Original Article

Factors Predicting Early Discontinuation of Methotrexate as a First-Line Treatment for Rheumatoid Arthritis in Italy: Results from the GISEA Registry

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Abstract

Objective: Despite the well-established efficacy of methotrexate (MTX) in rheumatoid arthritis (RA), monotherapy is not sufficient in almost half of patients. The aim of this registry-based study was to detect possible predictive factors for the early failure of MTX as a first-line treatment in early RA patients.

Materials and Methods: Five-hundred and ninety RA patients beginning MTX as the first-line treatment were included. Persistence on therapy was re-evaluated after 12 months. Baseline features of disease were evaluated by means of univariate Cox regression, and parameters significantly associated to the outcome were included in multivariate model.

Results: One hundred and forty-nine patients (25.3%) failed MTX during the 1st year, for inefficacy in 43.6% and adverse events in 37.5% of cases, respectively. At univariate analysis, patients who discontinued or failed treatment showed lower mean age, higher prevalence of anti-citrullinated peptide antibodies (ACPAs), and higher number of tender/swollen joints. The dose of MTX was correlated with the efficacy and the tolerance of the drug. In particular, patients treated with 7.5 mg of MTX weekly showed a higher rate of discontinuation for inefficacy than adverse events, and the contrary was detected for higher doses. On multivariate analysis, age, ACPA, and number of tender joints were directly associated with MTX discontinuation or failure.

Conclusions: More than 25% of RA patients treated with MTX as a first-line therapy failed treatment at 12 months. ACPA positivity, age, and number of tender joints were associated with early withdrawal of MTX in RA patients, while the dose of MTX was correlated to the efficacy and safety of the drug.

Key Words: *Anti-citrullinated protein antibodies, methotrexate, rheumatoid arthritis, treatment failure*

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Introduction

Methotrexate (MTX) is considered to be the anchor drug for patients with rheumatoid arthritis (RA), recommended as the first-line treatment in both early and long-standing diseases.[1,2] This is mainly based on strong data about its efficacy, safety, and the possibility to adjust the dose and route of administration. According to the last American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) recommendations for the management of RA with synthetic and biologic disease-modifying antirheumatic drugs (DMARDs), MTX should represent part of the first-treatment strategy in RA patients, both in monotherapy or in combination.[2,3] Despite this crucial role of MTX in RA, it is well defined that a percentage of patients fail the treatment.[4-12] To our knowledge, few studies have investigated the causes of early (within the 1st year) discontinuation or failure of MTX; in one of few available studies, a 2-year retention rate of about 66% is described for RA patients treated with MTX, showing a lower age and a longer disease duration as independent predictors for discontinuation.[13]

The aim of this study was to identify possible predictive factors for the early discontinuation or failure of MTX prescribed as the first-line treatment in early RA patients enrolled in the Italian Group for the Study of Early Arthritis (GISEA) registry.

Materials and Methods

Italian Group for the Study of Early Arthritis registry

The nationwide GISEA registry was launched in 2003 to record and monitor patients with early RA on the basis of the standard of clinical care. The registry involves hospital and community-based rheumatology units throughout Italy. Moreover, the GISEA registry included early RA patients with disease duration from diagnosis lower than 6 months. Patients aged >18 years are enrolled after giving their written informed consent, and the registry has been approved by the local Ethics Committee of Modena. Patient data are recorded at baseline and every 6 months thereafter. RA is diagnosed on the basis of the 1987 or 2010 ACR criteria.[14,15] The data collected include age, sex, disease duration, the time from diagnosis to beginning of treatment with a biological drug (latency), the intake of glucocorticoids and DMARD, smoking status, body mass index (BMI), the 28-joint disease activity score (DAS28), C-reactive protein, erythrocyte sedimentation rate (ESR; mm/h), rheumatoid factor (RF), anti-citrullinated peptide antibodies (ACPAs), and side effects. Comorbidities are recorded by monitoring the following: anemia, anxiety/depression, cardiopathy, cerebrovascular diseases, diabetes, gastropathies, hypertension, liver diseases, lung diseases, neoplasia, nephropathy, and peripheral vasculopathy. Extra-articular manifestations included Raynaud's phenomenon, rheumatoid nodules, lung involvement, and sicca syndrome.

