Egyptian Rheumatology and Rehabilitation

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Efficacy and gastrointestinal tolerability of methotrexate in late-onset rheumatoid arthritis patients: a prospective cohort study

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Abstract

Background The proportion of the late-onset forms of disease is growing in rheumatoid arthritis (RA) population. Concerns about comorbidities and drug adverse events lead to delay or ineffective treatment in these patients. The aim of this study is to analyze the tolerability and efficacy of methotrexate therapy in late-onset RA (LORA) patients and compare the baseline characteristics, efficacy, and gastrointestinal (GIT) adverse effects of methotrexate treatment between LORA and young-onset RA patients (YORA).

Results Patients whose symptoms began after 65 years or older were classified as LORA. Baseline characteristics, rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA) status, C-reactive proten (CRP) levels, disease activity scores, and radiographs of hands and feet were recorded. Patients were started to methotrexate therapy and followed for 6 months. Female gender was predominant in both LORA and YORA. LORA patients had less seropositivity (RF or anti-CCP), higher CRP levels, and higher DAS 28 scores. More than half of the patients (58%) had large joint involvement. Remission rates were higher in LORA patients, and total remission and low disease activity rates were similar. Methotrexate withdrawal due to gastrointestinal adverse events (nausea and vomiting) was lower than YORA patients. Logistic regression analysis demonstrated that DAS 28 score was the only predictor for disease remission (*p*: 0.000), and no predictive factor was found for methotrexate-related adverse events.

Conclusion Methotrexate-related gastrointestinal adverse events do not increase in LORA patients, and nausea-vomiting is seen lower than YORA. Methotrexate is well tolerated and effective in LORA patients, and a large amount of patients achieve treatment targets after 6 months of treatment with MTX. Methotrexate should be started immediately in LORA without additional concerns on adverse effects.

Keywords Late-onset rheumatoid arthritis, Methotrexate, Efficacy, GIT adverse events

Key summary points

This is the first prospective cohort study evaluating methotrexate efficacy and tolerability in late-onset rheumatoid arthritis patients. Our data demonstrated that methotrexate is effective, and drug withdrawal due to adverse events and nonresponse is low. A large amount of patients achieved treatment target (remission and low-disease activity) with methotrexate.

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Background

Rheumatoid arthritis (RA) is one of the most common chronic inflammatory autoimmune diseases, characterized by an inflammatory polyarthritis. The precise etiology of RA remains uncertain; multiple genetic, environmental, immunologic, and other factors contribute to the development of the disease [1, 2]. It is estimated that RA affects 0.24 to 1% of the population, and the prevalence was approximately two times higher in females than males [3–5]. RA commonly affects patients aged 30–50 years old, and incidence increases with age [6].

The clinical spectrum of RA is heterogeneous, and the primary goal of treatment is to control the symptoms, prevention of structural damage, and preservation of function. Methotrexate (MTX) is the anchor drug for RA. There is strong evidence about efficacy of MTX; studies demonstrated reduced symptoms and less joint damage with the use of MTX in RA patients [7, 8]. However, in observational studies, approximately 30% of patients discontinue MTX due to inefficacy and adverse events [9, 10]. Factors such as female gender, current smoking, disease duration, disease activity, RF, and anti-citrullinated protein antibody (ACPA) status are associated with MTX nonresponse. But these data from previous studies is obtained from retrospective data from small populations. It has been reported that 7 to 30% of patients discontinue MTX therapy within the first year of treatment due to toxicity [11, 12]. Common adverse events that cause MTX withdrawal are hematologic, gastrointestinal, pulmonary, infectious, mucocutaneous, renal, neuropsychiatric, and musculoskeletal adverse events [13]. Among these adverse events, GI side effects, especially nausea and vomiting, are the most limiting cause of optimal use of MTX in real-life experiences.

