Arthritis Research & Therapy

RESEARCH

Open Access

Obesity and fibromyalgia are associated with Difficult-to-Treat Rheumatoid Arthritis (D2T-RA) independent of age and gender

Nicoletta Luciano[1,2], Elisa Barone[1,2], Enrico Brunetta[1,2], Alessio D'Isanto[1], Maria De Santis[1,2], Angela Ceribelli[1,2], Marta Caprioli[2], Giacomo M. Guidelli[2], Daniela Renna[2] and Carlo Selmi[1,2*]

Abstract

Background There is still a significant proportion of patients with rheumatoid arthritis (RA) in whom multiple therapeutic lines are ineffective. These cases are defined by the EULAR criteria as Difficult-to-Treat RA (D2T-RA) for which there is limited knowledge of predisposing factors.

Objective To identify the clinical features associated with D2T-RA in real-life practice.

Methods We retrospectively collected demographic, clinical, and serological data on 458 patients consecutively seen for RA between January 2019 and January 2023. We compared patients fulfilling the D2T-RA criteria with the remaining RA cohort using univariate comparisons and logistic regression to determine the impact of clinical features, comorbidities on outcome variable, adjusted for confounders.

Results Seventy-one/458 (16%) patients fulfilled the 2021 EULAR criteria for D2T-RA with no significant differences for age (median 62 years interquartile range -IQR- 58- 65 vs. 62 IQR 60 – 63 in non-D2T), gender prevalence (23% in both groups) and positivity rates for rheumatoid factors (62% vs. 62% in non-D2T) and Anti-Citrullinated Protein Antibodies (ACPA) (69% vs. 61% in non-D2T). Conversely, D2T-RA cases had significant longer disease duration (median 15 years IQR 13–17 vs. 10 years IQR 9–11 in non-D2T; $p < 0.0001$). D2T-RA also had more erosions at baseline (24% vs. 11% in non-D2T; $p < 0.0001$) and higher disease activity index (CDAI) at the last follow up visit (15.7 ± 10.5 vs. 7.5 ± 8.8 in non-D2T; $p < 0.0001$). D2T-RA cases suffered with higher frequency of obesity (33% vs. 19% in non-D2T, $p = 0.021$) and fibromyalgia (25% vs. 10% in non-D2T, $p < 0.0001$). The multivariate analysis confirmed the correlations of D2T-RA with disease duration (Odds ratio -OR- 1.06, 95% confidence interval -CI—1.03–1.09; $p < 0.0001$), baseline erosions (OR 2.73, 95% CI 1.28–5.82; $p = 0.009$), obesity (OR 2.22, 95% CI 1.10–4.50; $p = 0.026$) and fibromyalgia (OR 3.91, 95% CI 1.76–8.70; $p = 0.001$), independent of age and gender.

Conclusions High disease activity, baseline erosions and disease duration are significantly associated with the D2T phenotype of RA while we confirm the importance of obesity and fibromyalgia.

Keywords Rheumatoid arthritis, Biologics, Treat-to-target

*Correspondence:
Carlo Selmi
carlo.selmi@hunimed.eu
[1] Department of Biomedical Sciences, Humanitas University, Via R Levi Montalcini 4, Pieve Emanuele, Milan 20090, Italy
[2] Rheumatology and Clinical Immunology, IRCCS Humanitas Research Hospital, Via A Manzoni 56, Rozzano, Milan 20089, Italy

Introduction

Difficult-to-Treat rheumatoid arthritis (D2T-RA) has been defined by a EULAR task force [1] through the fulfillment of three criteria, including a history of failure of at least 2 biologic or targeted synthetic disease modifying antirheumatic drugs (b/tsDMARDs) with different

mechanisms of action, the presence of active or symptomatic disease (defined as the presence of at least one of 5 established criteria), and the patient and/or physician's perception of difficulty in managing the disease. The estimated prevalence of D2T-RA has been reported to range between 5 and 20% in different cohorts [2–5]. Such wide variability may be influenced by various factors [6], including the timing of the pharmacological intervention [7].

It is unclear whether D2T-RA is a clinical entity with a yet unidentified pathogenic background that is present from the early disease stages or, vice versa, if the entity is intrinsically bound to the disease history. Indeed, risk factors for the development of D2T-RA are elusive. Proposed factors influencing such a risk include high disease activity and the presence of high-titer serum rheumatoid factors (RF) or anti-citrullinated peptide antibody (ACPA) [8], a triad that is often referred as *poor prognostic factors*. Moreover, comorbidities are observed in up to 70% of D2T-RA cases and potentially influence both patient evaluation and treatment choices [9]. Remarkably, comorbidities can represent pre-existing conditions impacting the overall prognosis and management, complications of the long-standing disease and associated inflammation, or sequelae of the prolonged glucocorticoid treatment, which may be in turn associated with a more aggressive disease per se [10]. Thus, it is crucial to define how comorbidities can influence the clinical picture of patients with RA, particularly associating to D2T cases [11–13].

Materials and methods

Study aim

This study represents an explorative cross-sectional analysis aimed at identifying potential features that are present at baseline (i.e., very early in the disease course of RA) and that may be associated to the subsequent development of D2T-RA.

Study population and data collection

We retrospectively collected data from 458 consecutive patients with RA fulfilling the ACR/EULAR 2010 classification criteria [14] attending the Rheumatology outpatients Clinic at Humanitas Research Hospital in Milan between January 2019 and January 2023, with a follow-up duration of at least 12 months. Patients were classified as having D2T-RA according to the 2021 EULAR criteria [1].

Data collection was performed through electronic clinical records review, and included demographic, clinical, laboratory, and instrumental information. Of note, 'baseline' data collection was performed prior to starting the first b/tsDMARD. Data concerning relevant comorbidities, including cardiovascular diseases, diabetes mellitus, neuropsychiatric syndromes, and fibromyalgia were collected. In particular, obesity was defined as a body mass index exceeding 30 kg/m^2, and fibromyalgia was defined according to 2016 classification criteria [15].

The Clinical Disease Activity Index (CDAI) was recorded at baseline (i.e., at the time of the diagnosis). The presence of erosions as well was checked at baseline and at the last follow-up using both X-ray and/or musculo-skeletal ultrasound (MSUS).

