Safety Profile of Methotrexate in Patients with Rheumatoid Arthritis

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Authors’ contributions
This work was carried out in collaboration among all authors. Authors ALK and PSP designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors PBM and ALK managed the analyses of the study and helped in literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: Methotrexate (MTX) is recommended as first-line therapy in patients with active Rheumatoid Arthritis (RA) as monotherapy or in combination with other disease-modifying anti-rheumatic drugs (DMARDs). Despite being considered a safe drug, some toxicities of MTX are inevitable and patients discontinue further treatment with MTX for the same.

Objective: To evaluate the safety profile of Methotrexate in patients with RA.

Methodology: An observational cross sectional study was conducted at a tertiary care hospital from 1st January 2020 to 31st December 2020 at rheumatology OPD in department of medicine.

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1. INTRODUCTION

Rheumatoid arthritis (RA) is one of the major systemic autoimmune diseases that affects humans across the world, with a prevalence of 0.4% to 1.3% worldwide and 0.28% to 0.7% in India [1,2]. RA is predominantly seen in females with a 2-3 times higher frequency than men and is characterized by symmetric bilateral involvement of joints associated with pain and swelling. Although the initial disease is associated with mild symptoms and fewer joint involvements, severity increases with the progression of the disease, characterized by inflammation of multiple joints with extra articular symptoms. If untreated, the inflammation of the synovial tissue can lead to permanent structural damage characterized by joint destruction, bone erosion, eventually leading to long-term disability and impaired quality of life [3].

Early diagnosis and treatment initiation within five months is paramount as it helps to substantially reduce the progression of joint changes and prevents irreversible damage to the joints. Different classes of drugs such as corticosteroids, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), and Disease-Modifying Anti-Rheumatic Drugs (DMARDs), are being used to treat RA. In India, >75% of patients with RA are prescribed DMARDs as the first line of treatment [3]. Among these, Methotrexate (MTX) is used as the first-line therapy drug in RA patients around the world, unless otherwise contraindicated or not tolerated by the patient [4]. Initial treatment with either MTX or a combination of MTX and glucocorticoid followed by sequential application of target therapies, including biologics, has shown significant improvement in disease outcome [5].

MTX, an anti-metabolite drug, is an analog of folic acid that interferes with dihydrofolate reductase enzyme activity, thereby preventing the synthesis of nucleotide and purine metabolism. These substances increase the production and release of adenosine, which is known to have anti-inflammatory properties [1]. Although methotrexate benefits many RA patients and is widely used due to its perceived efficacy, acceptable safety profile, and low cost, it is associated with side effects including hair loss, stomatitis, nausea, bone marrow toxicity, secondary infections, and hepatotoxicity [6]. The incidence of side effects has resulted in uncertainties among physicians while prescribing MTX in RA patients.

Usage of methotrexate under the recommended optimal weekly dose of up to 25mg is generally considered safe. While the safety profile of MTX under these circumstances is generally considered good, toxicities have been reported in the elderly population [7]. Studies determining the safety profile of MTX in the Indian population especially in the regions of Karnataka are limited. Hence, the present study was carried out to determine the incidence of patient reported side effects of MTX in RA patients in this part of Karnataka.

KLES, Dr. Prabhakar Kore Hospital, Belagavi. 117 patients diagnosed with RA who had been undergoing methotrexate treatment for at least six months as monotherapy or in combination with other DMARDs were included. Patient demographics, disease and treatment characteristics, side effects, and blood and laboratory markers specific to RA were studied with regards to methotrexate. Continuous variables were presented as mean and standard deviation, while categorical variables were presented as frequency and percentage. Association between categorical variables was done using Fisher exact test and chi square test.

Results: The study predominantly consisted of females (85.5%), and the mean age of patients was 47.92±13.398 years. Patient-reported side effects were seen/observed in 47% of patients. Commonly reported minor side effects were fatigue (17.1%), nausea (16.2%), anorexia (11.1%), stomatitis/oral ulcers (10.3%), epigastric burning (8.5%), hair fall (3.4%), and vomiting in 0.9% of patients. Demographic and clinical factors were not associated with side effects. There was no significant association between side effects and type of treatment.

