# Frequency and Causes of Methotrexate Intolerance and Discontinuation in Rheumatoid Arthritis Patients in Qena Governorate

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**Abstract**

**Background:** Methotrexate (MTX) is a conventional disease-modifying anti-rheumatic drug that has been used as first-line therapy for rheumatoid arthritis (RA), the frequency of MTX side effects and its discontinuation has been documented earlier, although it hasn't been fully investigated yet.

**Objectives:** To evaluate the causes and frequency of methotrexate therapy discontinuation in rheumatoid arthritis patients in Qena governorate and to determine risk factors that may increase the incidence of MTX intolerance.

**Patients and methods:** This hospital-based cross-sectional study was done on 200 patients with RA at the outpatient clinic of physical medicine, Rheumatology, and Rehabilitation Department of Qena University Hospital. All patients underwent a comprehensive history taking that included the reason for stopping methotrexate, a comprehensive clinical examination, a laboratory evaluation, and scoring of their disease activity. The patients were categorized into two groups based on their current MTX administration status.

**Results:** A total number of 90 (45%) patients stopped using MTX within 3months to 26 years duration for various reasons; the most frequent reasons for stopping were gastrointestinal and hepatic adverse effects, representing together 55.5% of causes of discontinuation. The two groups had a significant statistical difference regarding corticosteroid intake and the current steroid dose.

**Conclusion:** MTX appears to be a safe medication for RA patients to utilize for an extended period. To achieve the most benefit from an essential component of RA treatment, additional initiatives should be carried out to reduce the negative consequences and stoppage rate of methotrexate.

**Keywords**: Methotrexate; Gastritis; Side effects; Pancytopenia.

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## Introduction

Rheumatoid arthritis (RA) is a persistent autoimmune inflammatory condition that causes symmetrical polyarthritis in addition to systemic manifestations. It affects roughly 0.5–1% of people globally and is linked to serious physical function disorders and a decline in quality of life **(Silva-Fernández et al., 2020)**. Achieving clinical remission should now be the primary goal of treatment for early-stage RA to avoid physical disability and structural damage **(Tracey, 2017)**.

When treating RA, MTX is the most often prescribed disease-modifying anti-rheumatic drug (DMARD) **(Ren et al., 2018)**. It was recommended as first- line therapy for RA by the the European League Against Rheumatism (EULAR) and the the American College of Rheumatology (ACR) due to its powerful immunosuppressive and anti-inflammatory effect (Smolen et al., 2023). MTX acts by reducing cell division, raising adenosine release, and blocking enzymes involved in the metabolism of folate, In addition, MTX affects humoral responses, cellular adhesion molecule expression, cytokine production, and bone deposition and development **(Zhao et al., 2022)**.

Methotrexate administration is limited to once a week. More frequent administration of methotrexate has been linked to a greater incidence of acute and chronic toxicity. While the ideal dosage is unknown, 7.5-25.0 mg per week has been used in most cases **(Wang et al., 2018)**. MTX users may experience a relative folate deficiency because the medication interferes with pathways that are dependent on folate. The concurrent treatment of folic acid or folinic acid (7–10 mg weekly) reduces the adverse effects of MTX **(Bhoraniya et al., 2023)**.

The tolerability and safety of methotrexate have been evaluated and revised for more than 20 years with limited clinically significant side effects resulting from the regimen consisting of low doses every week used for RA management. The course of MTX intake shows a very long continuation rate reported in clinical practice, due to its efficacy and safety. The long duration of MTX intake denote that it is one of the safe mediation used for the treatment of autoimmune arthritis (Yazici, 2010). MTX has known side effects so the physicians should monitor every RA patient for early detection and treat these emerging side effects by doing laboratory investigations every 3 to 6 months mostly and completing history and examination every visit to the healthcare center. The most popular side effects include irritation of the gastrointestinal tract, liver toxicity, pulmonary complication, myelosuppression, and mucus membrane ulceration **(Almalag et al., 2020).**

