A paradigm of difficult-to-treat rheumatoid arthritis: subtypes and early identification

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Abstract

Objective

Multiple failures to biologic or targeted specific disease-modifying anti-rheumatic drugs (b/tsDMARDs) that lead to difficult-to-treat rheumatoid arthritis (D2TRA) may be the result of multi-drug inefficacy or reflect treatment problems related to adverse events, comorbidities, and/or poor adherence. We aimed to characterise a cohort of D2TRA patients in clinical practice, to analyse the differences between D2TRA due to inefficacy versus D2TRA from other causes, and to compare them with non-D2TRA.

Methods

The D2TRA group included patients who were receiving ≥2b/tsDMARDs due to inefficacy (D2TRA-inefficacy) or because of adverse events, poor adherence, contraindications, comorbidities, drug-intolerance, etc. (D2TRA-other). Patients who achieved low disease activity or remission with the first bDMARD were classified as non-D2TRA patients. For all patients, demographic, clinical characteristics and laboratory parameters were assessed prior to starting the first b/tsDMARD. Descriptive analysis was performed and bivariate logistic regression models were assembled.

Results

In total, 253 patients were included: 131 non-D2TRA and 122 D2TRA [86 (70.5%) D2TRA-inefficacy and 36 (29.5%) D2TRA-other]. Comparison of the two groups of D2TRA patients: no differences in gender, age at start of b/tsDMARD or age at RA diagnosis were found; this was also true of socioeconomic status, frequency of anxiety-depression and other comorbidities. Patients categorised as D2TRA-other had less extra-articular manifestations than D2TRA-inefficacy, as well as lower values of DAS28 at the start of the first b/tsDMARD. Comparisons of Non-D2TRA patients versus D2TRA-other resulted in the following observations: no differences in sociodemographic characteristics were evident nor were there any differences in terms of disease activity.

Conclusion

Patients with D2TRA-other are indistinguishable from non-D2TRA patients at baseline, indicating the former cohort does not appear to have any predictive value during the early stages of b/tsDMARD treatment, unlike what occurs in patients with D2TRA-inefficacy.

Key words

difficult-to-treat rheumatoid arthritis, biologic and targeted disease-modifying anti-rheumatic drugs, established rheumatoid arthritis

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Received on May 19, 2022; accepted in revised form on September 12, 2022.

Competing interests: M. Novella-Navarro reports grants from UCB, Lilly and Janssen outside the submitted work. R. Sanmartí reports grants from Abbvie, BMS, Gebro-Pharma, Lilly, MSD, Pfizer, Sanofi andRoche outside the submitted work. C. Plasencia-Rodríguez reports grants from Abbvie, Pfizer, Novartis, Lilly and Roche outside the submitted work. A. Balsa reports grants form Abbvie, Amgen, Pfizer, Galapagos, Novartis, Gilead, BMS, Nordic, Sanofi, Sandoz, Lilly, UCB and Roche outside the submitted work. The other authors have declared no competing interests.

Introduction

Difficult-to-treat rheumatoid arthritis (D2TRA) is an emerging healthcare concern (1). In fact, various studies suggest its prevalence ranges from 5 to 20% (2-5) among RA patients treated with biologic and targeted synthetic disease-modifying anti-rheumatic drugs (b/ts-DMARDs). Despite the increasing of therapeutic options, the greater knowledge of the treatments in terms of efficacy and safety, and the development of more tools for the approach to personalised medicine (6), these difficult-to-treat patients remain a challenge for clinicians.

D2TRA is a heterogeneous concept in which patients may experience difficulties in the management of their disease for different reasons. Thus, it has been postulated that within this group of patients there are, on the one hand, some who present multiple drug ineffectiveness due to the immune mechanisms intrinsic to RA, pharmacogenetics, etc. that lead to persistent inflammatory activity. On the other hand, there are those patients in whom the difficulty of RA management stems from various causes such as associated pain syndrome, lack of therapeutic adherence, adverse events, among others (4, 7).

