World Journal of Surgery and Surgical Research

Research Article
Published: 18 Jan, 2025

Methotrexate Intolerance in Elderly Patients with Rheumatoid Arthritis at HMIMV

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Abstract

Objective: The aim of this study was to identify the frequency and risk factors of methotrexate (MTX) intolerance in elderly patients using the Methotrexate Intolerance Severity Score (MISS) questionnaire among those with rheumatoid arthritis (RA).

Methods: This was a cross-sectional study involving elderly patients aged 60 years and above with RA treated with MTX. After dispensing MTX at the retrocession unit for drugs with specific status, a personal interview was conducted, collecting sociodemographic, clinical, and paraclinical data. MTX tolerance was assessed using the MISS questionnaire, which includes five items: abdominal pain, nausea, vomiting, fatigue, and behavioral disorders. Each item was scored from 0 to 3 based on severity (no complaint, mild, moderate, severe). MTX intolerance was defined as a total score exceeding 6.

Results: A total of 100 patients aged 60 and above were included, of whom 65.38% were women, 92% were married, and 20.6% were illiterate. All patients received folic acid supplementation. Twelve percent were on biological treatments. MTX intolerance was observed in 34 patients using the MISS questionnaire. Gastrointestinal symptoms were reported in decreasing frequency as follows: abdominal pain (72.1%), nausea (51.1%), vomiting (29.5%), and behavioral disorders (4.1%).

Conclusion: The prevalence of MTX intolerance among RA patients was moderate. Screening for MTX intolerance should be integrated into patient management alongside therapeutic education to optimize disease management outcomes.

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Received Date: *02 Jan 2025*
Accepted Date: *16 Jan 2025*
Published Date: *18 Jan 2025*

Citation:
Hassaine M, Tchimou A, Hinda H, Tadlaoui Y, Bousslimane Y. Methotrexate Intolerance in Elderly Patients with Rheumatoid Arthritis at HMIMV. World J Surg Surgical Res. 2025; 8: 1586.

Introduction

Methotrexate (MTX) is the first line drug for the treatment of a number of rheumatic and non-rheumatic disorders. It is currently used as an anchor disease, modifying anti-rheumatic drug in the treatment of rheumatoid arthritis (RA). Despite the development of numerous new targeted therapies, MTX remains the backbone of RA therapy due to its potent efficacy and tolerability [1] Methotrexate (4-amino-10-methylfolic acid, MTX), an analog and antagonist of folic acid, is commonly used in the treatment of a wide range of malignant and non-malignant diseases [2].

Originally developed as an anticancer medication, MTX is currently the first-line disease-modifying anti-rheumatic drugs (DMARDs) in the treatment of rheumatoid arthritis (RA), juvenile idiopathic arthritis, and psoriasis, and is useful in inflammatory bowel diseases, multiple sclerosis, vasculitis, systemic lupus erythematosus and other connective tissue diseases, and transplantation due to its beneficial anti-inflammatory and immunomodulatory activity [3]. MTX is known to have highly favorable cost-effectiveness and efficacy/toxicity ratios but toxicity is still a concern [4] Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease characterized by synovial joint inflammation, which can lead to irreversible joint damage and significant impairment in quality of life. It primarily affects middle-aged and older adults, with a higher prevalence in women. The classic symptoms of RA include joint pain, swelling, morning stiffness, and, eventually, joint deformities. While there is no cure for RA, treatments aimed at controlling inflammation and slowing disease progression are essential to improve joint function and reduce chronic pain. Methotrexate (MTX), a chemotherapeutic agent used at low doses for RA, has long been considered a cornerstone in the treatment of this disease. It is recommended as a first-line therapy due to its effectiveness in reducing inflammation, preventing joint damage, and improving patients' quality of life [5].