Studying the side effects of methotrexate shows that some depend on the dose of methotrexate, others appear to be due to folic acid deficiency, and are thus relieved by taking folic acid supplementation. The majority of methotrexate's side effects are moderate and do not result in stopping the medicine. Pneumonitis and other side effects that appear to be idiosyncratic allergies typically necessitate stopping methotrexate. Other side effects, like cirrhosis and liver fibrosis, appear to have multiple risk factors and may be influenced by the frequency of administration and total dose **(Song et al., 2022).**

In this study, we aimed to evaluate causes and frequency of methotrexate therapy discontinuation in rheumatoid arthritis patient

## Patients and methods

A descriptive cross-sectional study was conducted in the Department of

Rheumatology and Rehabilitation Qena University Hospital.

**Study Setting**: outpatient clinic and inpatient of physical medicine, Rheumatology, and Rehabilitation Department of Qena University Hospital.

**Study subjects**: a total of 200 RA patients were diagnosed according to EULAR/ACR 2010 classification criteria **(Humphreys, 2015)**.

**a. Inclusion criteria**: RA patients diagnosed according to EULAR/ACR 2010 classification criteria **(Humphreys, 2015)** with a history of taking MTX for at least 2 months, and age not less than 18 years old.

**b. Exclusion criteria**: patients with other autoimmune diseases, chronic liver disease including viral hepatitis B and viral hepatitis C, hematological malignancies, and those who are smaller than 18 years old.

**Study tools**: Complete history was taken from every patient involving personal history, history of present illness, therapeutic and surgery history, and Complete general examination, DAS 28 (calculated by the use of swollen joints count, tender joints count and ESR value) was calculated for all patients, and laboratory investigations including complete blood count (CBC), aspartate aminotransferase (AST), Alanine aminotransferase (ALT), serum creatinine, Random blood sugar (RBS) and Rheumatoid factor (RF), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP).

**Research outcome measures: Primary (main):** To evaluate causes and frequency of methotrexate therapy discontinuation in rheumatoid arthritis patients. **Secondary (subsidiary):** to determine the frequency of MTX side effects.

**Ethical approval code:** SVU/ MED/ PRR022/ 1/ 2023/2/542.

**Statistical analysis**

Data was analyzed and processed by utilizing the statistical package (IBM-SPSS), version 24 program. Mean ± standard deviation (±SD), or frequencies (n) and percentages (%) were used to describe the data. Chi Square test (v2) was utilized to test the Statistical differences between groups for qualitative variables, independent sample t-test and ANOVA were used for quantitative normally distributed variables, and nonparametric Mann Whitney test and Kruskal Wallis test were used for not normally distributed quantitative variables. A probability value (P value) is considered significant when it is <0.05.

**Results**

**Table 1. Age, sex, smoking state, and comorbidities of the studied patients**

| Variables | (N = 200) | |
|---|---|---|
| | Mean ± SD | Range |
| **Age** | 44.51 ± 11.85 | 20 – 70 |
| | N | % |
| **Sex (females)** | 176 | 88% |
| **Smoking** | 22 | 11% |
| **Diabetes mellites** | 34 | 17% |
| **Hypertension** | 43 | 21.5% |
| **Hypothyroidism** | 6 | 3% |

SD: standard deviation.

This study included 200 rheumatoid arthritis patients diagnosed according to the revised ACR classification criteria for RA **(Humphreys, 2015)**, Age ranged from 20 to 70 years with a mean value (± SD) of 44.5 (±11.85) years. There were 24 (12%) males and 176 (88%) females. Smokers represent 11% of the cases (22 patients). DM was

found in 34 (17%) patients, HTN was found in 43 (21.5%) patients, and hypothyroidism was found in 6 (3%) patients, (**Table.1**).

