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ORIGINAL RESEARCH

Patient and physician assessment in difficult-to-treat rheumatoid arthritis: patterns of subjective perception at early stages of b/tsDMARD treatment

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ABSTRACT

Objectives To analyse the trajectories of Disease Activity Score 28 (DAS28), patient global assessment (PGA) and physician global assessment (PhGA) and to assess their predictive capabilities on difficult-to-treat rheumatoid arthritis (D2TRA) classification.

Methods Longitudinal study of patients with rheumatoid arthritis (RA) from 2020 to 2022. Based on the D2TRA EULAR (European Alliance of Associations for Rheumatology) definition, patients were classified as D2TRA according to biological or targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) failure due to inefficacy (D2TRA-inefficacy) or other reasons (D2TRA-other). Patients who did not fulfil the D2TRA criteria were classified as NoD2TRA. DAS28, PGA and PhGA scores collected every 6 months during the first 24 months of b/tsDMARD treatment were used to identify different trajectories using latent class mixed models (LCMM).

Results The study population comprised 255 patients with RA, of whom 167 were NoD2TRA, 58 D2TRA-inefficacy and 30 D2TRA-other. LCMM stratified patients into two different trajectories for DAS28 and PhGA and three for PGA according to the most stable model. The most notable variation occurred during the first 6 months of treatment, thereafter remaining stable during the follow-up period. Most D2TRA-inefficacy patients fitted the trajectory, showing higher values of the studied parameters. NoD2TRA followed the trajectory with lower values, and D2TRA-other were distributed more homogeneously across all trajectories.

Conclusions The assessment of disease activity, together with patients' and physicians' perceptions, form a key element in the correct discrimination of patients who are going to develop D2TRA-inefficacy. However, identifying those patients who will be D2TRA-other remains challenging, whether by subjective or objective parameters.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Difficult-to-treat rheumatoid arthritis (D2TRA) encompasses a heterogeneous group of patients whose classification in D2TRA may be due to a multifactorial origin. One of the requirements for defining D2TRA is that the management of the disease is perceived as problematic by the physician and/or rheumatologist.

WHAT THIS STUDY ADDS

⇒ We found that from the early stages of treatment with biological or targeted synthetic disease-modifying antirheumatic drugs both physician and patient perception of the disease follow differentiated trajectories between patients with D2TRA (especially due to multidrug resistance) and those patients who do not develop D2TRA.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study contributes to the study of how the subjective perception of disease management is able to classify patients who will develop multidrug resistance due to inefficacy, so that probably within the whole group of patients with D2TRA, it is necessary to assess them separately according to the root of the difficulty of treatment.

BACKGROUND

Difficult-to-treat rheumatoid arthritis (D2TRA) is a multifactorial condition in which, for each individual patient, different factors may determine the persistence of signs and symptoms of rheumatoid arthritis (RA) that need not be due to drug resistance itself,[1 2] that ultimately results in patients being exposed to multiple lines of treatment.

In an attempt to establish a common scenario for this category of patients, the European Alliance of Associations for Rheumatology (EULAR) published a definition of D2TRA in 2020[3] comprised of three criteria: (1) treatment failure history, (2)

characterisation of active/symptomatic disease and (3) 'problematic' management of the disease as perceived by the rheumatologist and/or the patient.

Since the publication of the D2TRA definition, several studies have analysed the different reasons why patients may be difficult to treat, focusing in particular on the criterion of failure to multiple biological or targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs), which is easily traceable from medical records. Thus, two groups of patients have been distinguished: (1) those who fail multiple b/tsDMARDs due to inefficacy and persistence of inflammatory activity; and (2) those in whom other factors are at work, such as non-adherence, comorbidities, established structural damage, chronic pain syndromes. In short, non-inflammatory components predominate in this second patient group.[4–7]

However, to classify D2TRA, the third component of the definition must be fulfilled, and its predominantly subjective nature has made it difficult to evaluate being this fact is particularly evident in the case of data from patient registries. The aims of this study were: to analyse the values of patients' global assessment (PGA) and physicians' global assessment (PhGA) during the first 24 months of treatment with b/tsDMARDs as a surrogate marker of this problematic perception of disease management; and to observe their modification in order to determine whether they are capable of accurately predicting the classification of 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 (RA-Paz) University Hospital between January 2000 and December 2022.