LORA (late-onset RA) is defined as RA with an onset age over 60–65, which is almost 10–33% of the elderly RA population [9, 14]. It was reported in the literature that late-onset RA has a higher proportion of male gender, less frequent positivity for RF/ACPA, and higher titers for C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) [13, 14]. However, today, it is still unclear whether late-onset RA and young-onset RA are different diseases or same entitiy with minor differences. There is limited evidence on the efficacy of MTX in elderly, because clinicians tend to preferr less aggresive treatment choices in these patients. Clinical trials make restrictions due to age and comorbidities. Therefore, there is an ongoing need to identify the efficacy, side effects, and tolerability of MTX in late-onset RA patients.

The aim of this study is to evaluate the efficacy and tolerability of methotrexate, predictors of remission, and methotrexate nonresponse in late-onset RA patients and compare the baseline characteristics, efficacy, and adverse effects of methotrexate treatment between late-onset RA and young-onset RA patients.

Methods

This was a single-center prospective cohort study. Consecutive RA patients aged > 18 years and fulfilled the American College of Rheumatology/EULAR 2010 classification criteria for RA [15] were recruited between January 2020 and January 2021. In this cohort, patients whose symptoms began after 65 years or older were classified as LORA. Exclusion criteria were as follows: systemic rheumatic disease other than RA, history of DMARD use, malignancy, and pregnancy. All patients provided informed written consent.

The numbers of tender and swollen joints, the visual analog scale (VAS) scores, and physician's global assessment of disease were collected. Large joint involvement referred to shoulders, elbows, hips, knees, and ankles. Extraarticular manifestations include the following: skin (subcutaneous nodules, vasculitis), ocular (keratoconjunctivitis sicca, episcleritis, scleritis, keratitis), pulmonary (pulmonary nodules, interstitial lung disease, pleural effusion), cardiac (percardial effusion-pericarditis), and neurological(peripheral neuropathy/mononeuritis multiplex) manifestations. Patients who has renal disease due to RA or other diseases were excluded from the study. We followed up patients for gastrointestinal side effects as nausea-vomiting and hepatic adverse events, which are the most common causes of drug withdrawal.

Radiographs of hands and feet are obtained at the first visit. The term "erosive disease" indicated an erosion is seen in at least three separate joints at any of the following sites: the proximal interphalangeal, the metacarpophalangeal, the wrist (counted as one joint), and the metatarsophalangeal joints on radiographs of both hands and feet as defined in the 2010 ACR/EULAR RA classification criteria [16]. Seropositive RA was used for patients that have positive results for either RF (rheumatoid factor) or anti-CCP (anti-cyclic citrullinated peptide). Laboratory assessments include complete blood counts, liver tests (ALT, AST), serum creatinine/GFR, and CRP. Laboratory tests were first performed after 4 weeks and then every 12 weeks during follow-up. Disease activity was measured by DAS28 [17], SDAI [18], and CDAI [19] scores. PGA (Patient Global Assessment of Disease Activity) and EGA (Evaluator Global Assessment of Disease Activity) were asssessed on a 10-cm visual analogue scale. SJC and TJC each constitute 28 joint counts.

All patients started methotrexate as soon as they were diagnosed for RA. Folic acid in a dose of 5 mg was given the day after every methotrexate dose. The dosage was up-titrated from 10 to 15 mg over 3–4 weeks. No

subcutaneous dosing was used. Low-dose prednisone(≤ 5 mg) and NSAIDs were allowed during the study. Concomitant medications had to be stable for ≥ 3 months. Patients taking additional medications that could interact with MTX were excluded. Patients were categorized into responders to MTX and nonresponders to MTX according to the EULAR response criteria (improvement of ≤ 0.6 or improvement > 0.6 but ≤ 1.2 and a DAS 28 score attained during follow-up of > 3.7) [20]. Patients were reevaluted at 1st and 6th months of therapy. We assessed the frequency of remission and low disease activity (LDA) using American College of Rheumatology criteria in both groups after 24 weeks [21].

