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ORIGINAL PAPER

Methotrexate Survival in Early Rheumatoid Arthritis – Single-Center Data

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Abstract

Objective. The study aims to identify RA treatment patterns involving methotrexate and to estimate methotrexate survival and its determinants within the confines of a specific national environment of real-world data.

Methods. In this observational longitudinal retrospective study, data were obtained from a Romanian tertiary university hospital of rheumatology and included all adult csDMARD-naïve RA patients starting methotrexate between January 2000 and January 2024. Eary RA was defined as a symptom duration and disease duration of up to 24 months. Patients were followed until discontinuation of methotrexate, drop-out or up to an arbitrary duration of 60 months from their methotrexate initiation date.

Results. At baseline, the sample included 401 patients, mostly women (75.8%), with an average age of 56.0 years. Longitudinal analysis revealed a cumulative survival probability of methotrexate of 20% at 60 months (63.9% censored), with a median survival of 47 months (95%CI: 36-57 months). Methotrexate survival did not differ significantly according to sex (p=0.31), age above 50 years (p=0.13), symptom duration above 6 months (p=0.42), baseline HDA (p=0.80) and baseline glucocorticoid prescription (p=0.63). Baseline DAS28-CRP was significantly associated with methotrexate survival (HR=1.76; 95%CI 1.4-2.2; p<0.001). In case of methotrexate failure, step-up strategies consisted of adding hydroxychloroquine (36.3%), sulfasalazine (34.1%), b/tsDMARDs (18.7%), leflunomide (11.0%) or combinations. Methotrexate was discontinued mostly because of adverse events (55.1%), inefficacy (34.7%) and patient decision (9.2%). When methotrexate was stopped, it was most often replaced with leflunomide (66.3%), hydroxychloroquine (15.8%), sulfasalazine (11.6%) or b/tsDMARDs (6.3%), or combinations.

Conclusions. Methotrexate survival at 60 months after initiation is low and the risk of discontinuing methotrexate increases with baseline DAS28-defined RA activity. Methotrexate management in early RA needs refining based on clinical profiles of efficacy and tolerability.

Keywords: rheumatoid arthritis, methotrexate, persistence, survival.

Introduction

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disorder primarily affecting synovial joints, leading to inflammation, pain, and progressive joint destruction, which is associated with significant morbidity and disability. Early diagnosis and treatment are essential to improve long-term outcomes and quality of life.

Methotrexate is the cornerstone of RA treatment, serving as the first-line disease-modifying antirheumatic drug (DMARD). It effectively reduces joint inflammation, slows radiographic progression, and improves functional outcomes. Methotrexate is often used alone or in combination with other conventional synthetic DMARDs or with modern molecules, with a well-established safety and efficacy profile. Methotrexate exerts its remissive effect in RA mainly by inhibiting dihydrofolate reductase, reducing DNA synthesis and lymphocyte proliferation. It also increases extracellular adenosine, which suppresses pro-inflammatory cytokine production. These mechanisms collectively reduce synovial inflammation and joint damage, contributing to methotrexate's effectiveness as a DMARD. The drug is typically administered once weekly (to minimize toxicity) and the initial dose is usually from 7.5 to 15 mg per week, either orally, subcutaneously or intramuscularly. The dose may be titrated up based on clinical response and tolerance, usually to a maximum of 25 mg per week. Methotrexate is generally well-tolerated in the doses used for RA, but it requires regular monitoring due to potential clinical intolerance, hepatotoxicity, myelosuppression, and pulmonary toxicity. Adverse effects are dose-dependent and often mitigated with folic acid supplementation. Long-term safety is favorable when

appropriately monitored, supporting methotrexate's continued use as the "anchor drug" in RA management.

International expert recommendations and national prescription guidelines (health policies) uniquely interact to influence prescription patterns for early RA: while both agree that methotrexate should be part of any initiation regimen, adding to methotrexate or replacing methotrexate with conventional synthetic, biologic and targeted synthetic disease-modifying antirheumatic drugs (cs/b/tsDMARDs) may differ between European countries. While prescription patterns [1-7] and methotrexate survival [8-13] data exist for western countries, reports from eastern Europe are lacking. In this context, the study aims to identify RA treatment patterns involving methotrexate and to estimate methotrexate survival and its determinants within the confines of a specific national environment of real-world data.