The RA-Paz Registry is a database of all patients who have received, or who are receiving, treatment with b/tsDMARDs. This database enables rheumatologists to input clinical information on patients with RA from the very beginning of their b/tsDMARD treatment, as well as during follow-up, monitoring of clinical response and adverse events every 6 months.

Inclusion criteria were as follows: patients with RA (age ≥18 years) according to the 1987 American College of Rheumatology (ACR) or 2010 ACR EULAR classification criteria and treated with any b/tsDMARDs.

Patient classification

Based on the EULAR definition, patients who failed to achieve the treatment target with ≥2 classes of b/tsDMARDs were identified as D2TRA.[3] These patients were divided into two groups based on the reason they failed treatment: (1) those who had received ≥2 b/tsDMARDs due to inefficacy (D2TRA-inefficacy) or (2) because of adverse events, poor adherence, contraindications, comorbidities, drug intolerance, etc (D2TRA-other). This classification was based on a preliminary study where we observed that these two groups of patients with D2TRA exhibited sufficient differences that precluded their being analysed together.[7]

On the other hand, patients who did not fulfil the D2TRA criteria, according to the EULAR definition, were classified as NoD2TRA. In this group, we included patients who experienced low disease activity or remission (assessed by Disease Activity Score 28 -DAS28) with the first b/tsDMARD, or those who failed just one b/tsDMARD and continued with the same drug for at least 5 years.

Data collection

For all patients, the following data were collected just prior to start the first b/tsDMARD: demographic characteristics (age, sex, body mass index and smoking habit), age at diagnosis of RA, age at starting b/tsDMARD, previous and concomitant treatments (glucocorticoids and conventional synthetic), laboratory parameters, extra-articular manifestations and bone erosions. DAS28, PGA and PhGA were collected at the start of b/tsDMARD treatment and every 6 months during the 2 years following enrolment. This was done to ensure that data of sufficient granularity was obtained to accurately identify temporal changes in disease activity and patient's or physician's perception. PGA and PhGA were collected using a 0–100 mm Visual Analogue Scale (0=very good health status and 100=very bad).

Statistical analysis

Descriptive analysis are presented for categorical variables as frequencies and percentages, and for continuous variables as mean and SD.

Missing values were imputed using proximity from random forest, included in r-package random Forest V.4.7–11.[8]

Longitudinal analysis of DAS28, PGA and PhGA were performed by fitting a mixed-effects logistic regression that compared NoD2TRA versus D2TRA-inefficacy patients and NoD2TRA versus D2TRA-others. These analyses were carried out using lme4 V.1.1–34.[9]

In order to identify different trajectories during the first 24 months of follow-up for DAS28, PGA and PhGA, latent class mixed models (LCMM) were adjusted using linear link function, which is included in r-package LCMM V.2.0.0.[10] For each of these three parameters, LCMM were fitted taking into account the number of classes between 2 and 10. In all cases, the most suitable model was selected as that with the lowest value for the Bayesian information criterion (BIC). (online supplemental figure 1).

Univariate and multivariate multinomial logistic models were used to assess independent risk factors for becoming patients with D2TRA, included in r-package MASS V.7.3–58.2.[11] To avoid collinearity in the multivariate model fitting, we discarded all variables with an overall variance inflation factor (VIF) greater than 10.

RESULTS

Patient classification

In total, 255 patients with RA from the RA-Paz Registry treated with b/tsDMARDs and fulfilling the inclusion

criteria were included, of whom 167 were NoD2TRA, 58 were D2TRA-inefficacy and 30 D2TRA-other.

Demographic and clinical characteristics of the RA-Paz cohort

Of the total patients included, 82.4% were women with a mean age of 64.5 (12.2) years. Age at b/tsDMARD initiation was slightly younger in the D2TRA-inefficacy group than in the D2TRA-other or NoD2TRA groups (table 1). Mean time under b/tsDMARD in the entire cohort was 11.8 (5.1) years, which was higher in the D2TRA-inefficacy and NoD2TRA groups than in D2TRA-others. DAS28 values at the start of b/tsDMARDs treatment were higher in D2TRA-inefficacy 5.7 (1.2), as were PGA and PhGA, which measured 57.9 (22.4) and 52.3 (23.9), respectively (see table 1). Most of patients in D2TRA and NoD2TRA groups were treated at starting b/tsDMARD with tumor necrosis factor inhibitor (TNFi); for patients with D2TRA, frequencies and percentages of second b/tsDMARD prescription after failure to first b/tsDMARD are described in online supplemental table 1.