**Table 2.Laboratory features of the studied patients**

| Variables | (N=200) | |
|---|---|---|
| **Hemoglobin (g/dL)** | **Mean ± SD** | 11.7 ± 1.31 |
| | **Range** | 7.8 - 15.4 |
| **RBCs count ($10^9$/L)** | **Mean ± SD** | 4.2 ± 0.56 |
| | **Range** | 3.4 - 5.8 |
| **WBCS count ($10^9$/L)** | **Mean ± SD** | 6.98 ± 2.61 |
| | **Range** | 1.6 - 13.8 |
| **Platelets count ($10^9$/L)** | **Mean ± SD** | 280.2 ± 85.44 |
| | **Range** | 120 – 529 |
| **ALT (U/L)** | **Mean ± SD** | 25.5 ± 12.69 |
| | **Range** | 8 – 60 |
| **AST (U/L)** | **Mean ± SD** | 24.5 ± 8.19 |
| | **Range** | 13 – 45 |
| **Serum creatinine (mg/dL)** | **Mean ± SD** | 0.87 ± 0.29 |
| | **Range** | 0.57 - 3.20 |
| **ESR (mm in the first hour)** | **Mean ± SD** | 42 ± 27.48 |
| | **Range** | 5 – 135 |
| **CRP (mg/dL)** | **Mean ± SD** | 12.75 ± 10.45 |
| | **Range** | 1.22 – 46 |
| **RBS (mg/dL)** | **Mean ± SD** | 122 ± 50.14 |
| | **Range** | 60 – 302 |
| **RF** | **Positive** | 109 (54.5%) |
| | **Negative** | 91 (45.5%) |

RBCs: Red blood cells, WBCS: white blood cells, ALT: alanine aminotransferase, AST: aspartate aminotransferase, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, RBS: random blood sugar, RF: rheumatoid factor.

This table shows that hemoglobin ranged from 7.8 to 15.4 g/dL with a mean value (± SD) of 11.7 (±1.31) g/dL. RBCs ranged from 3.4 to 5.8 $10^9$/L with a mean value (± SD) of 4.2 (± 0.56) $10^9$/L. WBCs ranged from 1.6 to 13.8 $10^9$/L with a mean value (± SD) of 6.98 (±2.61) $10^9$/L. Platelets ranged from 120 to 529 $10^9$/L with a mean value (± SD) of 280.2 (±85.44) $10^9$/L. RBS ranged from 60 to 302 mg/dL with a mean value (± SD) of 122 (±50.14) mg/dL. ESR ranged from 5 to 135 with a mean value (± SD) of 41.99 (±27.48). CRP ranged from 1.22 to 46 mg/dL with a mean value (± SD) of 12.75 (±10.45) mg/dL. ALT ranged from 8 to 60 U/L with a mean value (± SD) of 25.5 (±12.69) U/L. AST ranged from 13 to 45 U/L with a mean value (± SD) of 24.5 (±8.19) U/L. Creatinine ranged from 0.2 to 3.2 mg/dL with a mean value (± SD) of 0.9 (±0.29) mg/Dl. rheumatoid factor was positive in 109 (54.5%) patients, (**Table.2**).

**Table 3.Articular manifestation and DAS28 score in the studied patients**

| Variables | | n = 200 |
|---|---|---|
| **Tender joints** | **Mean ± SD** | 5.96 ± 4.67 |
| | **Range** | 0 - 20 |
| **Swollen joints** | **Mean ± SD** | 1.99 ± 2.69 |

| | | |
|---|---|---|
| | **Range** | 1 - 16 |
| **DAS28 score** | **Mean ± SD** | 4.38 ± 1.38 |
| | **Range** | 1.68 – 7.88 |

DAS: disease activity score.

The disease duration has a range of 3 months to 27 years with a mean value of 7.75 ± 7.04. Counts of inflamed swollen joints in the cases ranged from 0 to 16 with a mean value of 1.99 ± 2.69, while tender joints ranged from 0 to 20 with a mean of 5.96 ± 4.67, Scoring disease activity in 28 joints (DAS 28) ranged from 1.68 to 7.88 with a mean of 4.38 ± 1.38, (**Table.3**).

