NIRRA group still represented one-third of cases (32.3%). This suggests that a substantial proportion of D2T-RA, including poly-refractory RA, may be cycling through different therapies without actual objective evidence of recalcitrant synovitis.

Table 2. Age and sex-adjusted logistic regression poly-refractory vs. non-poly-refractory

	OR (β)	95% CI	Sig.
Smoking[a]	5.067	1.774–14.472	0.002
Age[b]	1.010	0.984–1.036	0.450
Sex[c]	1.282	0.560–2.932	0.557

* Total Nagelkerke R^2 = 0.071. Logistic regression model adjusted for age and sex to explore associations with poly-refractory disease. The model included female and male, and age was used as a continuous variable. The adjusted-model found an association between poly-refractory disease and smoking (both active and past smokers).
[a] Considered both active and past smokers.
[b] Used as a continuous variable to adjust for age.
[c] The model included both male and female.

Because many mechanisms are operational in D2T-RA, the use of US to divide them into PIRRA and NIRRA to reduce the confounding factors was previously proposed.[14,23] The presence of objective signs of synovitis in the US (PIRRA) would imply that the b/tsDMARD is not adequately suppressing inflammation, indicating the need of cycling to a new drug, whereas their absence suggests that despite the symptoms, the drug is likely controlling the inflammation and switching the treatment would not necessarily resolve the problem. Noting that US-guided management of early RA was no better than "DAS-driven" treat-to-target strategies,[24,25] it will be interesting to see if US applied to NIRRA and PIRRA groups would predict responses to therapy switches. Regardless, considering that just 23 of 34 (67%) of patients with poly-refractory RA with recent US were PIRRA, the actual number of patients who have exhausted all available classes and may benefit from a further immunosuppressive approach is very low (23 of 1,469 of all patients treated with biologic and available clinical data or just 1.6%). These findings may be important for planning novel immunotherapy studies in genuinely refractory RA.

