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# Evolution from early to difficult-to-treat rheumatoid arthritis: incidence and risk factors in the ERA uclouvain Brussels cohort

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## Abstract

**Background** Despite an increasing number of targeted and biological disease-modifying anti-rheumatic drugs (ts or bDMARDs), a significant number of Rheumatoid Arthritis (RA) patients are refractory to multiple lines of treatments. The definition of Difficult-to-treat (D2T) RA patients has been proposed to harmonize research on this condition. While data on D2T in established RA are emerging, this is the first study to specifically address the evolution from early disease (ERA) to D2T-RA. To identify early clinical, laboratory, and radiographic predictors of progression from early rheumatoid arthritis to difficult-to-treat RA over a five-year follow-up.

**Methods** This was a retrospective monocentric cohort study of DMARD-naïve ERA patients (symptom duration ≤ 12 months), enrolled between 2010 and 2019. Patients were followed for 5 years with data collection at baseline, 6, 12, 36, and 60 months. The primary outcome was the development of D2T-RA, defined according to EULAR 2021 criteria. Baseline analyzed variables included clinical features, serology, radiographic damage, disease activity scores, patient-reported outcomes (PROs) and demographic features. Associations between baseline variables and D2T status were evaluated using univariate and multivariate logistic regression analyses.

**Results** We included 391 ERA patients [M/F 109/282, median age 48.2 years IQR (21.26)]. After 5 years, forty-one patients (10.5%) matched the D2T definition. A higher baseline radiographic damage, seropositivity, and baseline disease activity characterized these patients. Only radiographic damage was confirmed as an independent factor for progression to D2T-RA in a multivariate analysis [OR = 2.38 CI (1.09–5.54); $p = 0.03$]. During the follow-up, disease activity was consistently higher in the D2T group. D2T patients were exposed to a higher dose of glucocorticoids and more commonly suffered from infections and osteoporosis.

**Conclusions** Baseline radiographic damage, seropositivity, and high disease activity represent the major risk factors for the evolution from ERA to D2T-RA. Disease activity indices were consistently higher in D2T patients all along the five-year follow-up. In addition, D2T patients received higher GC doses and more commonly developed disease and treatment-related comorbidities.

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**Keywords** Difficult to treat rheumatoid arthritis, Rheumatoid Arthritis, D2T-RA, Early-RA, Predictors, Radiographic damage

## Background

Rheumatoid Arthritis (RA) is a chronic autoimmune disease that potentially leads to irreversible disability and joint damage [1]. Its prognosis has been deeply improved thanks to the development of biological disease-modifying anti-rheumatic drugs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs) [2]. According to the European Alliance of Associations for Rheumatology (EULAR) guidelines, together with the treat-to-target (T2T) approach, treatment should be tailored to reach disease remission or at least a low-disease activity (LDA) [3, 4]. Despite this approach, some RA patients do not reach disease control after failing multiple lines of targeted therapies [5–8]. These patients are exposed to long-term moderate or high disease activity, more drug toxicities, and higher glucocorticoid exposure [9, 10].

Recently, an EULAR Task Force defined the concept of "*difficult-to-treat*" Rheumatoid Arthritis (D2T-RA) as patients with persistent active disease despite being treated with at least two b/tsDMARDs with different mechanisms of action (MoA) [11]. This definition includes up to 20% of established RA patients with a significant socio-economic burden [12, 13].

Most studies to date have focused on cross-sectional analyses of patients with established D2T-RA, while little is known about the early factors that predispose patients with early rheumatoid arthritis (ERA) to progress to a difficult-to-treat phenotype.

Identifying early predictors at disease onset could facilitate the identification of patients at risk for D2T-RA and inform more personalized therapeutic strategies.

Therefore, this study aimed to analyse a large cohort of ERA patients to identify baseline factors—including clinical characteristics, laboratory markers, radiographic features, disease activity, and patient-reported outcomes (PROs)—associated with progression to D2T-RA over a 5-year follow-up period.

## Methods

We performed a retrospective monocentric cohort study. Between 2010 and 2019, patients ≥ 18 years old with an RA diagnosis according to the 2010 ACR/EULAR Criteria and with symptoms onset ≤ 12 months [Early-RA (ERA)] were included. Only patients with a minimum follow-up of five years were enrolled. All patients were disease-modifying anti-rheumatic drug (DMARDs) naïve. ERA patients were treated according to international guidelines, with remission or low disease activity as the target. Data were collected for a total follow-up of five years. During each evaluation as part of the routine clinical practice, the disease activity was recorded, including the tender and swollen joint count 28 (TJC28/SJC28), the disease activity score 28 joints (DAS28), the simplified disease activity index (SDAI), and clinical disease activity index (CDAI). Moreover, patients reported outcomes (PROs) as the VAS for patient global assessment (VASp), fatigue (VASf), and pain (VASpain) on a 0 -100 scale, together with the Health Assessment Questionnaire (HAQ) on a 0–3 scale, were obtained from each patient. The physician's global assessment (VASm) was also recorded. Hands and feet plain X-rays were performed at baseline for each patient to detect radiographic damage as a binary variable (Yes/No) including bone erosions (BE) and/or joint space narrowing (JSN). At each time point, treatment [glucocorticoid dose (Prednisone mg/day equivalent dose), classical DMARDs(cDMARDs), biological DMARDs (bDMARDs), and target synthetic DMARDs (tsDMARDs)], comorbidities (hypertension, diabetes, osteoporosis, and osteoporotic fractures) and severe infections leading to hospitalization were recorded. Data were collected at baseline, 6, 12, 36, and 60 months.