We considered treatments that were active at the last follow-up visit.

Statistical analysis

Continuous variables are reported as means (standard deviations) or medians (interquartile range – IQR), depending on their distribution. Categorical variables are reported as proportions and percentages.

Continuous variables were compared using the two-tailed t-test or the Mann Whitney U-test, according to their distribution. Categorical variables were compared using the Pearson chi-squared test (χ^2). Univariable logistic regression was performed to individuate potential features to be included in the multivariable model.

A multivariable logistic regression model was designed to assess the risk of developing D2T-RA, according to the presence of selected variables at the baseline evaluation, including those matching clinical relevance or those with $p < 0.10$ at the univariable analysis.

P-values < 0.05 were considered as statistically significant. The statistical analysis was performed using STATA 17.0 for Macintosh (Stata, College Station, TX).

Results

Characteristics of the entire cohort and of patients with D2T-RA

Demographic and clinical characteristics of the cohort are summarized in Table 1. The analysis included 458 consecutively enrolled patients with RA, 77% being female (352/458) with a median age of 62 years (IQR 52–73). Of the entire cohort, 22% (71/458) patients met the D2T-RA criteria. The features of patients with D2T-RA included the presence of erosions at baseline, with or without signs of active disease in 44/71 (62%), moderate or severe disease activity (CDAI > 10) in 25/71 (35%) with referred symptoms of active disease, including extra-articular manifestations, acute phase reactants and imaging signs in 63/71 (89%), persistent symptoms of RA impacting on quality of life, despite low disease activity in 46/71 (65%). In terms of disease management, D2T-RA was characterized by the inability to reduce glucocorticoid treatment below 7.5 mg/day of prednisone or equivalent in only 1/71 (1%), however, the disease was still

Table 1 Characteristics of the enrolled population arrayed according to the D2T criteria

	Total ($n=458$)	D2T-RA ($n=71$)	Non D2T-RA ($n=387$)	*P*-value
Male gender [n (%)]	106 (23.14)	16 (22.53)	90 (23.26)	0.895
Age (years) [median (IQR)]	62 (52–73)	62 (58- 65)	62 (60- 63)	0.980
Disease duration (years) [median (IQR)]	12 (10–14)	15 (13–17)	10 (9–11)	**< 0.0001**
RF pos [n (%)]	277 (60.48)	43 (61.43)	234 (61.74)	0.961
ACPA pos [n (%)]	278 (60.70)	48 (68.57)	230 (60.85)	0.223
Erosive disease [n (%)]	164 (35.81)	41 (58.57)	123 (32.28)	**< 0.0001**
Erosions at baseline [n (%)]	43 (9.39)	12 (23.53)	31 (10.62)	**0.012**
Surgery for RA [n (%)]	34 (7.42)	12 (16.90)	22 (5.70)	**0.002**
Poor prognostic factors [n (%)]	249 (54.37)	54 (76.06)	195 (51.05)	**< 0.0001**
Previous or current Smokers [n (%)]	140 (30.57)	14 (19.72)	126 (32.56)	0.237
Power Doppler pos [n (%)]	83 (18.12)	15 (31.25)	68 (31.63)	0.959
Morning Stiffness > 1 h [n (%)]	48 (10.48)	11 (15.49)	37 (9.56)	0.138
CRP > 0.5 mg/dL at diagnosis [n (%)]	119 (25.98)	10 (41.67)	109 (58.92)	0.113
CDAI at last follow up (mean + SD)	8.8 (6.5–9.5)	15.7 (12.9–18.5)	7.5 (6.5–8.5)	**< 0.0001**
CRP > 0.5 mg/dL at last follow up [n (%)]	35 (7.64)	6 (10.17)	29 (9.29)	0.833
csDMARDs [n (%)]	258 (56.33)	30 (42.25)	228 (58.91)	**0.009**
bDMARDs [n (%)]	174 (38.00)	30 (42.25)	144 (37.80)	0.478
tsDMARDs [n (%)]	151 (32.97)	40 (56.34)	111 (29.37)	**< 0.0001**
Glucocorticoids [n (%)]	110 (24.02)	20 (28.17)	90 (23.5)	0.399

Abbreviations: D2T-RA Difficult To Treat Rheumatoid Arthritis, *SD* Standard Deviation, *RF* Rheumatoid Factor, *ACPA* Anti Citrullinated Protein Autoantibodies, *CRP* C Reactive Protein, *CDAI* Clinical Disease Activity Index, *csDMARD* Conventional Synthetic Disease Modifying Antirheumatic Drugs, *bDMARD* Biological Disease Modifying Antirheumatic Drugs, *tsDMARD* Targeted Synthetic Disease Modifying Antirheumatic Drugs

perceived as "problematic to manage" by the physician in 58/71 (82%). Of note, the patient perspective could not be assessed due to the retrospective nature of the study.

Comparison of patients with and without D2T-RA

When patients with D2T-RA were compared with non-D2T cases, no significant differences were found in terms of age (62 years, IQR 58- 65 vs. 62 years, IQR 60- 63 in non-D2T, $p=0.98$), while disease duration was significantly longer in the D2T-RA group (15 years, IQR 13–17 vs. 10, IQR 9–11 in non-D2T, $p<0.0001$). No difference in terms of sex (22.5% vs. 23.6%) and serum autoantibodies (RF: 61.4% vs 61.7%; ACPA: 68.6% vs 60.9%) was noted when comparing patients meeting or not meeting the D2T-RA definition. The presence of at least one *poor prognostic factor* among erosive disease at baseline, positivity of serum autoantibodies, and high baseline disease activity [4], was more frequently found in D2T-RA (76% vs 51% in non-D2T; $p<0.0001$). Particularly, D2T-RA cases were characterized by higher disease activity at the last follow-up visit (CDAI 15.7, IQR 12.9–18.5 vs 7.5, IQR 6.5–8.5 in non-D2T, $p<0.0001$) and higher prevalence of early erosions (24% vs 11% in non-D2T, $p=0.012$). Conversely, no differences were found in terms of the presence of serum autoantibodies among two groups (ACPA 69% vs. 61% in non-D2T, $p=0.223$; rheumatoid factors 61% vs. 62% in non-D2T, $p=0.961$).