Table 3. PIRRA vs. NIRRA

	NIRRA n = 46	PIRRA n = 61	*P* value
Age, mean ± SD	58 ± 13	61 ± 15	0.110
Female, n (%)	35 (76)	49 (80)	0.640
BMI, median (IQR)	30.3 (27–37)	26.1 (23–30)	<0.001
Comorbidities			
Cardiovascular risk factors, n (%)			
Obese	24/44 (55)	15/57 (26)	0.004
Smoking	2/46 (4)	6/61 (10)	0.462
Hypertension	9/46 (20)	15/61 (25)	0.642
Diabetes	4/46 (9)	7/61 (12)	0.754
Ischemic heart disease	1/46 (2)	6/61 (10)	0.235
CVA/TIA	1/46 (2)	4/61 (7)	0.388
Dyslipidaemia	2/46 (4)	3/61 (5)	1.000
OSA	2/46 (4)	3/61 (5)	1.000
Number of cardiovascular risk factors, median (IQR)	1 (0–2)	1 (0–1)	0.321
Osteoarthritis, n (%)	30/46 (65)	43/61 (71)	0.676
Fibromyalgia, n (%)	7/46 (15)	2/61 (3)	0.037
Depression, n (%)	5/46 (11)	1/61 (2)	0.082
Chronic widespread pain, n (%)	3/46 (7)	7/61 (12)	0.510
Osteoporosis, n (%)	8/46 (17)	13/61 (21)	0.806
Osteoporotic fractures, median	0 (0–0)	0 (0–0)	0.098
Joint replacements, median	0 (0–0)	0 (0–1)	0.685
Patients with autoimmune diseases, n (%)			
Coeliac, n (%)	1/46 (2)	2/61 (3)	1.000
CTD overlap, n (%)	0/46 (0)	1/61 (2)	1.000
Sjogren syndrome, n (%)	1/46 (2)	1/61 (2)	1.000
Discoid lupus, n (%)	1/46 (2)	0/61 (0)	0.430
SLE, n (%)	0/46 (0)	0/61 (0)	CNC
IBD, n (%)	2/46 (4)	1/61 (2)	0.576
Hypothyroidism, n (%)	1/46 (2)	8/61 (13)	0.075
Age at diagnosis in years, mean ± SD	40 ± 12	43 ± 14	0.176
Disease duration in years, median (IQR)	17 (14–19)	16 (14–19)	0.876
TJC28, median (IQR)	14 (8–18)	11 (8–16)	0.258
SJC28, median (IQR)	2 (0–4)	5 (2–9)	<0.001
Main joint involvement, n (%)			
Small[a]	30/46 (65)	43/61 (71)	0.676
Large[b]	3/46 (6.5)	0/61 (0)	0.076
Both	13/46 (28)	18/61 (30)	1.000
VAS in mm, median (IQR)	70 (60–80)	70 (60–80)	0.198
DAS28, mean ± SD	4.93 (4.4–5.5)	5.30 (4.6–6.0)	0.017
Patients with extra-articular manifestations, n (%)			
Vasculitis	2/46 (4)	0/61 (0)	0.183
Glomerulonephritis	0/46 (0)	0/61 (0)	CNC
Scleritis	0/46 (0)	4/61 (7)	0.133
Pericarditis	2/46 (4)	1/61 (2)	0.576
CRP (mg/l), median (IQR)	5 (5–10)	10 (5–29)	0.007
CRP elevated (mg/l) >10, n (%)	11/46 (24)	30/61 (49)	0.009
RF positive, n (%)	29/46 (63)	44/61 (72)	0.403
Anti-CCP positive, n (%)	31/46 (67)	45/61 (74)	0.522
Drug-related characteristics			
Number of patients on current class, n (%)			
csDMARDs only	0/46 (0)	3/61 (5)	0.260
TNFi	7/46 (15.3)	13/61 (21)	0.616
Anti CD20	6/46 (13)	6/61 (10)	0.758
Anti-IL-6	2/46 (4.3)	8/61 (13)	0.184
JAKi	20/46 (43.5)	17/61 (28)	0.100
Abatacept	7/46 (15.3)	10/61 (16)	1.000
Other	2/46 (4.3)	0/61 (0)	0.178
None	2/46 (4.3)	4/61 (7)	0.392
Currently under glucocorticoid therapy, n (%)	7/46 (15)	25/61 (41)	0.005
Use of steroids in the last year (oral or IM), n (%)	11/46 (24)	29/61 (48)	0.016
Number of patients exposed to a specific class, n (%)			
TNFi	45/46 (98)	60/61 (98)	1.000
Anti CD20	32/46 (70)	44/61 (72)	0.831

(Continued)

Table 3. (*Cont'd*)

	NIRRA n = 46	PIRRA n = 61	*P* value
Anti IL-6	37/46 (80)	49/61 (80)	1.000
Abatacept	26/46 (57)	45/61 (74)	0.067
JAKi	30/46 (65)	40/61 (66)	1.000
Number of drugs tried in-class, median (IQR)			
csDMARDs	2 (2–2)	2 (2–3)	0.385
bDMARDs	4 (3–5)	5 (3–6)	0.102
tsDMARDs	1 (0–1)	1 (0–1)	0.819
Number of patients tried X classes, n (%)			
2	9/46 (20)	7/61 (12)	
3	7/46 (15)	15/61 (25)	
4	19/46 (41)	16/61 (26)	
5	11/46 (24)	23/61 (38)	