### Outcome of the study

The primary outcome of the study was the development of difficult-to-treat RA (D2T-RA) in a five-year follow-up, defined by fulfillment of the EULAR criteria at any follow-up time point. Secondary outcomes included the longitudinal evaluation of disease activity, cumulative glucocorticoid exposure, and the incidence of comorbidities and infections.

### D2T definition

At each time point, each patient was defined as D2T when fulfilling the recently proposed criteria [11]. In particular, each patient needs to respect all three criteria reported below:

1. Treatment according to EULAR recommendation and failure of ≥ 2 b/tsDMARDs (with different mechanisms of action) after failing csDMARD therapy (unless contraindicated).
2. Signs suggestive of active/progressive disease, defined as ≥ 1 of (a) at least moderate disease activity; (b) signs and/or symptoms suggestive of active disease; (c) Inability to taper glucocorticoid treatment below 7.5 mg/day prednisone; (d) Rapid radiographic progression (with or without signs of active disease); (e) RA symptoms that are causing a reduction in quality of life.

3. The management of signs and/or symptoms is perceived as problematic by the rheumatologist and/or the patient.

Patients fulfilling the D2T-RA criteria at any time point during the 5-year follow-up were included in the D2T-RA group. This study was performed in line with the principles of the Declaration of Helsinki and was approved by the local Ethics Committee.

### Statistical analysis

Descriptive statistics of clinical, demographic, and clinical characteristics, as well as disease activity and treatments, were reported as frequency (for qualitative variables) or as the mean ± SD or median (IQR) (for quantitative variables). To assess normality, the Shapiro-Wilk test and the Kolmogorov-Smirnov test were performed. A T-test was used for the comparison of normally distributed continuous variables. Variables with non-normal distribution were compared with the Mann-Whitney or the Kruskal-Wallis test. Fisher's test or $\chi^2$ was used for categorical variables. The Hodges–Lehmann method was used to estimate median differences between groups with 95% confidence intervals for non-normal variables. A multivariate logistic regression model was employed to assess the influence of baseline variables on the likelihood of being classified as D2T RA. The selection of variables for inclusion in the model was based on their statistical significance ($p$-value < 0.10) in the univariate analyses (Table 1): disease activity (DAS28CRP), seropositivity (ACPA and/or RF), the presence of baseline radiographic damage, and sex were considered. To avoid multicollinearity, composite indices (such as CDAI and SDAI) and individual components of DAS28 (e.g., TJC28, VAS) were not included in the final model. Analysis was performed with GraphPad 9.0 and SPSS 26.0.

## Results

We included 391 ERA patients [M/F 109/282, median age 48.2 years IQR (21.26)]. In a five-year follow-up, 41 patients (10.5%) matched the definition of D2T.

### Baseline

When comparing D2T and non-D2T patients (Table 2), the former were characterized by a higher prevalence of Rheumatoid Factor (RF) and anti-citrullinated peptide antibodies (ACPA), and higher baseline disease activity assessed with SDAI and CDAI, while a statistical tendency was observed for DAS28 (Table 2). Moreover, a significantly higher rate of baseline radiographic damage (70.7% *versus* % 46; $p = 0.003$) characterized those patients. The patient's and physician's disease evaluations according to the Visual Analogical Scale (VAS) for disease activity, pain, and fatigue were similar between groups.

### Objective measures of disease activity

During the 5-year follow-up, the disease activity (DAS28, CDAI, SDAI) was consistently higher in the D2T group (Fig. 1A-C; Supplementary Table S1). While at baseline the difference was minimal, from six months on we observed a consistent and stable difference.

To assess which items of the composite disease activity indices drove the persistently higher disease activity in D2T patients, we have individually analyzed each element that makes up the composite indices of disease

**Table 1** Predictors of D2T-RA

| | Univariate | | Multivariate | |
|---|---|---|---|---|
| | **OR (95% CI)** | ***p*-Value** | **OR (95% CI)** | ***p*-Value** |
| Baseline Erosions | 2.82 (1.42–5.91) | **0.004** | 2.35 (1.13–5.41) | **0.02** |
| ACPA and/or RF | 3.20 (1.24–10.91) | **0.03** | 2.85 (0.94–12.4) | 0.09 |
| Male Sex | 1.33 (0.65–2.61) | 0.44 | 1.72 (0.80–3.6) | 0.15 |
| TJC28 | 1.04 (1.003–1.09) | **0.03** | - | - |
| SJC28 | 1.03 (0.97–1.09) | 0.19 | - | - |
| CRP (mg/dL) | 1.05 (0.96–1.12) | 0.22 | - | - |
| VASm | 1.01 (1.001–1.03) | **0.03** | - | - |
| VASp | 1.007 (0.99–1.02) | 0.31 | - | - |
| VAS Pain | 1.005 (0.99–1.02) | 0.46 | - | - |
| VAS fatigue | 1.008 (0.99–1.02) | 0.22 | - | - |
| HAQ | 1.63 (1.04–2.62) | **0.03** | 1.65 (0.90–3.06) | 0.10 |
| DAS28 | 1.23 (0.97–1.58) | 0.08 | 1.07 (0.79–1.47) | 0.64 |
| CDAI | 1.03 (1.004–1.05) | **0.01** | - | - |
| SDAI | 1.03 (1.005–1.05) | **0.01** | - | - |