Assessment of parameter trajectories studied for patients

LCMM helped stratify patients according to longitudinal data on DAS28 (two classes), PGA (three classes) and PhGA (two classes). Taking into account their heterogeneity (figure 1), most suitable models were comprised of a number of classes determined by the lowest value of the BIC (online supplemental figure 1). The evolution of DAS28, PGA or PhGA during the first 2 years did not represent risk factors for patients response to treatment (online supplemental table 2).

For all parameters studied, the most notable variation occurred during the first 6 months following the onset of b/tsDMARD treatment, remaining stable thereafter during the established follow-up period.

Considering the differences in the distribution of treatment response between the classes and the fact that the different classes behave differently from baseline and especially at the 6-month measurement, these time points for the analysed characteristics were assessed as risk factors. The results of the univariate models revealed that the baseline and 6-month values of PhGA and DAS28 and PGA at 6 months were risk factors. All of these were used to fit a multivariate model to detect independent predictors. In this process, variables with VIF >10 were removed, so PGA and PhGA at 6 months turned out to be independent risk factors to differentiate NoD2TRA patients from D2TRA-inefficacy patients, (table 2).

Trajectories for DAS28

The evolution of DAS28 during the first 24 months of treatment showed the existence of two clear subpopulations: the so-called class-1 and class-2. Of the total number of patients analysed, 81% were classified as class-2, which was the one that showed lower DAS28 values during the entire trajectory. Meanwhile, class-1 consisted of 19% of the patients and corresponded to the highest DAS28 values. Class-1 contained the largest proportion of patients with D2TRA-inefficacy (50%) and class-2 contained a higher proportion of NoD2TRA (72.1%) (figure 1A–C).

Trajectories for PGA

By the same token, three latent classes were observed for PGA. PGA-class 1 contained 34.4% of patients with the highest PGA levels, of whom the greatest proportion were D2TRA-inefficacy patients (48.3%). PGA-class 2 consisted of 52.7% of patients and exhibited the lowest PGA levels, with a majority of them being NoD2TRA patients (77.9%). It is worth considering that class 3 may represent kind of a grey zone, representing 12.8% of patients who started with high levels of PGA. This group showed a greater change and a more pronounced decrease in the patients' perception of their disease. Even though this group consists mainly of NoD2TRA patients (59%), it contains a relevant proportion of D2T-inefficacy patients (27.7%) (figure 1D–F).

Trajectories for PhGA

Finally, latent classes for PhGA look pretty similar to subpopulations detected for DAS28. PhGA-class-1 contained 19.1% of patients and had the higher values since the baseline measures, a tendency that was maintained. In this class, 55.6% of patients were classified as D2TRA-inefficacy. However, PhGA-class-2 consisted of 88.8% of patients, who exhibited lower values of PhGA and contained almost 70.6% of NoD2TRA patients (figure 1G–I).

The distribution of overall patients in the different classes, as well as the intraclass distribution according to the D2TRA-inefficacy, D2TRA-others and NoD2TRA status are presented in figure 1D–I. There, it can be observed that the distributions of D2TRA-inefficay and NoD2TRA are more differentiated among the different classes than D2TRA-others, which follows a more homogeneous distribution pattern, making it impossible to a priori classify these patients as largely belonging to different classes. The median and IQRs at each time point for the resulting subpopulations, based on the longitudinal patterns of these three parameters, are depicted in figure 2.

DISCUSSION

The third point of the definition of patients with D2TRA has a large subjective component that is not only associated with activity indexes such as drug inefficacy. This study has therefore focused on analysing the evolution of clinical practice data reported by the patients and physicians during the first years under b/stDMARD treatment and comparing the results of D2TRA and NoD2TRA patients using a statistical model based on LCMM.