* Anti-CCP, anti-cyclic-citrullinated peptide; bDMARD, biological disease-modifying antirheumatic drug; BMI, body mass index; CNC, cannot be calculated; csDMARD, conventional synthetic disease-modifying antirheumatic drug; CTD, connective tissue disease; CVA, cerebral vascular accident; DAS-28-CRP, disease activity score C-reactive protein; IBD, inflammatory bowel disease; IL, interleukin; IQR, interquartile range; JAKi, Janus-kinase inhibitors; NIRRA, noninflammatory refractory rheumatoid arthritis; OSA, obstructive sleep apnoea; PIRRA, persistent inflammatory refractory rheumatoid arthritis; RF, rheumatoid factor; SD, standard deviation; SJC, swollen joint count; SLE, systemic lupus erythematosus; TIA, transient ischemic accident; TJC, tender joint count; TNFi tumour necrosis factor inhibitor; tsDMARD, target synthetic disease-modifying antirheumatic drug; US, ultrasound; VAS, visual analog scale.
[a] Small joints were considered: metacarpophalangeal, proximal interphalangeal, and metatarsophalangeal joints and wrists.
[b] Large were shoulders, elbows, hips, knees, and ankles.

For practical reasons, our study did not include all the factors typically considered as indicators of disease activity in the EULAR criteria for D2T-RA.[10] These factors include progressive radiographic changes, the challenge of tapering corticosteroids, and subjective symptoms that can affect the patient's quality of life, as assessed by either the physician or the patient.[10] The exclusion of these factors included lack of availability of community data on corticosteroid administration and tapering regimens by general physicians and the infrequent use of x-rays to assess rapid disease progression in our clinical practice. Additionally, patients' subjective impressions of disease activity were not consistently documented. As a result, individuals who would meet the D2T-RA criteria because of one of those three factors, but had a DAS-CRP score of less than 3.2 and lacked extra-articular manifestations, were not included in our study cohort. Furthermore, we did not have access to patients with RA who were solely on conventional DMARDs and had not been exposed to b/tsDMARDs so that we could have calculated the frequency of DT2 RA in the overall population of treated patients and not just on the biologic exposed cases as presently reported. Monitoring of such cases had shifted to the community, preventing us from determining the true prevalence of D2T in the overall RA population, including those who had never received b/tsDMARDs. Nevertheless, although the full gamut of suggested D2T components was lacking, the routine available clinical data tallied strongly with the sonographically determined NIRRA and PIRRA phenotypes.

Our study showed that patients with poly-refractory RA had a slightly higher disease activity than the rest of the D2T-RA cohort, with a higher DAS-28-CRP median score (5.4 vs 5.02) and a higher proportion of patients with increased CRP (53% vs 28%), which probably explains the higher rate of systemic (oral or intramuscular) corticosteroid use in the past year (62% vs 24%). Furthermore, there was a noticeably increased prevalence of smokers (current or past) among the poly-refractory group (that included patients with PIRRA and NIRRA) when compared with the other patients with D2T-RA (20% vs 4%), and smoking increased the odds of having poly-refractory RA nearly five-fold. This finding is consistent with studies demonstrating that smokers have a poorer response to TNF inhibitors,[26–28] which was the most used b/tsDMARD in our cohort. Our data suggest an adverse impact of smoking goes right through to the poly-refractory RA group, despite evidence that the JAKi response is unaffected by smoking status.[29–31]

We also noted that the poly-refractory RA group had longer disease duration than the remaining D2T RA group (18 vs 16 years), which was statistically significant ($P = 0.008$) and points to fact that at least in part, RA chronicity may be a factor in the emerging poly-refractory state, which needs further investigation.

Regarding the patients with PIRRA and NIRRA, we found results in keeping with previously reported literature, with one group with no objective inflammation (NIRRA) and commonly more patients with obesity (BMI median 30 vs 26) that are more likely to have fibromyalgia (15% vs 3%) and depression.[32] We did not find significant differences in depression rates between PIRRA and NIRRA groups, but no objective questionnaires were applied, and our data were exclusively extracted from EMR, possibly underestimating the depression prevalence rates. In general, anxiety and depression, as well as obesity and other cardiovascular risk factor conditions, were previously correlated to D2T-RA