Conclusion: Use of methotrexate in combination with other DMARDs is safe and should be encouraged as first line treatment of RA on routine basis. However, periodic blood and laboratory monitoring along with patient follow-ups are essential for early detection of toxicities.

Keywords: DMARD; methotrexate; rheumatoid arthritis; side effects.
2. MATERIALS AND METHODS

2.1 Study Design

An observational cross sectional study was conducted from 1st January 2020 to 31st December 2020 on 117 Rheumatoid Arthritis patients attending the Rheumatology OPD for follow up or admitted at KLES, Dr. Prabhakar Kore Hospital & MRC, Belagavi by universal sampling method.

All diagnosed cases of rheumatoid arthritis as per ACR/EULAR Criteria 2010 [8] already on methotrexate treatment at least for 6 months as monotherapy or in combination with other DMARDs and those willing to participate in the study were included. Patients with known hepatic and renal diseases, and known bone marrow disorders prior to initiation of treatment were excluded from the study.

All the collected data was documented in a study proforma designed specific for the study. The following data was collected:

• Patient demographics including, age and sex.

• Clinical characteristics including disease duration, disease activity (remission, low, moderate and high activity), RA factor and ACPA positivity.

• Treatment details including, DMARDs duration, type of treatment.

(Monotherapy and combination therapy) MTX dose (≥12.5mg = optimal dose; <12.5mg = suboptimal dose), MTX form (oral and subcutaneous).

• Laboratory investigations including Complete Hemogram, Liver function tests and Serum Creatinine (as and when required) were assessed to evaluate the presence of anemia, leukopenia, thrombocytopenia, hypoalbuminemia, elevated transaminases and creatinine.

After collecting the demographic details, a detailed history was taken to document patient reported side effects [6,9] whether it was absent or present, including:

• GI intolerance (Dyspepsia, Nausea, vomiting, Diarrhea, anorexia).

• Stomatitis, oral ulcers.

• Hair fall.

• Bone marrow toxicity like pancytopenia, anemia, leucopenia, thrombocytopenia.

• Infections like Herpes.

• Cough, shortness of breath and fever suggestive of Interstitial Pneumonitis, pleuritis, pleural effusion, interstitial fibrosis, non-cardiogenic pulmonary oedema.

• Methotrexate Flu (Nausea, Myalgia, low grade fever, chills).

The study was ethically approved by the Institutional Committee of Human Ethics (MDC/DOME/208). Informed written consent was obtained from all the subjects included in the study. All the subjects participating in the study were informed about the risks and benefits of the study and participant’s confidentiality was maintained.

2.2 Statistical Analysis

The obtained data was coded and entered into Microsoft Excel spreadsheet and then imported to SPSS for statistical analysis. Continuous variables were presented as mean and standard deviation, while the categorical variables were presented as frequency and percentage. Association between categorical variables was done using chi square test. ‘p’ value of <0.05 was considered statistically significant.

3. RESULTS AND DISCUSSION

In the current study, majority of the patients belonged to the age group of 41-60 years (n=57, 48.70%). While the youngest patient was aged 18 years, the oldest patient was 76 years with a mean age of 47.92±13.398 of the total. Out of 117 patients, 101 (86.30%) were females, while 16 (13.70%) were males, making it a study with female predominance with a ratio of 6:1 (Refer Table 1).
Table 1. Patient demographics

<table>
<thead>
<tr>
<th>Age (years) (n=117)</th>
<th>Minimum</th>
<th>Maximum</th>
<th>(Mean ±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>18</td>
<td>76</td>
<td>47.92 ± 13.398</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gender</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>101 (86.30%)</td>
<td>16 (13.70%)</td>
</tr>
</tbody>
</table>

Table 2 represents the mean, minimum and maximum duration of illness, DMARDs treatment and methotrexate treatment for RA in the study population. Among the 117 patients, only Rheumatoid factor was positive in 61 (52.10%) patients and only anti-citrin-citrulinated peptide antibody was positive in 3 (2.60%) patients. Both Rheumatoid factor and anti-citrin-citrulinated peptide antibody was present in 18 (15.40%) patients. Out of 117 patients, 57 (48.70%) patients were undergoing treatment with DMARDS for a year or less, 28 (23.90%) patients were undergoing treatment with DMARDS for >2 to 5 years. Duration of DMARDS was >1 to 2 years and >5 years in 19 (16.20%) patients and 13 (11.10%) patients, respectively.

