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Reasons for discontinuation of methotrexate in the treatment of rheumatoid arthritis and challenges of methotrexate resumption: a single-center, retrospective study

Hiroko Nagafuchi*, Yutaka Goto, Tomofumi Kiyokawa and Kimito Kawahata

Abstract

Background: Methotrexate (MTX) is an anchor drug used for the treatment of rheumatoid arthritis (RA); hence, understanding the reasons for MTX discontinuation in RA can help improve its treatment. Therefore, this study aimed to investigate the reasons for MTX discontinuation and to identify future challenges in RA treatment regarding the discontinuation and resumption of MTX treatment.

Results: MTX administration was discontinued in 771 patients with RA. The reasons for MTX discontinuation were as follows: (1) infectious diseases (20.0%), (2) malignancy (14.1%), and (3) respiratory problems (10.2%). Some patients did not resume MTX therapy even after the infections were cured. Liver dysfunction (8.0%) did not improve with MTX discontinuation and was often associated with fatty liver disease. In addition to adverse events, MTX discontinuation was due to patient preference (4.3%), planning for pregnancy (5.1%), invalidity (5.7%), remission (5.6%), remission with biologics (4.7%), old age (2.6%), and poor compliance (1.6%).

Conclusions: This study revealed diverse reasons for the discontinuation of MTX; there are cases in which MTX is discontinued but should be considered for resumption. Furthermore, issues such as the indications for MTX discontinuation should still be debated, and multicenter evidence must be collected and examined in future studies.

Keywords: Rheumatoid arthritis, Methotrexate, Discontinuation, Malignancy, Infection

Background

Methotrexate (MTX) is the first-line drug in the treatment of rheumatoid arthritis (RA) [1, 2], and medical guidelines have been established for such treatment [3, 4]. Previous reports revealed that MTX is associated with various adverse events [5, 6]. Nonetheless, there is sufficient evidence for MTX use in treating RA. However, the existing recommendations do not uniformly address all aspects related to MTX therapy and disagreements regarding its use remain [7]. Patients with RA requiring MTX therapy should generally be treated indefinitely [5].

On the other hand, 34–37% of patients with RA treated with MTX discontinue it. This is by no means a negligible percentage; hence, the reasons for MTX discontinuation need to be investigated [8, 9]. Furthermore, adverse events are not the only reason for MTX discontinuation in patients with RA [10]. Some studies have focused on the reasons for discontinuing MTX in treating RA [8, 11, 12]; however, most focused only on conventional adverse events and included small numbers of cases. Hence, there are insufficient data regarding this topic. Consequently, understanding the reasons for MTX discontinuation can help identify new challenges in the treatment of RA.

*Correspondence: h3naga@marianna-u.ac.jp

Division of Rheumatology, Department of Internal Medicine, St. Marianna University School of Medicine, 2-16-1 Sugao, Miyamae-ku, Kawasaki 216-8511, Japan

This study investigated the reasons for MTX discontinuation in the treatment of RA to clarify the issues related to the discontinuation and resumption of MTX therapy.

Patients and methods

This was a single-center, retrospective study. Data of 1402 patients who had discontinued MTX treatment at St. Marianna University Medical Center's Medical Information Office were extracted. After reviewing the electronic medical records, data of only 771 patients who had discontinued MTX were included in this study, excluding those who were transferred to other hospitals or had temporary reasons for MTX discontinuation. In this study, we included patients with RA that discontinued MTX from our outpatient department between January 2005 and October 2019 and investigated the reasons for the discontinuation. Reasons for MTX discontinuation included accompanying diseases that indicated the need for discontinuation, such as suspected cases of malignancy or infection. In some cases, multiple reasons were identified based on the attending physician's notes for MTX discontinuation in the medical records. Patients were not interviewed. Permanent MTX discontinuation was defined as failure to resume MTX during the observation period after discontinuation, while temporary MTX discontinuation excluded cases of MTX resumption after childbirth or surgery for malignancy. Patients with an observation period ≥1 year after MTX discontinuation were included. However, patients who died within 1 year of MTX discontinuation were also included in the study. In addition, data regarding sex, age at RA onset, time of MTX initiation, duration of MTX treatment, last MTX dose, laboratory data at the time of MTX discontinuation, and outcomes were extracted from the medical records. MTX dosage in Japan was approved at 8 mg/week in 1999 and a maximum dosage of 16 mg/week in 2011 [13]. The C-OPERA study revealed that, in Japan, efficacy is often achieved at 12 mg/week [13]. Thus, MTX doses for patients with RA are lower in Japan than in other countries.