The identification and management of these D2TRA patients should always be done in a holistic manner. In fact, considerable efforts are being undertaken to more accurately identify both subgroups, which may, in time, enable the development of more accurate therapeutic strategies (8, 9).

In a previous work conducted by our group, some risk factors associated with the development of multi-drug resistance were identified, including being younger at bDMARD initiation, having a higher baseline disease index, the presence of erosions, and poorer early response during the first 6 months of treatment with b/tsDMARDs. However, more evidence is needed to further understand this phenomenon and to develop an approach for classifying and identifying such patients. For these reasons, the objectives of this study were: i) to describe the characteristics of a cohort of D2TRA patients in clinical practice; ii) to compare the differences between D2TRA due to drug inefficacy *versus* D2TRA from other causes; iii) to compare D2TRA-other causes with non-D2TRA.

Patients and methods

This study involved subjects with RA from a prospective cohort of patients drawn from the Rheumatoid Arthritis Registry at La Paz University (RA Paz cohort) Hospital and Clínic University Hospital between 2000 and 2021. Patients (≥18 years of age) fulfilling 1987 ACR or 2010 ACR/EULAR classification criteria (10, 11), and treated with any b/tsDMARDs (TNFi, abatacept, tocilizumab, rituximab and JAK inhibitors) were included and classified into two groups according to the number of prior failures to b/tsDMARDs: difficult-to treat RA patients (D2TRA-patients), and non-difficult-to-treat patients (non-D2TRA patients). Ethical approval was obtained from the La Paz Ethics Committee (PI-1155).

Definitions for D2TRA patients and non-D2TRA patients

In this study, D2TRA-patients were defined according to EULAR criteria for D2TRA (1). Patients were divided in two groups: 1) those who had received ≥2b/tsDMARDs due to inefficacy (D2TRA-inefficacy) or 2) because of adverse events, poor adherence, contraindications, comorbidities, drug-intolerance, etc (D2TRA-other). Patients who achieved low disease activity or remission (as assessed by DAS28) with the first b/tsDMARD and continued with the same drug for at least 5 years were classified as non-D2TRA patients. We established the cut-off point for long-term follow-up at 5 years based on the data previously published by our group (5). Patients who failed to one b/tsDMARD were not included in the non-D2T group because we wanted to be in line with the classification we had used in previous work in order to compare clearly differentiated groups.

Patients who discontinued treatment, and the reason for their discontinuation, were not recorded in the database. In addition, those who lacked complete data or who did not fulfill pre-established inclusion criteria were excluded.