**Table 4. RA duration, MTX dose and duration of intake in the studied patients**

| **Variables** | | n = 200 |
|---|---|---|
| **Duration of RA in years** | Mean ± SD | 7.8 ± 7.04 |
| | Range | 0.25 - 27 |
| **MTX dose** | Mean ± SD | 15.2 ± 3.85 |
| | Range | 12.5 - 25 |
| **Duration of MTX intake in years** | Mean ± SD | 5.7 ± 6.4 |
| | Range | 0.25 - 26 |
| **Route of intake** | I.M | 143 (71.5%) |
| | S.C | 41 (20.5%) |
| | Oral | 16 (8%) |

The disease period ranged from 3 months to 27 years with a mean of 7.75 ± 7.04. The methotrexate dose ranged from 12.5 to 25 mg\wk. with a mean value (± SD) of 15.2 (±3.85) mg\wk., while the duration of intake ranged from 0.25 to 26 years with a mean value (± SD) of 5.7 (± 6.4) years. The Route of MTX intake was intramuscular in 143 (71.5%) patients, subcutaneous in 41 (20.5%) patients, and oral in 16 (8%), (**Table.4**).

**Table 5. Frequency of MTX side effects in the studied patients**

| **Variables** | n = 200 |
|---|---|
| Nausea and vomiting | 66 (33%) |
| Gastritis symptoms | 112 (56%) |
| Oral ulcers | 38 (19%) |
| Skin rash | 23 (11.5%) |
| Hair falling | 21 (10.5%) |
| Dry cough | 8 (4%) |
| Pneumonitis | 6 (3%) |
| Recurrent infection | 16 (8%) |
| Vasculitis | 0 (0%) |
| Nodulosis | 5 (2.5%) |
| Liver enzymes elevation | 13 (6.5%) |
| Kidney function elevation | 5 (2.5%) |
| Anemia | 12 (6%) |
| leukopenia | 11 (5.5%) |
| Pancytopenia | 6 (3%) |

Among the included patients (N= 200), Nausea and vomiting occurred in 66 (33%) patients, gastritis symptoms occurred in 112 (56%) patients, oral ulcers occurred in 38 (19%) patients, skin rash occurred in 23 (11.5%) patients, hair falling occurred in 21 (10.5%) patients, dry cough occurred in 8 (4%) patients, pneumonitis occurred in 6 (3%) patients, recurrent infection occurred in 16 (8%) patients, nodulosis occurred in 5 (2.5%) patients, liver enzyme elevation occurred in 13 (6.5%) patients, kidney function elevation occurred in 5 (2.5%), anemia occurred in 12 (6%) patients, leukopenia occurred in 11 (5.5%) patients, pancytopenia occurred in 6 (3%) patients and vasculitis was not recorded in any patient, (**Table.5**).

**Table 6. Causes of MTX discontinuation among the studied patients**

| Variables | n= 90 |
|---|---|
| **GIT problems (pain and vomiting)** | 37 (41.11%) |
| **Persistent liver enzymes elevation** | 13 (14.44%) |
| **Planning for pregnancy** | 11 (12.22%) |
| **Mucocutaneous side effects (oral ulcers)** | 6 (6.67%) |
| **Kidney functions elevation** | 5 (5.56%) |
| **Hypersensitivity** | 5 (5.56%) |
| **Myelosuppression** | 4 (4.44%) |
| **Respiratory problems (pneumonitis)** | 3 (3.33%) |
| **Poor response** | 6 (6.67%) |

Current study shows that a total number of 90 (45%) of the patients have discontinued MTX with gastrointestinal problems and liver enzymes elevation representing the most common causes. GIT problems were the causes of discontinuation in 37 (41.11%) of the patients, persistent liver enzymes elevation was the cause in 13 (14.44%) of the patients, planning for pregnancy was the cause in 11 (12.22%) of the patients, mucocutaneous side effects was the cause in 6 (6.67%) of the patients, kidney functions elevation was the cause in 5 (5.56%) of the patients, hypersensitivity was the cause in 5 (5.56%) of the patients, myelosuppression was the cause in 4 (4.44%) of the patients, respiratory problems was the cause in 3 (3.33%) of the patients and poor response was the cause in 6 (6.67%) of patients. (**Table.6 & Fig.1).**