Adverse events (AEs)

Adverse events were categorized as gastrointestinal (and this category subdivided for hepatic AEs and nausea-vomitting), hematologic (leukopenia, anemia, trombocytopenia), mucocutaneus (mouth sores, stomatitis, dry mouth, hair loss, rash), pulmonary (nodules, hypersensitivity pneumonitis), and neuropsychiatric. Subjects who had mild mucocutaneus adverse events or abnormal liver tests lower than 3 times of ULN (upper limits of normal) were advised to reduce methotrexate dosage (from 15 to 10 mg/weekly) and increased folic acid dose (5 to 10–15 mg/week). In case of severe adverse events, methotrexate was stopped. Hepatic adverse events were categorized based on 2 or 3 times of ULN.

The study was conducted in accordance with the Declaration of Helsinki and was in compliance with Good Clinical Practice Guidelines

Statistical analysis

The baseline characteristics of LORA and YORA were compared using a *t*-test or Mann-Whitney *U*-test for continuous variables and chi-square test for categorical measures or Fisher's exact test when chi-square test was not suitable. The significant independent variables in the univariate analyses were tested in multivariate stepwise regression models. The results were expressed as odds ratios (ORs) in logistic regression models and as regression coefficients in linear regression models. The 95% confidence interval (95% CI) was calculated, and a *p*-value less or equal 0.05 was considered significant. Power analysis is performed with a power of 0.80.

SPSS, version 26, was used for the data analysis.

Results

Baseline characteristics

Total of 250 patients (69 LORA and 181 YORA) were evalutated.

LORA

Mean age was 68.93 years. A total of 68% of patients were female; 62.2% patients had seropositive RA. A total of 58% of patients had large joint involvement.Twenty patients (29%) had erosive disease at the presentation. Five patients (7.2%) had extraarticular manifestations at first visit (1 NSIP, 1 pulmonary nodule, 2 sicca,1 cutaneous vasculitis). Eight patients (11.6%) had no response to MTX treatment at the end of the 6 months. Seven patients (10.1%) discontinued MTX due to adverse events (GIS: 3 patients, leucopenia: 1, pancytopenia: 1, ALTX3ULN: 2 patients). A total of 43% of patients met the criteria for remission and 40% for LDA.

In multivariate analysis, erosive disease was associated with age (*p*: 0.026), higher CRP (*p*: 0.048), SDAI (*p*: 0.032), and CDAI (*p*: 0.041) (Table 1). Logistic regression analysis demonstrated that DAS 28 score was the only predictor for disease remission (p: 0.000) (Table 2).

YORA

Mean age was 49.93 years. A total of 77% of patients were female, and 83.4% of patients had seropositive RA. A total of 48.1% of patients had large joint involvement. A total of 24.3% of patients had erosive disease at the presentation. Seven patients (3.9%) had extraarticular manifestations (2 pulmonary nodules, 4 sicca, and 1 peripheral neuropathy). Eighteen patients (9.9%) had no response to MTX. Twenty-nine patients discontinued MTX due to adverse events (GIS: 23 patients, leucopenia: 1, trombocytopenia: 1, ALTXx3ULN: 2, hair loss: 1). MTX withdrawal due to nausea-vomiting was seen in 23 patients (19 females, 4 males). A total of 30% of patients met the criteria for remission and 44% for LDA.

Comparison of LORA and YORA

Female/male ratio was similar between groups. Seropositive RA patients were statistically higher in YORA than LORA (*p*: 0.000). There were no differences in terms of symptom duration, large joint involvement, erosive disease, and extraarticular manifestations (*p*: 0.404, *p*: 0.104, *p*: 0.273, and *p*: 0.211, respectively). Mean CRP levels and DAS 28 scores at first visit were higher in LORA patients (*p*: 0.000). Remission rates were higher in LORA patients(*p*: 0.044), but there were no difference in LDA rates (*p*: 0.223). MTX nonresponse and adverse events were similar (*p*: 0.246 and *p*: 0.163). Total of 26 patients (21 females, 5 males) discontinued MTX due to nausea and vomitting both in LORA and YORA groups and correlated with younger age (*p*: 0.001). MTX discontination due to GIS adverse events (nausea and vomiting) was higher in YORA patients (*p*: 0.038) (Table 3).