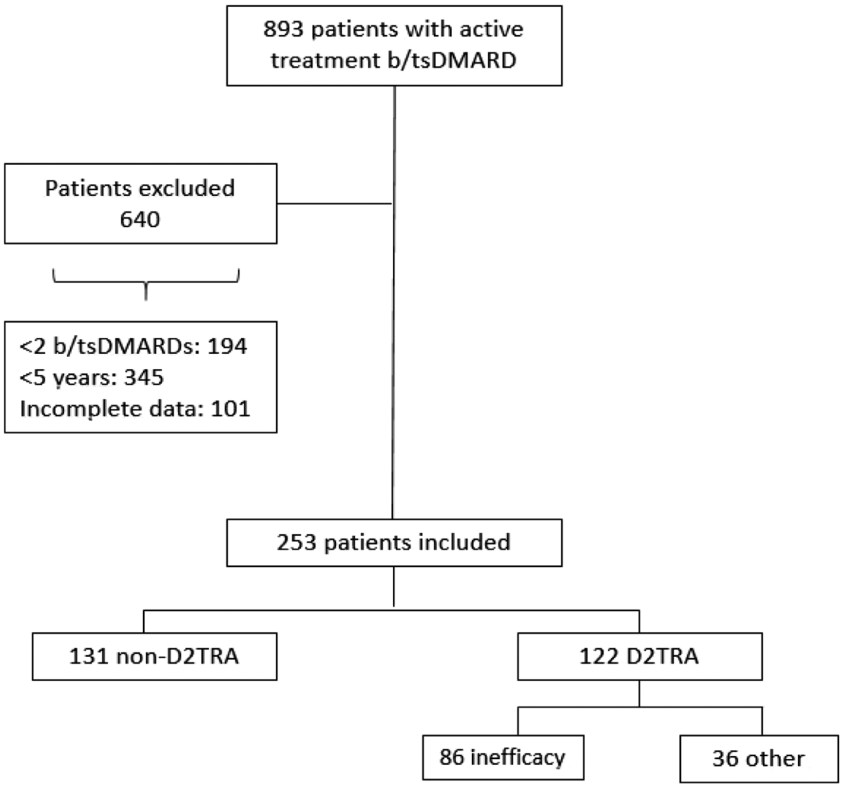

Fig. 1. Flowchart of patients included.

Data collection

For all patients, the following data were collected prior to starting the first b/tsDMARD: demographic characteristics (age, sex, Body Mass Index, smoking habit), age at diagnosis of RA, age at starting b/tsDMARDs, previous and concomitant treatments (glucocorticoids and conventional synthetic – csDMARDs), laboratory parameters such as rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPA). Presence of bone erosions (as assessed by simple radiography), extra-articular manifestations and comorbidities: hypertension, diabetes mellitus, dyslipidaemia, chronic respiratory disease, gastrointestinal disease, previous major adverse cardiovascular events, malignancies and severe or recurrent infections. In addition, a health assessment questionnaire (HAQ), pain visual analogue scale (VAS-Pain) and disease activity score with 28 joint-counts (DAS28) were assessed.

Statistical analysis

Descriptive analysis was performed. Qualitative variables are expressed as absolute numbers and frequencies; quantitative variables are reported as mean and standard deviation (SD) or median and interquartile range (IQR), depending on the data distribution. We analysed the sample in two steps: first, we analysed the D2TRA group in order to identify any differences between D2TRA-inefficacy and D2TRA-other; second, we compared D2TRA-other with Non-D2TRA patients. All analyses were carried out following the same rationale. Differences between qualitative variables were assessed using the Chi-square test; differences between quantitative variables were assessed using the t-test and Mann-Whitney test. Multiple bivariate logistic regression models were performed to identify which features were associated with this outcome and should therefore be considered in the multivariate analyses. Prior to adjusting the multivariate analysis, we performed a multi-collinearity test analysing the variance inflation factor (VIF >1) in order to check for any possible correlations between the independent variables. p-values <0.05 were considered statistically significant. Odds ratio (OR) and confidence intervals were also calculated (IBM SPSS 21.0).

Results

In total, 893 patients under active treatment with b/tsDMARD(s) were retrieved; 640 were not included because they did not fulfill the pre-established selection criteria according to the definitions of D2TRA and non-D2TRA, and 101 due to a lack of data. Finally, 253 patients were included in the study (Supplementary Table S1): 131 were non-D2TRA and 122 D2TRA [86 (70.5%) D2TRA-inefficacy and 36 (29.5%) D2TRA-other] (Fig. 1). Among reasons for discontinuation of treatment in D2TRA-other causes patients were: infections, infusional reactions, cutaneous reactions, laboratory abnormalities, lack of adherence, intolerance, interstitial lung disease and surgical procedures (Suppl. Table S2).

Demographic and clinical characteristics of D2TRA patients: D2TRA-inefficacy vs. D2TRA-other

Patient characteristics prior to start of a first b/tsDMARD are shown in Table I. No differences in age, gender, age at b/tsDMARD starting or age at RA diagnosis were found, nor were any concerning socioeconomic status, frequency of anxiety-depression or other comorbidities. The frequency of fibromyalgia at b/tsDMARD starting was higher in D2T-others *versus* D2T-inefficacy (25% *vs*. 18%), although the differences were not statistically significant. Forty-two patients (17%) had extra-articular manifestations at b/tsDMARD starting, among which the following were noteworthy: secondary Sjögren's syndrome, interstitial lung disease and rheumatoid nodulosis (Suppl. Table S3). Patients classified as D2TRA-other presented less frequency of extra-articular manifestations than D2TRA-inefficacy (8.3% *vs*. 26.7%; p=0.02) and experienced longer disease duration prior to start of a b/tsDMARD (9.5 *vs*. 5.6 years, p=0.01). Finally, D2TRA-other exhibited lower active disease by DAS28 before starting the first b/tsDMARD (4.9±1.4 *vs*. 5.7±1.2; p=0.01) than those with D2TRA-inefficacy.