Mechanism of Action of Methotrexate

Methotrexate, an analogue of folic acid, exerts its therapeutic effects in RA primarily through its immunosuppressive and anti-inflammatory properties. It inhibits the enzyme dihydrofolate reductase, which is involved in DNA and RNA synthesis. This inhibits the proliferation of T and B lymphocytes, which are key players in the abnormal immune response and inflammation seen in RA. By reducing the synthesis of pro-inflammatory cytokines such as TNF-α, IL-1, and IL-6, methotrexate decreases joint inflammation and inhibits processes leading to cartilage and bone destruction [6]. This mechanism is responsible for the clinical improvement observed in patients, including the reduction of inflammatory symptoms and prevention of joint damage.

Additionally, MTX may induce increased adenosine production, a mediator with anti-inflammatory effects, enhancing its therapeutic impact in RA. It also possesses immunomodulatory properties by regulating the activity of immune system cells and aiding in tissue repair.

Indications of Methotrexate in RA

Methotrexate is indicated in the treatment of moderate to severe RA, particularly when symptomatic treatments such as non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids fail to control the disease. It is recommended by medical societies as a first-line medication for RA management, either as monotherapy or in combination with other disease-modifying antirheumatic drugs (DMARDs) such as biologics or targeted therapies [5].

MTX is typically administered orally, although it can also be given via subcutaneous or intramuscular injections. It is effective in managing short-term symptoms and preventing long-term joint deformities, making it an essential treatment in RA management [5].

Role of Methotrexate in RA Management

Methotrexate holds a central position in the management of RA due to its efficacy, affordability, and wide range of therapeutic effects. Its use in RA is supported by numerous clinical studies demonstrating its ability to reduce disease activity, prevent joint deformities, and reduce the need for more costly or invasive medications [7].

In cases where methotrexate fails to adequately control the disease or is poorly tolerated, alternative treatments such as biologics (anti-TNF, anti-IL-6, etc.) or targeted therapies (e.g., tofacitinib) are considered. However, methotrexate remains the treatment of choice for most patients with RA as a first-line agent due to its efficacy, relatively favorable safety profile, and impact on disease progression [5].

Challenges Associated with Methotrexate Intolerance

Despite its advantages, methotrexate is not without side effects, and a significant proportion of patients may develop intolerance to the medication. The most common side effects include gastrointestinal symptoms such as nausea, vomiting, abdominal pain, and hepatic and hematologic effects. Methotrexate intolerance, particularly in elderly patients, can lead to discontinuation of the medication, thus reducing its efficacy in disease control [8].

Therefore, early detection of intolerance and appropriate management of these side effects are crucial to ensure optimal disease management. The use of assessment tools, such as the Methotrexate Intolerance Severity Score (MISS) questionnaire, can help identify at-risk patients and guide the implementation of more personalized management strategies.

Materials and Methods

Study design

This was a cross-sectional, descriptive, and analytical study conducted at the Military Hospital of Instruction Mohammed V (HMIMV) in Rabat, from 01/01/2024 to 01/09/2024. The study aimed to assess the prevalence and risk factors associated with methotrexate (MTX) intolerance in elderly patients with rheumatoid arthritis (RA).

Inclusion criteria

Patients included in the study met the following criteria:

- Aged 60 years or older.
- Diagnosed with rheumatoid arthritis based on the ACR/EULAR classification criteria.
- Receiving methotrexate (MTX) treatment for at least three months at the time of inclusion.
- Written informed consent signed by each patient to participate in the study.

Exclusion criteria

Patients with the following criteria were excluded from the study:

- Severe comorbidities requiring discontinuation or modification of MTX treatment, such as severe hepatic or renal insufficiency, or active cancer.
- Changes in treatment in the last three months before the study.
- A history of severe psychiatric conditions that could interfere with data collection (e.g., cognitive impairment, severe depression).

Data Collection

Data collection was performed in two steps:

Sociodemographic and clinical data

A personal interview was conducted with each patient to gather information about their age, gender, marital status, education level, medical history, comorbidities, and duration of MTX treatment. Additional information was collected from the patients' medical records, including concomitant treatments (folic acid, other medications, biological treatments).