Simple Logistic Regression and Multivariate Logistic Regression Analysis. **TJC28/** Tender Joint Count 28; **SJC28** = Swollen Joint Count 28; **CRP** = C-Reactive Protein; **HAQ** = Health Assessment Questionnaire; **DAS28** = Disease Activity Score 28 Joints; **CDAI** = Clinical Disease Activity Index; **SDAI** = Simplified Disease Activity Index; **ACPA** = anti-Citrullinated Protein Antibodies; **RF** = Rheumatoid Factor **VASp** = Visual Analog Scale patient; **VASm** = Visual Analog Scale physician; **VASf** = Visual Analog Scale for fatigue; **VASp** = Visual Analog Scale for pain; **Radiographic damage** = Presence of Bone Erosions and/or Joint Space Narrowing; **OR** = Odd Ratio

**Table 2** Baseline cohort features

| | D2T (*n* = 41) | No-D2T (*n* = 350) | *p* | Difference Between Means [95% CI] |
|---|---|---|---|---|
| | *N* (%) | | | |
| Age (Mean ± SD) | 44.09 ± 12.12 | 47.11 ± 14.98 | 0.23 | -3.02 ± 2.5 [-7.9 to 1.9] |
| Male | 14 (34.1) | 98 (19.8) | 0.46 | - |
| ACPA | 35 (85.4) | 232 (66.4) | 0.01 | - |
| RF | 34 (82.9) | 222 (63.6) | 0.01 | - |
| Seropositivity (ACPA and/or RF) | 37/41 (90.2) | 260/350 (74.3) | 0.02 | - |
| Duration of symptoms before diagnosis (months, IQR) | 4.24 (5.96) | 4.80 (5.96) | 0.95 | - |
| Radiographic damage | 29 (70.7) | 161 (46) | 0.003 | - |
| | Median (IQR) | | | Median Differences [95% CI] |
| TJC28 | 8 (12) | 6 (6) | 0.09 | 2.0 [0 to 4] |
| SJC28 | 6 (10) | 6 (6) | 0.66 | 0 [-2.0 to 2.0] |
| CRP (mg/dL) | 2 (3.5) | 1.24 (2.5) | 0.12 | 0.76 [-0.1 to 1.0] |
| HAQ | 1.5 (1.2) | 1.125 (0.05) | 0.05 | 0.25 [0 to 0.5] |
| $DAS28_{CRP}$ | 5.38 (2.54) | 4.78 (1.91) | 0.06 | 0.51 [-0.02 to 1.03] |
| CDAI | 27.8 (27.2) | 22.15 (17.9) | 0.04 | 5.6 [0.2 to 11.2] |
| SDAI | 31.7 (30.2) | 24.7 (19.8) | 0.02 | 6.9 [0.9 to 13] |
| VASp | 69 (30) | 60 (40) | 0.24 | 5 [-3 to 14.0] |
| VASm | 51.5 (40) | 44 (30) | 0.06 | 10 [0 to 19.0] |
| VASf | 69.5 (40.75) | 60 (50.75) | 0.25 | 6 [-4 to 17.0] |
| VASpain | 71.5 (41.25) | 66 (41) | 0.41 | -4.0 [-5 to 14.0] |

Comparison between D2T and No-D2T groups. *P* values refer to Mann-Whitney and Fisher's when appropriate. Hodges–Lehmann estimator applied for median differences between groups. **D2T** = Difficult-to-treat; **TJC28** = Tender Joint Count 28; **SJC28** = Swollen Joint Count 28; **CRP** = C-Reactive Protein; **HAQ** = Health Assessment Questionnaire; **DAS28** = Disease Activity Score 28 Joints; **CDAI** = Clinical Disease Activity Index; **SDAI** = Simplified Disease Activity Index; **ACPA** = anti-Citrullinated Protein Antibodies; **RF** = Rheumatoid Factor **VASp** = Visual Analogue Scale for patient global assessment; **VASm** = Visual Analogue Scale for physician global assessment; **VASf** = Visual Analogue Scale for fatigue; **VASp** = Visual Analogue Scale for pain; **Radiographic damage** = Presence of Bone Erosions and/or Joint Space Narrowing

activity (TJC28, SJC28, CRP). The results are represented in Fig. 2. After 6 months onwards D2T had a significantly higher number of TJC28 and SJC28, while the CRP levels did not differ across the timepoints.