Comparison between D2TRA-other causes and non-D2TRA patients

Patient characteristics at b/tsDMARD

initiation are shown in Table I. While patients with D2TRA-other had previously received more csDMARDs than non-D2TRA patients [2(1-3) *vs*. 2(2-3); $p<0.01$], no other differences were found either in sociodemographic characteristics or in baseline disease activity.

Risk factors associated to D2TRA-other causes

Taking into account those variables with significant differences in descriptive analysis, we analysed their association with D2TRA-other via a two-step process:

First, we performed a bivariate analysis establishing D2TRA-other *versus* D2TRA-ineficacy as an outcome variable. An association between extra-articular manifestations and disease duration at b/tsDMARD initiation was found. In addition, TJC, SJC, CRP, ESR at start of b/tsDMARD were also analysed. However, after checking for multi-collinearity, these variables were removed due to the correlations between them and the composite index DAS28. Finally, multivariate analysis showed that the absence of extraarticular manifestations (OR=5.82 95%CI 1.26–26.79), a lower DAS28 at b/tsDMARD initiation (OR=1.49 95%CI 1.05–2.12), and longer disease duration prior to starting a b/tsDMARD (OR=0.90 95%CI 0.85–0.97) were independently associated with being D2TRA-other.

Second, the same analysis was performed using D2TRA-other *versus* non-D2TRA as an outcome variable. In this case, bivariate analysis revealed only an association with number of previous csDMARDs (OR=1.93 95%CI 1.24–2.99).

Table I. Clinical characteristics and comparison between D2TRA patients (due to inefficacy and other causes) and D2TRA-other and non-D2TRA.

Variables	D2TRA-patients (n=122)		*p*-value*	Non-D2TRA (n=131)	*p*-value§
	D2TRA-inefficacy (n=86)	D2TRA-other (n=36)			
Age mean (SD)					
current	61.5 (12.6)	60.1 (12.8)	0.60	65.0 (12.5)	0.05
at diagnosis	43.9 (13.1)	40.1 (12.1)	0.14	46.0 (12.6)	**0.01**
at start b/tsDMARD	49.5 (12.0)	50.2 (11.5)	0.76	54.1 (11.9)	0.08
Sex (fem) n (%)	74 (86.1)	31 (86.0)	0.61	114 (87.0)	0.53
BMI mean (SD)	26.4 (5.4)	26.8 (6.1)	0.73	25.5 (5.5)	0.18
Smoking habit n (%)					
smokers	24 (27.9)	9 (25.0)		25 (19.1)	
ex smokers	17 (18.7)	7 (19.4)	0.93	32 (24.4)	0.68
never smokers	45 (52.3)	20 (55.6)		72 (55.0)	
Comorbidities mean (SD)	1.1 (1.0)	1.2 (1.0)	0.23	0.9 (1.1)	0.11
Anxiety-depression n (%)	25 (29.1)	10 (27.8)	0.53	21 (16.0)	0.14
Fibromyalgia n (%)	16 (18.6)	9 (25.0)	0.28	20 (15.2)	0.21
Previous csDMARDs	2 (2-3)	2 (2-3)	0.79	2 (1-3)	**<0.01**
Erosions n (%)	48 (55.8)	17 (47.2)	0.25	44 (33.8)	0.17
Extraarticular manifestations n (%)	23 (26.7)	3 (8.3)	0.02	17 (13.0)	0.32
Time between diagnosis and starting bDMARD mean (SD)	5.0 (5.6)	9.5 (9.1)	**0.01**	7.5 (7.0)	0.16
Current CE n (%)	81 (94.2)	33 (91.7)	0.22	115 (87.8)	0.49
Current MTX n (%)	74 (86.0)	28 (76.8)	0.28	99 (75.6)	0.48
1st bDMARD n (%)					
TNFi	76 (88.4)	33 (91.7)	0.63	98 (74.8)	0.06
Non TNFi	10 (11.6)	3 (8.3)	0.51	33 (25.2)	
Immunological parameters n (%)					
RF positive	72 (83.7)	30 (82.3)	0.49	106 (80.2)	0.52
ACPA positive	72 (83.7)	27 (75.3)	0.19	110 (84.0)	0.13
TJC mean (SD)	10.5 (7.0)	6.9 (6.2)	**0.02**	7.9 (5.7)	0.74
SJC mean (SD)	8.9 (5.6)	6.5 (4.5)	**<0.01**	6.7 (3.5)	0.34
CRP mean (SD)	10.0 (3.2-28.2)	4.5 (0.6-11)	**<0.01**	6.4 (2.5-18-8)	0.66
ESR mean (SD)	38.8 (26.3)	27.2 (21.3)	**0.01**	30.2 (20.2)	0.52
VAS mean (SD)	61.2 (20.9)	54.4 (24.6)	0.12	54.8 (20.6)	0.91
PGA mean (SD)	53.7 (24.4)	40.1 (22.3)	**0.03**	48.1 (21.5)	0.12
DAS28 mean (SD)	5.7 (1.2)	4.9 (1.4)	**0.01**	5.1 (1.0)	0.33
HAQ mean (SD)	10.3 (6.2)	9.0 (5.9)	0.32	7.9 (5.1)	0.37

