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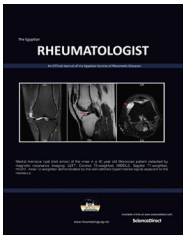

ORIGINAL ARTICLE

# Leading causes of methotrexate and antimalarial drugs discontinuation in Iranian patients with rheumatoid arthritis

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**KEYWORDS**

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**Abstract** *Background:* Methotrexate (MTX) and anti-malarial drugs are widely prescribed for rheumatoid arthritis (RA) as disease-modifying anti-rheumatic drugs (DMARDs). Some patients discontinue treatment because of their adverse effects which could induce disease reactivation.

*Aim of the work:* We aimed to evaluate common causes of DMARD discontinuation such as MTX, chloroquine (CQ) and hydroxychloroquine (HCQ) in patients with rheumatoid arthritis.

*Patients and methods:* We reviewed the records of RA patients referred to the rheumatologic clinic of Shariati Hospital in 2006 and their records were retrospectively reviewed till 1991. Patients who received MTX (with or without CQ or HCQ consumption) for at least one month were included to determine the frequency and more prevalent causes of drug discontinuation.

*Results:* Among 295 RA patients, 28.5% discontinued MTX. Adverse drug effects were found in 27.4% of the patients. However, no serious adverse events such as cirrhosis were reported. Among 271 patients who received antimalarial agents, 41.3% discontinued treatment. 51.3% of drug withdrawals were because of ophthalmological consultation and presence of retinopathy, macular pigmentation, and keratopathy, without any persistent or serious ocular complication such as blindness. Only patients who discontinued treatment due to retinopathy were significantly older than the others.

*Conclusion:* With respect to the relatively low rate of discontinuation due to adverse effects, MTX seems to be a safe drug for long-term use in RA patients. Serial eye examination for those using antimalarial drug will protect them against ocular toxicity which could further lead to higher rates of drug discontinuation.



## 1. Introduction

Rheumatoid arthritis (RA) is the most common form of chronic inflammatory arthritis [1]. It is a multi-factorial disease

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sustained by environmental and genetic factors with substantial evidence implicating cytokines in its pathogenesis and determining the effectiveness of RA treatment with methotrexate (MTX) and glucocorticoids [2]. With respect to the widespread prescription of disease-modifying anti-rheumatic drugs (DMARDs) in RA patients [3], more attention should be paid to adverse drug effects, especially those that lead to drug discontinuation. This could prevent any harm to the patients and facilitate the establishment of better practical guideline for routine medical practice [4]. Also sudden DMARD withdrawal may precipitate disease reactivation [5]. A considerable relation was reported between the MTX dose and disease activity in RA patients [6]. Common DMARDs prescribed for RA include MTX [7] and antimalarial agents such as chloroquine (CQ) or hydroxychloroquine (HCQ) [8]. MTX is a safe, effective and useful therapy for RA. An aspect of the evolving optimism in RA treatment has been the use of multiple agents in combination therapy [9]. Many patients stop medications because of their physicians' order, while others discontinue medication because of experiencing unwanted adverse effects [8].

In a retrospective multicenter study of 760 RA patients that analyzed reasons for DMARD discontinuation, 47.1%, 43.2% and 9% interrupted therapy due to lack of efficacy, adverse events, or undefined reasons, respectively [10]. The most serious toxicities of MTX include hepatic fibrosis, cirrhosis, pneumonitis and myelosuppression which require serial monitoring of the complete blood cells count (CBC), aspartate aminotransferase (AST), albumin and creatinine every 4–8 weeks [11]. *Antimalarials* require intensive monitoring to avoid severe retinal damage that can lead to blindness. Appropriate examinations should be performed regularly in order to decide whether to taper or stop when damage is still mild, preclinical or reversible [12]. A randomized clinical trial showed that adverse effects of HCQ led to permanent discontinuation in 10 of 120 patients due to gastrointestinal complaints in 5, mucocutaneous problems in 4 and disturbed vision in 1 patient [13].