Different trajectory patterns were identifiable and emerged within a few months of treatment initiation. All trajectories followed a similar profile, with an initial change (at 6 months) in DAS28, PGA and PhGA, followed

Table 1 Demographic characteristics of the total cohort

Variables	Total (n=255)	Non-D2TRA (n=167)	D2TRA (n=88)	
			D2TRA-inefficacy (n=58)	D2TRA-others (n=30)
Age, mean (SD)				
Current	64.5 (12.2)	64.8 (12.2)	64.9 (11.6)	61.9 (12.7)
At diagnosis	42.9 (13.2)	43.3 (13.5)	42.3 (12.4)	41.8 (13.1)
At start of b/tsDMARD	52.2 (12.0)	53.1 (12.1)	49.9 (11.8)	51.9 (11.5)
Sex (female), n (%)	210 (82.4)	139 (83.2)	50 (86.2)	24 (80.0)
BMI, mean (SD)	26.4 (5.0)	26.1 (4.3)	27.0 (5.8)	27.8 (6.5)
Smoking habit, n (%)				
Smokers	45 (17.6)	24 (14.6)	14 (24.1)	7 (23.3)
Ex-smokers	76 (29.8)	51 (30.5)	16 (27.6)	9 (30.0)
Never smokers	134 (52.5)	92 (55.1)	28 (48.3)	24 (80.0)
Comorbidities, mean (SD)	1 (0–2)	1 (1–2)	1 (0–1)	1 (1–2)
Fibromyalgia, n (%)	41 (16.1)	26 (15.6)	8 (13.8)	7 (23.3)
Erosions, n (%)	91 (35.7)	50 (29.9)	31 (53.4)	10 (23.3)
Extra-articular manifestations, n (%)	39 (15.3)	23 (13.8)	13 (22.4)	7 (10.0)
Time between diagnosis and starting bDMARD, mean(SD)	8.8 (8.1)	9.2 (8.0)	7.1 (7.2)	9.6 (9.7)
Total time under bDMARD, mean (SD)	11.8 (5.1)	11.3 (4.8)	14.4 (4.8)	9.6 (5.6)
Current CE, n (%)	231 (90.6)	156 (93.4)	58 (100)	27 (94.4)
Current MTX, n (%)	209 (82.0)	138 (82.6)	48 (82.8)	23 (76.7)
First bDMARD, n (%)				
TNFi	217 (85.1)	138 (82.6)	54 (93.1)	25 (83.4)
Non-TNFi	38 (14.9)	29 (17.4)	4 (6.9)	5 (16.6)
IL6i	20 (7.9)	14 (8.4)	3 (5.2)	3 (10.0)
Abatacept	9 (3.5)	8 (4.8)	1 (1.7)	0 (0)
Rituximab	8 (3.1)	7 (4.2)	0 (0)	1 (3.3)
JAKi	1 (0.4)	0 (0)	0 (0)	1 (3.3)
Immunological parameters, n (%)				
RF+	218 (85.5)	145 (86.8)	50 (86.2)	23 (82.1)
ACPA+	208 (81.6)	139 (83.2)	49 (84.5)	20 (71.4)
TJC mean (SD)	8.6 (6.5)	7.6 (5.7)	11.7 (7.4)	7.9 (7.7)
SJC mean (SD)	7.5 (4.9)	7.1 (4.4)	9.1 (5.9)	7.1 (5.4)
CRP mean (SD)	6.2 (2.6–16.6)	5.4 (2.6–14.4)	8.1 (3.1–28.2)	5.2 (1.4–15.2)
ESR mean (SD)	31.6 (19.8)	30.4 (19.1)	36.9 (21.0)	28.4 (21.1)
PGA mean (SD)	52.9 (23.1)	51.6 (22.4)	57.9 (22.4)	51.2 (27.4)
PhGA mean (SD)	49.0 (21.8)	49.1 (20.7)	52.3 (23.9)	43.1 (23.2)
DAS28 mean (SD)	5.2 (1.2)	5.0 (1.0)	5.7 (1.2)	5.1 (1.5)
HAQ mean (SD)	9.5 (5.3)	8.9 (5.1)	11.6 (5.4)	9.6 (6.1)

Results are expressed as frequencies and % for categorical variables, mean and SD or median and IQR for quantitative variables.
ACPA, anti-citrullinated peptide antibody; BMI, body mass index (kg/m^2); b/tsDMARD, biological and/or targeted synthetic disease-modifying antirheumatic drug; CE, corticosteroids; CRP, C-reactive protein; DAS28, Disease Activity Score 28; D2TRA, difficult-to-treat rheumatoid arthritis; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; IL6i, interleukin 6 inhibitor; JAKi, Janus kinase inhibitor; MTX, methotrexate; PGA, patient global assessment; PhGA, physician global assessment; RF, rheumatoid factor; SJC, swollen joint count; TJC, tender joint count; TNFi, tumour necrosis factor inhibitor.

