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Timely escalation to second-line therapies after failure of methotrexate in patients with early rheumatoid arthritis does not reduce the risk of becoming difficult-to-treat

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Abstract

Background To investigate the frequency of difficult-to-treat (D2T) rheumatoid arthritis (RA) in patients early escalated to biologic/targeted synthetic disease modifying anti-rheumatic drugs (b/tsDMARDs) after failure of treat-to-target with methotrexate (MTX).

Methods From a prospective cohort of early RA, all patients with their first access in the years 2005–2018, and eventually starting a b/tsDMARD before the end of 2022, were included and followed-up until April 2024. Study outcomes included drug survival on each consecutive b/tsDMARDs, development of D2T (according to the EULAR definition and subsequent modifications), and its predictors.

Results Of a total cohort of 722 early RA patients treated with initial MTX and followed-up for at least 3 years from diagnosis, 155 (21.5%) had started a b/tsDMARD after a median of 19 months. In more than 70% of the cases, RA was uncontrolled despite optimal doses of MTX of ≥ 15 mg/day. The retention rates of the first and the second b/tsDMARD were approximatively 70% after 1 year but dropped to 40% after 5 years. After a median (IQR) follow up of 72.6 (34.5-134.2) months, 45 patients (29%) fulfilled the EULAR D2T criteria. At multivariable analysis, higher number of swollen joints and worse pain scores were confirmed as predictors of D2T. Furthermore, in this early RA cohort, shorter disease duration at the start of treatment with b/tsDMARDs, together with negativity for autoantibodies, were also independent predictors of D2T.

Conclusions Early implementation of treatment after failure of treat-to-target with MTX may not prevent the development of D2T in RA. Patients showing early refractoriness to conventional drugs and those lacking autoantibodies are at higher risk of multiple treatment failures.

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Keywords Rheumatoid arthritis, Early, Difficult-to-treat, Refractory, Methotrexate, Treat-to-target, Seronegative, Anti-citrullinated protein antibodies, ACPA, Rheumatoid factor

Introduction

The increasing availability of biological (b) and targeted synthetic (ts) disease modifying anti-rheumatic drugs (DMARDs) has significantly modified the outcomes of patients with rheumatoid arthritis (RA) over the past twenty years [1]. However, a variable proportion of patients still require access to multiple drugs with different mechanisms of action without ever achieving adequate disease control [2–4]. Although the correct estimate of treatment-resistant and difficult-to-treat (D2T) RA is hampered by several factors, including variability in its definition and heterogeneity in patient populations, the most recent studies adopting the criteria for D2T endorsed by the European Alliance of Associations for Rheumatology (EULAR) [5] are roughly in agreement in indicating a frequency of around 15-18% of all b/tsDMARD-experienced patients [6–11].

Along with the expansion of treatment options, the prognosis of RA has been greatly improved through early diagnosis and timely introduction and implementation of effective therapies [12, 13]. Accordingly, longer disease duration negatively affects the response to DMARDs [14]. Based on data from several registries, however, the access to the first bDMARDs still appears to be significantly delayed in real practice, with a disease duration of about 8–14 years in most cohorts [15, 16], and only a trend toward shorter times in recent years [17, 18]. It could be expected that earlier escalation to second-line therapies after failure of initial treat-to-target with conventional synthetic (cs) DMARDs would improve the rates of response and thus reduce the proportion of D2T RA. However, the effect of timely introduction of b/tsDMARD in the context of early arthritis clinics (EAC) has never been specifically investigated.

Aim of this study was to analyse the retention rate of the first and subsequent lines of b/tsDMARDs, and the frequency of D2T, in patients with RA who had undergone early diagnosis, prompt initiation of methotrexate (MTX), and treatment guided by a target-oriented approach, with rapid escalation to second-line therapies.

Patients and methods

Patients

We performed a retrospective analysis of prospectively collected data from a monocentric inception cohort of patients with new-onset RA (≤12 months of symptoms at inclusion) referred to the EAC of the IRCCS Policlinico San Matteo University Hospital of Pavia, Italy [19–21]. All patients with their first access to the EAC in the years 2005–2018, and eventually starting a b/tsDMARD before the end of 2022, were included and followed-up until April 2024. Per protocol of our EAC, patients had to fulfill the 1987 and/or the 2010 classification criteria for RA [22, 23]. Patients with changes in diagnosis during follow-up were excluded from analyses.