Some researchers emphasize that follow-up eye examinations should be performed with 6–12 months intervals [14,15] while others suggest routine ophthalmic screening is not necessary in patients whose renal function is normal, if the daily dosage is $<6.5$ mg/kg [16]. A multicenter study on 1162 patients to evaluate the causes of DMARD discontinuation showed that antimalarial agents were the second most frequent DMARDs to be discontinued [17].

We aimed to evaluate the common causes for discontinuation of methotrexate, chloroquine, and hydroxychloroquine in a cohort of Iranian RA patients. Possible risk factors and irreversible outcome of adverse effects were also studied in relation to drug discontinuation.

## 2. Patients and methods

In this retrospective study, 295 patients with RA who received $\geqslant 7.5$ mg MTX weekly for at least one month and who had been referred to the Rheumatology Clinic of Shariati Hospital in 2006, Tehran, Iran were included. All the patients included fulfilled the 1987 revised American Rheumatism Association criteria for classification of RA [18]. Ethics committee of Tehran University of Medical Science approved the study proposal and all of data were gathered in numbered coding system to obscure patient's name. Samples were collected among patients who were visited at the Clinic in 2006 and their records were retrospectively reviewed reaching back to 1991. All of the patients had serial follow-up and serial laboratory findings were documented.

These records were reviewed for finding any evidence of MTX prescription and those who received it for at least one month were included. Simultaneously their charts were reviewed for CQ or HCQ prescription and any discontinuation (temporary or permanent discontinuation until data gathering time in 2006) were noted. Finally, the patients were divided into two groups: those who discontinued the drugs and those who continued them (for each drug group). MTX dose was calculated as mean dose per month instead of weekly dosage because of the better presentation of changing dosage in the previous visit [19].

Our data collection form consisted of items regarding the patients' characteristics: age, sex, body mass index (BMI), disease activity, dosage and duration of prednisolone consumption and any concurrent DMARD consumption as CQ or HCQ; their dosages and duration and weekly MTX; dose, duration and cumulative dose. The results of serial laboratory tests at each visit were also recorded such as: CBC, blood urea nitrogen (BUN), creatinine, creatinine clearance (CrCl) calculated by Cockroft-Gault equation [20], AST, alanine aminotransferase (ALT), alkaline phosphatase (ALP), serum albumin, prothrombin time and bilirubin as well as liver sonography (if available). Biannual ophthalmological consultations were obtained from the patients' records for those who used CQ or HCQ to evaluate ocular complications leading to drug discontinuation. Any cause of drug discontinuation was identified based on the records and was added. Finally, initiation of the same drug (compared with persistent drug discontinuation) was noted and their following laboratory findings were collected to evaluate other adverse drug reactions.

### 2.1. Statistical analysis

Data were analyzed using SPSS software, version 12. The data were summarized using descriptive statistics: mean ± standard deviation (±SD), or frequencies (number) and percentages (%). *T*-test and Chi-square test were used as appropriated. A probability value $p < 0.05$ was considered statistically significant.

## 3. Results

Among the 295 patients with RA who received MTX, 271 (91.9%) also used CQ or HCQ during their follow-up course at the clinic during the study period. The age of the patients was 49.4 ± 12.8 years and 84.4% were women. Their CrCl was 105.2 ± 36.6 cc/min/1.73 $m^2$ and no evidence of severe renal insufficiency (CrCl < 30 cc/min/1.73 $m^2$) was observed. The mean duration of MTX treatment was 40.5 ± 34.6 months and the mean dose was 35.7 ± 11.4 mg/month. Body mass index, disease activity and laboratory features of the RA patients are presented in Table 1.

Eighty-four (28.5%) patients discontinued MTX temporarily but only 23 (7.8%) discontinued it permanently. None of them developed severe or irreversible clinical or laboratory complication such as cirrhosis or pulmonary fibrosis. In most