Table 4. PIRRA vs. NIRRA characteristics among poly-refractory RA*

	Poly-refractory RA valid with US scan N= 34		
	NIRRA n = 11	PIRRA n = 23	Significance
Demographics			
Age, median (IQR)	59 (46–69)	64 (57–73)	0.543
Female, n (%)	6 (55)	19 (83)	0.111
BMI, median (IQR)	30 (26–33)	27 (23–31)	0.344
Cardiovascular risk factors, n (%)			
Obese	6 (55)	15 (65)	0.458
Smoking	1 (9)	4 (17)	1.000
Hypertension	2 (18)	7 (30)	0.682
Diabetes	1 (9)	2 (9)	1.000
Ischemic heart disease	1 (9)	2 (9)	1.000
CVA/TIA	0 (0)	2 (9)	1.000
Dyslipidaemia	0 (0)	1 (4)	1.000
OSA	1 (9)	0 (0)	0.324
Patients with autoimmune diseases, n (%)			
Coeliac	0 (0)	1 (4)	1.000
CTD overlap	0 (0)	1 (4)	1.000
Sjogren syndrome	0 (0)	1 (4)	1.000
Discoid lupus	1 (9)	0 (0)	0.324
SLE	0 (0)	0 (0)	CNC
IBD	1 (9)	0 (0)	0.324
Hypothyroidism	1 (9)	3 (13)	1.000
Current use of steroids, n (%)	3 (27)	17 (74)	0.023
Current use of oral glucocorticoid therapy, n (%)	1 (9)	14 (61)	0.008
Osteoarthritis, n (%)	9 (82)	16 (70)	0.682
Fibromyalgia, n (%)	1 (9)	0 (0)	0.324
Depression, n (%)	0 (0)	1 (4)	1.000
Chronic widespread pain	1 (9)	2 (9)	1.000
Osteoporosis, n (%)	4 (36)	4 (17)	0.388
Osteoporotic fractures, median	0 (0–0)	0 (0–0)	0.580
Joint replacements, median	1 (0–3)	0.5 (0–1)	0.458
Disease characteristics			
Age at onset	45 (31–51)	45 (34–49)	0.824
Disease duration in years, median (IQR)	18 (14–19)	18 (15–20)	0.915
TJC28, median (IQR)	15 (7–21)	11 (9–15)	0.630
SJC28, median (IQR)	1 (0–2)	7 (5–9)	<0.001
Main joint involvement, n (%)			
Small[a]	8 (72)	17 (74)	1.000
Large[b]	1 (9)	0 (0)	0.324
Both	2 (18)	6 (26)	1.000
VAS in mm, median (IQR)	60 (50–70)	70 (60–80)	0.095
DAS28, mean ± SD	4.75 (4.1–5.6)	5.42 (4.9–6.1)	0.05
Patients with extra-articular manifestations, n (%)			
Vasculitis	1 (9)	0 (0)	0.324
Glomerulonephritis	0 (0)	0 (0)	CNC
Scleritis	0 (0)	3 (13)	0.535
Pericarditis	1 (9)	0 (0)	0.324
CRP, median (IQR)	5 (5–16)	15 (5–29)	0.069
CRP elevated >10, n (%)	3 (27)	13 (57)	0.152
RF positive, n (%)	9 (82)	17 (74)	1.000
Anti-CCP positive, n (%)	11 (100)	18 (78)	0.150

* CNC, value of 0.

Anti-CCP, anti-cyclic-citrullinated peptide; BMI, body mass index; CNC, cannot be calculated; CTD, connective tissue disease; CVA, cerebral vascular accident; DAS-28-CRP, disease activity score C-reactive protein; IBD, inflammatory bowel disease; IQR, interquartile range; NIRRA, noninflammatory refractory rheumatoid arthritis; OSA, obstructive sleep apnoea; PIRRA, persistent inflammatory refractory rheumatoid arthritis; RA, rheumatoid arthritis; RF, rheumatoid factor; SD, standard deviation; SJC, swollen joint count; SLE, systemic lupus erythematosus; TIA, transient ischemic accident; TJC, tender joint count; US, ultrasound; VAS, visual analogue scale.

[a] Small joints were considered: metacarpophalangeal, proximal interphalangeal, and metatarsophalangeal joints and wrists.