Materials and Methods

Methotrexate use for RA in Romania

Romanian clinical guidelines mandate methotrexate as the first-line csDMARD in RA management. If not contraindicated, methotrexate is introduced at diagnosis or as early as possible, starting usually with 10 mg/week, up to 25 mg/week in subcutaneous or oral (less frequent, due to commercial unavailability of pills), frequently alongside folate supplementation to reduce side effects. Methotrexate is prescribed alone or in combination with other csDMARDs (usually sulfasalazine, hydroxychloroquine), especially when aiming for rapid disease control. The Romanian National Health Insurance House fully reimburses methotrexate under the standard RA treatment protocol. Previously published data from the Romanian Registry of Rheumatic Diseases (RRBR) show that about 48.7 % of b/tsDMARD-treated RA patients are on methotrexate, with 41.9 % receiving at least 20 mg/week, while 18.1 % are on moderate doses (15-20 mg/week), and 40% on lower doses (≤ 12.5 mg/week) [14].

Data source

In this observational longitudinal retrospective study, data were obtained from a Romanian tertiary university hospital of rheumatology and included all adult csDMARD-naïve RA patients starting methotrexate between January 2000 and January 2024. All RA diagnoses fulfilled the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria [15]. The following exclusion criteria were applied: previous csDMARD or b/tsDMARD use prior to methotrexate initiation; concomitant diagnosis of other inflammatory rheumatic diseases (e.g., systemic lupus erythematosus, systemic sclerosis, spondyloarthritis); incomplete medical records regarding methotrexate initiation date, duration, or reason for discontinuation; patients enrolled in interventional clinical trials; pregnancy at baseline or within follow-up; methotrexate initiated for non-rheumatoid indications (e.g., psoriasis, inflammatory bowel diseases). Eary RA was defined as a symptom duration and disease duration of up to 24 months. Patients were followed until discontinuation of methotrexate, drop-out or up to an arbitrary duration of 60 months from their methotrexate initiation date.

The following variables were collected for each patient at baseline and every available visit until censoring: demographics (age at study observation start, sex), RA timeframe (date of symptom duration, date of RA diagnosis), RA phenotype (status of rheumatoid factor – RF, and anti-citrullinated protein antibodies – ACPA), acute phase reactants (C-reactive protein – CRP, normal < 5 mg/L; erythrocyte sedimentation rate – ESR, normal < 20 mm/h), RA activity (tender joint count, swollen joint count, patient global assessment on a 100 mm visual analogue scale, DAS28 calculated with both CRP and ESR, defining remission as DAS28 < 2.6, low disease activity - LDA as 2.6-3.2, moderate disease activity – MDA as 3.2-5.1, and high disease activity - HDA as > 5.1) and RA treatment (DMARDs, glucocorticoids).

Statistics

The normality of the data distribution was assessed using descriptive statistics, normality, stem plots and leaves, and Kolmogorov-Smirnov tests corrected by Lilliefors. Continuous variables describing patient characteristics are reported as "average ± standard deviation" (if normally distributed) or "median (first quartile - third quartile)" (if non-normally distributed). Survival of methotrexate therapy (time to discontinuation of methotrexate) were assessed with Kaplan Meier analysis, factoring for sex, age above 50 years, symptom duration above 6 months, DAS28-CRP-defined high disease activity (HDA) at baseline, glucocorticoid prescription at baseline (all compared by log rank). An unadjusted Cox proportional hazards regression model was used to evaluate the association between baseline DAS28-CRP and time to methotrexate discontinuation in months. Tests were considered significant if $p < 0.05$ and were performed using IBM SPSS Statistics version 25.0 forWindows (IBM Corp., Armonk, NY, USA).