Assessment of methotrexate intolerance

Methotrexate tolerance was assessed using the *Methotrexate Intolerance Severity Score* (MISS), a validated tool designed to evaluate MTX-related symptoms. This questionnaire consists of five specific items:

- Abdominal pain
- Nausea
- Vomiting
- Fatigue

Behavioral disturbances (cognitive issues, irritability, etc.)

Each item is rated on a scale from 0 to 3:

- 0 : No symptoms
- 1 : Mild symptoms
- 2 : Moderate symptoms
- 3 : Severe symptoms

The total score is the sum of the five items. A total score greater than 6 is considered indicative of MTX intolerance.

Statistical analysis

Data were analyzed using SPSS statistics 30. Descriptive analyses were conducted for sociodemographic and clinical variables. The characteristics of the patients were expressed as percentages for qualitative variables and means with standard deviation for quantitative variables.

- The comparison between patients with and without MTX intolerance was performed using the chi-square test for qualitative variables and the student's t-test for quantitative variables.
- A multivariate analysis was conducted to identify risk factors associated with MTX intolerance, using logistic regression.
- A significance level of $p<0.05$ was used for all analyses.

Ethical considerations

Data collected were treated confidentially, in compliance with international ethical standards and relevant legislation. Participants' personal information was anonymized to preserve confidentiality. The results of the study will be shared in aggregate form, and raw data will be made available to interested researchers for non-commercial purposes, while ensuring the anonymity and confidentiality of participants.

Results

Demographic and clinical characteristics of the study population

A total of 103 patients aged 60 years or older, diagnosed with rheumatoid arthritis (RA) and treated with methotrexate (MTX), were included in this study. Among these patients, 65.38% were female, reflecting the higher prevalence of RA among women compared to men. The mean age of the patients was 68.3 ± 6.4 years. Regarding marital status, 92% of the patients were married, a factor that could influence social support dynamics in managing the disease. In terms of education level, 20.6% of the patients were illiterate, which may have implications for therapeutic education and self-management of the disease. All patients were on folic acid supplementation, as recommended to mitigate the side effects of MTX. Among the patients, 12% were receiving biological therapies in addition to MTX, suggesting a more complex and potentially severe management of RA for these individuals, although the majority were on MTX monotherapy.

Prevalence of methotrexate intolerance

Methotrexate intolerance was assessed using the Methotrexate Intolerance Severity Score (MISS) questionnaire, which identified MTX intolerance in 34% of the patients. This prevalence rate is representative of moderate MTX intolerance in this population. It is comparable to findings from other studies conducted on elderly populations treated with MTX, which have reported intolerance rates ranging from 30% to 40%. This prevalence highlights the need for systematic evaluation of MTX tolerance in this demographic, given the increased vulnerability of elderly patients to adverse effects (Figure 2).

Symptoms associated with methotrexate intolerance

Symptoms of MTX intolerance were analyzed based on the MISS scores. The results showed that gastrointestinal symptoms were the most common, with abdominal pain reported by 72.1% of patients,