### Patient reported outcomes (PROs) and physician disease activity assessment

As for the TJC28 and SJC28, the difference between the groups in terms of PROs and Physician VAS evaluation was evident across the 5-year evaluation (Fig. 3). Specifically, at 6 months (M), 36 M, and 60 M D2T patients had higher VASp, VASm, and VASpain. VASf did not statistically differ between the two groups except for the 36 M evaluation. The HAQ difference between the two groups has increased in a time-dependent manner, mainly linked to a decrease in No-D2T compared to the stable values in D2T.

### bDMARDs prescription sequence in D2T-RA

The prescription sequence is summarized in Fig. 4. Twenty-three patients (56%) were treated with 2 bDMARDs, ten (24.4%) with 3 bDMARDs, four (7.8%) with 4 bDMARDs, and the remaining four with 5 (9.7%) bDMARDs. Tumour Necrosis Factor inhibitors (TNFi) were the most prescribed treatment as the first bDMARD in 21 patients (51.2%), followed by anti-IL-6R (9 patients, 21.9%), abatacept (7 patients, 17.1%), and Janus Kinase inhibitors (JAKi) (4 patients, 9.7%). As second-line bDMARDs, TNFi was again the most prescribed treatment (23 patients, 56%), while 10 patients (24.4%) received Rituximab, and the remaining were treated by JAKi and anti-IL6R (both 4 patients, 9.7%).

### Patients failing two bDMARDs with the same MoA

As a supplementary analysis, we compared the D2T Cohort with the patients treated with 2 bDMARDs with the same mechanism of action (MoA), hence not fulfilling the strict definition of D2T-RA. Sixteen patients were treated with two TNFi and one with two anti-IL6. The two cohorts were similar, including the baseline and the follow-up evaluation. No statistical difference emerged in disease activity and PROs between the two groups (Supplementary Table S2).

### Predictors of D2T evolution

We explored the potential role of discriminant variables [baseline radiographic damage, sex, seropositivity, disease activity ($DAS28_{CRP}$), and HAQ] as predictors of evolution toward a D2T profile. Table 1 reports complete data. Variables that differed between D2T and non-D2T ($p < 0.10$) were included in a logistic regression model: baseline radiographic damage, ACPA and/or RF, HAQ, and DAS28. Only the presence of radiographic damage at baseline was confirmed as a strong independent factor of D2T progression in the multivariate analysis [OR = 2.35 CI (1.13–5.41); $p = 0.025$].

### Comorbidities during follow-up

After five years of follow-up, the number of infections was higher in the D2T patients (51.2% versus 27.5%; $p = 0.0015$) as well as osteoporosis (25% versus 8.1%; $p = 0.005$). Moreover, they were exposed to a higher cumulative dose of glucocorticoids [> 1 gram] (52.5% versus 35.5%; $p = 0.035$) while only a tendency emerged for severe infection [requiring hospitalization and/or IV therapy] (12.2% versus 8.3%; $p = 0.08$). No difference

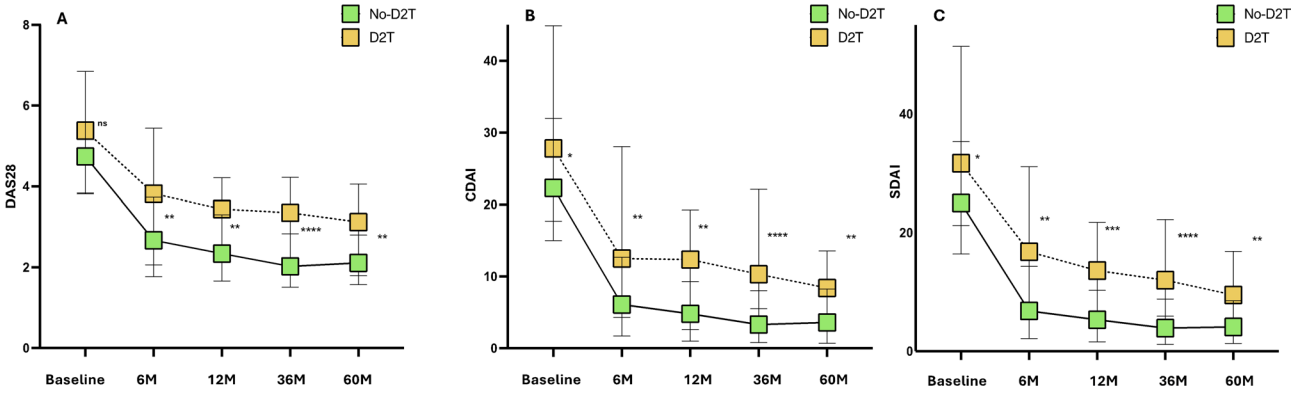


**Fig. 1** 5 Years of disease activity comparison between D2T versus No-D2T. Whisker Plots showing disease activity trajectories comparison in D2T and No-D2T patients for **(A)** DAS28, **(B)** CDAI, and **(C)** SDAI; ns = non-significant *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, **** $p < 0.0001$. A Mann-Whitney t-test was performed

emerged for other comorbidities, including diabetes (9.7 versus 29.3%; $p = 0.06$) and hypertension (34.1% versus 31.2%, $p = 0.70$).