This was a retrospective observational study on patients treated according to routine clinical practice, who gave comprehensive and informed consent before proceeding with all examinations as part of an approved service evaluation (clinical audit) of the Early Arthritis Clinic of the IRCCS Policlinico San Matteo Foundation, Pavia, Italy.

Treatments

Upon enrollement in the EAC, all patients were treated according to a treat-to-target protocol aimed at low disease activity based on the 28-joints disease activity score (DAS28 < 3.2). MTX monotherapy was used as first-line treatment in all patients unless contraindicated, with slight variations in the initial and maximal doses, which were increased from 10 to 15 mg/wk and from 20 to 25 mg/wk, respectively, after 2010 [20]. Bridging with glucocorticoids was modified during the study period, with part of the patients enrolled before 2010 randomised to receive or not receive low dose prednisone for two years as a part of an open-label trial [19], and patients enrolled after 2010 all receiving prednisone 5 mg for 12 months [20, 21].

In case of failure to achieve the therapeutic target with csDMARDs, patients could be escalated to second-line treatment strategies taking into account poor prognostic factors as follows: combination of csDMARDs (MTX + sulfasalazine 2 g/day); start of a b/tsDMARD. The proportion of patients in combination therapy with csDMARD was however very small (~ 5% of our cohort). The decision to start a b/tsDMARDs was partially disconnected from the DAS28 and, as per clinical practice, could take into account demographic variables, comorbidities, prognostic factors, and others [1]. The choice of the first and subsequent b/tsDMARDs was based on drug availability, intolerance/contraindications, autoantibody status, medical and social costs.

Assessments and follow-up

During the EAC phase, patients were seen every two months in the first semester, tri-monthly until month 24, and every six months thereafter. Once a b/tsDMARD was started, follow-up occurred every two months for the first six months, then every four months, with the target of low disease activity (DAS28 < 3.2). If the target was not

met at six months, patients were treated in accordance with the rheumatologist's opinion (increase or reintroduction of conventional therapy, short-term treatment with prednisone, switch or swap of the b/tsDMARD).

Demographic characteristics, comorbidities and treatment history were recorded at enrollment in the EAC and at the start of the first b/tsDMARD. In detail, comorbidities were collected according to the Charlson Comorbidity Index (CCI) that could be extracted from manual review of the medical records, with further recording of hypertension, obesity, interstitial lung disease and depression. Previous history of MTX during the EAC phase included: failure (uncontrolled disease despite maximal MTX dose); intolerance (complete intolerance or inability to increase MTX > 10 mg/week); contraindication (never able to start MTX). Serostatus for rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) was centrally determined on baseline sera. The presence of erosions - ≥1 point according to the Sharp/van der Heijde score [24] - on conventional radiographs of the hands and feet was determined at the start of the first b/tsDMARD. Disease activity measures including joint counts, acute phase reactants and patient reported outcomes (PROs), were collected at each time point during follow-up.

Outcomes

We assessed the effectiveness of each consecutive b/tsDMARDs as drug survival, defined as duration between start and stop dates for each line of therapy. Analyses were performed with right-censoring at the last follow-up visit date before April 2024. Reasons for drug discontinuation were classified as primary failure (inability to ever achieve DAS28 < 3.2), secondary failure (disease relapse after achieving DAS28 < 3.2), safety, and others.

According to the EULAR definition [5], we defined D2T patients those who had failed two or more b/tsDMARD classes (criterion 1 of the original publication, 'treatment failure history'), or were receiving a second b/tsDMARD class therapy, but either DAS28 was ≥ 3.2 after 6 months, or glucocorticoids were taken at dosages > 7.5 mg/day (criterion 2 of the original publication, 'presence of active disease'). Radiographic progression was not available and thus not included in the definition of active/progressive disease. Also, criterion 3 ('clinical perception of problematic disease') could not be reliably extrapolated from the manual review of the medical charts. Because of possible intra-class switches and of the different availability of targeted drugs over the study period, we also considered the alternative definition of D2T proposed by recent studies [25], consisting in failure of ≥2 b/tsDMARDs, irrespective of their mechanism of action. Finally, we defined treatment-refractory those patients with primary failure (never achieving low disease activity after initiating the medication) to their first two prescribed mechanisms of action [9].