Results

At baseline (Table 1), the sample included 401 patients, mostly women (75.8%), with an average age of 56.0 years, diagnosed with early RA. Most RA cases were seropositive (59.4% RF positive; 65.4% ACPA positive), with highly active disease (average DAS28-ESR of 5.9 and average DAS28CRP of 5.3). All patients were started on methotrexate: 86.1% started with a dose of 10 mg/week and in 94.6% of cases the administration route was subcutaneous. Also, 79.5% of them received concomitant oral glucocorticoids.

Table 1. *Baseline characteristics (n = 401)*

women	75.8%
age (years)	56.0 ± 13.4
symptom duration (years)	0.5 (0.3-2.0)

disease duration (years)	0.3 (0.0-1.7)
RF positive	59.4%
ACPA positive	65.4%
RF and ACPA positive	54.6%
CRP (mg/L)	15.3 (6.5-41.6)
ESR (mm/h)	43 ± 26
tender joint count/28	7 (4-12)
swollen joint count/28	5 (3-10)
PGA (mm)	44 ± 31
DAS28-CRP	5.3 ± 1.3
DAS28-ESR	5.9 ± 1.3
% initiating 10 mg MTX	86.1%
% initiating SC MTX	94.6%
% concomitant oral GC	79.5%

Abbreviations: ACPA – anti-citrullinated protein antibodies; CRP – C-reactive protein; DAS – disease activity score; ESR – erythrocyte sedimentation rate; GC – glucocorticoids; MTX – methotrexate; PGA – patient's global assessment; RF – rheumatoid factor; SC – subcutaneous.

Longitudinal analysis revealed a cumulative survival probability of methotrexate of 20% at 60 months (63.9% were censored; Figure 1), with a median survival of 47 months (95% CI: 36-57 months). Methotrexate survival did not differ significantly according to sex (p = 0.31), age above 50 years (p = 0.13), symptom duration above 6 months (p = 0.42), baseline HDA (p = 0.80) and baseline glucocorticoid prescription (p = 0.63).

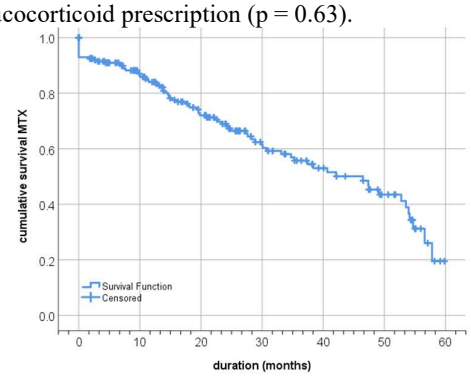

Figure 1. *Methotrexate survival in early RA at 60 months.*

Baseline DAS28-CRP was significantly associated with methotrexate survival (Wald = 25.1; df = 1; p < 0.001): for every unit increase in baseline DAS28-CRP, the risk of methotrexate discontinuation increased by 76% (hazard ratio = 1.76; 95% CI 1.4-2.2; Figure 2).

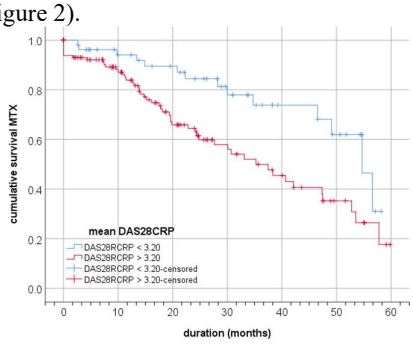

Figure 2. *Methotrexate survival according to baseline DAS28-CRP category (log rank $\chi 2$ = 7.9, p = 0.005): either < 3.2 (55 months, 95% CI 47-60 months) or > 3.2 (35 months, 95% CI 26-45 months).*

In case of methotrexate failure to reach treatment target, step-up strategies consisted of adding hydroxychloroquine (36.3%), sulfasalazine (34.1%), b/tsDMARDs (18.7%), leflunomide (11.0%) or combinations of these additional drugs. Methotrexate was discontinued mostly because of adverse events (55.1%), inefficacy (34.7%) and patient decision (9.2%), while other causes were underrepresented (death 1.0%) or absent (pregnancy, persistent remission). When methotrexate was stopped, it was most often replaced with leflunomide (66.3%), hydroxychloroquine (15.8%), sulfasalazine (11.6%) or b/tsDMARDs (6.3%), or combinations of these replacements.