The use of JAK inhibitors was more common in D2T-RA (56% vs. 29% in non-D2T, $p<0.0001$) while it should be noted that 20/40 (50%) D2T-RA prescritions of this class of DMARDs were made in 2022. Conventional synthetic DMARDs were more frequently used in non-D2T (59% vs. 42% in D2T, $p=0.009$). The autoantibody status, C-reactive protein levels and the prevalence of extra-articular manifestations were not significantly correlated with D2T-RA.

Table 2 reports the distribution of extra-articular RA manifestations and comorbidities according to the D2T-RA status. Among comorbidities, obesity (33% vs. 19% in non-D2T, $p=0.021$) and fibromyalgia (25% vs. 10% in non-D2T, $p<0.0001$) were more commonly observed in patients with D2T-RA, compared to the counterpart.

At the univariate analysis (Table 3) D2T-RA correlated with disease duration (OR 1.05, 95% CI 1.02- 1.08, $p<0.0001$), the presence of erosions at baseline evaluation (OR 2.6, 95% CI 1.23–5.47, $p=0.012$), CDAI values at last follow-up visit (per CDAI additional point OR 1.08, 95% CI 1.05–1.11, $p<0.0001$), and history of previous surgery to treat RA (OR 3.37, 95% CI 1.58- 7.16; p 0.002). A significant association between D2T-RA and ongoing tsDMARDs (OR 3.10, 95% CI 1.85–5.21; $p<0.0001$), obesity (OR 2.16, 95% CI 1.13–4.14; $p=0.021$) and concomitant fibromyalgia (OR 3.21, 95% CI 1.71–6.05; $p<0.0001$) was observed.

Table 2 Comorbidities and extra-articular manifestations of the disease according to the D2T criteria

	D2T-RA (*n* = 71)	Non D2T-*RA* (*n* = 387)	*P*-value
Hypertension [n (%)]	28 (39.44%)	133 (34.37%)	0.411
Dyslipidemia [n (%)]	26 (36.62%)	118 (30.89%)	0.342
Major Cardiovascular Events [n (%)]	10 (14.08%)	30 (7.75%)	0.087
Obesity [n (%)]	17 (33.33%)	58 (19.21%)	**0.021**
Diabetes [n (%)]	9 (12.68%)	33 (8.53%)	0.269
Diverticular Disease [n (%)]	7 (9.86%)	21 (5.43%)	0.158
Sjogren Disease [n (%)]	4 (5.63%)	10 (2.58%)	0.181
Thyroid disease [n (%)]	17 (33.33%)	98 (23.94%)	0.805
GERD [n (%)]	13 (18.31%)	47 (12.14%)	0.160
Thrombotic Events [n (%)]	6 (8.45%)	21 (5.43%)	0.324
Malignancies [n (%)]	23 (32.39%)	126 (32.56%)	0.978
Asthma/COPD [n (%)]	10 (14.08%)	54 (13.95%)	0.977
Anxious or Depressive Syndrome [n (%)]	9 (12.68%)	35 (9.04%)	0.342
Osteoporosis	25 (53.19%)	140 (59.07%)	0.456
Fibromyalgia [n (%)]	18 (25.35%)	37 (9.56%)	**< 0.0001**
ILD [n (%)]	13 (23.21%)	64 (23.27%)	0.992
Rheumatoid Nodules [n (%)]	5 (7.04%)	12 (3.10%)	0.116

Abbreviations: *D2T-RA* Difficult To Treat Rheumatoid Arthritis, *GERD* Gastroesophageal Reflux Disease, *COPD* Chronic Obstructive Pulmonary Disease, *ILD* Interstitial Lung Disease

Multivariable logistic regression confirmed the association between D2T-RA with disease duration (per additional year OR 1.06, 95% CI 1.03–1.09; $p < 0.0001$), baseline erosions (OR 2.73, 95% CI 1.28–5.82; $p = 0.009$), obesity (OR 2.22, 95% CI 1.10–4.50; $p = 0.026$) and fibromyalgia (OR 3.91, 95% CI 1.76–8.70; $p = 0.001$), independent of age and sex.

Discussion

In this retrospective cross-sectional study, we report a prevalence of D2T-RA reaching 22% among a monocentric cohort of patients with RA, followed-up for at least 12 months. We describe the association between the development of D2T-RA with baseline evidence of erosive disease and comorbidities, particularly obesity and fibromyalgia.

A significant proportion of patients with RA will manifest a D2T disease as mainly defined by the failure of multiple DMARDs with persistence of symptoms despite the numerous available innovative treatments. Since an early treatment seems to be able to reduce the risk of developing D2T-RA, a timely identification of patients at risk becomes of major relevance [16, 17]. In our cohort, among disease characteristics, only disease duration and baseline erosions increased the risk of D2T-RA, while the autoantibody status or gender did not. Conversely, obesity and fibromyalgia, two comorbidities frequently reported in RA cohorts, seem to play a key role in the predisposition to a D2T disease.

Indeed, RA-associated comorbidities influence therapeutic efficacy and safety and we observed that fibromyalgia and obesity increase the risk of D2T-RA by nearly 4 and over 2 times, respectively, in agreement with the data reported in a previous study identifying patients with "pain syndromes and obesity" as a group of D2T cases most distant to the concept of true refractory RA [18]. Most of these patients affected by pain syndromes and obesity were characterized by persistent signs and symptoms, mainly pain and fatigue, fitting the non inflammatory phenotype [19, 20]. Expert opinion has suggested that non-pharmacological strategies, including regular psychologist and physiotherapist evaluation, should regularly performed in patients with D2T-RA [21]. Moreover, weight loss programmes have shown significant beneficial effects on disease activity, physical functioning, and pain control in obese patients with D2T-RA [21].