Patients

Patients with early RA who began MTX as the first-line treatment were included in the study. For all patients, age, sex, disease duration, smoking status, the intake of glucocorticoids, clinical and serological data, comorbidities, and extra-articular manifestations were collected at baseline, before starting MTX. For all enrolled patients, clinical status was re-evaluated after 12 months, focusing on disease activity and the persistence with MTX therapy.

When MTX was discontinued or a biologic drug was added, the time and the causes of the therapy change were also recorded.

Failure was defined according to the EULAR nonresponse criteria after 12 months[16] or the association of a biologic DMARD during the 1st year of follow-up. Discontinuation was defined as other cause of withdrawal of MTX, both intolerance and adverse events, requiring the suspension of the drug.

Statistical analysis

The differences among patients stopping or continuing at the 1st year of therapy with MTX were analyzed using the Mann–Whitney U-test for the continuous variables (median values and interquartile ranges [IQR]) and the Chi-square test for the categorical variables (absolute numbers and percentages) regarding baseline characteristics.

The univariate analysis was performed using binomial Cox regression model to select parameters to be included in multiple Cox regression analysis (only parameters significantly different in univariate analysis were included in multiple model).

The baseline variables considered were sex, disease duration, ESR, DAS28, the concurrent use of glucocorticoids and DMARDs, comorbidities, extra-articular manifestations, BMI, and smoking habit.

All analyses were made using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA), and a $P \leq 0.05$ was considered statistically significant. The data are expressed as percentages or median values and IQR unless otherwise indicated.[17]

Results

The registry included 1123 patients with early RA. Five hundred and eleven were excluded because they were treated with a DMARD other than MTX or because they were lost to follow-up. Twenty-two patients who stopped MTX during the 1st year of treatment for disease remission were excluded to avoid possible cases of self-limiting arthritis mimicking RA. For the inclusion in the registry, the percentage of missing data had to be <10%.

We analyzed 590 RA patients (female/male 458/132, mean age 55.78 ± 14.5 years; mean DAS28 5.35 ± 1.2). RF was positive in 65.1%, and ACPA was positive in 39%. Comorbidities were observed in 19% of patients, mainly cardiovascular diseases, while extra-articular RA manifestations were recorded in 1.5%. Sixty-eight percent of subjects used low doses of steroids. MTX was administered by parenteral route (577/590, 97.8%) and only 13 patients took oral MTX. A summary of demographic and serological data, comorbidities, and treatment is presented in Table 1.

One hundred and forty-nine patients (25.3%) discontinued or failed MTX during the 1st year (mean period of treatment 4.7 ± 3.4 months). The causes were inefficacy for 65/149 patients (43.6%; namely 31.5% for primary inefficacy and 12.1% for loss of efficacy, respectively) and adverse events in 56/149 (37.5%, mainly liver function alteration, while only one patient discontinued the treatment for an infection of the lower respiratory tract); other reasons/not recorded in 28/149 (18.8%).

When we compared RA patients who continued MTX (Group A) with patients who discontinued or failed treatment during the 1st year (Group B), the latter group showed a lower mean age (P = 0.05) and a higher number of tender and swollen joints on 28 joints (P = 0.001 and P = 0.031, respectively) at baseline; the rate of discontinuation of MTX (P = 0.041) was reduced by the association of MTX with another DMARDs during the 1st year in 19 patients (hydroxychloroquine in 17 patients and leflunomide in 2); finally, DAS28 was higher in patients in Group B than Group A, but the difference was not significant. No differences were observed regarding the association with steroids [Table 2].

Stratifying the causes of failure or discontinuation according to the baseline dosage of MTX, we observed a different impact for adverse events or inefficacy [Table 3];

Table 1: Demographic, clinical and serological features of rheumatoid arthritis patients treated with methotrexate as first-line therapy

Nr	590
Male/female ratio	132/458 (0.29)
Age (median, IQR)	57 (20)
Smoke (%)	183 (31)
ACPA (%)	361 (61.2)
Rhematoid factor (%)	383 (64.9)
ACPA + RF	165 (27.9)
Isolated RF	218 (36.9)
Isolated ACPA	176 (29.8)
None	31 (5.2)
Comorbidities (%)	112 (18.8)
Cardiovascular diseases	99 (16.8)
Lung diseases	37 (6.2)
Liver diseases	11 (1.9)
Skin disorders	68 (11.6)
Diabetes	24 (4.1)
Anemia	57 (9.7)
Hyperuricemia	54 (9.2)
Depression	40 (6.8)
Other/not reported	199 (33.7)
Extra-articular manifestations (%)	9 (1.5)
Steroid therapy (%)	405 (68.6)
Mean methotrexate dose	10 (5)
ERS	31 (32)
CRP >5 mg/L (%)	406 (68.8)
Tender joints count 28	7 (9)
Swollen joints count 28	5 (7)
DAS28	5.45 (1.61)
BMI	42.6 (4.78)