## Discussion

In this study, we analyzed the evolution of an ERA cohort towards a D2T phenotype during a 5-year follow-up. In a real-world scenario, we highlight that patients who will evolve to D2T-RA are characterized at baseline by the presence of negative prognostic factors: baseline radiographic damage, RF/ACPA seropositivity, and disease activity. A higher overall disease activity over time also characterizes D2T patients. When deconstructing the components of disease activity indices, D2T patients are characterized, from six months onwards, by a higher number of SJC28 and TJC28, higher pain perception, and also by more severe disease evaluation by the rheumatologist. Previous studies classified ERA patients as being at high or low risk of a worsening disease based on disease activity at baseline and negative prognostic factors (erosive disease, seropositivity for ACPA or RF), tailoring the first treatment to maximize the outcome with the lower possible GCs dose [14–16] They demonstrated the safety and efficacy of more intense regimens in achieving remission with excellent outcomes also in long-term follow-up [17]. However, the results were inconclusive when stratifying patients into high-risk and low-risk groups. Our study, in a real-life setting and with a different outcome, confirms the presence of predictors of more aggressive disease in the short and long term, identifying a phenotype of patients more prone to fail multiple bDMARDs and have persistent active disease. In particular, 10.5% of our patients matched the D2T definition. This prevalence is slightly superior compared to previous ERA cohorts' studies (5.87%-7.9%) [18, 19]. Several variables discriminate D2T patients. At baseline, seropositivity, disease activity, and radiographic damage were identified as predictors of evolution toward D2T, but only the latter was confirmed as a strong independent factor associated with the outcome. The presence of radiographic damage, and in particular of bone erosions, is a validated marker of disease severity [20, 21] and has already been demonstrated as a predictor for D2TRA, although in an established RA cohort [22]. Besides radiographic damage, the disease activity and seropositivity were the stronger associated factors with D2T-RA. However, at baseline, it was hard to discriminate D2T only based on clinical evaluation: the number of TJC28, SJC28, CRP VASp, and VASm were comparable, while the assessment with disease activity indexes allowed to the perception of a slight difference between the two groups, at least with CDAI and SDAI.

Interestingly, a previous study that included newly diagnosed, treatment-naïve RA patients [19, 23]—even though some exceeded the 12-month threshold used in the definition—reported similar findings: DAS28 difference at baseline is not a discriminant between D2T and non-D2T before treatment.

As we show, apart from the baseline evaluation, the higher disease activity was a distinctive feature from the first evaluation onwards, highlighting that a poor response to the induction treatment or a delay in MTX prescription [23] is a major determinant for the development of the D2T phenotype. In our cohort, we analyzed the time between symptom onset and diagnosis as a proxy of early management. We found no significant difference between D2T and non-D2T patients. This finding contrasts with the results from Giollo et al. [23], who showed that treatment delay—particularly MTX initiation after >12 months—was significantly associated with D2T-RA development. In our setting, however, all patients were diagnosed within 12 months from symptom onset. Furthermore, we did not capture the time to MTX initiation, preventing a direct comparison. Despite these differences, our findings support the same conceptual framework: poor early disease control is associated