Statistical analysis

Descriptive statistical analysis was performed using Microsoft Excel 16.54 (Microsoft Corporation, Redmond, WA, USA). Additionally, differences between the reasons for discontinuation groups in the MTX treatment period (time from MTX initiation to discontinuation) were tested using the Kruskal-Wallis test. This analysis was performed using Prism 5.0 (Graph Pad Software, Inc., San Diego, CA, USA). The statistical significance was set at $P \leq 0.05$.

Results

Patient background

Among the 771 patients with RA who discontinued MTX, 590 (76.5%) were female. The median age at the onset of RA was 58.0 (interquartile range [IQR]: 46.0–67.0) years. The overall observation period was 7.0 (3.5–13.5) years, and the observation period after MTX discontinuation was 2.0 (0.5–4.4) years, including the period of patients who died after MTX discontinuation. Of the 771 included patients, 59 (7.7%) died in the observation period. Of these, 28 (47.5%) died owing to the reason for MTX discontinuation, 20 of whom (71.4%) died within 1 year of MTX discontinuation. The most common cause of death was malignancy (18 of 28 cases, 64.3%). The time from RA onset to initiation of MTX administration was 0.8 (0–5.6) years, and 56.8% of the patients started MTX within 3 months of onset; the final dose of MTX was 6.0 (4.0–8.0) mg/week, and the duration of MTX treatment was 3.0 (0.8–7.0) years.

Reasons for discontinuation of MTX in patients with RA

The reasons for MTX discontinuation in patients with RA are shown in Table 1. Pneumonia was classified as an infectious disease, and lymphoproliferative disease (LPD) was included in malignancies. The most common reasons for MTX discontinuation were (1) infectious diseases ($n = 154$, 20.0%), (2) malignancy ($n = 109$, 14.1%), and (3) respiratory problems ($n = 79$, 10.2%).

The details regarding infectious diseases (n=154) are as follows. Respiratory infections accounted for 104 (67.5%) cases, urinary tract infections for 11 (7.1%), skin infections for 10 (6.5%), sepsis for six (3.9%), and others for

Table 1 Reasons for discontinuation of methotrexate in patients with rheumatoid arthritis

Reasons	*n* (%)	Reasons	*n* (%)
Infectious diseases	154 (20.0)	Improved with biologics	36 (4.7)
Malignancy	109 (14.1)	Patient preference	33 (4.3)
Respiratory problems[a]	79 (10.2)	Renal dysfunction	32 (4.2)
Liver dysfunction	62 (8.0)	Older age	20 (2.6)
Gastrointestinal disease	51 (6.6)	Heart failure, pleural effusion, oedema	19 (2.5)
Haematological disease[b]	46 (6.0)	Fever	12 (1.6)
Invalidity of methotrexate	44 (5.7)	Poor compliance	12 (1.6)
Rheumatoid arthritis remission	43 (5.6)	Surgery	6 (0.8)
Mucocutaneous disease	41 (5.3)	Neurological disease	6 (0.8)
Wish for pregnancy	39 (5.1)	Others	51 (6.5)

Total number = 771, multiple answers allowed

[a] Respiratory disease and symptoms were included as respiratory problems. Pneumonia was included as an infectious disease

[b] Lymphoproliferative disease was included as a malignancy

23 (14.9%). Respiratory infections ($n = 104$) included pneumonia in 58 patients (55.8%), pneumocystis pneumonia in 17 (16.3%), nontuberculous mycobacteriosis in six (5.8%), and pyothorax in three (2.9%). In addition, MTX discontinuation because of upper respiratory tract inflammation or bronchitis was observed in 20 patients (19.2%), and six of the ten patients with skin infections had cellulitis. The recorded malignancies ($n = 109$) were LPD in 44 patients (40.4%), lung cancer in 16 (14.7%), stomach cancer in eight (7.3%), uterine cancer in six (5.5%), breast cancer in six (5.5%), colorectal cancer in five (4.6%), and others in 24 (22.0%).