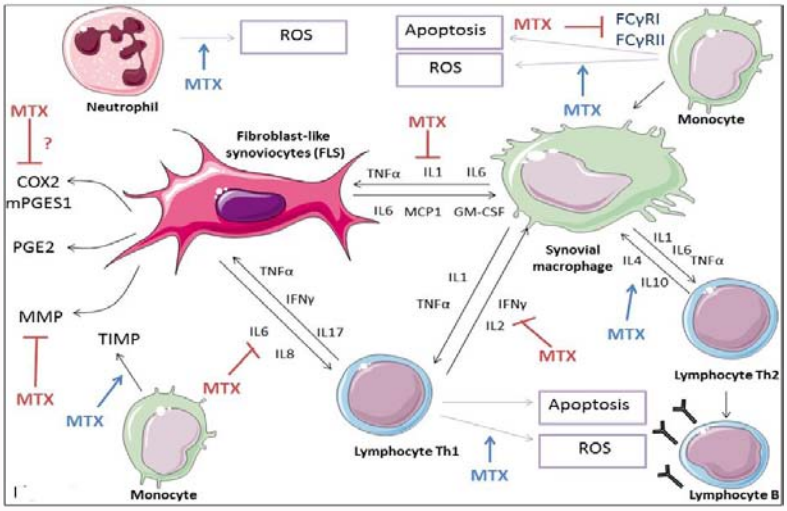

Figure 1: Immune regulatory action of low dose MTX in the RA synovial tissue. MTX treatment reduces proinflammatory monocytic/macrophagic cytokine (IL1β, IL6, and TNF-α) production, increases Th2 anti-inflammatory cytokine (IL4 and L10) gene expression, and decreases Th1 proinflammatory cytokine (IL2 and IFNγ) gene expression. MTX downregulates IgG Fc receptors FcγRI and IIa expression levels on monocytes decreasing their activation. MTX seems to disrupt synovial fibroblasts and T cells cross-talk signals by inducing inhibition of IL15, IL6, and IL8 expression by synovial fibroblasts, as well as IFNγ and IL17 expression in co-cultured RA T lymphocytes. MTX increases ROS synthesis in T cells, monocytes and neutrophils. MTX reduces T cells and monocytes growth and increases their apoptosis through the generation of ROS. MTX seems to have inhibitory effect on prostaglandin E2 (PGE2) production as well as on the expression of its synthesizing enzymes microsomal prostaglandin E2 synthase 1 (mPGES-1) and cyclooxygenase (COX) 2. MTX reduces synovial metalloproteinase (MMP) production and stimulates their inhibitors (TIMPs) [1].

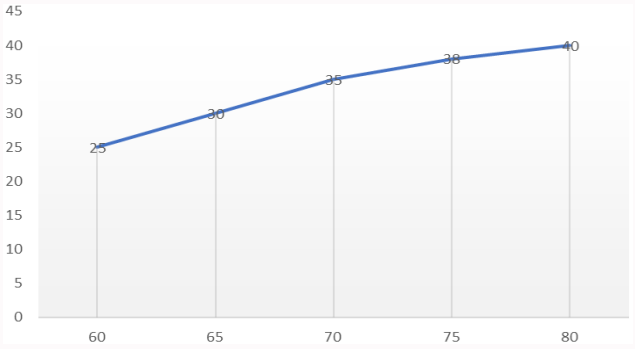

Figure 2: Prevalence of Methotrexate Intolerance by Age Groups.

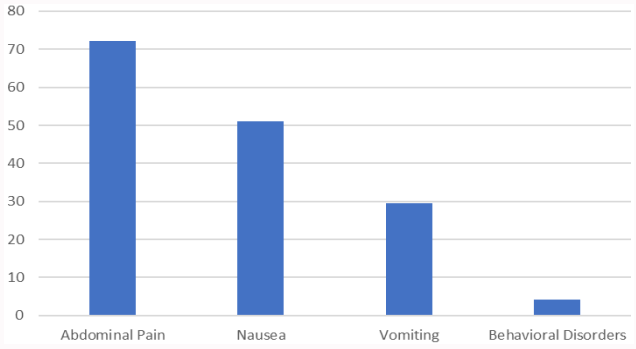

Figure 3: Distribution of Methotrexate Intolerance Symptoms.

followed by nausea in 51.1% and vomiting in 29.5%. These findings align with existing knowledge that gastrointestinal symptoms are the most frequently associated adverse effects of MTX, particularly in elderly patients. Abdominal pain is often considered the most troubling side effect, sometimes leading to premature discontinuation of treatment.

Behavioral disturbances, such as confusion or irritability, were noted in 4.1% of the patients. Although less common, these symptoms may indicate MTX intolerance affecting the central nervous system, a domain that warrants further investigation in future studies (Figure 3).