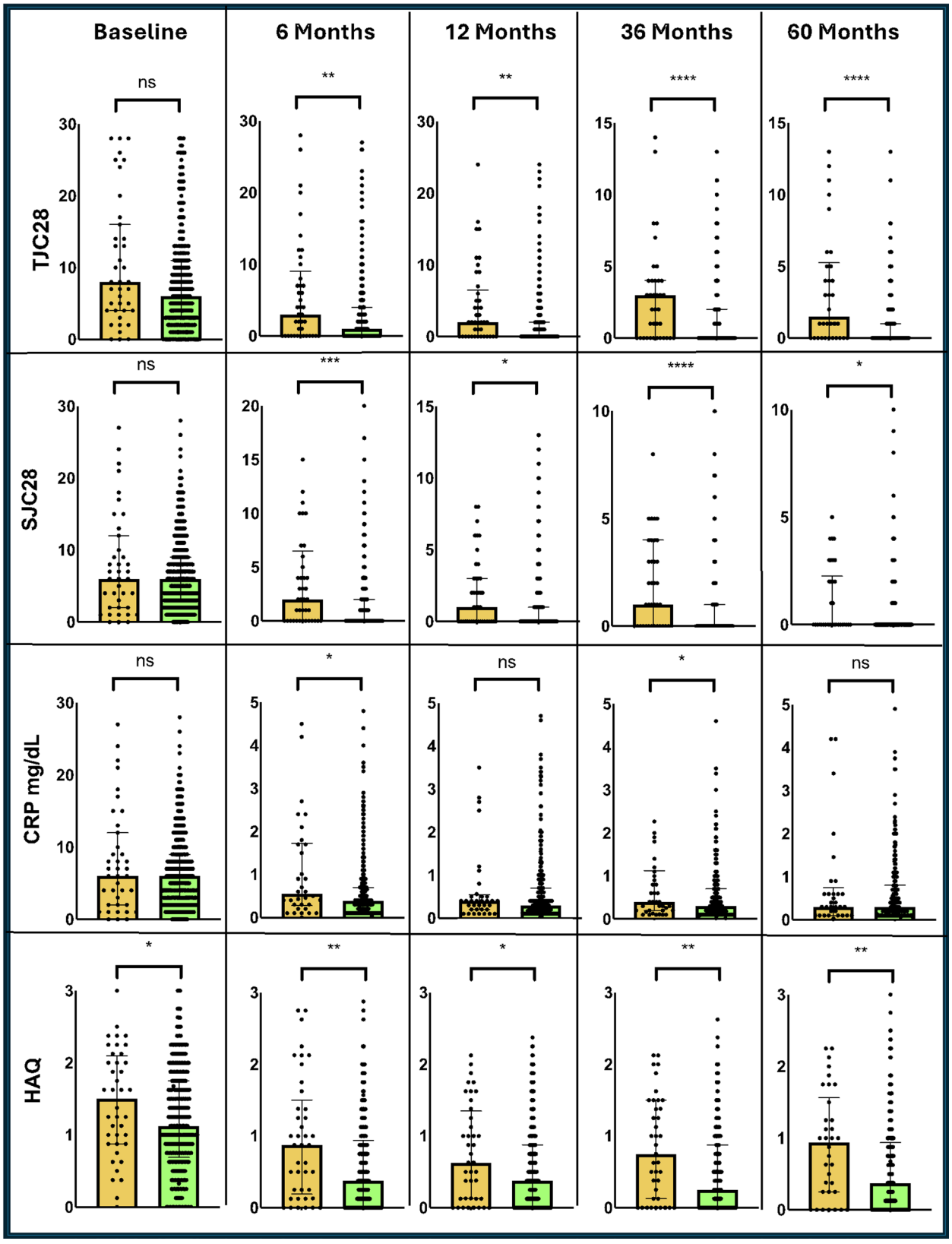


**Fig. 2** Mann-Whitney non-parametric t-test comparison showing D2T (Orange) versus No-D2T (Green) at different time points. **TJC** = Tender Joint Count 28 Joints; **SJC28** = Tender Joint Count 28 Joints; **CRP** = C-Reactive Protein; **HAQ** = Health Assessment Questionnaire. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$