Respiratory problems ($n = 79$) included interstitial pneumonia ($n = 46$, 58.2%), suspected MTX-associated pneumonia ($n = 22$, 27.8%), cough ($n = 19$, 24.1%), and other diseases ($n = 13$, 16.5%). Among the patients with interstitial pneumonia, 14 (30.4%) had organizing pneumonia. In this study, only nine patients received >15 mg of MTX weekly and 24 received >12 mg of MTX weekly. In the latter group of patients, seven had infectious diseases, and eight had malignancies, including four patients with LPD. Owing to the small number of cases, a comparison of reasons for MTX discontinuation between patients receiving high-dose MTX and those receiving low-dose MTX was not performed.

Liver dysfunction

MTX was discontinued owing to liver dysfunction in 57 patients (7.4%). The median aspartate aminotransferase (AST) level was 70 (IQR 51–99) IU/L, and alanine aminotransferase level was 103 (65.5–129) IU/L in 55 patients, excluding two patients who had no available data owing to MTX discontinuation at other hospitals. Excluding five patients with an unknown long-term course following MTX discontinuation, 29 (55.8%) of the remaining 52 patients had normalized liver function within 3 months of MTX discontinuation.

Abdominal sonography was performed in 30 patients, and fatty liver was found in 15 (50.0%). In addition to fatty liver, hepatitis C was diagnosed in three patients, autoimmune hepatitis in two, liver cirrhosis in one, liver cancer in one, liver metastasis in one, portal hypertension in one, alcohol consumption in three, and drug use in one; these were considered factors of liver damage, apart from MTX. Of the 30 patients who underwent abdominal sonography, the remaining two had no abnormal findings. A comparison of liver function in patients with and those without fatty liver showed that AST was significantly lower in patients with fatty liver (62.9 [46.5–77.5] IU/L vs. 115.1 [58.0–143.0]; P=0.0305). However, the two groups of patients could not be divided based on liver function test findings.

Renal dysfunction

Renal dysfunction was the cause of MTX discontinuation in 32 patients (4.25%), and the estimated glomerular filtration rate was 33.5 (26.3–42.5) mL/min at the time of MTX discontinuation. In addition, three of the 32 patients (9.4%) had pancytopenia caused by renal dysfunction.

Reasons for MTX discontinuation other than adverse events

Other reasons for MTX discontinuation (apart from adverse events) included patient preference, pregnancy plans, the invalidity of MTX use or the RA diagnosis, remission, and remission with biologics. Some patients discontinued MTX owing to their old age and poor compliance. The age of the older patients at the time of MTX discontinuation was 81.0 (76.0–85.0) years.

Time to MTX discontinuation associated with the reason for MTX discontinuation

The duration of treatment until MTX discontinuation in patients with RA, according to the reason for MTX discontinuation, was analyzed (Fig. 1). Gastrointestinal disorders, mucosal skin disorders, and fever occurred