Statistical analysis

Patient demographics and disease characteristics at baseline were analysed using standard descriptive statistics. Categorical data were presented as percentages, while normally distributed continuous variables were expressed as mean ± 1 standard deviation (SD).

The crude drug retention rates were estimated using the Kaplan–Meier life-table method. Time to discontinuation was defined as the period between the initiation of b/tsDMARD therapy and the last administration. Any treatment interruption longer than 6 months was considered as discontinuation. Patients who were lost to follow-up or who discontinued treatment for reasons unrelated to treatment were right-censored.

Baseline differences between D2T and non-D2T patients were compared using the $\chi 2$ test or the unpaired t test, as appropriate. Predictors of D2T were estimated using a multivariate stepwise backward regression model. We limited the number of variables in the multivariate model following the rule of Freeman and the value of 10 events per variable to ensure that it was reliable. The final model was corrected for calendar year of b/tsDMARD start (2005–2010; 2011–2016; 2017–2022). Factors with P-values < 0.10 were stepwise removed until the final multivariate model was selected. Missing data were minimal and were not imputed.

Results

Baseline characteristics of the study population

Of a total cohort of 905 patients newly diagnosed with RA in the years 2005–2018, 722 (79.8%) had follow-up data available for at least 3 years after the first access to the EAC. At referral, patients had median (IQR) symptom duration of 17 (10.7–28.5) weeks and mean (SD) DAS28 of 4.74 (1.22); 72% were female, with a mean (SD) age of 60 (14.4) years. MTX was started in 78% of the cases, and bridging with prednisone in 72%.

Five-hundred and thirteen patients (71%) were at least in DAS28 low disease activity at their last available visit. One-hundred and fifty-five patients (21.5%) had started a b/tsDMARD after a median (IQR) of approximatively 19 (10-39.8) months (36.1% within month 12, 66.5% within month 24, 75.5% within month 36). Demographic and clinical characteristics at the time of the start of the first b/tsDMARD are shown in Table 1. The population consisted of predominantly female, relatively young subjects, overweight in 43.9% of the cases, with 21.3% being obese; although 75 patients (48.4%) had at least 1 comorbidity, the CCI was low (mean [SD] 0.9 [1.2]). Patients had moderate disease activity, and 36.8% were negative for both RF and ACPA. In more than 70% of the cases,

Table 1 Demographic and clinical characteristics of the study population at the start of treatment with the first ts/bDMARD

	***n*=155**
Age, mean (SD), yrs	53.2 (13.7)
Female gender, n. (%)	122 (78.7)
BMI, mean (SD)	26.2 (6.6)
Current smoker, n. (%)	35 (22.6)
Hypertension, n. (%)	73 (47.1)
CCI, mean (SD)	0.9 (1.2)
ILD, n. (%)	10 (6.5)
Depression, n. (%)	23 (14.8)
Disease duration, median (IQR), months	18.7 (10.1–39.8)
DAS28, mean (SD)	4.5 (1.1)
SJC28, mean (SD)	4.2 (3.5)
TJC28, mean (SD)	6.8 (5.7)
VAS pain, mean (SD), mm	58.9 (23.7)
VAS PGA, mean (SD), mm	59.3 (23.5)
ESR, mean (SD), mm/1 h	24.3 (17.4)
CRP, mean (SD), mg/dl	1.2 (1.7)
RF and/or ACPA positive, n. (%)	98 (63.2)
SHS erosions ≥ 1, n. (%)	67 (43.2)
MTX status at b/tsDMARD escalation, n. (%)	
- failure	116 (74.8)
- intolerance*	33 (21.3)
- never started	6 (3.9)
current csDMARD, n. (%)	
- none/HCQ	12 (7.7)
- MTX	127 (81.9)
- others	16 (10.4)
MTX dose, mean (SD)	18.7 (4.8)
Current prednisone, n. (%)	124 (80)
Prednisone dose, mean (SD), mg/day	6.1 (2.5)