Table 3 summarises the distribution of type of treatment received. 82 (70.10%) of patients received the optimal dose (<12.5mg). 104 (88.90%) of patients received MTX in oral form; while, 13 (11.10%) of patients received subcutaneous MTX.

Disease activity was categorized based on the CDAI/DAS28CRP scores. Nearly half the patients (n=58, 49.60%) had moderate disease activity followed by high activity in 40 (34.20%) patients, remission in 10 (8.50%) patients and low disease activity in 9 (7.70%) patients.

Following MTX therapy, the blood parameters including anemia, leukopenia, thrombocytopenia and transaminitis were evaluated in this study. Among the 117 patients, 75 (64.1%) patients had anemia, 2 (1.7%) had leukopenia, 5 (4.3%) patients had thrombocytopenia and 16 (13.7%) of patients had transaminitis. Out of 117 patients, hypoalbuminemia was observed in 17 (14.5%) of patients; while, in 8 (6.8%) patients the creatinine levels were abnormal.

Table 2. Descriptive statistics of disease duration, DMARDs duration and methotrexate dose in the study population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease duration (years)</td>
<td>0.5</td>
<td>20</td>
<td>4.18 ± 4.29</td>
</tr>
<tr>
<td>DMARDs duration (years)</td>
<td>0.5</td>
<td>15</td>
<td>2.61 ± 2.79</td>
</tr>
<tr>
<td>Methotrexate dose (mg/week)</td>
<td>7.5</td>
<td>25</td>
<td>15.598 ± 4.93</td>
</tr>
</tbody>
</table>

Table 3. Frequency distribution of type of treatment received by the patients

<table>
<thead>
<tr>
<th>RA treatment</th>
<th>Frequency</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTX monotherapy</td>
<td>2</td>
<td>1.7</td>
</tr>
<tr>
<td>Combination of MTX and DMARDS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX + low dose steroid</td>
<td>8</td>
<td>6.8</td>
</tr>
<tr>
<td>MTX+HCQ</td>
<td>10</td>
<td>8.5</td>
</tr>
<tr>
<td>MTX + low dose steroid + HCQ</td>
<td>71</td>
<td>60.7</td>
</tr>
<tr>
<td>MTX + low dose steroid + HCQ + Leflunomide</td>
<td>22</td>
<td>18.8</td>
</tr>
<tr>
<td>MTX + low dose steroid + HCQ + Sulfasalazine</td>
<td>3</td>
<td>2.6</td>
</tr>
<tr>
<td>MTX + HCQ + Leflunomide</td>
<td>1</td>
<td>0.9</td>
</tr>
<tr>
<td>Total (n)</td>
<td>117</td>
<td>100.0</td>
</tr>
</tbody>
</table>
In the study population, 55 (47%) patients reported side effects and 62 (53%) patients had no reported side effects following MTX therapy. Frequency distribution of patient reported side effects is summarized in Table 4.

**Table 4. Frequency distribution of reported side effects in the study population**

<table>
<thead>
<tr>
<th>Reported Side Effects</th>
<th>Frequency (n=117)</th>
<th>Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epigastric burning</td>
<td>10</td>
<td>8.5</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
<td>0.9</td>
</tr>
<tr>
<td>Nausea</td>
<td>19</td>
<td>16.2</td>
</tr>
<tr>
<td>Anorexia</td>
<td>13</td>
<td>11.1</td>
</tr>
<tr>
<td>Stomatitis/oral ulcers</td>
<td>12</td>
<td>10.3</td>
</tr>
<tr>
<td>Hair fall</td>
<td>4</td>
<td>3.4</td>
</tr>
<tr>
<td>Fatigue</td>
<td>20</td>
<td>17.1</td>
</tr>
<tr>
<td>None</td>
<td>62</td>
<td>53</td>
</tr>
</tbody>
</table>

No significant association was noted between incidence of side effects and age (p=0.774) as analysed by Chi Square Test. There was no significant association between gender and patient reported side effects (p=0.058) and between the duration of DMARDs therapy and side effects (p=0.079). No significant association between MTX dose and reported side effects (p=0.321) was found as well as no significant association was noted between the type of treatment and side effects (p=0.610).