The pysician and patient perception are milestones in defining D2T-RA, and have shown different trajectories since the early disease stages comparing patients who subsequently develop D2T disease from those who do not [22]. Moreover, it has been suggested that D2TRA encompasses two different subsets, the first one being linked to true drug inefficacy, while the other is mainly due to the presence of factors limiting the therapeutic choices or efficacy. In particular, the first subset is more often accompanied by extra-articular manifestations and shows shorter disease duration at b/tsDMARD initiation, while the other is characterized by more concomitant

Table 3 Univariate and multivariate analysis of factors associated with the D2T criteria in RA

Variable	Univariate analysis	*P* Value	Multivariate analysis	*P* value
Mean age	1.00 ± 0.01 (CI 0.98- 1.02)	0.980	1.00 ± 0.01 (CI 0.99- 1.03)	0.444
Male gender	0.96 ± 0.30 (CI 0.52- 1.76)	0.895	1.78 ± 0.62 (CI 0.90- 3.51)	0.096
Mean Disease duration	**1.05 ± 0.01 (CI 1.02- 1.08)**	**< 0.0001**	**1.06 ± 0.02 (CI 1.02- 1.09)**	**0.001**
Rheumatoid Factor +	0.99 ± 0.26 (CI 0.58- 1.67)	0.961		
ACPA +	1.40 ± 0.40 (CI 0.81- 2.42)	0.223		
Erosions at diagnosis	**2.6 ± 0.99 (CI 1.23- 5.47)**	**0.012**	**2.73 ± 1.05 (CI 1.28- 5.82)**	**0.009**
Erosive disease	**2.96 ± 0.80 (CI 1.76- 5.00)**	**< 0.0001**		
CDAI at last follow up	**1.08 ± 0.02 (CI 1.05- 1.11)**	**< 0.0001**		
CRP > 1 mg/dL at diagnosis	0.5 ± 0.22 (CI 0.21- 1.20)	0.113		
CRP > 1 mg/dL (last follow-up)	1.10 ± 0.52 (CI 0.44- 2.80)	0.833		
Surgery for RA	**3.37 ± 1.30 (CI 1.58- 7.16)**	**0.002**		
Poor prognostic factors	**3.05 ± 0.90 (CI 1.70- 5.44)**	**< 0.0001**		
Former or current Smokers	0.65 ± 0.24 (CI 0.31- 1.33)	0.237		
Ongoing therapies				
OGC	1.28 ± 0.37 (CI 0.72- 2.25)	0.400		
Hydroxychloroquine	0.69 ± 0.26 (CI 0.34- 1.41)	0.304		
Methotrexate	0.65 ± 0.19 (CI 0.37- 1.14)	0.134		
tsDMARD	**3.10 ± 0.82 (CI 1.85- 5.21)**	**< 0.0001**		
bDMARD	1.20 ± 0.32 (CI 0.72- 2.01)	0.479		
Comorbidities/Extra-articular manifestations				
Hypertension	1.24 ± 0.33 (CI 0.74- 2.09)	0.411		
Dyslipidemia	1.29 ± 0.35 (CI 0.76- 2.19)	0.342		
Major Cardiovascular Events	1.95 ± 0.76 (CI 0.91- 4.19)	0.087		
Obesity	**2.16 ± 0.72 (CI 1.13- 4.14)**	**0.021**	**2.32 ± 0.85 (CI 1.14- 4.72)**	**0.020**
Diabetes	1.56 ± 0.62 (CI 0.71- 3.41)	0.269		
Diverticular Disease	1.91 ± 0.87 (CI 0.78- 4.67)	0.158		
Sjogren Disease	2.25 ± 1.36 (CI 0.69- 7.40)	0.181		
Thyroid disease	0.93 ± 0.28 (CI 0.51- 1.68)	0.805		
Thrombotic Events	1.61 ± 0.78 (CI 0.63- 4.14)	0.324		
Malignancies	1 ± 0.27 (CI 0.58- 1.70)	0.978		
Asthma/COPD	1.01 ± 0.38 (CI 0.49- 2.10)	0.977		
Anxiety and depression	1.46 ± 0.58 (CI 0.67- 3.19)	0.342		
Osteoporosis	0.79 ± 0.25 (CI 0.42- 1.48	0.456		
Fibromyalgia	**3.21 ± 1.03 (CI 1.71- 6.05)**	**< 0.0001**	**3.79 ± 1.55 (CI 1.69- 8.47)**	**0.001**
ILD	1 ± 0.35 (CI 0.50- 1.97)	0.992		
Rheumatoid Nodules	2.37 ± 1.30 (CI 0.81- 6.94)	0.116		

Abbreviations: *RA* Rheumatoid Arthritis, *ACPA* Anti Citrullinated Protein Autoantibodies, *CRP* C-Reactive Protein, *CDAI* Clinical Disease Activity Index, bDMARD Biological Disease Modifying Antirheumatic Drugs, *tsDMARD* Targeted Synthetic Disease Modifying Antirheumatic Drugs, *OGC* Oral Glucocorticoids, *COPD* Chronic Obstructive Pulmonary Disease, *ILD* Interstitial Lung Disease

fibromyalgia and comorbidities [23]. In our study, the importance of disease perception in D2T-RA is supported by the observation that C reactive protein levels did not differ significantly while patient reported outcomes were significantly worse in the D2T-RA group, further supporting a large non inflammatory component. The lack of association at multivariate analysis for disease activity measures such as CDAI should be interpreted in the same fashion.

Numerous studies have focused on the negative impact of obesity on RA prognosis, demonstrating low rates of response to treatment in patients with higher baseline BMI [24–26]. The SWEFOT trial demonstrated that obesity in early RA was the strongest independent predictor of non-remission with more than a fivefold increased odds 2 years after diagnosis despite a treat-to-target approach [27]. The negative impact of obesity on therapeutic outcomes came by the "meta-inflammation"

hypothesis associated with pro-inflammatory cytokines and adipokines production by adipose tissue cells. Two biomarkers that could have a role in RA disease progression are adiponectin and leptin. Adiponectin is an adipokine able to promote extracellular matrix degradation and joint distruption [28]; its serum/plasma levels in RA are directly related to radiographic damage [29], DAS-28 and erythrocyte sedimentation rate [30, 31]. Leptin is generally considered a proinflammatory adipokine that stimulates the production of proinflammatory cytokines, such as TNF-α and IL-6. A strong relation with serum/synovial fluid ratios of leptin levels and RA erosive disease and duration were demonstrated [32] as well as a correlation between serum levels and disease activity [33]. Obesity might contribute to the definition of D2T-RA through different mechanisms, including the possibly decreased absorption of drugs administered subcutaneously, poorer health-related quality enhancing chronic pain, and risk of underestimation of RA disease activity, for instance, by compromising the correct assessment of the swollen joint count. As a result, lower rates of DAS28 remission are observed in obese patients with RA, counterposed to similar rates in the decrease of objective inflammation measures, compared to non-obese patients [34, 35].