Table 1 Multiple linear and logistic regression analysis of LORA

Variable	Gender	Seropositive RA	Erosive RA	MTX nonresponder	MTX withdrawal due to adverse event
Large joint involvement	*p*: 0.350 *OR*: 0.707	*p*: 0.237 *OR*: 0.609	*p*: 0.315 *OR*: 1.513	*p*: 0.193 *OR*: 0.389	*p*: 0.368 *OR*: 1.929
Only large joint involvement	*p*: 0.629 *OR*: 0.930	*p*: 0.594 *OR*: 1.231	*p*: 0.435 *OR*: 0.463	*p*: 0.463 *OR*: 1.109	*p*: 0.109 *OR*: 5.80
Extraarticular manifestations	*p*: 0.136 *OR*: 0.894	*p*: 0.371 *OR*: 2.56	*p*: 0.453 *OR*: 1.704	*p*: 0.471 *OR*: 2.036	*p*: 0.077 *OR*: 7.86
MTX nonresponders	*p*: 0.203 *OR*: 3.675	*p*: 0.654 *OR*: 1.009	*p*: 0.577 *OR*: 0.796	NA	*p*: 0.030 *OR*: 8.55
MTX withdrawal due to adverse events	*p*: 0.606 *OR*: 1.190	*p*: 0.236 *OR*: 0.413	*p*: 0.339 *OR*: 0.377	*p*: 0.030 *OR*: 8.55	NA
Symptom duration	*p*: 0.653 *β*: −0.063	*p*: 0.470 *β*: −0.100	*p*: 0.085 *β*: −0.218	*p*: 0.323 *β*: 0.131	*p*: 0.991 *β*: −0.002
Age	*p*: 0.844 *β*: 0.028	*p*: 0.065 *β*: 0.259	*p*: 0.026* *β*: −0.284	*p*: 0.592 *β*: −0.071	*p*: 0.968 *β*: 0.006
DAS28	*p*: 0.627 *β*: 0.489	*p*: 0.753 *β*: 0.126	p:0.881 *β*: −0.054	*p*: 0.381 *β*: −0.335	*p*: 0.781 *β*: 0.114
SDAI	*p*: 0.869 *β*: 0.180	*p*: 0.728 *β*: 0.373	*p*: 0.032* *β*: 2.12	*p*: 0.949 *β*: −0.066	*p*: 0.361 *β*: −1.008
CDAI	*p*: 0.763 β: −0.023	*p*: 0.690 *β*: −0.348	*p*: 0.041* *β*: −1.64	*p*: 0.892 *β*: −0.113	*p*: 0.449 *β*: 0.681
CRP	p: 0.986 β: 0.009	*p*: 0.630 *β*: −0.248	*p*: 0.048* *β*: −0.933	*p*: 0.476 *β*: 0.350	*p*: 0.481 *β*: 0.373

LORA late-onet rheumatoid arthritis, *RA* rheumatoid arthritis, *MTX* methotrexate, *DAS28* disease activity score-28, *SDAI* simple disease activity index, *CDAI* clinical disease activity index, *CRP* C-reactive protein, *OR* odds ratio, *NA* not applicable.

* Means significance ($p \leq 0.05$ is statistically significant)

Table 2 Logistic regression analysis of the impact factors on remission in LORA patients

Variable	*p*-value	OR	95% *CI* for OR
Age	0.430	0.990	0.967–1.015
Seropositivity	0.980	0.991	0.495–1.985
Large joint inv.	0.743	1.111	0.593–2.080
Only large joint	0.657	0.786	0.271–2.279
Erosive RA	0.936	1.028	0.522–2.023
Extraarticular man.	0.456	0.606	0.163–2.257
Disease duration	0.763	1.010	0.947–1.076
DAS 28	0.000*	3.688	2.013–6.755
CRP	0.323	0.994	0.981–1.006

LORA late-onset rheumatoid arthritis, *RA* rheumatoid arthritis, *DAS28* disease activity score-28, *CRP* C-reactive protein, *OR* odds ratio

* Means significance ($p \leq 0.05$ is statistically significant)

Discussion

This is a prospective observational cohort study to describe the clinical, serological characteristics of LORA and to assess the efficacy and tolerability of methotrexate in these patients. To our knowledge, this is the first prospective analysis on the efficacy and intolerance of methotrexate therapy in LORA patients.