There was neither significant association between the form of MTX and incidence of side effects (p=0.600) nor between the disease activity and patient reported side effects (p=0.220).

Among 75 patients with anemia, 43 reported side effects and 32 patients had no side effects. The difference was statistically significant (p=0.003). Association between anemia and MTX dose (p=0.854), transaminases (p=0.886), leukopenia (p=0.180), thrombocytopenia (p=0.428), hypoalbuminemia (p=0.955) and creatinine (p=0.494) were not statistically significant (Refer Table 5).

None of the patients with leukopenia reported side effects (p=0.109). Association between leukopenia and MTX dose (p=0.231), transaminases (p=0.441), thrombocytopenia (p=0.675), hypoalbuminemia (p=0.426) and creatinine (p=0.593) was not statistically significant. Only one patient with thrombocytopenia reported side effects (p=0.199). Association between thrombocytopenia and MTX dose (p=0.624), transaminases (p=0.134), hypoalbuminemia (p=0.734) and creatinine (p=0.395) were not statistically significant. Among 16 patients with elevated transaminases levels, 7 patients reported side effects and 9 patients had no side effects. No statistically significant difference noted (p=0.778). Association between thrombocytopenia and MTX dose (p=0.275), hypoalbuminemia (p=0.62) and creatinine (p=0.374) were not statistically significant. Out of 17 patients with hypoalbuminemia, 8 patients reported side effects and 9 patients had no side effects. No statistically significant difference noted (p=0.996). Association between hypoalbuminemia and MTX dose (p=0.961) and creatinine (p=0.418) were not statistically significant.

Among 8 patients with elevated creatinine levels, 4 patients reported side effects (p=0.861). Association between elevated creatinine levels and MTX dose (p=0.217) was not statistically significant. Out of 117 patients, 10 patients had reported side effects only, 42 patients had deranged laboratory- blood parameters only, 45 patients had both side effects and deranged laboratory-blood parameters. No statistically significant association between the type of treatment and adverse treatment outcome was noted (p=0.686). Similarly, difference between the dose of MTX and adverse treatment outcomes were not significant (p= 0.725).

**Table 5. Association of anemia with patient reported side effects**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Anemia Present (n=75)</th>
<th>Absent (n=42)</th>
<th>Total (N=117)</th>
<th>Chi square value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient reported Side effects</td>
<td>Present</td>
<td>43 (78.2%)</td>
<td>12 (21.8%)</td>
<td>55 (100.0%)</td>
<td>8.941</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>32 (51.6%)</td>
<td>30 (48.4%)</td>
<td>62 (100.0%)</td>
<td></td>
</tr>
</tbody>
</table>

p<0.05 considered significant. Cochran rule for applying the chi square test was met.
3.1 Discussion

Mean age of the patients in the current study cohort was 47.92 years which is lower than the mean age 55.6 years noted by Myasoedova et al. [10], and higher than 41.72 reported by Mittal et al. [11]. Previous studies have suggested that RA diagnosis is higher in the sixth decade of life [1]. In this study, although 19.7% patients belonged to age group >60 years, majority patients (48.7%) belonged to the age group of 41-60 years. According to Myasoedova et al. [10] women are affected 3-4 times that of men. In their study, incidence of RA increased by 2.5% per year from 1995 to 2007 in women as compared to men in whom there was a decrease in 0.5% incidence of RA per year. Similar female predominance (85.5%) was noted in the study with a female to male ratio of 6:1, and can be attributed to the fact that RA affects more commonly in women.