Continuous values are reported as median (IQR) dicotomic values are reported as percentage. ACPA: Anti-citrullinated peptide antibodies, RF: Rheumatoid factor, ERS: Erythrosedimentation rate, DAS: Disease activity index, BMI: Body mass index, IQR: Interquartile range, CRP: C-reactive protein

Table 2: Demographic, clinical and serological features of rheumatoid arthritis patients treated with methotrexate after 1-year therapy

	Continuing MTX 441 (74.7%)	Failure MTX 149 (25.3%)	*P*
Age	57 (20)	57 (19)	0.037
BMI	24.7 (4.9)	24.8 (5.9)	0.5576
ESR	33 (32)	28 (36)	0.0458
Tender joints 28	8 (8)	9 (9)	≤0.001
Swollen joints 28	5 (6)	7 (8)	0.027
DAS28	5.4 (1.5)	5.7 (1.8)	0.1146
Mean dosage MTX	10 (5)	15 (5)	0.024
Male gender (%)	99 (22.4)	33 (22.1)	0.88
Smoke (%)	131 (29.7)	52 (35)	0.32
Rheumatoid factor (%)	284 (64.4)	99 (66.3)	0.558
ACPA (%)	283 (64.1)	78 (52.3)	0.016
RF + ACPA +	131 (29.7)	34 (23.2)	0.108
RF alone	153 (34.7)	65 (43.6)	
ACPA alone	131 (29.7)	45 (29.1)	
None	26 (5.9)	5 (3.3)	
Comorbidities (%)	79 (17.9)	32 (21.6)	0.255
Extra-articular manifestations (%)	5 (1.1)	4 (2.7)%	0.182
Steroid therapy (%)	306 (69.4)	99 (66.4)	0.641
Combination therapy (%)	18 (4.1)	1 (0.7)	0.041
Reactive C protein >5 mg/L (%)	312 (70.8)	94 (63.1)	0.135

Continuous values are reported as median and IQR, dicotomic values are reported as percentage. Mann–Whitney U-test was performed to evaluate association between continuous variables and MTX failure. Contingency table with Chi-square test was used to evaluate associations between dicotomic variables and MTX failure. IQR: Interquartile range, MTX: Methotrexate, ACPA: Anti-citrullinated peptide antibodies, DAS: Disease activity index, RF: Rheumatoid factor, ESR: Erythrosedimentation rate, BMI: Body mass index

in particular, patients treated with 7.5 mg of MTX weekly did not have adverse events, but inefficacy was the cause of failure or discontinuation in 91.7% of cases at this dosage. On the contrary, adverse events were recorded in 68.4% and inefficacy only in 5.3% of patients with a dosage of 20 mg weekly or higher. During the 1st year, 30% of patients increased the dose of MTX, without significant changes in 1 year efficacy or safety of the drug.

We performed a multivariate analysis including tender joints, age, the baseline dosage of MTX, the presence of ACPA, and the combination therapy. Since both tender and swollen joints are correlated with MTX discontinuation or failure at univariate analysis, and considering that these data clearly influence each other, we decided to include in the model only the tender joints, showing a higher significance than swollen joints with respect to MTX failure. ACPA, age, and number of tender joints at baseline were confirmed to be directly associated with early MTX discontinuation or failure, also when corrected for the gender [Table 4].

Discussion

Our study aimed to reveal possible predictive factors of early failure or discontinuation of MTX used as the first-line treatment in RA patients during the 1st year of therapy. This topic has been investigated in only a few studies, mainly with long-term treatments, without conclusive data.

