



The effect of methotrexate on blood, liver, and renal parameters in patients with rheumatoid arthritis

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Abstract

Background: Rheumatoid arthritis (RA) is a long-term autoimmune disorder that primarily affects joints. The disease may also affect other parts of the body, including the skin, eyes, lungs, heart, nerves, and blood. This study aimed to evaluate the effect of methotrexate on blood, liver, and renal parameters in patients with RA.

Methods: A six-month cross-sectional study was carried out on 60 consecutive patients aged 19-70 years diagnosed with RA on methotrexate treatment (10 mg) orally per week. A questionnaire was taken from participants, and laboratory tests were done on renal and liver function and complete blood count (CBC), erythrocyte sedimentation rate (ESR), glutamic oxaloacetic transaminase (SGOT or AST), glutamate pyruvate transaminase (SGPT or ALT), Creatinine, C-reactive protein (CRP), and rheumatoid factor (RF) as a follow-up to drug intake.

Results: At the end of sample collection, participants ranged in age from 19 to 70 years, with a female-to-male ratio of 1.5:1. Significant differences in platelet (PLT) levels were observed only between days 1 and 14 of the treatment ($p < 0.05$). Similarly, SGPT levels showed significant variation between days 1 and 30 of the treatment ($p < 0.05$). Additionally, RF levels exhibited significant differences between days 1 and 14 ($p < 0.01$) and between days 1 and 30 of the treatment ($p < 0.04$).

Conclusion: The recommended medication for all kinds of patients with RA is methotrexate, which has had a notable impact on blood, liver, and kidney parameters. These characteristics can serve as indicators for monitoring the medication's effectiveness, safety, and patient follow-up.

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Introduction

Rheumatoid arthritis (RA) is a chronic, symmetrical, inflammatory autoimmune disease that initially affects small joints, progressing to larger joints, and eventually the skin, eyes, heart, kidneys, and lungs. Often, the bone and cartilage of joints are destroyed, and tendons and ligaments weaken (1).

The onset of this disease is usually from the age of 35 to 60 years, with remission and exacerbation. It can also afflict young children even before the age of 16 years, referred to as juvenile RA (JRA), which is similar to RA except that rheumatoid factor (RF) is not found (2-4). In the West, the prevalence of RA is believed to be 1-2% (5,6), and 1% worldwide (7).

One of the most common screening procedures in rheumatologic therapies is liver enzyme testing, as recommendations, such as the widely used American College of Rheumatology guidelines, urge monitoring liver enzymes at intervals of at least 8-12 weeks in all RA patients treated with methotrexate (MTX) (8). Additionally, since MTX precipitates in the renal tubules and is primarily excreted by the kidneys, high doses used for oncological treatments may lead to acute kidney injury (AKI) (9). Therefore, close monitoring of renal function is essential when administering MTX.

Although low-dose MTX therapy is regarded as an anchor therapy in RA, full details of its mechanism of action and off-target effects are still incompletely understood (10).

Considering MTX's effects on folic acid metabolism, MTX treatment can result in alterations of mean corpuscular volume (MCV), which may impact red cell distribution width (RDW), as MCV levels feed into RDW calculation (11). We thus questioned, whether RDW levels and subsequently its diagnostic utility and potential in RA subjects, as reported before, are influenced by ongoing MTX therapy (10,12-14). This study aimed to evaluate the effect of methotrexate on blood, liver, and renal parameters in patients with RA.

Methods

This cross-sectional study was conducted at Duhok Rheumatology Center from October 2023 to March 2024. Build statistics and a basis to standardize future practice and Hospital protocol.