*complete intolerance or inability to increase MTX > 10 mg/w

BMI=body mass index; CCI=Charlson comorbidity index; ILD=interstitial lung disease; DAS28=disease activity score on 28 joints; SJC28=swollen joint count on 28 joints; TJC28=tender joint count on 28 joints; VAS=visual analogue scale; PGA=patient global assessment; ESR=erythrocyte sedimentation rate; CRP=C-reactive protein; RF=rheumatoid factor; ACPA=anti-citrullinated peptide antibodies; SHS=Sharp score; MTX=methotrexate; csDMARD=conventional synthetic disease-modifying anti-rheumatic drug; HCQ=hydroxychloroquine

RA was uncontrolled despite optimal doses of MTX of ≥15 mg/day; 80% of the patients were on glucocorticoids, at a mean (SD) dose of 6.1 (2.5) mg/day. The first b/tsDMARD was a tumor necrosis factor inhibitor (TNFi) in 52.9% of the cases, followed by abatacept (26.4%), a Janus Kinase inhibitor (JAKi) (12.3%), or an interleukin (IL)-6R antagonist (8.4%).

Survival on the first b/tsDMARD

Median (IQR) duration of observation of patients started on a b/tsDMARD was 72.6 (34.5-134.2) months. The retention rate of the first b/tsDMARD dropped from 72.3% at 12 months to 61% at 36 months and 41.6% at 60 months, further declining thereafter (Fig. 1A). Collectively, 95 patients (61.3%) globally discontinued treatment after a median (IQR) of 23.5 (8–60) months. Reason for discontinuation was primary failure in 23.3% of the cases, secondary failure in 46.7%, and safety in 30% (Fig. 1B).

Survival analysis was repeated in the subgroup of patients starting a TNFi ($n=82$), resulting in similar retention rates. In particular, the retention rate was 72.3% at 12 months, 64.2% at 36 months and 44.9% at 60 months.

Survival on the second b/tsDMARD

Among the 95 patients discontinuing the first b/tsDMARD, 72 (75.7%) started a second b/tsDMARD. The retention rate is shown in Fig. 1C. Similarly to the first b/tsDMARD, treatment persistence dropped from 73.1% at 12 months to 53.9% at 36 months, further declining to 35.8% at 60 months. Also, reasons for discontinuation showed an overall similar pattern, apart from a slight decrease of secondary failures in favour of an increase in safety issues (Fig. 1D).

Survival analysis was repeated in those patients starting a second b/tsDMARD with a different mechanism of action ($n=53$). The retention rate was numerically higher at 12 months (78.9%), but dropped to 56.6% at 36 months, declining further to 45.3% thereafter.

D2T RA: frequency and predictors

Altogether, after a global median (IQR) follow up of 72.6 (34.5-134.2) months, the mean (SD) number of failed lines of therapy was 1.1 (1.4), and 48/155 (31%) patients had failed ≥2 b/tsDMARDs (mean [SD] number 2.8 [1.4]) irrespective of the mechanism of action (alternative D2T definition). Of them, 45 (29%) fulfilled the EULAR D2T criteria because of failure of ≥2 different mechanisms of action, including 3 patients who were still on their second mechanism but were concomitantly receiving >7.5 mg/day of prednisone after 6 months. Of note, the proportion of EULAR D2T was comparable across calendar years (31.7%, 31.3% and 25.8%). Nine patients (5.8%) had evidence of refractory disease (primary failure to the first two prescribed mechanisms of action).

Factors at the time of b/tsDMARD start associated with EULAR D2T RA are shown in Table 2. This subgroup of patients had significantly higher female predominance, tended to be younger and more overweight. Baseline disease activity was higher, with higher numbers of swollen joints and more frequent need of glucocorticoids. Also, and apparently paradoxically, D2T RA patients were those more rapidly escalated to b/tsDMARD after failure of MTX, as indicated by their significantly shorter disease duration in the range of 15 months. Together with higher inflammation, patients also had higher joint and generalised pain, with disproportionate joint tenderness (ΔTJC28-SJC28 ≥7 in nearly 25% vs. 13%) and worse pain