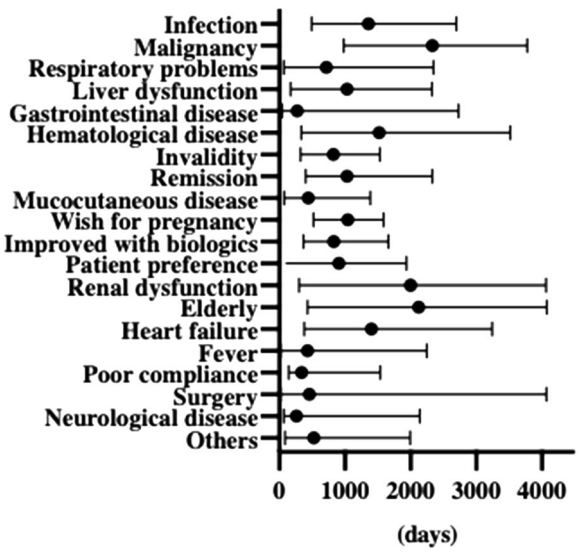

Fig. 1 Time to methotrexate (MTX) discontinuation according to the reason for MTX discontinuation. Duration of treatment until MTX discontinuation in patients with RA according to the reason for MTX discontinuation. Results are shown in days (median with interquartile range) according to the reasons; the time to MTX discontinuation was found to vary in accordance with the reasons (P<0.0001). Gastrointestinal disorders, mucosal skin disorders, and fever occurred relatively early after MTX initiation, and MTX was discontinued. In contrast, patients who discontinued MTX because of malignancy, old age, or renal dysfunction tended to have longer durations of MTX therapy before discontinuation

relatively early after MTX initiation, and MTX was immediately discontinued in such cases. In contrast, patients who discontinued MTX because of malignancy, old age, or renal dysfunction tended to have longer treatment durations prior to discontinuation.

Discussion

Only a few studies have examined the reasons for MTX discontinuation [8, 10–12]; however, none of them have focused on reasons other than adverse events. In the present study, the reasons for MTX discontinuation were diverse, and the most common reasons were the following: (1) infectious diseases (including pneumonia), (2) malignancy, and (3) respiratory problems.

In this study, many patients discontinued MTX owing to infectious diseases and did not resume MTX treatment after the infections were cured. In addition to severe infections, MTX was discontinued owing to upper respiratory tract infections. Patients with RA reportedly have a higher incidence of infections than the general population [14, 15]. Previous studies reveal that RA severity, corticosteroid use, and increased complications are associated with an increased risk of infection in patients with RA [16–18]. However, MTX has not been included as a risk factor for infectious diseases in RA [19]. Conversely, reports have suggested an association between low-dose MTX and opportunistic infections, as well as between MTX and various vaccines [20–24].

Whether continuing or halting MTX treatment at the onset of infection in patients with RA improves the outcome of infection has not been adequately studied. The Japanese MTX Clinical Practice Guideline for the Treatment of RA 2016 states that, in patients on long-term MTX therapy, MTX should be discontinued immediately upon onset of infection [13]. McLean-Tooke et al. proposed discontinuing MTX therapy in patients with RA with infections and resuming MTX after the infection is cured [19]. However, there is no clear evidence or guideline regarding the timing of MTX resumption after recovery from infection [3, 4]. This is an important issue that should be considered in future research.

MTX should be discontinued immediately in cases of LPD [13]; however, the data in many reports are insufficient to fully assess the risk of MTX in malignancy [9, 25, 26]. Furthermore, other than with LPD, there is no evidence for MTX discontinuation owing to complications associated with malignancy. However, the present study found that many physicians discontinued MTX due to malignancies, which were also cited as a reason for the discontinuation of MTX in a previous study [8]. According to the Adverse Event Reporting System of the Food and Drug Administration, from the first quarter of 2004 to the end of 2015, MTX was significantly associated with all malignancies except liver cancer [27]. Two studies reported an increased risk of lung cancer in patients with RA treated with MTX [28, 29]. Conversely, several reports have shown that, apart from drug-induced malignancies, RA also increases the incidence of malignancies, especially LPD [30–32]. However, the American College of Rheumatology (ACR) and Spanish guidelines do not address the treatment of RA at the onset of malignancy [3, 33]. Canadian guidelines generally state that patients with RA with active malignancies should delay or refrain from treatment with conventional or biologic disease-modifying antirheumatic drugs while receiving chemotherapy or radiation therapy since immunity is compromised [34]. This study did not examine the malignancy status behind MTX discontinuation, but MTX discontinuation due to malignancy was based on the physician's decision. This lack of evidence emphasises that issues of concern remain. The development and subsequent course of malignancy are complicated by many factors, including the stage of malignancy, differences in treatment strategies, and variances in patient background. It is also important to determine who should screen for malignancy during MTX administration [35].