Sixty consecutive patients aged 19-70 years with diagnosed RA on methotrexate treatment (10 mg) orally per week participated in this study. A questionnaire was taken from the participants after obtaining ethics approval from the Research Ethics Committee of Duhok Directorate of Health (13122023-11-17). Biochemical tests for renal and liver function, including creatinine, glutamic oxaloacetic transaminase (SGOT/AST), and glutamate pyruvate transaminase (SGPT/ALT), were performed alongside hematological tests such

as complete blood count (CBC) and erythrocyte sedimentation rate (ESR). Additionally, serological tests, including C-reactive protein (CRP) and rheumatoid factor (RF), were conducted to monitor drug administration. A total of 6 mL of venous blood was collected from each participant, with 3 mL placed in an EDTA tube for hematological tests and the remaining 3 mL used for biochemical analysis. Instruments for data collection were as follows: Roche Cobas c 311 biochemical auto analyzer machine for serum CRP, SGOT, SGPT, and Creatinine levels, and Boule Medonic hematological auto analyzer machine for hemoglobin (Hb), white blood cell (WBC), and platelet (PLT) levels. Patients undergoing MTX treatment were included in the study, while those receiving anti-rheumatoid drug therapies other than MTX, as well as individuals with blood, renal, or liver diseases, were excluded.

Results

Age and hematological changes during 1st, 14th, and 30th days of the treatment

Age and hematological changes [Mean±Standard Deviation (SD)] were as follows: age (44.13±10.31) years, while Hb, WBC, PLT counts, and ESR on the first day of the treatment were 12.30±1.67 gm/dl, 8.85±2.68×10⁹/L, 287.67±68.42×10³/L, 31.37±20.19 mmHg/hr, respectively; on the day 14th of the treatment were 12.20±1.59, 8.79±2.65, 270.38±73.96, and 28.12±14.97, respectively; and on day 30th of the treatment were 12.20±1.92, 9.06 ±2.98, 278.38±35.96, and 26.86±17.03, respectively (Table 1).

Biochemical changes during 1st, 14th, and 30th days of the treatment

Also, biochemical changes in Creatinine, SGOT, and SGPT levels were as follows: on the first day of the treatment were 0.74±0.34, 24.38±16.76, and 25.58±17.26 gm/dl, respectively; on day 14th of the treatment were 0.71±0.32, 20.66±7.62, and 21.18±7.77 gm/dl, respectively; and on day thirty after treatment were 0.72±0.34, 20.32 ±8.11, and 20.53±8.07 gm/dl, respectively (Table 2).

Serological changes during 1st, 14th, and 30th days of the treatment

Serological changes in CRP and RF levels were as follows: on the first day of the treatment were 21.29±53.84 gm/dl and 76.20±77.15 U/ml, respectively; on day 14th of the treatment were 12.39±18.97 gm/dl and 44.46 ± 46.52 U/ml, respectively; on day thirty after treatment were 11.82 ±14.04 gm/dl, 43.26 ± 59.41 U/ml, respectively (Table 3).

Comparison of hematological changes during 1st, 14th, and 30th days of the treatment

There were no significant differences between Hb, WBC, and ESR on all treatment days (1st, 14th, and 30th) ($p > 0.05$), while the only significant differences in PLT levels were between 1st and 14th days ($p < 0.05$) (Table 4).

Comparison of biochemical changes during 1st, 14th, and 30th days of the treatment

There were no significant differences between Creatinine and SGOT on all treatment days (1st, 14th, and 30th) ($p > 0.05$), while the only significant differences in SGPT levels were between 1st and 30th days ($p < 0.05$) (Table 5).

Comparison of serological changes during 1st, 14th, and 30th days of the treatment:

There were no significant differences between CRP levels on all treatment days (1st, 14th, and 30th) ($p > 0.05$), while there were significant differences in RF levels between 1st and 14th days, as well as 1st and 30th days ($p < 0.01$ and $p < 0.04$, respectively) (Table 6).