[b] Large joints were shoulders, elbows, hips, knees, and ankles.

when compared with patients with non-D2T-RA,[32,33] and although the studies did not compare between those with objective and nonobjective inflammation, they suggest that those variables to possibly contribute to a misclassification as D2T-RA.

In our study, the PIRRA group had higher SJC (median 5 vs 2) and DAS-28-CRP score (median 5.3 vs 4.93), as well as higher CRP levels (median 10 vs 5), suggesting a genuinely greater inflammatory disease burden. In line with this, patients with PIRRA had a higher rate of current (at the moment of US) corticosteroid use than NIRRA (41% vs 15%). A recent study also associated the use of steroids with patients with PIRRA, although their PIRRA definition was examiner-based and not defined by objective signs on US.[34] Our findings showed how US could help stratify the NIRRA and PIRRA phenotypes, which could be relevant for therapy switching or not, but we recognize that US may not be widely available in clinical practice to facilitate this decision. Clinically, the presence of multiple swollen joints instead of one or a few joints and elevation of CRP in the absence of obesity and chronic pain/fibromyalgia may best identify the groups with genuinely active synovitis that targeted therapy should be switched from a clinical perspective. The mechanisms responsible for the NIRRA phenotype are still unclear, but factors including secondary OA, fibromyalgia, peripheral nerve sensitization, and central sensitization are likely important.[16] For example, apart from fibromyalgia, when specifically looking into patients with poly-refractory RA (Table 4), although not statistically significant, numerically, the OA prevalence was higher in patients with NIRRA (82%), against 70% of patients with PIRRA. This is of extreme importance because the management of secondary OA in advance RA is clearly different from the one of actual active RA disease. Hence, these patients may not benefit from b/tsDMARD cycling, because of the absence of inflammation. In the real-world setting, the presence or absence of US inflammation has been widely used to help rheumatologists with decision-making on continuing or switching the cs/b/tsDMARD, being especially useful in patients with a low SJC and DAS-28-CRP pointing to only moderate disease, because SJC was shown to be closely related to US synovitis and a high SJC may suggest a higher likelihood of PIRRA status.[35]

Our study had some limitations. Firstly, although, all patients met the three essential EULAR criteria for D2T-RA, as a cross-sectional study based on EMR, patients that would be considered D2T-RA because of (1) difficulty tapering down corticosteroids under 7.5 mg were not included because of incomplete, data including primary care corticosteroid data; (2) rapid radiographic progression because routine follow up radiographs is not part of our standard of care; and (3) RA symptoms deemed to impair quality of life as documented by either patient or physician, were not included. So, despite of all our patients having symptoms reducing their quality of life, some might have been left out too because of a disease activity score of less than moderate, possibly underestimating the total number of D2T-RA. On the other hand, our study could overestimate the prevalence of D2T and poly-refractory patients among patients with RA because our center is in a tertiary hospital and receives referrals from difficult cases from other cities nearby. Secondly, as our data comes from a "real-world" clinical setting, the US was not taken according to a prespecified protocol but performed only in clinically swollen joints and according to the physician's examination and opinion, which could possibly underestimate subclinical synovitis at other sites. Nevertheless, the combined use of US and clinical data clearly showed evidence for two distinct phenotypes in D2T-RA encompassing poly-refractory RA, namely a PIRRA and NIRRA phenotype, with our univariate analysis still showing differences between the groups, specifically in the NIRRA group with more obesity and fibromyalgia.

In conclusion, only 2.7% of patients on b/tsDMARD cases could be classified as poly-refractory RA, having explored at least one drug of each available class and was linked to smoking. Of the patients with D2T-RA, including poly-refractory RA that had US, 57% were PIRRA and 43% had no US detected synovitis or NIRRA, and this group was shown to have a higher fibromyalgia prevalence rate and also obesity. US may be useful for phenotyping D2T-RA and to guide the next step in management, especially in patients with a lower SJC and DAS-28-CRP that are not under steroid treatment. The use of US to stratify NIRRA and PIRRA strongly correlated with obesity and fibromyalgia and lower CRP in the NIRRA group and suggests that this US-driven designation is clinically robust. Our study highlights the existence of the poly-refractory RA subgroup as an important clinical challenge with no therapeutic options and also suggests that patients with D2T-RA have at least two different clinical profiles that could benefit from different therapeutic strategies.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. McGonagle had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. David, Saleem, McGonagle.
Acquisition of data. David, Di Matteo, Dass, Nam, Saleem, McGonagle.
Analysis and interpretation of data. David, Di Matteo, Hen, Ortega, Wakefield, Bissell, Mankia, Emery, Saleem, McGonagle.