We could not identify any association between the patients smoking history and the development of D2T-RA. Smoking is one of the factors universally associated with a more aggressive form of RA [36, 37] and also to multiple treatment failures [19] that failed to be linked with D2T in our analysis, if not for a higher proportion of smokers among controls to D2T cases, thus stressing the unclear role of smoking on determining treatment responses and outcomes in established RA [37–40].

Our study confirms previous observations regarding the independent association between evidence of erosive disease at baseline and the risk of developing D2T-RA [41, 42]. Remarkably, while not confirmed at multivariable analysis, the presence of at least one poor prognostic factor among seropositivity, presence of erosions at diagnosis, and high disease activity at baseline was associated with D2T-RA, pointing to the need to carefully assess patients since the moment that RA is diagnosed for the risk of the subsequent development of D2T disease. From this point of view, particular attention should be dedicated to individuating relevant comorbidities, including obesity and fibromyalgia, as possible contributors. Further research is needed to assess whether the early management of such comorbidities can contribute to reduce the risk of subsequent development of D2T-RA.

The analysis of treatments used in D2T-RA cases showed that in this group there was a more limited use of conventional synthetic DMARDs and a higher use of tsDMARDs without reacting statistical significance. The wider use of tsDMARDs (in the case of RA including only JAK inhibitors) may reflect the timing of their availability in Italy, but also may be secondary to their effect on residual pain despite the achievement of remission or low disease activity [43–45], based on the role of the JAK-STAT pathway in the production of both pronociceptive and anti-inflammatory cytokine [46]. Furthermore, data from the FIRST registry support an advantage for tsDMARDs compared to bDMARDs in D2T-RA patients translating into a higher proportion of rapid responders and better outcomes in CDAI, in MTX- and glucocorticoid-free individuals associated with JAK inhibitors [47]. Our results might suggest that JAK inhibition may exceed in efficacy bDMARDs due to their ability to modulate non-immune (or not directly immune-mediated) pathways that contribute to define D2T-RA, such as residual pain. Moreover, while caution must be exerted with JAK inhibitors in patients with a high cardiovascular risk profile, including obesity, further evidence is required to define whether their glucocorticoid-sparing effect may exceed in benefits compared to harms in this specific target population.

This study has strengths and limitations, among the former are the real-world setting with a standardized approach to patients' care in a single tertiary center and the adoption of an accepted definition of D2T-RA which found a prevalence in line with the literature [2, 4, 5]. Limitations include the retrospective nature of the study and the absence of some variables, i.e. socioeconomic status and adherence, which have been previously described as associated to an higher risk of D2T-RA [2, 48, 49]. We were not able to derive disease activity measures at baseline for a significant proportion of patients, so these were not included in the analysis. The patients' perspective on the problematic nature of the disease management could not be precisely assessed, as would be required per D2T-RA criteria [1]. Moreover, while fibromyalgia was defined according to the latest classification criteria, we acknowledge that the pathophysiology and clinical features may differ in patients with chronic conditions associated to pain. Last, in our study, D2T-RA represents a heterogeneous population, embracing patients with high disease activity and multiple drug failure, as well as the counterpart characterized by low inflammation biomarkers but still uncontrolled symptoms, reflecting what recently reported in another cohort [50].

Conclusion

In conclusion, our data identify erosions at diagnosis, the presence of fibromyalgia and obesity at baseline as characteristics independently associated with the development of D2T-RA. Our explorative analysis suggests that

further characterization is warranted to better phenotype patients with D2T-RA, particularly to understand the contribution of chronic inflammation, altered pain perception, and the role of both organic and psychological comorbidities in assessing disease activity and residual pain. The implementation of biopsy- and biomarker-driven trials [51–53] will allow to better elucidate such important issues, and, hopefully, to progressively abandon the "trial-and-error" approach in favour of a precision medicine model aimed at controlling the disease earlier, thus possibly reducing the risk of developing D2T-RA.

Acknowledgements
Not applicable.

Authors' contributions
N.L., E.Ba., A.D.I. and C.S. contributed to the design of the research and to the writing of the manuscript. N.L., M. D. S., A.C., M.C., G.M.G., D.R. and C.S. contributed to patients' data collection. E.Ba. and E.Br. performed the statistical analysis of the results. All authors discussed the results and commented on the manuscript.

Funding
Not applicable.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
N.L. and G.M.G.: Consulting / speakers fee AbbVie, BMS, Eli-Lilly, Galapagos, Janssen, Novartis; D.R.: Consulting / speakers fee AbbVie, Eli-Lilly, Janssen, Novartis; C.S.: Consulting / speakers fee (AbbVie, Amgen, Alfa-Wassermann, Biogen, Eli-Lilly, Galapagos, Janssen, Novartis, Pfizer, SOBI); Research support (AbbVie, Amgen, Pfizer).

Received: 4 March 2024 Accepted: 3 November 2024
Published online: 03 January 2025