There is some evidence of MTX-induced fatty liver [36, 37], and its pathogenesis has been elucidated at the molecular level [38, 39]. The 2021 ACR guidelines recommend that MTX be administered to patients with RA and non-alcoholic fatty liver disease when liver enzyme levels are normal [3]. Studies have investigated MTX-induced fatty liver in patients with RA [40, 41]; however, no studies have followed the long-term prognosis of fatty liver with MTX. In addition, there is no index to determine whether MTX treatment should be continued in RA complicated by fatty liver disease. However, if the liver damage is mild and fatty liver is present on abdominal sonography, it might be possible to follow up without discontinuing MTX.

In previous reports, the main reasons for MTX discontinuation were adverse events, such as gastrointestinal symptoms and abnormal laboratory values [8, 10–12]. In addition, drug eruptions, gastrointestinal disorders, and abnormal laboratory data are acceptable reasons for discontinuing MTX. The present study revealed various reasons other than adverse events that were associated with MTX discontinuation. Although old age is not a reason for discontinuing MTX, older patients are more likely to discontinue MTX early owing to decreased compliance [42], increased adverse events associated with decreased renal function [43], and susceptibility to infections owing to age-related decline in physiological function [44, 45].

It is controversial whether MTX or biologics should be discontinued when RA is relieved by the concomitant use of biologics [46]; however, in some cases, MTX was

discontinued in the present study. In addition, an article examining MTX reinduction showed that patients with high RA disease activity, older age, and comorbidities are less likely to resume MTX treatment; however, details regarding the comorbidities were not described [47].

This study had a few limitations, including that it was a single-centre, retrospective study. Hence, the analysis of the impact of combination therapy on MTX discontinuation was insufficient, and institution-specific decisions to discontinue MTX may have contributed to bias. Furthermore, the impact of concomitant therapies other than MTX was not studied. Finally, the overall number of patients with RA receiving MTX in the department was unknown in this study; hence, the frequency of cases in which MTX was discontinued was unknown.

Conclusions

In conclusion, this study revealed that the reasons for the discontinuation of MTX are diverse. The following remaining challenges were determined in this study: (1) when MTX administration should be restarted after infections have subsided, (2) whether MTX administration should be discontinued when malignancy develops, and (3) management of fatty liver that develops owing to MTX administration. Resolving these problems of MTX discontinuation may convince more patients to recommence MTX therapy. Hence, collecting and examining evidence from multiple institutions in the future is recommended.

Abbreviations

MTX: Methotrexate; RA: Rheumatoid arthritis; IQR: Interquartile range; LPD: Lymphoproliferative disease; AST: Aspartate aminotransferase.

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Authors' contributions

All authors contributed to the conception and design of the study. Material preparation, data collection, and analysis were performed by H. N., Y. G., T. K., and K. K. The first draft of the manuscript was drafted by H. N. All authors commented on the previous versions of the manuscript. The authors have read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author, H. Nagafuchi, on reasonable request.

Declarations

Ethics approval and consent to participate

The Ethics Committee of St. Marianna University School of Medicine (protocol number 4678) approved the study protocol as well as the collection and publication of data. Informed consent was obtained in the form of opt-out on the website (https://www.marianna-u.ac.jp/houjin/disclosure/clinical-research/marianna/file/ichiran.pdf. in Japanese). All procedures were performed in accordance with the ethical standards outlined in the Declaration of Helsinki.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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References