Choice of treatment is related to either patient preference or physician recommendation [12]. According to Quach et al. [13] only 30% RA patients reach a low disease activity with MTX monotherapy with a dose of 20 mg/week, while the rest of them need additional medications for improvements. In a study by Dubey et al. [14] systemic corticosteroids (54.4%) were the commonly used additional DMARDs followed by hydroxychloroquine (53.9%), NSAIDS (47.5%), sulfasalazine (20.1%) and leflunomide (15.7%). In the study, the mean duration of DMARDs treatment was 2.63 years; among 117 patients, only 1.7% of patients received MTX monotherapy, while 98.3% patients received combination therapy (different combinations of MTX, steroid, hydroxychloroquine and leflunomide), since most rheumatologists prefer a combination therapy to ensure adherence and minimize side effects.

Studies have shown that the prevalence of side effects related to MTX toxicity ranges from 10-40% [15,16]. Patient reported side effects following MTX therapy in this study were comparatively higher (47%). Frequency of patient reported side effects differs in different regions due to patient related and physician related factors [12]. Literature enumerates the following toxicities associated with MTX irrespective of clinical doses including hematologic, gastrointestinal, pulmonary, infectious, mucocutaneous, renal, neuropsychiatric and musculoskeletal side effects [9,17,18,19]. Most common symptoms in a study by Attar [20] were gastrointestinal upset (31%), central nervous system symptoms (18.3%), abnormal liver function tests (14.1%), stomatitis (9.9%), alopecia (9.9%), macrocytic red blood cells picture (7%), fever with no infection (4.2%), macular rash (4.2%) and pancytopenia (4.2%).

A 30% incidence of gastrointestinal side effects was reported by Shea et al (2014). Accumulation of MTX for a prolonged period in the intestinal mucosal cells leads to sensitivity of the epithelium resulting in gastrointestinal symptoms [21]. Similar to the literature, in this study, majority of symptoms were gastrointestinal related including nausea (16.2%), anorexia (11.1%), epigastric burning (8.5%) and vomiting (9.0%). The gastrointestinal symptoms can be managed with drugs including H2 blockers, antacids, folate supplementation. Incidence of fatigue (17.1%) was the next common side effect after gastrointestinal side effects.

Pedrazas et al. [22] in their study showed that RA patients undergoing low dose MTX therapy (78.6%) had higher relative risk (11.73; CI: 2.57-58.98) of developing oral events than patients using other combination of drugs (23.8%). Mucocutaneous changes are due to impairment of oral mucosa and immunosuppression. Frequency of stomatitis/oral ulcers was relatively lower (10.3%) in the study cohort. Although mild pulmonary side effects such as cough and dyspnea are common with MTX, hypersensitivity pneumonitis is also reported by Conway et al. [23]. Patients on MTX therapy are prone to infection due to immunosuppressive nature of MTX [24]. In the current study cohort, pulmonary side effects were not experienced by any patients. Incidence of alopecia was comparatively lower (3.4%) than previous reports with MTX therapy (10%), occurrence is which is troublesome especially in young females which may hinder them from treatment continuation [20].

Frequency of hematological side effects ranges from 1-25% and comprise of mild leukopenia and pancytopenia are common in elderly patients with baseline folate deficiency [15,25]. Myelotoxicity is mainly due to increased serum MTX levels caused by delayed elimination, renal dysfunction, or hypoalbuminemia secondary to inflammation or liver disease [26]. Pancytopenia has also been seen after accidental methotrexate overdose in patients with hypoalbuminemia. We observed anemia in 64.1% patients, leukopenia in 1.7% patients, thrombocytopenia in 4.3%
patients and hypoalbuminemia in 14.5% patients. Higher frequency of anemia and hypoalbuminemia seen in the study could be related to predefined anemia and hypoproteinemia present at baseline in many patients, making them more vulnerable to MTX toxicity. Elevated transaminases were seen in 13.7% of patients in the study which is in accordance with the results of Gilani et al. [17] that reported raised transaminases by 13% (twice the normal ULR) in MTX therapy.