References

1. Nagy G, Roodenrijs NMT, Welsing PMJ, Kedves M, Hamar A, Van Der Goes MC, et al. EULAR definition of difficult-to-treat rheumatoid arthritis. Ann Rheum Dis. 2021;80(1):31–5. Available from: https://pubmed.ncbi.nlm.nih.gov/33004335/. [cited 2023 Nov 27].
2. Roodenrijs NMT, De Hair MJH, Van Der Goes MC, Jacobs JWG, Welsing PMJ, Van Der Heijde D, et al. Characteristics of difficult-to-treat rheumatoid arthritis: results of an international survey. Ann Rheum Dis. 2018;77(12):1705–9. Available from: https://pubmed.ncbi.nlm.nih.gov/30194273/. [cited 2023 Nov 27].
3. MJH de H, JWG J, JLM S, JM van L. Difficult-to-treat rheumatoid arthritis: an area of unmet clinical need. Rheumatology (Oxford). 2018;57(7). Available from: https://pubmed.ncbi.nlm.nih.gov/29029308/. [cited 2023 Nov 27].
4. Watanabe R, Hashimoto M, Murata K, Murakami K, Tanaka M, Ohmura K, et al. Prevalence and predictive factors of difficult-to-treat rheumatoid arthritis: the KURAMA cohort. Immunol Med. 2022;45(1):35–44. Available from: https://pubmed.ncbi.nlm.nih.gov/34033729/. [cited 2023 Nov 27].
5. Batko B, Urbański K, Świerkot J, Wiland P, Raciborski F, Jędrzejewski M, et al. Comorbidity burden and clinical characteristics of patients with difficult-to-control rheumatoid arthritis. Clin Rheumatol. 2019;38(9):2473–81. Available from: https://pubmed.ncbi.nlm.nih.gov/31076943/. [cited 2023 Nov 27].
6. Roodenrijs NMT, Welsing PMJ, Van Roon J, Schoneveld JLM, Van Der Goes MC, Nagy G, et al. Mechanisms underlying DMARD inefficacy in difficult-to-treat rheumatoid arthritis: a narrative review with systematic literature search. Rheumatology (Oxford). 2022;61(9):3552–66. Available from: https://pubmed.ncbi.nlm.nih.gov/35238332/. [cited 2023 Nov 27].
7. Giollo A, Zen M, Larosa M, Astorri D, Salvato M, Calligaro A, et al. Early characterization of difficult-to-treat rheumatoid arthritis by suboptimal initial management: a multicentre cohort study. Rheumatology (Oxford). 2023;62(6):2083–9. Available from: https://pubmed.ncbi.nlm.nih.gov/36190344/. [cited 2023 Nov 27].
8. Roodenrijs NMT, Kedves M, Hamar A, Nagy G, Van Laar JM, Van Der Heijde D, et al. Diagnostic issues in difficult-to-treat rheumatoid arthritis: a systematic literature review informing the EULAR recommendations for the management of difficult-to-treat rheumatoid arthritis. RMD Open. 2021;7(1). Available from: https://pubmed.ncbi.nlm.nih.gov/33514671/. [cited 2023 Nov 27].
9. Luciano N, Barone E, Timilsina S, Gershwin ME, Selmi C. Tumor Necrosis Factor Alpha Inhibitors and Cardiovascular Risk in Rheumatoid Arthritis. Clin Rev Allergy Immunol. 2023;65(3):403–19. Available from: https://pubmed.ncbi.nlm.nih.gov/38157095/. [cited 2024 Sep 9].
10. Dey M, Nagy G, Nikiphorou E. Comorbidities or extra-articular manifestations: time to reconsider the terminology? Rheumatology (Oxford). 2022;61(10):3881–3. Available from: https://pubmed.ncbi.nlm.nih.gov/35244149/. [cited 2023 Nov 27].
11. Messelink MA, Roodenrijs NMT, van Es B, Hulsbergen-Veelken CAR, Jong S, Overmars LM, et al. Identification and prediction of difficult-to-treat rheumatoid arthritis patients in structured and unstructured routine care data: results from a hackathon. Arthritis Res Ther. 2021;23(1). Available from: https://pubmed.ncbi.nlm.nih.gov/34238346/. [cited 2023 Nov 27].
12. Hecquet S, Combier A, Steelandt A, Pons M, Wendling D, Molto A, et al. Characteristics of patients with difficult-to-treat rheumatoid arthritis in a French single-centre hospital. Rheumatology (Oxford). 2023. Available from: https://pubmed.ncbi.nlm.nih.gov/36961324/. [cited 2023 Nov 27].
13. Novella-Navarro M, Plasencia C, Tornero C, Navarro-Compán V, Cabrera-Alarcón JL, Peiteado-López D, et al. Clinical predictors of multiple failure to biological therapy in patients with rheumatoid arthritis. Arthritis Res Ther. 2020;22(1). Available from: https://pubmed.ncbi.nlm.nih.gov/33298140/. [cited 2024 Feb 10].
14. Kay J, Upchurch KS. ACR/EULAR 2010 rheumatoid arthritis classification criteria. Rheumatology (Oxford). 2012;51 Suppl 6(SUPPL. 6). Available from: https://pubmed.ncbi.nlm.nih.gov/23221588/. [cited 2023 Nov 27].
15. Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Häuser W, Katz RL, et al. 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria. Semin Arthritis Rheum. 2016Dec 1;46(3):319–29.
16. Nagy G, Roodenrijs NMT, Welsing PMJ, Kedves M, Hamar A, van der Goes MC, et al. EULAR points to consider for the management of difficult-to-treat rheumatoid arthritis. Ann Rheum Dis. 2022;81(1):20–33. Available from: https://pubmed.ncbi.nlm.nih.gov/34407926/. [cited 2023 Nov 27].
17. Tan Y, Buch MH. "Difficult to treat" rheumatoid arthritis: current position and considerations for next steps. RMD Open. 2022;8(2). Available from: https://pubmed.ncbi.nlm.nih.gov/35896282/. [cited 2023 Nov 26].
18. Roodenrijs NMT, Van Der Goes MC, Welsing PMJ, Tekstra J, Lafeber FPJG, Jacobs JWG, et al. Difficult-to-treat rheumatoid arthritis: contributing factors and burden of disease. Rheumatology (Oxford). 2021;60(8):3778–88. Available from: https://pubmed.ncbi.nlm.nih.gov/33331946/.[cited 2023 Nov 27].
19. Buch MH, Eyre S, McGonagle D. Persistent inflammatory and non-inflammatory mechanisms in refractory rheumatoid arthritis. Nat Rev Rheumatol. 2021;17(1):17–33. Available from: https://pubmed.ncbi.nlm.nih.gov/33293696/. [cited 2023 Nov 27].
20. Joharatnam N, McWilliams DF, Wilson D, Wheeler M, Pande I, Walsh DA. A cross-sectional study of pain sensitivity, disease-activity assessment, mental health, and fibromyalgia status in rheumatoid arthritis. Arthritis Res