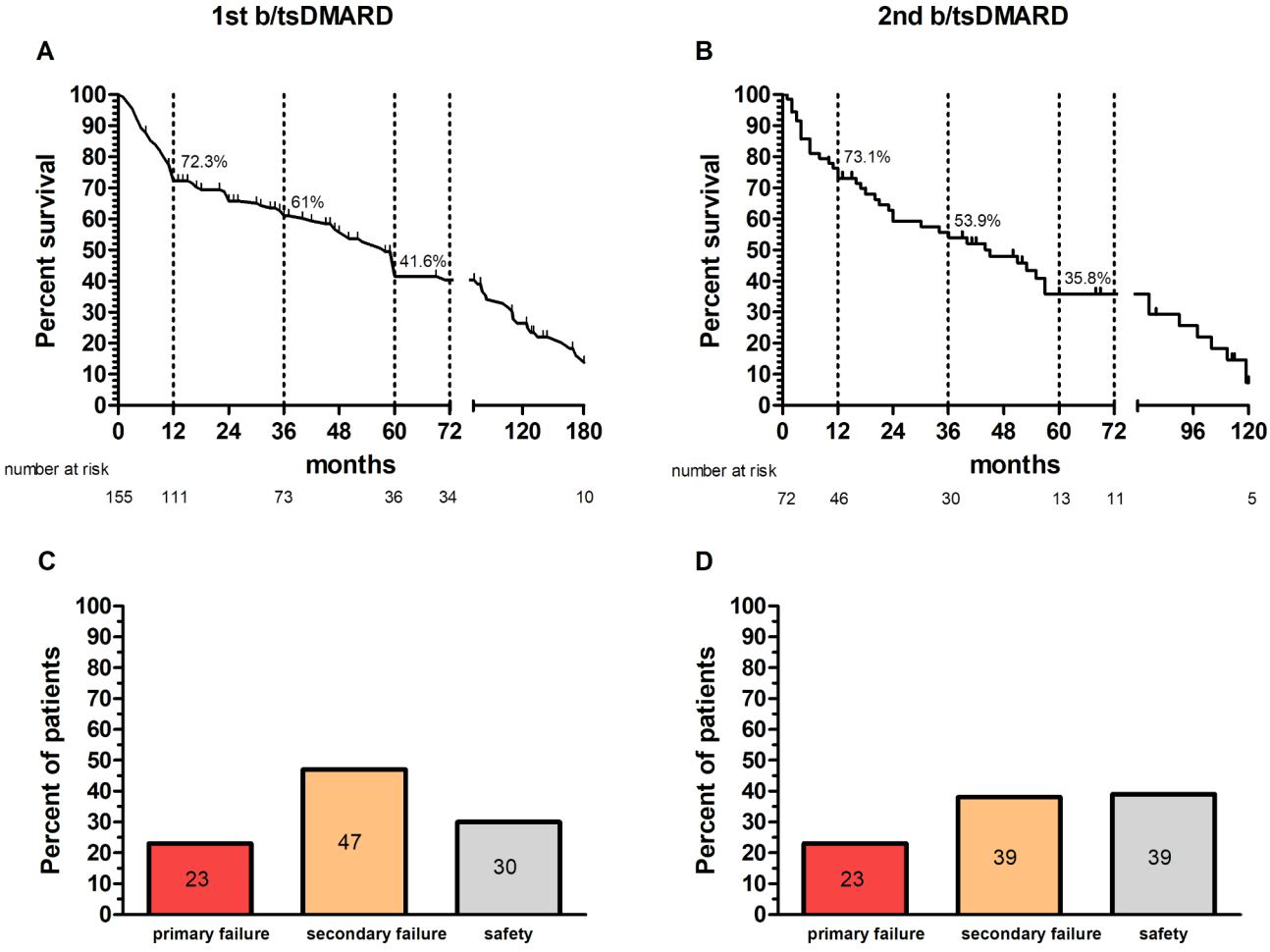

Fig. 1 Retention rate and causes of discontinuation of sequential lines of b/tsDMARD over follow-up. (**A**, **C**) Kaplan-Meier survival curves showing the retention rate of the first b/tsDMARD (**A**) and the second b/tsDMARD (**C**). (**B**, **D**) Histograms showing causes of discontinuation of the first (**B**) and the second (**D**) b/tsDMARD

scores (VAS pain>40 mm in 91.1% vs. 73.6%, $p=0.03$). Furthermore, D2T RA patients were more frequently negative for both RF and ACPA. Patients' characteristics in the alternative D2T definition were comparable (data not shown).