Previous studies have suggested high BMI, female gender, concomitant NSAIDs use, gastrointestinal events prior to MTX therapy and creatinine clearance as the possible risk factors for developing MTX toxicity [20]. Islam et al. [27] observed a decreased rate of side effects in injectable form than oral MTX. Although Edelman et al. [28] and Dubey et al. [14] have reported age as a potential risk factor for MTX toxicity, however the mechanism remains unknown. MTX toxicity related adverse effects is one of the major reasons for treatment discontinuation in approximately 12% patients after mid-long term therapy [29]. Gastrointestinal symptoms are higher with oral form leading to treatment switch from oral to parenteral forms [18]. However, despite treatment switch persistence of GI symptoms are reported Calasan et al. [29]. Compared to oral therapies with repeated dosages, Pulse dosage schedules of MTX therapy induces lower and short duration blood levels, thus reducing toxicity [17].

In accordance with reports by Hoekstra et al. [30], Dubey et al. [14], Drosos et al. [31], and Berkun et al. [32], who reported no correlation between age, MTX dose and oral lesions, demographic and clinical factors including age (p=0.774), gender (p=0.058), disease activity (p=0.220), duration of treatment (p=0.079), MTX dose (p=0.321), type of treatment i.e. MTX monotherapy or in combination therapy with other DMARDs (p=0.610), MTX form i.e. oral or subcutaneous (p=0.600) were not associated with side effects in this study. Similarly, none of the blood and laboratory parameters were correlated with each other and with MTX dose and side effects (p>0.05) except for anemia (p=0.003) suggesting that the abnormalities are not dose related and independent of the MTX dose, type of treatment and side effects. Adverse outcome was further categorized as side effects only, deranged laboratory-blood parameters only and those with both side effects and deranged lab-blood parameters. Nearly half of patients had both side effects and deranged laboratory-blood parameters. However, type of treatment (p=0.686), dose of MTX (p= 0.725) and adverse treatment outcome were not related to each other.

4. CONCLUSION

MTX is relatively safe drug. Despite the fact that almost all patients received MTX as a part of combination therapy, the incidence of patient reported side effects was 47%. Apart from common reported minor side effects such as fatigue (17.1%), nausea (16.2%), anorexia (11.1%), stomatitis/oral ulcers (10.3%), epigastric burning (8.5%), hair fall (3.4%), and vomiting in 0.9% of patients, no serious or life-threatening side effects were reported. In this study, 64.1% patients were anemic, 1.7% patients had leukopenia, 4.3% patients had thrombocytopenia and 13.7% patients had elevated transaminas levels.

As observed in the study, demographic and clinical factors include age (p=0.774), gender (p=0.058), disease activity (p=0.220), duration of treatment (p=0.079), MTX dose (p=0.321), type of treatment i.e. MTX monotherapy or in combination therapy with other DMARDs (p=0.610), MTX form i.e. oral or subcutaneous (p=0.600) and were not associated with side effects. Similarly, no significant association between side effects and type of treatment (p=0.686), a dose of MTX (p= 0.725) was observed. Hence, this study proposes that this group of study population tolerated methotrexate well without any life-threatening side-effects. Hence, use of methotrexate in combination with other DMARDs is safe and should be encouraged as first line treatment of RA on routine basis.

5. LIMITATION OF THE STUDY

In this study, different patient reported symptoms based on routes of administration, dose of MTX (suboptimal vs optimal) and different drug combinations was assessed to give a detailed understanding of the causal relationship. Cross sectional nature of the study is one of the major limitations of the study. Although with the available sample size, the side effects and its relationships were assessed, more robust results would be possible with larger sample and prospective study design. Therefore, further prospective controlled trials with in depth laboratory investigations and regular monitoring.
of the patient reported symptoms are warranted to validate the cross-sectional study. Along with demographic features and pretreatment characteristics, genetic polymorphism has been implicated as a predictive factor for MTX toxicity. Further research is warranted in this regard.

CONSENT

All authors declare that written informed consent was obtained from the patient (or other approved parties) for publication of this original article.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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