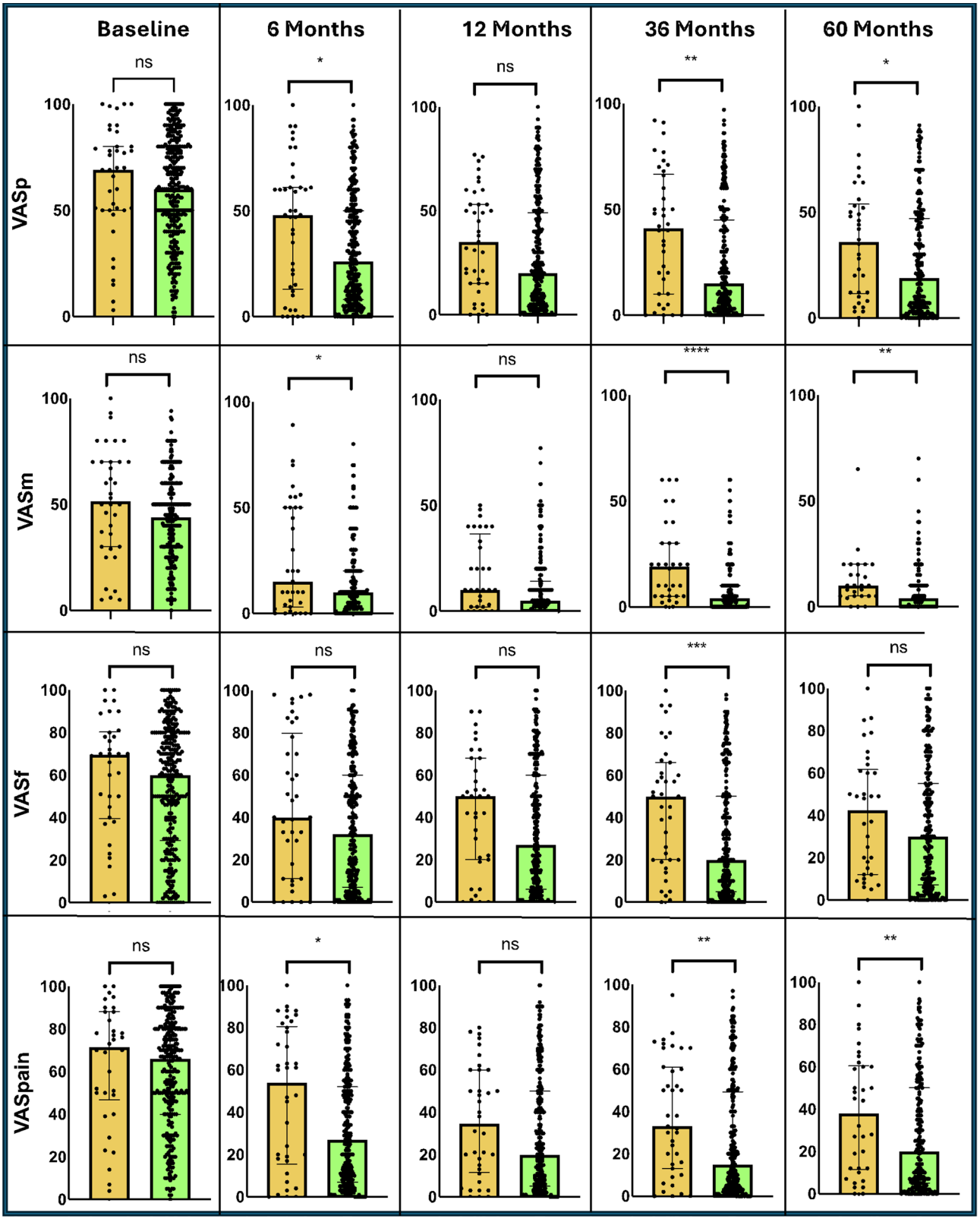


**Fig. 3** Mann-Whitney non-parametric t-test comparison showing D2T (Orange) versus No-D2T (Green) at different time points. **VASp** = Visual Analogue Scale for patient global assessment; **VASm** = Visual Analogue Scale for physician global assessment; **VASf** = VAS fatigue. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, **** $p < 0.0001$

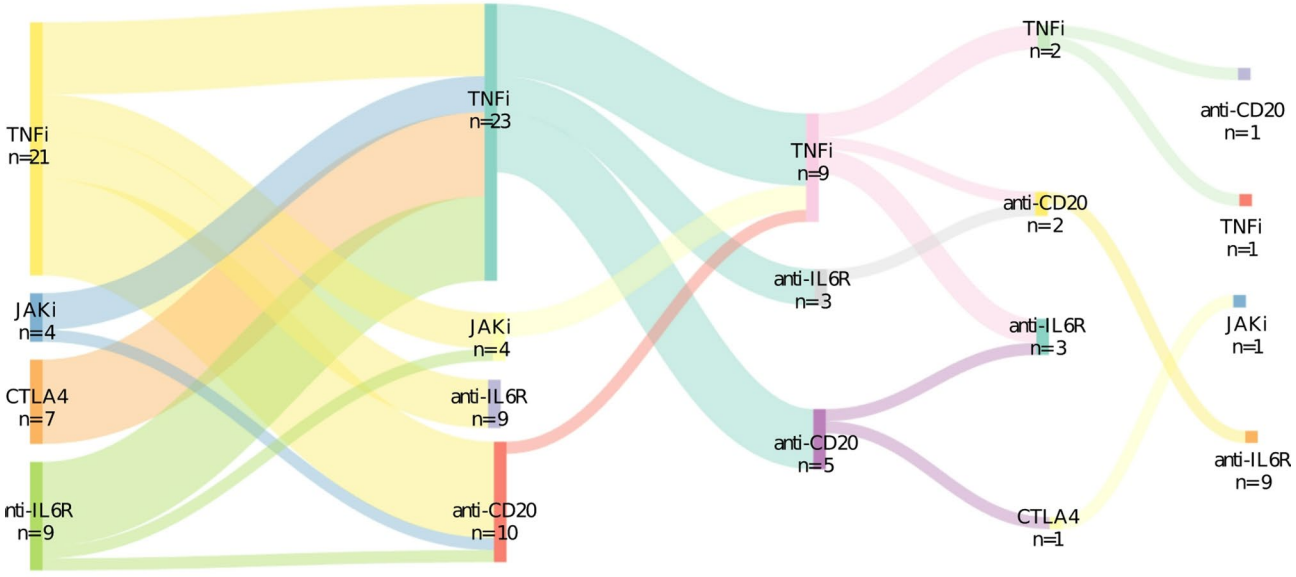


**Fig. 4** Sankey plot depicting prescription sequence in D2T-RA ($n=41$). Sankey Plot for b/tsDMARDs prescription. **TNFi** = Tumour Necrosis Factor Inhibitors; **JAKi** = Janus-Kinase Inhibitors; **CTLA4** = Cytotoxic T-Lymphocyte Antigen 4 (Abatacept); **anti-IL6R** = anti-interleukin 6 Receptor; **anti-CD20** = B-Lymphocyte Cluster Differentiation 20 (Rituximab)

with the emergence of D2T-RA. This observation reinforces the established evidence that early and effective disease control is critical to long-term outcomes. In fact, early response to treatment has been consistently correlated with better clinical and radiographic outcomes [24], as the ability to predict the mid-long-term evolution: non-response to MTX predicts joint destruction at 2 years and the prompt response is related to lower disease activity [25–27].

While disease activity indexes (CDAI, SDAI, DAS28) are a reliable and powerful tool in daily clinical practice, they combine a multidimensional evaluation including an objective evaluation, the physician and patient's evaluation, and blood test. We then deconstruct them, analyzing the contribution of each item (TJC28, SJC28, CRP, VASm, VASp, CRP) to the global effect on disease activity evaluation. In general, we identify a good concordance between the PROs and pain perception (TJC28 VASp, VASpain) and the physician estimate of disease activity (SJC28 and VASm). These patients showed both higher pain perception and a genuinely more severe disease. While the existence of different D2T phenotypes has been proposed [24] we observed a contemporary involvement of pain perception, PROs, and physician evaluation. Further confirmations derive from the weak predictive value of these variables considered separately. We showed how none of the objective and subjective components is sufficient *per sé* to explain the evolution of the D2T phenotype.