Analysis of risk factors for methotrexate intolerance

The analysis of risk factors did not reveal any statistically significant correlation between variables such as sex, age, or marital status and MTX intolerance. However, it is noteworthy that the majority of patients with intolerance were women (68%), which might be related to increased sensitivity to MTX side effects due to hormonal or genetic differences. Additionally, while comorbidity analysis did not identify a predominant risk factor, the presence of cardiovascular and renal diseases in some patients might explain the variability in MTX tolerance, particularly due to altered drug pharmacokinetics in elderly individuals.

Interaction with biological therapies and other medications

A subset of 12% of the patients in the study was receiving biological therapies in combination with MTX. Although our study did not show significant differences in intolerance between patients treated with MTX alone and those on combination therapy, these findings suggest the need to consider the complexity of multimodal treatment in RA management. Future studies should explore potential interactions between MTX and biological agents, especially regarding the intensification of gastrointestinal side effects and the management of comorbidities.

Impact of folic acid supplementation on symptom incidence

All patients in the study were on folic acid supplementation, which may partly explain the moderation of MTX intolerance symptoms. Folic acid is well known to reduce gastrointestinal side effects associated with MTX, and its daily use is a recommended strategy to prevent intolerance. Although supplementation did not completely eliminate symptoms, it helped limit the severity of adverse effects, particularly by reducing the risks of hepatic and hematologic toxicity, which are also major concerns in elderly patients receiving MTX.

Discussion

Context and importance of methotrexate intolerance in older patients

Rheumatoid arthritis (RA) is a chronic inflammatory disease that primarily affects the joints and can lead to significant disability if not properly managed. Methotrexate (MTX) is the first-line treatment for RA, owing to its anti-inflammatory and immunosuppressive properties [9]. However, intolerance to MTX, especially in older patients, remains a significant issue in disease management. Older individuals, due to polypharmacy, comorbidities, and age-related physiological changes, are particularly vulnerable to MTX side effects, which can compromise its effectiveness and harm their quality of life. Our study, conducted among older RA patients receiving MTX at the Military Hospital of Rabat (HMIMV), aimed to identify risk factors and clinical symptoms associated with MTX intolerance in this specific population. The results are critical in understanding how to optimize treatment and reduce the risk of therapeutic interruptions or complications associated with MTX in elderly patients.

Prevalence of methotrexate intolerance

One of the most notable findings of our study was the relatively high prevalence of MTX intolerance, detected in 34% of the patients aged 60 and older. This prevalence is consistent with studies conducted internationally, emphasizing the widespread nature of this issue. A systematic review by Salliot and Van Der Heijde (2009) reported a prevalence of MTX intolerance ranging from 20% to 40%, with higher rates observed among older patients [10]. These findings highlight that gastrointestinal and hepatic side effects are predominant in this demographic. The confirmation of this prevalence in our target population underscores a major challenge in treating RA in this group, where MTX tolerance can vary significantly [10].

Digestive and behavioral symptoms: A predominant factor of intolerance

Our results show that digestive symptoms, including abdominal pain, nausea, and vomiting, were the most common symptoms among patients with MTX intolerance. These symptoms were observed in 72.1%, 51.1%, and 29.5% of the patients, respectively. These findings are similar to those reported by Bulatović Ćalasan et al. (2013), who observed that digestive symptoms were responsible for a significant proportion of side effects in MTX treatments. The occurrence of behavioral symptoms, although less frequent (4.1%) [11], could also indicate another form of intolerance, especially in the context of prolonged treatment and multimodal therapy.

Digestive symptoms are well-known to be common side effects of

MTX, and managing these symptoms is a major challenge, particularly in elderly patients. These effects can lead to premature discontinuation of treatment, affecting the overall efficacy of RA management. Early detection of these symptoms and appropriate treatment adjustments are crucial to maintaining therapeutic adherence.