REFERENCES

1. Watts RA, Mooney J, Lane SE, et al. Rheumatoid vasculitis: becoming extinct? Rheumatology (Oxford) 2004;43:920–923.
2. Furst DE, Keystone EC, Braun J, et al. Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2011. Ann Rheum Dis 2012;71 Suppl 2:i2–45.
3. Ntatsaki E, Mooney J, Scott DGI, et al. Systemic rheumatoid vasculitis in the era of modern immunosuppressive therapy. Rheumatology (Oxford) 2014;53:145–152.
4. Asai S, Takahashi N, Asai N, et al. Characteristics of patients with rheumatoid arthritis undergoing primary total joint replacement: a

14-year trend analysis (2004-2017). Mod Rheumatol 2020;30: 657–663.
5. Turesson C, O'Fallon WM, Crowson CS, et al. Extra-articular disease manifestations in rheumatoid arthritis: incidence trends and risk factors over 46 years. Ann Rheum Dis 2003;62:722–727.
6. Watts RA, Lane SE, Scott DGI. Decrease over time in the incidence of systemic rheumatoid vasculitis: comment on the article by Turesson et al. Arthritis Rheum 2005;52:1620–1621; author reply 1621.
7. Young BL, Watson SL, Perez JL, et al. Trends in joint replacement surgery in patients with rheumatoid arthritis. J Rheumatol 2018;45: 158–164.
8. Mazzucchelli R, Pérez Fernandez E, Crespí-Villarías N, et al. Trends in hip fracture in patients with rheumatoid arthritis: results from the Spanish National Inpatient Registry over a 17-year period (1999-2015). TREND-AR study. RMD Open 2018;4:e000671.
9. Smolen JS, Landewé RBM, Bijlsma JWJ, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Ann Rheum Dis 2020;79:685–699.
10. Nagy G, Roodenrijs NMT, Welsing PMJ, et al. EULAR definition of difficult-to-treat rheumatoid arthritis. Ann Rheum Dis 2021;80:31–35.
11. Buch MH. Defining refractory rheumatoid arthritis. Ann Rheum Dis 2018;77:966–969.
12. Kearsley-Fleet L, Davies R, Cock D De, et al. Biologic refractory disease in rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. Ann Rheum Dis 2018;77:1405–1412.
13. Hair MJH de, Jacobs JWG, Schoneveld JLM, et al. Difficult-to-treat rheumatoid arthritis: an area of unmet clinical need. Rheumatology (Oxford) 2018;57:1135–1144.
14. Roodenrijs NMT, Welsing PMJ, Van Roon J, et al. Mechanisms underlying DMARD inefficacy in difficult-to-treat rheumatoid arthritis: a narrative review with systematic literature search. Rheumatology (Oxford) 2022;61:3552–3566.
15. McWilliams DF, Kiely PDW, Young A, et al. Interpretation of DAS28 and its components in the assessment of inflammatory and non-inflammatory aspects of rheumatoid arthritis. BMC Rheumatol 2018;2:8.
16. Buch MH, Eyre S, McGonagle D. Persistent inflammatory and non-inflammatory mechanisms in refractory rheumatoid arthritis. Nat Rev Rheumatol 2021;17:17–33.
17. Von Elm E, Altman DG, Egger M, et al. Strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ 2007;335:806–808.
18. Sreerangaiah D, Grayer M, Fisher BA, et al. Quantitative power Doppler ultrasound measures of peripheral joint synovitis in poor prognosis early rheumatoid arthritis predict radiographic progression. Rheumatology (Oxford) 2016;55:89–93.
19. Bhasin S, Cheung PP. The role of power Doppler ultrasonography as disease activity marker in rheumatoid arthritis. Dis Markers 2015; 2015:325909.