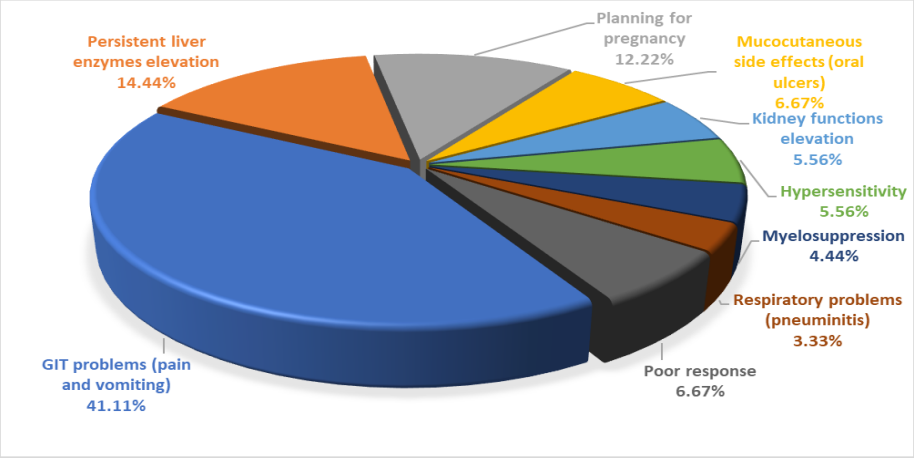


**Fig.1. Causes of MTX discontinuation among the studied patients**

**Table 7. Steroidal and non-steroidal anti-inflammatory drugs (NSAIDs) among the studied group**

| Variables | | MTX tolerant group(n=110) | MTX intolerant group (n=90) | P value |
|---|---|---|---|---|
| **Steroid intake (oral prednisolone)** | **(yes)** | 75 (68.18%) | 82 (91.11%) | <0.001* |
| **Current steroid dose** | **Mean ± SD** | 5.86 ± 5.01 | 7.72 ± 6.14 | 0.019* |
| | **Range** | 5 – 20 | 5 - 40 | |
| **Diclofenac** | **(yes)** | 15 (13.64%) | 9 (10%) | 0.208 |
| **Etoricoxib** | **(yes)** | 8 (7.27%) | 5 (5.56%) | |
| Paracetamol | (yes) | 4 (3.64%) | 0 (0%) | |

P value >0.05 =not statistically significant, P value <0.05= statistically significant**.**

Regarding steroid drug intake, there is a statistically significant difference between the two groups with P value <0.001. 75 (68.18%) patients in the MTX tolerant group were taking oral prednisolone, while 82 (91.11%) of the patients in the MTX intolerant group were taking oral prednisolone. Also, there was a statistically significant difference (P value = 0.019) between the two groups regarding the current steroid dose, the Current steroid dose ranged from 5 to 20 with a mean (±SD) of 5.86 (±5.01) in the MTX tolerant group and ranged from 5 to 40 with a mean of (±SD) of 7.72 (±6.14) in the MTX intolerant group. Regarding NSAIDs and paracetamol intake, there is no statistically significant difference between the two groups (P value = 0.208), In the patients of MTX-tolerant group 15 (13.64%) patients were given diclofenac, 8 (7.27%) patients were given etoricoxib and 4 (3.64%) patients were given paracetamol , While in the patients of MTX-intolerant group 9 (10%) patients were given diclofenac, 5 (5.49%) patients were given etoricoxib and no one was given paracetamol, (**Table.7**).

**Discussion**

In the present study which included 200 RA patients with a mean disease duration of 7.8 (±7.04) years, 110 (55%) patients were currently on MTX with a mean dose of 15.1 (±3.97) mg\wk. and a mean duration of intake of 5.7 (±6.4) years, while 90 (45%) of the patients stopped MTX due to different causes.