At multivariate regression analysis for demographic variables, age, body weight and comorbidities dropped for the model, with only female gender remaining significant. In a final full model including disease variables, and corrected for calendar year, shorter disease duration, higher number of swollen joints, worse pain scores and negativity for RF and ACPA were all independent predictors of EULAR D2T with an AUC (95% CI) of 0.82 (0.74 to 0.88) (Table 3). The same variables also predicted the alternative D2T definition. Due to the low number of refractory RA, no prediction models could be tested.

Discussion

Results from our study indicate that, in patients with newly diagnosed RA undergoing early treatment and treat-to-target with MTX, the prognosis is mostly favourable, with few escalations to second-line therapy. However, when patients are refractory to MTX, the chances of treatment persistence on b/tsDMARDs, even started early, are still unsatisfactory, and about one-third of cases remain resistant to multiple lines of treatment. In addition to measures of disease activity and impact, predictors of D2T in this early RA cohort are shorter disease duration and autoantibody negativity.

Most of the recent inception cohorts of RA show improved outcomes as a result of early referral and DMARDs start, regular monitoring, and adherence to therapeutic recommendations [26–28]. Progresses appear to be in great part attributable to the correct use of MTX, as only 20-30% of patients from large independent cohorts need escalation to b/tsDMARDs [26–29]. The 20% rate of patients starting second-line treatment

Table 2 Characteristics of D2T* and non-D2T patients at the start of treatment with the first b/tsDMARD

	D2T *n.* 45	non-D2T *n.* 110	*p*
Age, mean (SD), yrs	50.1 (10.9)	54.5 (14.6)	0.07
Female gender, n. (%)	41 (91.1)	81 (73.6)	**0.03**
BMI, mean (SD)	27.2 (8.3)	25.7 (5.7)	0.27
Overweight, n. (%)	25 (55.6)	43 (39.1)	0.09
Current smoker, n. (%)	11 (24.4)	24 (21.8)	0.89
Hypertension, n. (%)	24 (53.3)	49 (44.5)	0.41
CCI, mean (SD)	1.1 (1.3)	0.9 (1.2)	0.36
Depression, n. (%)	9 (20)	14 (12.7)	0.36
Disease duration, median (IQR), months	15.1 (8-29.6)	21.5 (11-46.1)	**0.02**
DAS28, mean (SD)	5.2 (0.7)	4.1 (1.1)	**< 0.001**
SJC28, mean (SD)	5.6 (3.3)	3.5 (3.4)	**0.001**
TJC28, mean (SD)	10 (6.6)	5.4 (4.6)	**< 0.001**
VAS pain, mean (SD), mm	66.9 (19.9)	55.6 (24.5)	**0.02**
CRP, mean (SD), mg/dl	1.2 (1.3)	1.2 (1.8)	0.87
RF and/or ACPA positive, n. (%)	22 (48.9)	76 (69.1)	**0.03**
SHS erosions ≥ 1, n. (%)	20 (44.4)	47 (42.7)	0.99
MTX, n. (%)	39 (86.7)	88 (80)	0.45
MTX dose, mean (SD)	19.5 (4.8)	18.4 (4.7)	0.20
Prednisone, n. (%)	42 (93.3)	82 (74.5)	**0.02**
Prednisone dose, mean (SD), mg/day	6.5 (3)	5.9 (2.2)	0.17

D2T = Difficult-to-Treat; BMI = body mass index; CCI = Charlson comorbidity index; DAS28 = disease activity score on 28 joints; SJC28 = swollen joint count on 28 joints; TJC28 = tender joint count on 28 joints; VAS = visual analogue scale; CRP = C-reactive protein; RF = rheumatoid factor; ACPA = anti-citrullinated peptide antibodies; SHS = Sharp score; MTX = methotrexate

*D2T according to the EULAR definition [5].

Table 3 Multivariate regression analysis for D2T*

	OR	95% CI	*p*
female gender	5.11	1.20 to 21.86	0.03
disease duration	0.98	0.96 to 0.99	0.04
number of swollen joints	1.26	1.05 to 1.51	0.01
VAS pain	1.02	1.01 to 1.03	0.04
RF and ACPA negative	2.58	1.09 to 6.91	0.03

D2T = Difficult-to-Treat; VAS = visual analogue scale; RF = rheumatoid factor; ACPA = anti-citrullinated peptide antibodies

*D2T according to the EULAR definition [5].

in our EAC is in line with similar data from the ESPOIR cohort [28, 29], and confirms that more than 70% of early RA in the new millennium can expect to achieve favourable outcomes with csDMARDs alone [26].