1. Favalli EG, Biggioggero M, Meroni PL (2014) Methotrexate for the treatment of rheumatoid arthritis in the biologic era: still an "anchor" drug. Autoimmun Rev 13(11):1102–1108. https://doi.org/10.1016/j.autrev.2014.08.026
2. Pincus T, Yazici Y, Sokka T, Aletaha D, Smolen JS (2003) Methotrexate as the "anchor drug" for the treatment of early rheumatoid arthritis. Clin Exp Rheumatol 21(Supplement 31):S179–S185
3. Fraenkel L, Bathon JM, England BR et al (2021) 2021 American College of Rheumatology Guideline for the treatment of rheumatoid arthritis. Arthritis Care Res (Hoboken) 73(7):924–939. https://doi.org/10.1002/acr.24596
4. Smolen JS, Landewé RBM, Bijlsma JWJ et al (2020) EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Ann Rheum Dis 79(6):685–699. https://doi.org/10.1136/annrheumdis-2019-216655
5. Wang W, Zhou H, Liu L (2018) Side effects of methotrexate therapy for rheumatoid arthritis: a systematic review. Eur J Med Chem 158:502–516. https://doi.org/10.1016/j.ejmech.2018.09.027
6. Gilani ST, Khan DA, Khan FA, Ahmed M (2012) Adverse effects of low dose methotrexate in rheumatoid arthritis patients. J Coll Physicians Surg Pak 22(2):101–104
7. Valerio V, Kwok M, Loewen H et al (2021) Systematic review of recommendations on the use of methotrexate in rheumatoid arthritis. Clin Rheumatol 40(4):1259–1271. https://doi.org/10.1007/s10067-020-05363-2
8. Nikiphorou E, Negoescu A, Fitzpatrick JD et al (2014) Indispensable or intolerable? Methotrexate in patients with rheumatoid and psoriatic arthritis: a retrospective review of discontinuation rates from a large UK cohort. Clin Rheumatol 33(5):609–614. https://doi.org/10.1007/s10067-014-2546-x
9. Salliot C, van der Heijde D (2009) Long-term safety of methotrexate monotherapy in patients with rheumatoid arthritis: a systematic literature research. Ann Rheum Dis 68(7):1100–1104. https://doi.org/10.1136/ard.2008.093690
10. Alarcón GS, Tracy IC, Strand GM, Singh K, Macaluso M (1995) Survival and drug discontinuation analyses in a large cohort of methotrexate treated rheumatoid arthritis patients. Ann Rheum Dis 54(9):708–712. https://doi.org/10.1136/ard.54.9.708
11. Gomides APM, de Albuquerque CP, Santos ABV et al (2019) Causes of synthetic disease-modifying drug discontinuation in rheumatoid arthritis: data from a large real-life cohort. PLoS One 14(3):e0213219. https://doi.org/10.1371/journal.pone.0213219
12. Wluka A, Buchbinder R, Mylvaganam A et al (2000) Longterm methotrexate use in rheumatoid arthritis: 12 year followup of 460 patients treated in community practice. J Rheumatol 27(8):1864–1871
13. Kameda H, Fujii T, Nakajima A et al (2019) Japan College of Rheumatology guideline for the use of methotrexate in patients with rheumatoid arthritis. Mod Rheumatol 29(1):31–40. https://doi.org/10.1080/14397595.2018.1472358
14. Smitten AL, Choi HK, Hochberg MC et al (2008) The risk of hospitalized infection in patients with rheumatoid arthritis. J Rheumatol 35(3):387–393
15. Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE (2002) Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. Arthritis Rheum 46(9):2287–2293. https://doi.org/10.1002/art.10524

16. Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE (2002) Predictors of infection in rheumatoid arthritis. Arthritis Rheum 46(9):2294–2300. https://doi.org/10.1002/art.10529
17. Au K, Reed G, Curtis JR et al (2011) High disease activity is associated with an increased risk of infection in patients with rheumatoid arthritis. Ann Rheum Dis 70(5):785–791. https://doi.org/10.1136/ard.2010.128637
18. Lacaille D, Guh DP, Abrahamowicz M, Anis AH, Esdaile JM (2008) Use of nonbiologic disease-modifying antirheumatic drugs and risk of infection in patients with rheumatoid arthritis. Arthritis Rheum 59(8):1074–1081. https://doi.org/10.1002/art.23913
19. McLean-Tooke A, Aldridge C, Waugh S, Spickett GP, Kay L (2009) Methotrexate, rheumatoid arthritis and infection risk: what is the evidence. Rheumatology (Oxford) 48(8):867–871. https://doi.org/10.1093/rheumatology/kep101
20. Oien KA, Black A, Hunter JA, Madhok R (1995) Pneumocystis carinii pneumonia in a patient with rheumatoid arthritis, not on immunosuppressive therapy and in the absence of human immunodeficiency virus infection. Br J Rheumatol 34(7):677–679. https://doi.org/10.1093/rheumatology/34.7.677
21. Antonelli MA, Moreland LW, Brick JE (1991) Herpes zoster in patients with rheumatoid arthritis treated with weekly, low-dose methotrexate. Am J Med 90:295–298. https://doi.org/10.1016/0002-9343(91)90568-I
22. Boyarsky BJ, Ruddy JA, Connolly CM et al (2021) Antibody response to a single dose of SARS-CoV-2 mRNA vaccine in patients with rheumatic and musculoskeletal diseases. Ann Rheum Dis 80(8):1098–1099. https://doi.org/10.1136/annrheumdis-2021-220289
23. Hua C, Barnetche T, Combe B, Morel J (2014) Effect of methotrexate, anti-tumor necrosis factor α, and rituximab on the immune response to influenza and pneumococcal vaccines in patients with rheumatoid arthritis: a systematic review and meta-analysis. Arthritis Care Res (Hoboken) 66(7):1016–1026. https://doi.org/10.1002/acr.22246
24. Park JK, Lee YJ, Shin K et al (2018) Impact of temporary methotrexate discontinuation for 2 weeks on immunogenicity of seasonal influenza vaccination in patients with rheumatoid arthritis: a randomised clinical trial. Ann Rheum Dis 77(6):898–904. https://doi.org/10.1136/annrheumdis-2018-213222
25. De Cock D, Hyrich K (2018) Malignancy and rheumatoid arthritis: epidemiology, risk factors and management. Best Pract Res Clin Rheumatol 32(6):869–886. https://doi.org/10.1016/j.berh.2019.03.011
26. Smitten AL, Simon TA, Hochberg MC, Suissa S (2008) A meta-analysis of the incidence of malignancy in adult patients with rheumatoid arthritis. Arthritis Res Ther 10(2):R45. https://doi.org/10.1186/ar2404
27. Inose R, Hashimoto N, Hosomi K, Yokoyama S, Takada M (2020) Association between malignancy and methotrexate and biological disease-modifying antirheumatic drugs in patients with rheumatoid arthritis. Int J Clin Pharmacol Ther 58(3):131–138. https://doi.org/10.5414/CP203604
28. Buchbinder R, Barber M, Heuzenroeder L et al (2008) Incidence of melanoma and other malignancies among rheumatoid arthritis patients treated with methotrexate. Arthritis Rheum 59(6):794–799. https://doi.org/10.1002/art.23716
29. Abásolo L, Júdez E, Descalzo MA et al (2008) Cancer in rheumatoid arthritis: occurrence, mortality, and associated factors in a South European population. Semin Arthritis Rheum 37(6):388–397. https://doi.org/10.1016/j.semarthrit.2007.08.006
30. Simon TA, Thompson A, Gandhi KK, Hochberg MC, Suissa S (2015) Incidence of malignancy in adult patients with rheumatoid arthritis: a meta-analysis. Arthritis Res Ther 17:212. https://doi.org/10.1186/s13075-015-0728-9
31. Wilton KM, Matteson EL (2017) Malignancy incidence, management, and prevention in patients with rheumatoid arthritis. Rheumatol Ther 4(2):333–347. https://doi.org/10.1007/s40744-017-0064-4