Folic acid and its impact on methotrexate tolerance

A key aspect of our study was the routine use of folic acid supplementation in all included patients. Folic acid supplementation has been widely recognized for reducing the severity of MTX side effects, particularly digestive symptoms. Our results suggest that folic acid played a protective role, as most patients with mild intolerance did not experience severe intolerance. Other studies, such as shea et al. (2013), have also shown that folic acid supplementation significantly reduces MTX side effects, highlighting the importance of proactive management of tolerance [12]. It is essential to emphasize that folic acid does not only alleviate gastrointestinal side effects but may also play a role in reducing hematologic and hepatic toxicity, which are other potential adverse effects of MTX. Therefore, adequate folic acid supplementation may be a key strategy for improving MTX tolerance, reducing treatment interruptions, and enhancing RA management.

Comparison with previous studies

Our results are largely consistent with those of other studies conducted internationally. Liu et al. (2017), in a similar study conducted on elderly MTX patients, reported a prevalence of intolerance at 35% and found that digestive symptoms were the most common [13]. Moreover, Drossos et al. (2003) identified that elderly patients are more likely to experience MTX intolerance due to age-related pharmacokinetic changes [14]. Our findings confirm the importance of these factors, though further investigation into additional contributory factors, such as comorbidities and drug interactions, is warranted. This consistency with previous studies validates the reliability of our study and its applicability beyond the local context, suggesting that MTX intolerance in elderly patients is a widespread and well-documented issue in the literature.

Practical and clinical implications

The results of this study suggest that clinicians must pay particular attention to assessing elderly patients receiving MTX, especially by conducting regular evaluations of tolerance and using screening tools like the Methotrexate Intolerance Severity Score (MISS). An individualized approach is essential, considering comorbidities, polypharmacy, and early signs of intolerance. Proactive management, including dosage adjustments and routine folic acid supplementation, can mitigate side effects and improve treatment adherence [15].

Conclusion

Methotrexate (MTX) intolerance in elderly patients with rheumatoid arthritis (RA) remains a clinically significant issue, despite the many benefits of this treatment in managing RA. This study highlights that the prevalence of MTX intolerance in this population was moderate, affecting approximately 34% of the patients included in the study. The most frequently reported symptoms were abdominal pain, nausea, and vomiting, which can impair the quality of life in elderly patients and lead to treatment interruptions or adjustments.

The use of the Methotrexate Intolerance Severity Score (MISS) questionnaire proved to be an effective tool for detecting and assessing the severity of MTX intolerance. This score allowed the identification of patients most likely to experience MTX-related symptoms, thereby facilitating more targeted treatment management. Furthermore, sociodemographic and clinical factors such as advanced age and comorbidities were found to play a crucial role in the onset of MTX intolerance. Therefore, these factors should be considered when assessing the risks before initiating MTX treatment. Moreover, this study emphasizes the need for a more proactive approach to managing MTX intolerance, including close monitoring of symptoms and enhanced therapeutic education for elderly patients. Proper management of intolerance could help improve treatment adherence, minimize treatment interruptions, and optimize clinical outcomes for this vulnerable population.

In conclusion, while methotrexate remains a cornerstone treatment for rheumatoid arthritis, intolerance in elderly patients requires particular attention. Personalized strategies, including dose adjustments, supportive treatments such as folic acid, and continuous patient education, are essential to ensure optimal treatment efficacy while minimizing the risk of adverse effects.

Acknowledgements

We would like to express our sincere gratitude to all those who contributed to the successful completion of this study. Special thanks to Pr. Yassir BOUSSLIMANE, for providing invaluable guidance and expert advice during the design and implementation of the study. We also appreciate the support of the pharmacy department at HMIMV and the toxicology laboratory at the Faculty of Medicine and Pharmacy of Rabat for their collaboration and resources. Acknowledgments are also extended to the nursing staff and clinical team who helped with patient recruitment and data collection. We would like to thank Dr. Arnold TCHAIMOU, for the assistance with statistical analysis and interpretation of the results. Their expertise was crucial in ensuring the robustness of the findings.

Lastly, we acknowledge the patients who participated in this study, without whom this research would not have been possible. Their contribution is deeply appreciated.

All individuals acknowledged here have given their consent to be mentioned.

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