Ther. 2015;17(1). Available from: https://www.pmc/articles/PMC4363056/. [cited 2024 Feb 10].
21. Majnik J, Császár-Nagy N, Böcskei G, Bender T, Nagy G. Non-pharmacological treatment in difficult-to-treat rheumatoid arthritis. Front Med (Lausanne). 2022;9. Available from: https://pubmed.ncbi.nlm.nih.gov/36106320/. [cited 2024 Sep 17].
22. Novella-Navarro M, Cabrera-Alarcón J, López-Juanes N, Villalba A, Fernández EF, Monjo I, et al. Patient and physician assessment in difficult-to-treat rheumatoid arthritis: patterns of subjective perception at early stages of b/tsDMARD treatment. RMD Open. 2023;9(3). Available from: https://pubmed.ncbi.nlm.nih.gov/37775112/. [cited 2024 Sep 17].
23. Novella-Navarro M, Ruiz-Esquide V, Torres-Ortiz G, Chacur CA, Tornero C, Fernández-Fernandez E, et al. A paradigm of difficult-to-treat rheumatoid arthritis: subtypes and early identification. Clin Exp Rheumatol. 2023;41(5):1114–9. Available from: https://pubmed.ncbi.nlm.nih.gov/36377568/. [cited 2024 Sep 17].
24. Ajeganova S, Andersson ML, Hafström I. Association of obesity with worse disease severity in rheumatoid arthritis as well as with comorbidities: a long-term followup from disease onset. Arthritis Care Res (Hoboken). 2013;65(1):78–87. Available from: https://pubmed.ncbi.nlm.nih.gov/22514159/ . [cited 2023 Nov 27].
25. Abuhelwa AY, Hopkins AM, Sorich MJ, Proudman S, Foster DJR, Wiese MD. Association between obesity and remission in rheumatoid arthritis patients treated with disease-modifying anti-rheumatic drugs. Sci Rep. 2020;10(1). Available from: https://pubmed.ncbi.nlm.nih.gov/33122725/. [cited 2023 Nov 27].
26. Gremese E, Carletto A, Padovan M, Atzeni F, Raffeiner B, Giardina AR, et al. Obesity and reduction of the response rate to anti-tumor necrosis factor α in rheumatoid arthritis: an approach to a personalized medicine. Arthritis Care Res (Hoboken). 2013;65(1):94–100. Available from: https://pubmed.ncbi.nlm.nih.gov/22730143/. [cited 2023 Nov 27].
27. Levitsky A, Brismar K, Hafström I, Hambardzumyan K, Lourdudoss C, Van Vollenhoven RF, et al. Obesity is a strong predictor of worse clinical outcomes and treatment responses in early rheumatoid arthritis: results from the SWEFOT trial. Open. 2017;3:458. Available from: http://rmdopen.bmj.com/. [cited 2023 Nov 27].
28. Del Prete A, Salvi V, Sozzani S. Adipokines as potential biomarkers in rheumatoid arthritis. Mediators Inflamm. 2014;2014 . Available from: https://pubmed.ncbi.nlm.nih.gov/24799765/. [cited 2023 Nov 27].
29. Giles JT, Allison M, Bingham CO, Scott WM, Bathon JM. Adiponectin is a mediator of the inverse association of adiposity with radiographic damage in rheumatoid arthritis. Arthritis Rheum. 2009;61(9):1248–56. Available from: https://pubmed.ncbi.nlm.nih.gov/19714593/. [cited 2023 Nov 27].
30. Chen X, Lu J, Bao J, Guo J, Shi J, Wang Y. Adiponectin: a biomarker for rheumatoid arthritis? Cytokine Growth Factor Rev. 2013;24(1):83–9. Available from: https://pubmed.ncbi.nlm.nih.gov/22910140/. [cited 2023 Nov 27].
31. Meyer M, Sellam J, Fellahi S, Kotti S, Bastard JP, Meyer O, et al. Serum level of adiponectin is a surrogate independent biomarker of radiographic disease progression in early rheumatoid arthritis: results from the ESPOIR cohort. Arthritis Res Ther. 2013;15(6). Available from: https://pubmed.ncbi.nlm.nih.gov/24314299/. [cited 2023 Nov 27].
32. Olama SM, Senna MK, Elarman M. Synovial/serum leptin ratio in rheumatoid arthritis: the association with activity and erosion. Rheumatol Int. 2012;32(3):683–90. Available from: https://pubmed.ncbi.nlm.nih.gov/21140264/. [cited 2023 Nov 27].
33. Lee YH, Song GG. Circulating leptin and its correlation with rheumatoid arthritis activity: a meta-analysis. J Rheum Dis. 2023;30(2):116–25. Available from: https://pubmed.ncbi.nlm.nih.gov/37483475/. [cited 2023 Nov 28].
34. Dey M, Nagy G, Nikiphorou E. Comorbidities and extra-articular manifestations in difficult-to-treat rheumatoid arthritis: different sides of the same coin? Rheumatology (Oxford). 2023;62(5):1773–9. Available from: https://pubmed.ncbi.nlm.nih.gov/36205537/. [cited 2024 Sep 17].
35. Bertsias A, Flouri ID, Repa A, Avgoustidis N, Kalogiannaki E, Pitsigavdaki S, et al. Patterns of comorbidities differentially affect long-term functional evolution and disease activity in patients with "difficult to treat" rheumatoid arthritis. RMD Open. 2024;10(1). Available from: https://pubmed.ncbi.nlm.nih.gov/38242549/. [cited 2024 Sep 17].
36. Chang K, Yang SM, Kim SH, Han KH, Park SJ, Shin JII. Smoking and rheumatoid arthritis. Int J Mol Sci. 2014;15(12):22279–95. Available from: https://pubmed.ncbi.nlm.nih.gov/25479074/. [cited 2023 Nov 27].
37. Ishikawa Y, Terao C. The Impact of Cigarette Smoking on Risk of Rheumatoid Arthritis: A Narrative Review. Cells. 2020;9(2). Available from: https://pubmed.ncbi.nlm.nih.gov/32092988/. [cited 2023 Nov 27].