20. Aletaha D, Smolen JS. Joint damage in rheumatoid arthritis progresses in remission according to the disease activity score in 28 joints and is driven by residual swollen joints. Arthritis Rheum 2011;63: 3702–3711.
21. Gessl I, Popescu M, Schimpl V, et al. Role of joint damage, malalignment and inflammation in articular tenderness in rheumatoid arthritis, psoriatic arthritis and osteoarthritis. Ann Rheum Dis 2021;80: 884–890.
22. D'Agostino MA, Terslev L, Aegerter P, et al. Scoring ultrasound synovitis in rheumatoid arthritis: a EULAR-OMERACT ultrasound taskforce-Part 1: definition and development of a standardised, consensus-based scoring system. RMD Open 2017;3:e000428.
23. Tan Y, Buch MH. "Difficult to treat" rheumatoid arthritis: current position and considerations for next steps. RMD Open 2022;8:e002387.
24. Dale J, Stirling A, Zhang R, et al. Targeting ultrasound remission in early rheumatoid arthritis: the results of the TaSER study, a randomised clinical trial. Ann Rheum Dis 2016;75:1043–1050.
25. Haavardsholm EA, Aga A-B, Olsen IC, et al. Ultrasound in management of rheumatoid arthritis: ARCTIC randomised controlled strategy trial. BMJ 2016;354:i4205.
26. Mattey DL, Brownfield A, Dawes PT. Relationship between pack-year history of smoking and response to tumor necrosis factor antagonists in patients with rheumatoid arthritis. J Rheumatol 2009;36: 1180–1187.
27. Söderlin MK, Petersson IF, Geborek P. The effect of smoking on response and drug survival in rheumatoid arthritis patients treated with their first anti-TNF drug. Scand J Rheumatol 2012;41:1–9.
28. Hyrich KL, Watson KD, Silman AJ, et al; British Society for Rheumatology Biologics Register. Predictors of response to anti-TNF-alpha therapy among patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. Rheumatology (Oxford) 2006;45:1558–1565.
29. Emery P, Downie B, Liu J, et al. POS0536 filgotinib demonstrates clinical efficacy in rheumatoid arthritis independent of smoking status: a post-hoc subgroup analysis of three phase 3 clinical trials. Ann Rheum Dis 2021;80:502.
30. Curtis J, Emery P, Burmester G, et al. THU0114 effects of smoking on baricitinib efficacy in patients with rheumatoid arthritis: pooled analysis from two phase 3 clinical trials. Ann Rheum Dis 2017;76:244.
31. Rubin DT, Torres J, Regueiro M, et al. P563 Association between smoking status and the efficacy and safety of tofacitinib in patients with ulcerative colitis: data from the tofacitinib clinical programme. J Crohns Colitis 2022;16:i506–i507.
32. Roodenrijs NMT, van der Goes MC, Welsing PMJ, et al. Difficult-to-treat rheumatoid arthritis: contributing factors and burden of disease. Rheumatology (Oxford) 2021;60:3778–3788.
33. Dey M, Nagy G, Nikiphorou E. Comorbidities and extra-articular manifestations in difficult-to-treat rheumatoid arthritis: different sides of the same coin? Rheumatology 2023;62:1773–1779.
34. Giollo A, Zen M, Larosa M, et al. Early characterization of difficult-to-treat rheumatoid arthritis by suboptimal initial management: a multicentre cohort study. Rheumatology (Oxford) 2023;62:2083–2089.
35. Coras R, Sturchio GA, Bru MB, et al. Analysis of the correlation between disease activity score 28 and its ultrasonographic equivalent in rheumatoid arthritis patients. Eur J Rheumatol 2020;7:118–123.