Results are expressed as frequencies and % for categorical variables, mean and standard deviation (SD) or median and interquartile range (IQR) for quantitative variables. *p*-values were calculated using the Chi-square test for categorical variables, and the T-student and U-Man-Whitney tests for continuous variables.

**p*-value: comparison between D2TRA-inefficacy and D2TRA-other causes

§*p*-value: comparison between D2TRA-other causes and non-D2TRA.

bDMARD: biologic disease-modifying anti-rheumatic drug; BMI: Body Mass Index (kg/m^2); csDMARD: conventional synthetic disease modifying antirheumatic drug; CE: corticosteroids; MTX: methotrexate; TNFi: tumour necrosis alpha inhibitor; RF: rheumatoid factor; ACPA: anti citrullinated peptide antibody; TJC: tender joint count; SJC: swollen joint count; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; VAS: visual analogue scale-patient; PGA: patient global assessment; DAS28: Disease activity score-28; HAQ: health assessment questionnaire.

Discussion

In this study, we found that approximately 13% of our cohort met the criteria for D2TRA, of which approximately two-thirds were due to multi-drug resistance stemming from inefficacy while the remaining patients for causes other than inefficacy.

In an attempt to identify and predict those clinical characteristics that would allow us to determine which patients are most likely to develop D2TRA, we found that those with D2TRA-inefficacy and D2TRA-other presented different baseline clinical characteristics. Patients who developed multi-drug resistance during the course of the disease had a higher DAS28 at the start of b/tsDMARD compared to those who switched b/tsDMARDs for other reasons. We also found that D2TRA-inefficacy was more closely linked to a prevalence of extra-articular manifestations and shorter disease duration at b/tsDMARD initiation than D2TRA-other, which may signify that those patients have more severe disease at start of b/tsDMARDs treatment.

Since D2TRA was first defined, some studies have attempted to characterise and break down the various reasons and clinical features associated with the difficulties of managing these patients. Thus, the study carried out by Takanashi *et al*. revealed that 10% of the

patients in their cohort were D2TRA, of whom 34% were due to multidrug resistance, 10% to comorbidities and 56% to socioeconomic reasons (12). While Roodenrijs *et al*. identified 52 patients who met D2TRA criteria, 27 (52%) were so classified due to what they considered to be "true inefficacy" while the remainder were attributed to "non-inflammatory" causes (13). Differences in the frequencies of causes of D2TRA between these two studies and ours may be due to the fact that many such causes are included in the "non-inflammatory" category and it is not always easy to distinguish one from the other, which is particularly true of fibromyalgia and chronic pain.