Our results demonstrated that LORA patients had less seropositivity (RF or anti-CCP), higher CRP levels, and higher DAS 28 score. Remission rates were higher in LORA patients, and total remission and LDA rates were similar with YORA. MTX withdrawal due to GI adverse events (nausea and vomiting) is much lower than YORA patients. The current study found clear support for the effective, safe, and well-tolerated use of MTX in LORA patients. Nausea and vomitting are the most limiting cause of MTX use, and from our results, it is evident that these GI adverse events are mostly seen in young female patients.

Early studies that focus on clinical features showed no differences in clinical findings and radiographic progression between LORA and YORA patients [22–24]. A similar pattern of results was also obtained by the current study that baseline characteristics, female predominance, symptom duration, large joint involvement, erosive disease course, and extraarticular manifestations, were similar between LORA and YORA patients. But the proportion of male patients did not increase in LORA group. In our study, we classified patients as "seropositive RA" if RF or anti-CCP was positive. Previous studies reported prevalence of anti-CCP antibodies in LORA varies between 65 and 77% and between 69 and 92% in YORA

Table 3 Comparison of LORA and YORA patients

Variable	LORA ($n = 69$)	EORA ($n = 181$)	*p*-value
Age (mean)	68.93 ± 6.5	49.93 ± 9.68	
Gender (female/male)	47/22	141/40	0.201
Seropositivity (*n*/%)	43 (62.3%)	151 (83.4%)	0.000*
Symptom duration (mean/years)	2.59 ± 3.06	3.48 ± 5.17	0.404
Large joint involvement (*n*/%)	40 (58%)	87 (48.1%)	0.104
Only large joint involvement (*n*/%)	6 (8.7%)	14 (7.7%)	0.491
Erosive disease (*n*/%)	20 (29%)	44 (24.3%)	0.273
Extraarticular manifestations (*n*/%)	5 (7.2%)	7 (3.9%)	0.211
CRP (mean/mg/L)	31.9 ± 28.24	22.56 ± 31.6	0.000*
DAS 28 (mean)	4.8 ± 0.69	4.58 ± 0.65	0.024*
SDAI (mean)	12.5 ± 5.97	14.37 ± 4.4	0.066
CDAI (mean)	14.89 ± 5.42	11.01 ± 5.56	0.443
Remission (*n*/%)	30 (43%)	56 (30%)	0.044*
LDA (*n*/%)	28 (40%)	85 (44%)	0.223
MTX nonresponders (*n*/%)	8 (11.6%)	18 (9.9%)	0.246
MTX withdrawal due to adverse events (*n*/%)	7 (10.1%)	29 (16%)	0.163
MTX withdrawal due to nausea-vomiting (*n*/%)	3 (4%)	23 (12%)	0.038*

LORA late-onset rheumatoid arthritis, *EORA* early-onset rheumatoid arthritis, *MTX* methotrexate, *DAS28* disease activity score-28, *SDAI* simple disease activity index, *CDAI* clinical disease activity index, *CRP* C-reactive protein, *LDA* low disease activity.

* Means significance ($p \leq 0.05$) is statistically significant)

patients [25, 26]. Consistent with these data, our findings showed that seropositivity (RF/CCP positivity) was lower (62.3%) in LORA than (83.4%) YORA patients. Decrease in autoantibody response with aging can be explained by the decline in the function of the adaptive immune system as a consequence of immunosenescence [27]. Also, DAS 28-CRP scores and CRP levels were higher than YORA, and these findings support the previous studies [23, 28].