When required, treatment escalation occurred rather early in our cohort, within 3 years of disease onset in three quarters of cases. Such rapid access to second-line therapies clearly contrasts with the 7-years delay that still affects most b/tsDMARD cohorts [15–18]. Despite short disease duration, however, retention on the first b/tsDMARD was suboptimal and decreased from 70% after 1 year to 40% after 5 years. The retention rate of a second b/tsDMARD showed a similar slope. These patterns mirror those observed in other cohorts with similarly short disease duration from Northern Europe [30]. One of the largest datasets from the British Society for Rheumatology, covering patients with a treatment delay of about 12 years, demonstrates much lower one- and three-year survivals, in the range of 65%-40% for the first bDMARD and 55%-30% for the second [31]. However, the prescription rules from the National Institute for Health and Care Excellence (NICE) limit the use of biologics to patients with severely active disease [32]. In areas were the use of b/tsDMARDs is not restricted, the retention rates of our RA patients starting treatment early appear instead comparable to those of patients with long-standing disease [33, 34].

As a result of multiple treatment failures, a proportion of our early RA patients could classify as D2T. Together with the EULAR definition [5], we also used the modification proposed by Hecquet S et al., [25] which is based on the number of molecules used and not on the mechanism of action (alternative D2T), to correct for the different drug availability over the years and for possible practice of intra-class switches. The interpretation of the prevalence of D2T and of its predictive factors deserves some consideration. When referred to the overall number of new RA diagnoses, the frequency of D2T in our cohort was certainly low. Indeed, less than 50 of the 722 RA patients (6.2–6.6%) enrolled in our EAC cohort failed two or more targeted therapies, a proportion similar to that recently described in a Spanish longitudinal cohort of early RA [35]. However, these numbers are the result of dilution from the general RA population, of which a part achieved favorable outcomes with csDMARDs alone. The picture is completely reversed if only patients who failed conventional treatment are analysed. Here, nearly one third (29–31% depending on the definition of D2T) failed more than 2 b/tsDMARDs. Again, recalculating the number of D2T in relation to those who started a b/tsDMARD (17%) in the Spanish longitudinal cohort of early RA, a similar proportion of 33% emerges [35]. The cross-sectional nature of most of the studies on patients with long-standing disease at the time of their first b/tsDMARDs, as well as the heterogeneous definitions of D2T [7–11], make the results hardly comparable. However, among b/tsDMARD-initiators with established RA, those who fail > 2 drugs/mechanisms of action appear in the range of 10-20% [7–11], which is almost half compared with our early D2T. The finding that earlier intensification of therapies does not modify treatment persistence would appear paradoxical and, even more counterintuitive, shorter disease duration was even a poor prognostic factor in our cohort. Treatment delay and disease duration have been reported as either risk factors [6, 36, 37] or protective [8, 9, 38] for D2T. Our results are not in contrast with the overall notion that timely and optimal

treatment with MTX is a prerequisite for reducing the risk of disease refractoriness. In a recent study, it was indeed clearly shown that nearly half of the patients with D2T had started MTX with a delay of >12 months from diagnosis [37]. Our cohort, however, had fairly homogeneous baseline management, with early institution of MTX within 12 months of symptom onset, up-titration to optimal doses according to a treat-to-target strategy, and rapid escalation to second-line therapies. A possible explanation of our findings could be the ceiling effect of appropriate initial management with MTX, with smaller gains from further treatment intensification. Lack of improvements upon expedient addition of TNFi after failure of treat-to-target with MTX in the 'Very early Etanercept and MTX versus MTX with Delayed Etanercept in RA' (VEDERA) study [39] supports this idea. If confirmed, these data would indicate the need to identify early (ideally at diagnosis) those patients who could benefit from more aggressive therapies from the onset.