Table 1. Age and hematological changes during 1st, 14th, and 30th days of the treatment

Parameter	Age	HB1	HB2	HB3	WBC1	WBC2	WBC3	PLT1	PLT2	PLT3	ESR1	ESR2	ESR3
N	Valid	60	60	60	60	60	60	60	60	60	60	60	60
	Missing	0	0	0	0	0	0	0	0	0	0	0	0
Mean	44.13	12.30	12.20	12.20	8.85	8.79	9.06	287.67	270.38	278.35	31.37	28.12	26.86
Median	44.00	12.30	12.40	12.30	8.95	8.55	9.70	281.50	265.00	270.00	27.00	25.00	25.00
Std. Deviation	10.31	1.68	1.59	1.92	2.68	2.65	2.98	68.41	73.96	60.44	20.19	14.97	17.03
Minimum	19	9.3	9.2	8.5	1.3	3.5	3.5	135	118.0	148	4	3.0	1.0
Maximum	70	16.0	15.5	16.0	17.0	16.0	16.1	417	450.0	400	85	69.0	75.0

HB1: Hemoglobin 1st day, **HB2:** Hemoglobin 14th day, **HB3:** Hemoglobin 30th day, **WBC1:** WBC 1st day, **WBC2:** WBC 14th day, **WBC3:** WBC 30th day, **PLT1:** PLT 1st day, **PLT2:** PLT 14th day, **PLT3:** PLT 30th day, **ESR1:** ESR 1st day, **ESR2:** ESR 14th day, **ESR3:** ESR 30th day.

Table 2. Biochemical changes during 1st, 14th, and 30th days of the treatment

Parameter	Creatinine1	Creatinine2	Creatinine3	GOT1	GOT2	GOT3	GPT1	GPT2	GPT3
N	Valid	60	60	60	60	60	60	60	60
	Missing	0	0	0	0	0	0	0	0
Mean	0.74	0.71	0.72	24.38	20.66	20.32	25.58	21.18	20.53
Median	0.70	0.65	0.68	20.00	20.00	18.00	22.00	20.00	18.00
Std. Deviation	0.34	0.32	0.34	16.76	7.62	8.11	17.26	7.77	8.07
Minimum	0.10	0.00	0.12	0.9	1	0.2	6.00	2.00	0.20
Maximum	1.84	2.09	1.97	135.0	40	40.0	140.00	41.00	40.00

Creatinine 1: creatinine 1st day, **Creatinine 2:** creatinine 14th day, **Creatinine 3:** creatinine 30th day, **GOT1:** GOT 1st day, **GOT2:** GOT 14th day, **GOT3:** GOT 30th day, **GPT1:** GPT 1st day, **GPT 2:** GPT 14th day, **GPT3:** GPT 30th day.

Table 3. Serological changes during 1st, 14th, and 30th days of the treatment

Parameter	CRP1	CRP2	CRP3	RF1	RF2	RF3
N	Valid	60	60	60	60	60
	Missing	0	0	0	0	0
Mean	21.291	12.391	11.829	76.200	44.462	43.268
Median	10.820	9.400	9.400	64.000	32.000	17.500
Std. Deviation	53.848	18.974	14.044	77.151	46.529	59.413
Minimum	0.0	0.0	0.0	0.0	0.0	0.0
Maximum	409.0	130.0	90.0	256.0	232.6	256.0

CRP1: CRP 1st day, **CRP 2:** CRP 14th day, **CRP 3:** CRP 30th day, **RF1:** RF 1st day, **RF2:** RF 14th day, **RF3:** RF 30th day.

Table 4. Comparison of hematological changes during 1st, 14th, and 30th days of the treatment

Paired samples T-Test									
Parameter		Paired differences					t	Df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence interval of the difference				
					Lower	Upper			
Pair 1	HB1 - HB2	0.103	0.780	0.100	-0.098	0.305	1.025	59	0.310
Pair 2	HB1 - HB3	0.100	1.078	0.139	-0.178	0.378	0.721	59	0.474
Pair 3	HB2 - HB3	-0.003	0.997	0.128	-0.260	0.254	-0.023	59	0.981
Pair 4	WBC1 - WBC2	0.054	2.189	0.282	-0.511	0.620	0.193	59	0.848
Pair 5	WBC1 - WBC3	-0.211	2.766	0.357	-0.926	0.503	-0.593	59	0.556
Pair 6	WBC2 - WBC3	-0.266	2.445	0.315	-0.897	0.365	-0.843	59	0.403
Pair 7	PLT1 - PLT2	17.283	64.356	8.308	0.658	33.908	2.080	59	0.042
Pair 8	PLT1 - PLT3	9.317	40.449	5.222	-1.133	19.766	1.784	59	0.080
Pair 9	PLT2 - PLT3	-7.966	59.585	7.692	-23.359	7.426	-1.036	59	0.305
Pair 10	ESR1 - ESR2	3.245	14.726	1.901	-0.559	7.049	1.707	59	0.093
Pair 11	ESR1 - ESR3	4.503	18.831	2.431	-0.361	9.368	1.852	59	0.069
Pair 12	ESR2 - ESR3	1.258	9.967	1.286	-1.316	3.833	.978	59	0.332