by a plateau phase during which these scores remained stable. Class-2 contained the vast majority of NoD2TRA patients, while class-1 contained the higher proportion of D2TRA-inefficacy, in which the levels of the analysed parameters were higher compared with the baseline measures. Thus, in this study we demonstrate that these

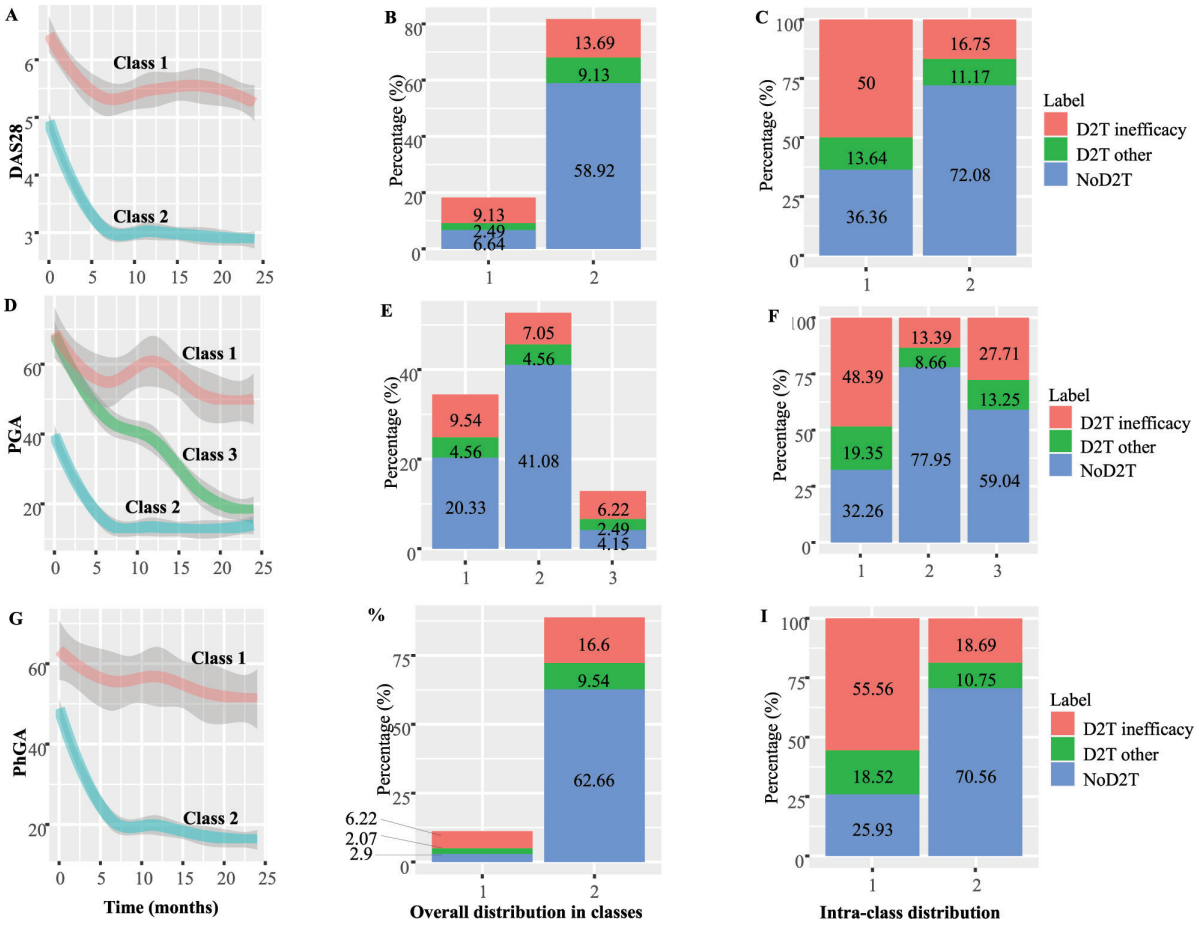

Figure 1 Shows the different trajectory plots for the DAS28 (A), PGA (D) and PhGA (G) classes. Overall patients distribution according to the different classes: DAS28 (B) PGA (E) and PhGA (H); intra-class distribution of patients for DAS28 (C), PGA (F) and PhGA (I). DAS28, Disease Activity Score 28; PGA, patient global assessment; PhGA, physician global assessment.

parameters do, by themselves, show predictive power for stratifying patients according to their treatment response. In addition, our results show that the responses observed at 6 months are representative of long-term outcomes.