Although well tolerated by most, some patients develop important adverse events such as myelosuppression, gastrointestinal side effects (vomiting, nausea or abdominal pain), increased infection rate, or abnormal liver function tests, which may limit its use and may result in additional health care costs. Among causes of discontinuation of MTX in our patients, gastrointestinal side effects were the most common representing 41.11%, while liver problems were the second cause representing 14.44%, thus gastric problems and liver problems together represent 55.55% of causes of discontinuation of MTX in this group of patients. Other causes include planning for pregnancy (12.22%), mucocutaneous side effects (6.67%), kidney functions elevation (5.56%),

hypersensitivity (5.56%), myelosuppression (4.44%), respiratory problems (3.33%), and poor response (6.67%).

These results match with **Ćalasan et al. (2013)** who figured out that 42.3% of RA patients reported suffering from gastrointestinal symptoms while on MTX therapy. Moreover, **Curtis et al. (2016)** agreed with our findings as they reported that the most reported adverse effects included gastrointestinal symptoms. Also, **El-Zorkany et al. (2013)** found that gastrointestinal side effects accounted for 56.5% of the MTX discontinuation causes and liver issues came in second at 13%, together they represent 69.5% of the reasons. While **Vidal-Montal et al. (2023)** noted that gastrointestinal side effects occur in 19% of the patients, liver enzyme elevation in 5% of the patients, infection in 1% of the patients, and hematological side effects did not occur in any patient.

**Anvari (2016)** did not match our results. According to his study, just 23 individuals (7.8%) permanently stopped taking MTX, while 84 patients (28.5%) did so temporarily. The most common causes of discontinuation were abnormal liver function test (11.9%), pregnancy (8.3%), nausea and vomiting (5.9%), and neutropenia or pancytopenia (3.6%),
**Manfredi et al. (2019)** found that 149 patients (25.3%) stopped taking MTX during the initial year of treatment (mean treatment duration 4.7 ± 3.4 months). The reasons were ineffectiveness in 65 patients, drug complications predominantly liver function alteration in 56 patients (37.5%), and other unidentified reasons in 28 patients (18.8%). Moreover**, Alarcón et al. (1995)** listed the explanations for stopping MTX with complications and lack of effectiveness accounting for around 53% of all irreversible discontinuations. There were no cases of severe liver disease detected, and there was no correlation between higher blood creatinine levels.

Regarding steroid drug intake, a higher percentage of patients were taking oral prednisolone in the MTX-intolerant group (91.11%) with a statistically significant difference between the two groups (P value <0.001). Also, there was a statistically significant difference between the two groups regarding current steroid dose (P value = 0.019) with higher mean dose in the MTX-intolerant group (7.72 ± 6.14), this highlights the significant GIT adverse effects of steroids which adds to the gastrointestinal irritating effect of MTX. As regarding analgesics and anti-inflammatory drugs intake, small percentage of our patients were chronically taking NSAIDs or paracetamol with no statistically significant difference between the two groups (P value = 0.208).

**Park et al. (2020)** was in consistent to our findings as they found that Patients in the MTX-hold group had slightly higher glucocorticoid dose at baseline. On the other hand, **El-Zorkany et al. (2013)** showed different outcomes as they stated that current steroid dose was insignificantly different between MTX-hold group and MTX discontinuation group (P=0.435). Also, **Manfredi et al. (2019)** stated that current steroid dose was insignificantly different between MTX-hold group and MTX discontinuation group (P=0.641).

**Conclusion**

In conclusion, methotrexate is considered to be a safe medication for prolonged administration in RA patients provided by the comparatively low rate of medication cessation due to side effects and the lack of serious or irreversible organ damage, however steroid drug use appears to increase the risk of gastrointestinal adverse event. To lessen the rate of methotrexate cessation and make the most benefit of a medication considered an essential component of RA

therapy regimens, more efforts should be made to mitigate its side effects, particularly gastrointestinal and hepatic problems.

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