In 1991, Scully *et al*. reported a discontinuation rate of 69% for MTX after 5 years, in 124 RA patients;[8] patients who persisted in treatment were younger and with a shorter disease duration. The main causes of discontinuation were the poor efficacy and the adverse drug reactions.[4] The percentage of discontinuation of MTX varies largely in literature, from a maximum of 55% after 48 weeks to 50% after 50 months.[5-7] In particular, Keysser showed a drop-out rate due to toxicity of 15.9% for MTX, mainly within the 1st year of treatment.[9]

In 2016, a Cochrane meta-analysis compared the efficacy of MTX in monotherapy or combination therapy, including 158 randomized controlled trials (over 37,000 patients) with a duration of at least 12 weeks. The authors concluded that monotherapy was less effective in controlling disease and in preventing joint damage than triple therapy (MTX, sulfasalazine, and hydroxychloroquine) or the association with biologic DMARDs or tofacitinib.[12]

Finally, the PRESERVE trial aimed to analyze features predicting the loss of remission in patients with moderately active RA who received full-dose combination etanercept plus MTX induction therapy, followed by a reduced-dose of etanercept or etanercept withdrawal. Although in a subset of patients with a different clinical history (no early RA, no MTX as first-line therapy), the authors detected, in the MTX monotherapy subgroup, predictive factors for the loss of remission similar to our study, namely the number of tender or swollen joints, other than DAS28, and low ESR levels.[11]

In our study, the majority of patients discontinued treatment with MTX because of inefficacy, followed by adverse events. At univariate analysis, MTX monotherapy, lower age, positivity of ACPA, a higher number of tender and swollen joints, and surprisingly a higher dose of MTX were associated with the failure or early discontinuation of MTX during the 1st year of treatment.

These results have not previously been reported. Furthermore, it is noted that some previous studies relate back to a period in which the measurement of ACPA was not used in clinical practice.

Evaluating the possible correlation between the dose of the drug and the causes of discontinuation, we have observed that a lower dosage was more frequently associated with discontinuation for inefficacy than adverse events and the contrary was detected for higher doses. Interestingly, 49 patients (9.1%) were treated with 7.5 mg of MTX weekly.

Intuitively, a low dosage of drug can contribute to early discontinuation due to inefficacy. It is surprising that about 10% of early RA patients are still treated with a very low dosage of MTX. This topic was previously investigated in the MTX for RA in Italy study, highlighting that in Italy, the first dose of MTX is often lower than or equal to 10 mg weekly and, in this regard, an initial low dose of MTX could contribute to an increase drug discontinuation for inefficacy. The authors argued that in common practice, rheumatologists tend to prescribe the lowest possible dose, even when complete remission is not achieved.[18]

Both EULAR and ACR recommend an initial therapeutic dose of 15 mg/week, although it is recognized that

Table 3: Causes of therapy failure according to dosage of methotrexate

	≤7.5 mg	10 mg	15 mg	≥20 mg
Adverse events (%)	0.0	28.0	41.4	68.4
Inefficacy (%)	91.7	48.0	44.9	5.3

Table 4: Multivariate analysis

Parameter	OR	95% CI	*P*
Age	0.98	0.971-0.998	0.025
ACPA	1.531	1.019-2.300	0.04
Combination therapy	0.148	0.019-1.138	0.066
MTX weekly dosage	1.039	0.985-1.095	0.16
Tender joint count	1.035	1.001-1.071	0.044

Factors associated to early discontinuation of methotrexate. ACPA: Anti-cyclic citrullinated peptide antibodies, MTX: Methotrexate, CI: Confidence interval, OR: Odd ratio

the average tolerable effective dose ranges between 15 and 20 mg/week.[2,3,19,20]

In GISEA registry, a titration of initial dose of MTX is not reported; the absence of a titration of MTX dose could contribute to the development of gastrointestinal side effects and therefore to MTX discontinuation.

Finally, ACPA positivity in younger patients and the higher count of tender joints regardless of the value of acute-phase reactant levels could be helpful in the identification of a cluster of patients to be strictly evaluated at the early stage of the disease to consider the addition of other drugs. In case of MTX failure, and in the presence of poor prognostic factors, the addition of another DMARDs is not recommended, and a targeted synthetic or a biologic DMARDs should always be considered.

Conclusions

During the year of treatment, about a quarter of patients with early RA failed MTX therapy, mainly for inefficacy (43.6% of cases) or adverse events (37.5%). The presence of ACPA, the age of the patient, and the number of tender joints at baseline were directly associated with early MTX failure, while the dose of MTX was correlated to the efficacy and safety of the drug.

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Conflicts of interest

There are no conflicts of interest.

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