These results are in line with other studies showing that the initial response to treatment can condition a patient's later response and can be maintained over time. For example, in a study carried out on patients who initiated treatment with TNFi, the different trajectories of response identified at 6 months proved to be indicative of future outcomes.[12] Other studies have found that the level of disease activity at baseline and especially during

Table 2 Results from univariate and multivariate multinomial logistic regression

	Univariate						Multivariate					
	NoD2TRA vs D2TRA-inefficacy			NoD2TRA vs D2TRA-other			NoD2TRA vs D2TRA-inefficacy			NoD2TRA vs D2TRA-other		
Predictor	OR	CI	P value	OR	CI	P value	OR	CI	P value	OR	CI	P value
DAS28 baseline	1.74	1.32 to 2.30	<0.001	0.94	0.66 to 1.33	n.s.	–	–	–	–	–	–
DAS28 6 months	1.8	1.42 to 2.28	<0.001	1.5	1.12 to 1.99	<0.01	–	–	–	–	–	–
PGA baseline	1.01	0.998 to 1.03	n.s.	1.002	0.99 to 1.02	n.s.	–	–	–	–	–	–
PGA 6 months	1.03	1.02 to 1.04	<0.001	1.02	1.01 to 1.04	<0.05	1.02	1.003 to 1.04	<0.05	1.007	0.99 to 1.03	n.s.
PhGA baseline	1.02	1.001 to 1.03	<0.05	0.99	0.97 to 1.01	n.s.	–	–	–	–	–	–
PhGA 6 months	1.04	1.02 to 1.05	<0.001	1.03	1.01 to 1.05	<0.01	1.02	1.01 to 1.04	<0.05	1.02	0.999 to 1.05	n.s.

DAS28, Disease Activity Score 28; D2TRA, difficult-to-treat rheumatoid arthritis; n.s., non significant; PGA, patients global assessment; PhGA, physicians global assessment.

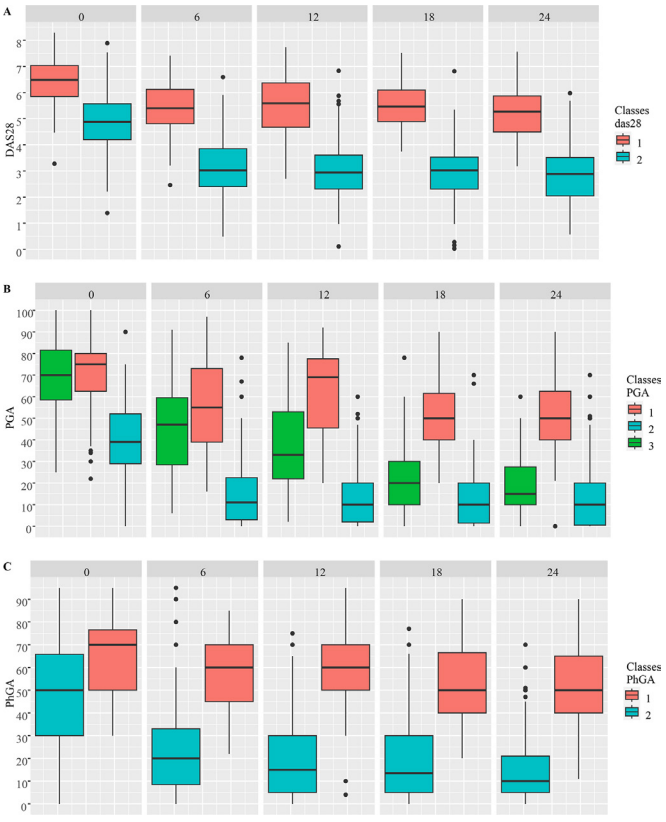

Figure 2 Median and IQR of all parameters studied in each point of follow-up for different classes. DAS28, Disease Activity Score 28; PGA, patient global assessment; PhGA, physician global assessment.

the first 3 months of treatment is significantly related to the level of disease activity at 1 year.[13 14] However, to date there has been no study that accounts for the combination of possible trajectories that activity parameters may follow in unison with disease the perception parameters provided by patient and physician assessments.