Table 5. Comparison of biochemical changes during 1st, 14th, 30th days of the treatment

Paired Samples T-Test									
Parameter		Paired Differences					t	Df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	Creatinine1- Creatinine 2	0.026	0.224	0.029	-0.031	0.084	0.913	59	0.365
Pair 2	Creatinine1- Creatinine 3	0.021	0.332	0.042	-0.064	0.10707	0.491	59	0.626
Pair 3	Creatinine2- Creatinine 3	-0.005	0.313	0.040	-0.086	0.075	-0.133	59	0.894
Pair 4	GOT1 - GOT2	3.719	16.679	2.153	-0.589	8.028	1.727	59	0.089
Pair 5	GOT1 - GOT3	4.057	16.293	2.103	-0.151	8.266	1.929	59	0.059
Pair 6	GOT2 - GOT3	0.338	5.482	0.707	-1.078	1.754	0.478	59	0.635
Pair 7	GPT1 - GPT2	4.400	17.108	2.208	-0.0194	8.819	1.992	59	0.051
Pair 8	GPT1 - GPT3	5.048	16.870	2.177	0.690	9.406	2.318	59	0.024
Pair 9	GPT2 - GPT3	0.648	5.527	0.713	-0.779	2.076	0.909	59	0.367

Table 6. Comparison of serological changes during 1st, 14th, and 30th days of the treatment

Paired samples T-Test									
Parameter		Paired differences					t	Df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence interval of the difference				
					Lower	Upper			
Pair 1	CRP1 - CRP2	8.900	49.537	6.395	-3.896	21.697	1.392	59	0.169
Pair 2	CRP1 - CRP3	9.462	50.557	6.527	-3.598	22.523	1.450	59	0.152
Pair 3	CRP2 - CRP3	0.562	11.184	1.444	-2.327	3.451	0.389	59	0.699
Pair 4	RF1 - RF2	31.737	67.822	8.755	14.217	49.258	3.625	59	0.001
Pair 5	RF1 - RF3	32.931	84.154	10.864	11.191	54.670	3.031	59	0.004
Pair 6	RF2 - RF3	1.193	33.173	4.282	-7.376	9.763	0.279	59	0.781

Abbreviations:

CrCl: Creatinine Clearance, **CRP:** C-Reactive Protein, **csDMARDs:** conventional synthetic Disease-Modifying Anti-Rheumatic Drugs, **EDTA:** Ethylenediaminetetraacetic Acid, **ESR:** Erythrocyte Sedimentation Rate, **EULAR:** European Alliance of Association for Rheumatology, **GOT:** Glutamic Oxaloacetic Transaminase, **GPT:** Glutamic Pyruvic Transaminase, **Hb:** Hemoglobin, **JRA:** Juvenile Rheumatoid Arthritis, **MCV:** Mean Corpuscular Volume, **Mg:** Milligram, **ml:** Milliliter, **MTX:** Methotrexate, **PLT:** Platelet, **RA:** Rheumatoid Arthritis, **RDW:** Red Cell Distribution Width, **RF:** Rheumatoid Factor, **SD:** Standard Deviation, **WBC:** White blood cell.