Discussions

In this longitudinal retrospective study of 401 patients with early RA, the median observed methotrexate survival was 47 months, with a cumulative survival probability of only 20% at 60 months. These findings reflect the real-world complexity of long-term methotrexate persistence in routine clinical practice and underscore the substantial attrition observed over time, with nearly two-thirds of patients censored due to incomplete follow-up or alternative treatment pathways. Importantly, methotrexate survival was not significantly influenced by demographic factors such as sex or age, nor by clinical parameters such as baseline HDA, symptom duration over six months, or concomitant glucocorticoid use. This suggests that these commonly recorded baseline characteristics may not be reliable predictors of long-term methotrexate survival. In contrast, baseline disease activity measured by DAS28-CRP was significantly associated with methotrexate survival. For every unit increase in DAS28-CRP, the hazard of discontinuing MTX increased by 76%, highlighting that patients with higher inflammatory burden may require earlier treatment intensification or alternative therapeutic approaches. The main reasons for methotrexate discontinuation were adverse events (55.1%) and inefficacy (34.7%), in line with previous European cohort data. Notably, patient-driven discontinuation accounted for nearly 10% of cases, reflecting the role of individual preferences, perceived tolerability, and possibly inadequate shared decision-making. Pregnancy and persistent remission were not observed as causes for discontinuation in this cohort, likely due to the relatively short median disease duration and the structure of care pathways in Romanian practice. In cases where methotrexate failed to achieve treatment targets, step-up strategies varied, with hydroxychloroquine (36.3%) and sulfasalazine (34.1%) being the most common csDMARDs added. Only 18.7% of patients transitioned to b/tsDMARDs, reflecting both reimbursement constraints and guideline-based requirements for csDMARD failure

before escalation. When methotrexate was discontinued entirely, leflunomide (66.3%) emerged as the most frequent replacement, consistent with its availability and csDMARD status in national protocols.

These findings are consistent with real-world data from other settings, although median methotrexate survival in this Romanian cohort appears somewhat shorter than in countries with more aggressive early treatment strategies and easier access to biologics. For example, in a recent study by Perrotta et al. among 242 Italian methotrexate users, the survival rate of methotrexate at 24 months was approximately 60%, while at 48 months and 96 months, it was 40% and 20%, respectively [13]. Different populations show higher methotrexate survival: Ideguchi et al. reported that the cumulative methotrexate survival probability after 5 years was 61.9% in group of 273 RA patients for Japan [11]. Older studies report even greater methotrexate survival, probably illustrating the lack of advanced therapies [8]. Interestingly, methotrexate persistence does not seem to be strongly genetically determined [16], genome-wide association studies reporting a polygenic architecture associated with methotrexate survival and an inverse correlation of methotrexate persistence with greater genetic disposition for RA. Since methotrexate persistence is not strongly determined by genetics alone, clinical factors (such as disease activity, disease severity, comorbidities, and adverse effects) likely play a more dominant role in the discontinuation of methotrexate, as outlined in this study.

The results also emphasize the need for close monitoring of patients with high baseline disease activity, who appear at higher risk for methotrexate failure. Additionally, the observed patterns of methotrexate replacement and step-up strategies reflect national prescribing behaviors and could inform local health policy and therapeutic algorithms.

This study has several limitations, including its retrospective design, the potential for residual confounding, and the lack of systematic adverse event recording. However, the large sample size, real-world setting, and longitudinal follow-up enhance the generalizability of our findings and provide valuable insights into the long-term use and limitations of methotrexate in early RA management.

Conclusions

Methotrexate survival at 60 months after initiation is low and the risk of discontinuing methotrexate increases with baseline DAS28-defined RA activity. Methotrexate failure determines most often a step-up csDMARD strategy, not addition of b/tsDMARDs, which represents a constraint of the national regulations. The leading causes of methotrexate discontinuation are adverse events, followed by inefficacy. In conclusion, methotrexate management in early RA needs refining based on clinical profiles of efficacy and tolerability.

Conflicts of Interest: The authors declare no conflicts of interest.

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