In a previous study conducted by our group, we observed that baseline and 6-month DAS28 values were able to correctly classify 87.5% of patients with multiple biological failures, as well as 94.1% of patients with a good response to the first b/tsDMARD (AUC 0.89, 95% CI 0.74 to 1.00). The use of this composite index during the early stages of treatment with b/tsDMARDs provides an objective measurement that is able to not only predict the outcome of multidrug failure, but also to discriminate between D2TRA-inefficacy patients vs good responders.[15]

With regard to our previous data,[7 15] in this study we have modified the inclusion criteria for the NoD2TRA group, including those patients who responded well to the first b/tsDMARD and those who failed a line of treatment, but who did not meet the D2TRA definition. Likewise, by using a different statistical model, we corroborated that DAS28 is a robust classification measure for assessing multiple drug failure, taking into account these subgroups of patients. This was shown by the two very different trajectories observed with DAS28, not only at baseline and 6 months, but also over a longer follow-up time.

On the other hand, and in response to the main aim of the study, PGA and PhGA values have similarly proven to be important in classifying patients into D2TRA-inefficacy versus NoD2TRA, providing an additional assessment that complements and is in line with what has already been described by DAS28 values.

In the case of PGA, we see that there are three classes, two of which are very differentiated and in which the 'worst' class includes those patients who are more likely to be part of the D2TRA-inefficacy group and the 'best' class those who are likely to be NoD2TRA. This was to be expected, since PGA is included in the DAS28 index although it carries relatively little weight compared with that of tender joint count, swollen joint count and erythrocyte sedimentation rate.[16] Another component that was added to this study is the physician's perception of the patient's disease, which can be observed in the two different trajectories, and which is also in line with DAS28. This means that in terms of both activity (for which we have parameters that can be measured objectively) and patient and physician perceptions of the disease, there are similar trajectories that are without any discordance in the categories considered.[17]

Although other indexes such as Clinical Disease Activity Index (CDAI) or Simplified Disease Activity Index (SDAI) are used to assess disease activity and include in their calculation the PGA and/or PhGA components.[17] We used DAS28 in our study because it is the index of choice in the definition of D2TRA, referring to persistent disease activity in the second criterion (DAS28>3.2).[3 18] DAS28, CDAI and SDAI have a good correlation when it comes to the assessment of disease activity. Probably, using these other indices and taking into account the established cut-off points for considering moderate disease activity (equivalent to DAS28>3.2), this criterion for persistent activity would not differ significantly.

As for the D2TRA-other patients, in a previously published study we were unable to predict their evolution using the baseline characteristics during the first 6 months.[7] Therefore, in this study we also considered it important to analyse the trajectories of the clinical variables over 2 years. This would allow us to corroborate whether by following these patients for a longer period of time we could find some reference value to better identify them. However, we have come to the realisation that these outcomes are not predictable and do not follow a clearly identifiable trajectory, as opposed to what occurs among the NoD2TRA and D2TRA-inefficacy patients.

The third criterion of the D2TRA definition encompasses a diverse spectrum of patient circumstances adding to the complexity of RA. Thus, these components will probably have to be refined in the future in order to tighten the definition, thereby facilitating a more objective approach that allows clinicians to better assess the issue of 'problematic perception' when managing RA.[1 19] However, these results raise the possibility that

both PGA and PhGA could act as surrogate markers of problematic disease management. In fact, these data can be easily extracted from the retrospective registries, and help characterise patients with D2TRA early on and with greater clarity, especially those with D2TRA-inefficacy.[20]

Our study is not without limitations. First, the heterogeneity of patients with D2TRA means that we have to consider a distinction between the D2TRA-inefficacy and D2TRA-other groups, which means we must contend with smaller sample sizes for these subpopulations. Nevertheless, the heterogeneity of patients with D2TRA is shown by the different cohorts of patients that have been studied. We chose PGA and PhGA because we considered them to be widely used determinations, although other markers can be taken into account when performing such analyses. In contrast, this is the first study that has attempted to provide an objective measure of the third point of the definition of D2TRA. It may therefore represent the first step towards a nuanced understanding and treatment of these challenging patient groups.

In conclusion, the evolution of DAS28, PGA and PhGA follow different trajectories during the first 2 years of treatment with b/tsDMARDs, reflecting the classification of patients into D2TRA and NoD2TRA groups. So that, the assessments of the disease made by physicians and the patients, in tandem with the activity indexes, are a key element to correctly discriminating those patients who are going to present multidrug failures due to inefficacy from those who are good responders. However, attempting to identify, a priori, those patients who will be D2TRA for reasons other than inefficacy remains difficult, whether by subjective or objective parameters.

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Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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