Discussion

According to EULAR guidelines, conventional synthetic Disease-Modifying Anti-Rheumatic Drugs (csDMARDs), particularly MTX in combination with low-dose glucocorticoids, should be used as the first-line treatment for RA. Despite being considered an essential therapy for RA, low-dose MTX therapy's exact mechanism of action and side effects are yet unknown (10). Changes in hemoglobin (Hb) and mean corpuscular volume (MCV) due to MTX treatment may influence red cell distribution width (RDW), as RDW is calculated based on MCV levels (11). In addition to biochemical analysis, which helps predict potential toxicities, clinicians prioritize managing adverse effects through clinical monitoring. However, no studies have identified a widespread occurrence of these disturbances in the general population. This gap in research motivated the present study, aiming to develop a more effective approach for improved patient care.

Furthermore, in this study, no significant increase in transaminase levels was observed at an MTX cumulative dose of 1.5 g. This finding suggests that RA patients included in the study may tolerate MTX better than psoriatic patients, which could explain the absence of notable liver enzyme elevations (15,16). Even though, there is minimal correlation between elevated concentration of transaminases and the likelihood of fibrosis and histological alterations (17,18). A meta-analysis of randomized controlled trials examined the risk of liver injury in MTX users. The study published in *Seminars in Arthritis and Rheumatism*, 45(2), 156-162, revealed that the frequency of raised liver enzyme concentrations during MTX treatment in patients with psoriasis was more than that of RA patients (14.5% vs. 7.5%) (19). Research on other populations indicates a modest association between cumulative MTX dose and fibrosis. Moreover, liver enzymes were particularly monitored among the biochemical markers examined during prolonged MTX treatment (20).

Additionally, a 50% dose reduction in the event that Creatinine clearance (CrCl) is less than 45 mL/min may result from a decrease in CrCl, which is another important factor in renal-based treatment (21).

Effects of moderate renal insufficiency on pharmacokinetics of MTX in patients with RA (22). Renal disease in RA patients: The results of this study indicate that the cumulative MTX dose has a significant impact on renal function ($p = 0.037$ for creatinine and $p = 0.036$ for CrCl), particularly in female patients. A significantly higher prevalence of CrCl disturbances is also observed when compared to creatinine (13.18% vs. 1.09%, respectively, $p < 0.001$), indicating that CrCl should be prioritized in renal monitoring (23). The results of another

study indicate that the cumulative MTX dose has a significant impact on renal function ($p = 0.037$ for creatinine and $p = 0.036$ for CrCl), particularly in female patients. Considering renal function tests, creatinine levels were observed on days 1, 14, and 30, and the results were compared with those reported by (24). Similarly, in the evaluation of liver function tests, SGOT and SGPT levels were measured on days 1, 14, and 30, and the findings aligned with those of (25). The observed significant changes in GOT levels during treatment follow-up suggest that MTX may not always be toxic to the liver or kidneys when administered at low doses with proper clinical monitoring and investigations. Regarding serological tests, the current study found no significant differences in CRP levels between days 1st, 14th, and 30th, which is consistent with the findings of Ismaili et al. (2019) (26).

Conclusion

Methotrexate is the primary medication recommended for patients with RA, demonstrating significant effects on hematological, hepatic, and renal parameters. Although the administration of low-dose MTX on a weekly basis for autoimmune conditions may result in certain adverse effects, it is generally well-tolerated and exhibits considerable efficacy. Proper monitoring is essential to mitigate potential negative outcomes. Given that many of these serious complications can be detected early and potentially avoided, it is imperative for primary care physicians and hematologists to be aware of these issues and the associated guidelines. Prolonged MTX therapy may result in elevated liver enzyme levels. Serological assessments, such as CRP and RF tests, are critical for monitoring disease progression and the side effects of MTX. Additionally, conducting bone marrow examinations in relation to MTX treatment is advisable, as bone marrow suppression may provide valuable insights. If laboratory test abnormalities occur during treatment, it is recommended to reduce the methotrexate dosage or consider switching to an alternative medication with fewer side effects until the patient's condition stabilizes.

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Ethical statement

A questionnaire was taken from the participants after obtaining ethics approval from the Research Ethics Committee of Duhok Directorate of Health (13122023-11-17).

Conflicts of interest

The authors declare that they have no conflicts of interest.

Author contributions

BT: Data collection, filling questionnaire by asking patients, investigations, and drafting the manuscript; BR: Data collection, analysis of data, and drafting the manuscript.

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