38. Gianfrancesco MA, Trupin L, Shiboski S, Van Der Laan M, Graf J, Imboden J, et al. Smoking Is Associated with Higher Disease Activity in Rheumatoid Arthritis: A Longitudinal Study Controlling for Time-varying Covariates. J Rheumatol. 2019;46(4):370–5. Available from: https://pubmed.ncbi.nlm.nih.gov/30504507/. [cited 2023 Nov 27].
39. Roelsgaard IK, Ikdahl E, Rollefstad S, Wibetoe G, Esbensen BA, Kitas GD, et al. Smoking cessation is associated with lower disease activity and predicts cardiovascular risk reduction in rheumatoid arthritis patients. Rheumatology (Oxford). 2020;59(8):1997–2004. Available from: https://pubmed.ncbi.nlm.nih.gov/31782789/. [cited 2023 Nov 27].
40. Nayebirad S, Javinani A, Javadi M, Yousefi-Koma H, Farahmand K, Atef Yekta R, et al. The effect of smoking on response to methotrexate in rheumatoid arthritis patients: A systematic review and meta-analysis. Mod Rheumatol. 2023. Available from: https://pubmed.ncbi.nlm.nih.gov/36688574/. [cited 2023 Nov 27].
41. Garcia-Salinas R, Sanchez-Prado E, Mareco J, Ronald P, Ruta S, Gomez R, et al. Difficult to treat rheumatoid arthritis in a comprehensive evaluation program: frequency according to different objective evaluations. Rheumatol Int. 2023;43(10):1821–8. Available from: https://pubmed.ncbi.nlm.nih.gov/37269430/. [cited 2024 Sep 17].
42. Alp G, Cinakli H, Aysin İK, Solmaz D, Akar S. Challenges and insights in managing difficult-to-treat rheumatoid arthritis: real-world clinical perspectives. Clin Exp Rheumatol. 2024;42(7):1398–406. Available from: https://pubmed.ncbi.nlm.nih.gov/38372714/. [cited 2024 Sep 17].
43. Fautrel B, Kirkham B, Pope JE, Takeuchi T, Gaich C, Quebe A, et al. Effect of Baricitinib and Adalimumab in Reducing Pain and Improving Function in Patients with Rheumatoid Arthritis in Low Disease Activity: Exploratory Analyses from RA-BEAM. J Clin Med. 2019;8(9). Available from: https://pubmed.ncbi.nlm.nih.gov/31492040/ . [cited 2023 Nov 27].
44. Dougados M, Taylor PC, Bingham CO, Fallon L, Brault Y, Roychoudhury S, et al. The effect of tofacitinib on residual pain in patients with rheumatoid arthritis and psoriatic arthritis. RMD Open. 2022;8(2). Available from: https://pubmed.ncbi.nlm.nih.gov/36814062/. [cited 2023 Nov 27].
45. De Stefano L, Bozzalla Cassione E, Bottazzi F, Marazzi E, Maggiore F, Morandi V, et al. Janus kinase inhibitors effectively improve pain across different disease activity states in rheumatoid arthritis. Intern Emerg Med. 2023;18(6):1733–4. Available from: https://pubmed.ncbi.nlm.nih.gov/37500945/. [cited 2023 Nov 27].
46. Simon LS, Taylor PC, Choy EH, Sebba A, Quebe A, Knopp KL, et al. The Jak/STAT pathway: A focus on pain in rheumatoid arthritis. Semin Arthritis Rheum. 2021;51(1):278–84. Available from: https://pubmed.ncbi.nlm.nih.gov/33412435/. [cited 2023 Nov 27].
47. Ochi S, Sonomoto K, Nakayamada S, Tanaka Y. Preferable outcome of Janus kinase inhibitors for a group of difficult-to-treat rheumatoid arthritis patients: from the FIRST Registry. Arthritis Res Ther. 2022;24(1). Available from: https://pubmed.ncbi.nlm.nih.gov/35232462/. [cited 2023 Nov 27].
48. Roodenrijs NMT, Van Der Goes MC, Welsing PMJ, Van Oorschot EPC, Nikiphorou E, Nijhof NC, et al. Non-adherence in difficult-to-treat rheumatoid arthritis from the perspectives of patients and rheumatologists: a concept mapping study. Rheumatology (Oxford). 2021;60(11):5105–16. Available from: https://pubmed.ncbi.nlm.nih.gov/33560301/. [cited 2023 Nov 27].
49. Van Den Bemt BJF, Zwikker HE, Van Den Ende CHM. Medication adherence in patients with rheumatoid arthritis: a critical appraisal of the existing literature. Expert Rev Clin Immunol. 2012;8(4):337–51. Available from: https://pubmed.ncbi.nlm.nih.gov/22607180/. [cited 2023 Nov 27].
50. Novella-Navarro M, Ruiz-Esquide V, Torres-Ortiz G, Chacur CA, Tornero C, Fernández-Fernandez E, et al. A paradigm of difficult-to-treat rheumatoid arthritis: subtypes and early identification. Clin Exp Rheumatol. 2023;41(5):1114–9. Available from: https://pubmed.ncbi.nlm.nih.gov/36377568/. [cited 2024 Sep 17].
51. Humby F, Durez P, Buch MH, Lewis MJ, Rizvi H, Rivellese F, et al. Rituximab versus tocilizumab in anti-TNF inadequate responder patients with rheumatoid arthritis (R4RA): 16-week outcomes of a stratified, biopsy-driven,

multicentre, open-label, phase 4 randomised controlled trial. Lancet. 2021;397(10271):305–17. Available from: https://pubmed.ncbi.nlm.nih.gov/33485455/. [cited 2023 Nov 27].
52. Rivellese F, Nerviani A, Giorli G, Warren L, Jaworska E, Bombardieri M, et al. Stratification of biological therapies by pathobiology in biologic-naive patients with rheumatoid arthritis (STRAP and STRAP-EU): two parallel, open-label, biopsy-driven, randomised trials. Lancet Rheumatol. 2023;5(11):e648–59. Available from: http://www.thelancet.com/article/S2665991323002412/fulltext . [cited 2023 Nov 27].
53. Pitzalis C, Choy EHS, Buch MH. Transforming clinical trials in rheumatology: towards patient-centric precision medicine. Nature Rev Rheumatol. 2020;16(10):590–9. Available from: https://www.nature.com/articles/s41584-020-0491-4. [cited 2024 Feb 1].

Publisher's Note