Methotrexate is the cornerstone for rheumatoid arthritis therapy. There have been studies evaluating efficacy and toxicity of methotrexate in RA patients using biomarkers. Active MTX polyglutamate levels (MTXPGs) have been shown to be related to clinical outcomes in rheumatoid arthritis (RA) and juvenile idiopathic arthritis (JIA). Higher concentrations of long-chain MTXPGs were also associated with favorable outcomes in RA [29] and risk of gastrointestinal toxicity in JIA [30]. Also, several genes have been studied to investigate the association with the efficacy and toxicity of methotrexate, but the results were controversial [31–35]. Yet, it still seems not possible to predict the outcomes of patients on methotrexate based on biomarkers or genetic investigations. A retrospective analysis of clinical predictors of methotrexate response conducted by Duong et al. showed that baseline disease activity score-28-eryhtrocyte sedimentation rate (DAS28-ESR), positive ACPA, and health assessment questionnare (HAQ) score were the predictors for drug response [36]. Our study demonstrated that only higher DAS 28 score is the predictor for remission in the methotrexate therapy both in LORA and YORA patients.

Another important issue is that there has been no evidence that methotrexate pharmacokinetics and pharmacodynamics change significantly with age. Bresolle et al. showed that drug pharmocokinetics are not significantly different from younger ages, but dose adjustments should be made in patients who have renal impairment [37]. Besides, previous studies confirmed that age does not affect MTX efficacy or the rate of side effects; patients had similar response rates to MTX [38, 39]. Our data also showed that with same MTX dosages, LORA patients had better remission rates, and achievement of treatment targets was similar after 24 weeks.

A study conducted by Yazici et al. showed that the probability of continuing methotrexate over 5 years was 79%, and permanent discontinuations due to adverse events were 10% of all patients [40]. A recent study from UK also demonstrated that gastrointestinal adverse events were less reported in older age, and these gastrointestinal adverse events were most prevalent in the first year of MTX therapy [41]. Our data also proved that gastrointestinal side effects, especially nausea and vomiting, were much less common in LORA patients. Nausea and vomiting were seen mostly in young female patients and is the leading cause of MTX withdrawal.

Conclusıon

Late-onset rheumatoid arthritis (LORA) is not a different clinical entity from RA. Our results suggest that methotrexate-related adverse events do not increase in LORA patients, and nausea and vomiting are seen lower than YORA. Remission and LDA rates are similar with methotrexte therapy, and the only predictor for remission is higher DAS-28. The present findings confirm that methotrexate is well tolerated and effective in LORA patients, and a large amount of patients achieve treatment targets after 6 months of treatment with MTX.

Abbreviations

ACR	American College of Rheumatology
AEs	Adverse events
Anti-CCP	Anti-cyclic citrullinated peptide
CDAI	Clinical Disease Activity Index
CI	Confidence interval
CRP	C-reactive protein
DAS 28	Disease activity score-28
DMARD	Disease-modifying antirheumatic drugs
EGA	Evaluator Global Assessment of Disease Activity
EULAR	European Alliance of Associations for Rheumatology
GIT	Gastrointestinal
LDA	Low disease activity
LORA	Late-onset rheumatoid arthritis
MTX	Methotrexate
MTXPGs	Methotrexate polyglutamate levels
NSAID	Nonsteroidal anti-inflammatory drug
OR	Odds ratio
PGA	Patient Global Assessment of Disease Activity
RF	Rheumatoid factor
SDAI	Simple Disease Activity Index
SJC	Swollen joint count
TJC	Tender joint count
ULN	Upper limits of normal
VAS	Visual analog scale
YORA	Young-onset rheumatoid arthritis

Acknowledgements
Not applicable

Authors' contributions
Study conception and design, EDB and IA; data collection, EDB; analysis and interpretation of results, EDB and IA; draft manuscript preparation, EDB. The authors read and approved the final manuscript.

Funding
This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Availability of data and materials
The data that support the findings of this study are available from the corresponding author (E. D. Bayrak), upon reasonable request

Declarations

Ethics approval and consent to participate
A written informed concent was taken from all participants. The protocol was approved by the institutional ethic review board of Acıbadem University (protocol number: 2022-15/36) and conducted in accordance with the Declaration of Helsinki.

Consent for publication
Not applicable

Competing interests
The authors declare that they have no competing interests.

Received: 16 December 2022 Accepted: 7 February 2023
Published online: 13 February 2023

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