Moreover, we registered the most common disease and treatment-related comorbidities as well as the cumulative dose of glucocorticoids. As expected, The D2T group was more exposed to glucocorticoid and was more prone to develop side effects such as osteoporosis and infections. This observation opens debate on the role of GC: their usefulness is not questioned as bridge therapy or short-term disease control, but the physician should be prompted to manage the well-known side effects early.

A necessary criterion of the recent D2T-RA definition is the failure of ≥ 2 b/tsDMARDs with different MoA. However, we found that patients failing ≥ 2 bDMARDs with the same MoA seem to have outcomes similar to D2T-RA patients. Switching of bDMARDs class after a first TNFi failure does not increase the response rate to the second drug [3, 28], suggesting that patients failing ≥ 2 bDMARDs with the same MoA are not intrinsically "more refractory" (than those failing two drugs with the same MoA). However, in our cohort, patients who failed ≥ 2 bDMARDs within the same MoA class appeared to have similar clinical outcomes to those fulfilling the D2T-RA criteria. Moreover, switching to a different bDMARD class after failure of a first TNFi does not consistently improve treatment response [3, 28]. These observations suggest that patients failing multiple bDMARDs—even within the same MoA—may still exhibit a difficult-to-treat phenotype, despite not formally meeting the definition.

Although confirmation on larger cohorts is necessary, our observation questions the legitimacy of excluding patients failing ≥ 2 bDMARDs with the same MoA from the D2T-RA definition. Our study has several strengths and some limitations. First of all, to the best of our

knowledge, this is the first study evaluating the trajectory evolution of a large monocentric cohort of ERA naïve to DMARDs from the diagnosis up to 5 years. The advantage of including only early RA naïve to therapy significantly reduces various biases in the treatment efficacy on disease activity and pain perception. Moreover, we systematically collected PROs, and each component of the disease activity score; we were then able to analyze each component separately. The monocentric design ensures homogeneous management of patients, especially concerning the T2T approach and the prescription of targeted therapies.

## Conclusion

In conclusion, we analyzed a large cohort of early untreated rheumatoid arthritis through the evolution toward the D2T phenotype, identifying the presence of radiographic damage as the stronger predictor of poor evolution, along with seropositivity for ACPA and RF. D2T patients have a higher disease activity and self-disease activity perception from baseline. The disease burden and higher glucocorticoid exposure may be responsible for the higher rate of comorbidities such as infections and osteoporosis. Our results enhance the knowledge of the evolution from ERA toward D2T-RA, but we are still far from predicting treatment response only with clinical and radiological features. Further studies are necessary to identify biomarkers of D2T evolution.

### Abbreviations

| | |
|---|---|
| ACPA | Anti–citrullinated proteins antibodies |
| ACR | American College of Rheumatology |
| BE | Bone Erosion |
| bDMARDs | Biological DMARDs |
| BMI | Body Mass Index |
| CDAI | Clinical Disease Activity Index |
| cDMARDs | Classic DMARDs |
| CRP | C–Reactive Protein |
| DAS 28 | Disease Activity Score 28 Joint |
| D2T | Difficult–to–treat |
| DMARDs | Disease Modifying Anti Rheumatic Drugs |
| ERA | Early rheumatoid arthritis |
| EULAR | European League Against Rheumatism |
| GCs | Glucocorticoids |
| HAQ | Health Assessment Questionnaire |
| IQR | Interquantile range |
| JSN | Joint Space Narrowing |
| LDA | Low Disease Activity |
| MTX | Methotrexate |
| PDN | Prednisone |
| RA | Rheumatoid Arthritis |
| RF | Rheumatoid Factor |
| SJC | Swollen Joint Count |
| SDAI | Serological Disease Activity Index |
| TJC | Tender Joint Count |
| TNFi | Tumor Necrosis Factor Inhibitor |
| tsDMARDs | Target synthetic DMARDs |
| VAS | Visual Analogue Scale |
| VASf | Visual Analogue Scale for fatigue |
| VASp | Visual Analogue Scale for patient global assessment |
| VASm | Visual Analogue Scale for physician global assessment |
| VASp | Visual Analogue Scale for pain |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13075-025-03645-1.

**Additional File 1**: **Supplementary Table S1**. Detailed comparison between D2T and no-D2T from baseline to 60M.

**Additional File 2**: **Supplementary Table S2**. Comparison between D2T classic definition and patients who failed at least 2 bDMARDs with the same mechanism of action.

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### Author contributions

Conceptualization: F.N., C.T., P.D. Writing – original draft: F.N., C.T., P.D. Writing – review & editing: F.N., C.T., P.D. Statistical analysis: F.N. T.S. Data curation: T.S., A.A. Resources: E.S., S.D., C.V.M., S.D.M . Supervision: P.D. All authors read and approved the final manuscript.

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### Data availability

No datasets were generated or analysed during the current study.

## Declarations

### Ethics approval and consent to participate

The study was conducted according to the Declaration of Helsinki. All patients provided informed consent.

### Consent for publication

Not applicable.

### Competing interests

The authors declare no competing interests.

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