Fibromyalgia is a prevalent feature in RA patients (14), according to different studies it ranges from 5 to 52% of the population with established RA (15). As fibromyalgia shares many symptoms with rheumatic diseases, such as pain and fatigue, these individuals frequently present a diagnostic challenge to the rheumatologist. This entity has profound implications for the management of inflammatory arthritis because non inflammatory pain may lead to unnecessary escalation of anti-rheumatic treatment (15, 16). In our study, we did not find differences in frequency of fibromyalgia between patient groups but, numerically, this percentage was higher in both subgroups of D2TRA-patients, mainly in D2TRA-other. Thus, RA patients with concomitant fibromyalgia could erroneously classify with high activity in the scores, resulting in an early switch to a b/tsDMARD, and thereby potentially accelerating refractoriness. Predictors of incident fibromyalgia among patients with RA are limited and there is need for guidance regarding the management of comorbid fibromyalgia. Nevertheless, in a recent publication by Nagy *et al*., if a patient is suspected to be D2TRA, the possibility of the presence of a concomitant mimicking disease such as fibromyalgia should be considered as first step precisely to avoid misclassification of patients (9).

When comparing the characteristics of patients with D2TRA-other causes with those who maintain a good response to treatment over a long follow-up period (non-D2TRA), in the bivariate analysis we found that only the number of previous csDMARDs was associated as a risk factor for developing D2TRA-other. The other baseline characteristics proved very similar in both groups. This led us to believe that patients with multiple drug failure due to causes other than inefficacy are not *a priori* distinguishable before starting a b/tsDMARD, from those who might show a good therapeutic response. Therefore, multi-drug resistance due to inefficacy may be easier to predict during early stages since, since as we described in a previous study, clinical features that clearly differentiate these risk factors are present in this population (5).

This is the first study that attempts to assess whether D2TRA, for reasons other than inefficacy, can be identified during the early stages; to date, previous studies have only attempted to predict those patients who will develop D2TRA overall (17-19). Thus, the importance of these findings is supported by the fact that, as has already been described, D2TRA is heterogeneous and multifactorial. In this way we can differentiate persistent inflammatory refractory RA, which presents as a lack of efficacy to multiple targeted therapies in which immunologic mechanisms, genetic/epigenetic alterations, pharmacogenetics or immunogenicity of bDMARDs are involved. In addition, it is important to note aspects of non-inflammatory persistent disease, in which factors not necessarily intrinsic to the pathophysiology of RA but rather to a patient's comorbidities, socioeconomic status, expectations, self-assessment etc., must be taken into account (7, 20). Therefore, therapeutic management in D2TRA must be approached in a different manner, depending on the underlying mechanisms. In those patients susceptible to developing multidrug resistance due to "true inefficacy", it is crucial (and arguably easier) to identify them during initial stages of treatment with b/tsDMARDs in order to tailor therapeutic strategies based on personalised medicine. On the other hand, in those D2TRA-other patients whose baseline characteristics do not *a priori* suggest that they will develop multi-drug resistance, therapeutic strategies should be more focused on a patient-centered management approach (8, 9, 21-23).

A limitation of this study could be the fact that patients who had failed only one b/tsDMARD were not included in the non-D2T group, decreasing the sample size. However, having defined the non-D2T patients as those on treatment with the same b/tsDMARD for at least 5 years, allows us to make comparisons of two clearly differentiated groups, as we did in our previous study (5).

In conclusion, this study corroborates the hypothesis that D2TRA is a heterogeneous entity in which it is easier to predict, *a priori*, those patients who will be resistant to multiple drugs from those who will switch from b/tsDMARD for different reasons. This could have important implications in terms of the initiation and monitoring of treatment in order to achieve optimal disease management.

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