Together with classical measures of disease activity and PROs, also reported by others [7, 8, 10, 38], negativity for RF and ACPA emerged as a factor associated with D2T. We acknowledge that misdiagnosis may increase the prevalence of autoantibody-negative RA, and be a risk factor for refractoriness to treatments that are ineffective in conditions other than RA. However, changes in diagnosis more frequently occur in the early phases [40], and autoantibody-negative patients started on b/tsDMARDs in our cohort had severe polyarthritis not explained by other diseases at study entry and over follow-up. The autoantibody-negative subset of RA continues to be surrounded by uncertainties regarding diagnosis, evolution, and response to therapy [41–43]. Although the effect of cs and bDMARDs is reported to be generally comparable in patients with and without antibodies, a recent meta-analysis of randomised controlled trials indicates that in autoantibody-negative RA the response to further bDMARDs after failure of TNFi might be lower [44]. The suboptimal response in this subgroup is certainly also driven by subjective dissatisfaction poorly amenable to immunosuppressive treatment [45, 46]. However, the association of autoantibody negative status with D2T was independent of PROs, suggesting the intervention of additional factors that need to be addressed, including later access to care [47], more severe disease activity at treatment start [48], predominance of immunopathological mechanisms that are not targeted by current approaches [49], , and others.

There are limitations to our study. Despite the treat-to-target approach with MTX adopted in our early RA patients upon diagnosis, escalation to b/tsDMARDs and further treatment changes were not strictly guided by disease activity scores, and the prevalence of D2T may thus reflect clinical practice. Our analysis was not comprehensive of all variables that contribute to D2T, including socio-economic factors, access to care, adherence, and others. Consequently, the definition of D2T cannot be used interchangeably with refractory RA, intended as inefficacy of multiple agents [50]. However, treatment costs are covered by the national health system in Italy and, according to administrative databases in our area, adherence is satisfactory [51, 52]. Failure of multiple b/tsDMARDs may thus be primarily driven by inefficacy in our cohort. The burden of comorbidities in our early RA population, extrapolated from the manual review of the medical records, was expectedly low and not significantly affecting the outcome. Larger numbers from multicentric cohorts are needed to address specific reasons of treatment failure, including inflammatory and non-inflammatory refractoriness [50], also in relation to the autoantibody status.

Conclusions

The effect of timely introduction of b/tsDMARD after failure of first-line treatments with MTX on the occurrence of D2T in patients with early RA had never been specifically investigated. Our study is based on a unique setting of RA patients diagnosed shortly after the onset of symptoms, treated early with csDMARDs, and escalated to second-line therapies mostly within the first three years from diagnosis. We demonstrate that only a minority of early RA patients require treatment with b/tsDMARDs. However, among b/tsDMARDs initiators, nearly 30% remain D2T. Apart from measures of disease activity and impact, significant predictors of D2T are shorter disease duration and autoantibody-negative status.

We conclude that early implementation of treatment after failure of treat-to-target with MTX may not prevent the development of D2T in patients with RA. Further studies are needed to identify personalised strategies from the onset, especially in cases of early refractoriness to conventional drugs and in autoantibody-negative patients.

Abbreviations

ACPA	anti-citrullinated protein antibodies
b/tsDMARDs	biological/targeted synthetic disease modifying anti-rheumatic drugs
CCI	Charlson Comorbidity Index
csDMARD	conventional synthetic disease modifying anti-rheumatic drugs
DAS28	28-joints disease activity score
D2T	difficult-to-treat
EAC	early arthritis clinic
EULAR	European Alliance of Associations for Rheumatology
MTX	methotrexate
PRO	patient reported outcomes
RA	rheumatoid arthritis
RF	rheumatoid factor

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None.

Author contributions
"BDO, SB and CM conceived the work. BDO, LDS and SB contributed to the analysis and interpretation of data and drafted the manuscript. EBC, VM, FC and GS contributed to the acquisition and the analysis of data and revised the manuscript critically. GS, AM and CM contributed to the interpretation of data and revised the manuscript critically for important intellectual content. All the authors provided final approval of the version to be published."

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Data availability
Data relevant to the study are included in the manuscript. De-identified participant rough data are available from the corresponding author (serena.bugatti@unipv.it) upon reasonable request.

Declarations

Ethical approval
IRCCS Policlinico San Matteo Foundation Ethics Committee n.20070001302.

Patient and public involvement
Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Consent for publication
Not applicable. The manuscript does not include identifying details of the participants that were studied.

Competing interests
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