32. Baecklund E, Iliadou A, Askling J et al (2006) Association of chronic inflammation, not its treatment, with increased lymphoma risk in rheumatoid arthritis. Arthritis Rheum 54(3):692–701. https://doi.org/10.1002/art.21675
33. García-Vicuña R, Martín-Martínez MA, Gonzalez-Crespo MR et al (2017) Recommendations by the Spanish Society of Rheumatology for the management of patients diagnosed with rheumatoid arthritis who cannot be treated with methotrexate. Reumatol Clin 13(3):127–138. https://doi.org/10.1016/j.reuma.2016.10.002
34. Bombardier C, Hazlewood GS, Akhavan P et al (2012) Canadian Rheumatology Association recommendations for the pharmacological management of rheumatoid arthritis with traditional and biologic disease-modifying antirheumatic drugs: part II safety. J Rheumatol 39(8):1583–1602. https://doi.org/10.3899/jrheum.120165
35. Pundole X, Suarez-Almazor ME (2020) Cancer and rheumatoid arthritis. Rheum Dis Clin North Am 46(3):445–462. https://doi.org/10.1016/j.rdc.2020.05.003
36. Langman G, Hall PM, Todd G (2001) Role of non-alcoholic steatohepatitis in methotrexate-induced liver injury. J Gastroenterol Hepatol 16(12):1395–1401. https://doi.org/10.1046/j.1440-1746.2001.02644.x
37. Shetty A, Cho W, Alazawi W, Syn WK (2017) Methotrexate hepatotoxicity and the impact of nonalcoholic fatty liver disease. Am J Med Sci 354(2):172–181. https://doi.org/10.1016/j.amjms.2017.03.014
38. Lee MH, Hong I, Kim M et al (2008) Gene expression profiles of murine fatty liver induced by the administration of methotrexate. Toxicology 249(1):75–84. https://doi.org/10.1016/j.tox.2008.04.011
39. Ezhilarasan D (2021) Hepatotoxic potentials of methotrexate: understanding the possible toxicological molecular mechanisms. Toxicology 458:152840. https://doi.org/10.1016/j.tox.2021.152840
40. Mori S, Arima N, Ito M, Fujiyama S, Kamo Y, Ueki Y (2018) Non-alcoholic steatohepatitis-like pattern in liver biopsy of rheumatoid arthritis patients with persistent transaminitis during low-dose methotrexate treatment. PLoS One 13(8):e0203084. https://doi.org/10.1371/journal.pone.0203084
41. Quintin E, Scoazec JY, Marotte H, Miossec P (2010) Rare incidence of methotrexate-specific lesions in liver biopsy of patients with arthritis and elevated liver enzymes. Arthritis Res Ther 12(4):R143. https://doi.org/10.1186/ar3085
42. Harrold LR, Briesacher BA, Peterson D et al (2013) Cost-related medication nonadherence in older patients with rheumatoid arthritis. J Rheumatol 40(2):137–143. https://doi.org/10.3899/jrheum.120441
43. Secora A, Alexander GC, Ballew SH, Coresh J, Grams ME (2018) Kidney function, polypharmacy, and potentially inappropriate medication use in a community-based cohort of older adults. Drugs Aging 35(8):735–750. https://doi.org/10.1007/s40266-018-0563-1
44. Maggini S, Pierre A, Calder PC (2018) Immune function and micronutrient requirements change over the life course. Nutrients 10(10):E1531. https://doi.org/10.3390/nu10101531
45. Schoevaerdts D, Sibille FX, Gavazzi G (2021) Infections in the older population: what do we know. Aging Clin Exp Res 33(3):689–701. https://doi.org/10.1007/s40520-019-01375-4
46. Tornero-Molina J, Alperi-López M, Castellví I et al (2022) Experts document on methotrexate use in combined therapy with biological or targeted synthetic disease modifying drugs in patients with rheumatoid arthritis. Reumatol Clin (Engl Ed) 18(1):33–41. https://doi.org/10.1016/j.reuma.2020.08.009
47. de Thurah A, Nørgaard M, Stengaard-Pedersen K (2015) Methotrexate utilization in rheumatoid arthritis. A register-based cohort-study of treatment re-starts after gabs of at least 90 days. Springerplus 4:227. https://doi.org/10.1186/s40064-015-0975-x

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