Adverse effects of low dose methotrexate in rheumatoid arthritis patients

A hospital-based study

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ABSTRACT

الأهداف: إلقاء الضوء على الأعراض الجانبية لعقار ميثوتريكسيت (MTX) الذي يُستخدم في علاج التهاب المفاصل الروماتويدي (RA) وربط هذه الأعراض بالعوامل المساعدة التي تزيد من خطر الإصابة .

الطريقة: تم عمل دراسة استرجاعية لجميع المرضى المصابين بالتهاب المفاصل والذين استخدموا عقار (MTX) لمدة 3 أعوام خلال الفترة من يناير 2006م إلى ديسمبر 2008م وذلك في مستشفى جامعة الملك عبدالعزيز، جدة، المملكة العربية السعودية. ولقد تم تسجيل الأعراض الجانبية لـ (MTX) وتحليلها إحصائياً.

النتائج: لقد استخدم 71 مصاباً بـ (RA) من أصل 116مصاباً عقار (MTX). وكَانَ اضطراب المعدة والأمعاء في 31% مِنْ المرضى، تَلى ذلك بعض الأعراض العصبية في 18% من المرضى, وتسمم الكبد في 14%،والتهاب المعِدة في 10% وكذلك الثعلبة في 10% من المرضى، وكبر كريات الدم في 7%، وتبلغ نسبة المصابين 4% وذلك لأمراض الحمى والطفح الخدي وقلة الكريات الشاملة. هذا بالإضافة إلى قدرة العقار على تحفيز تضرر الرئة مع زيادة حجم العقيدة الروماتويدية في 1% من المرضى. يعد القصور الكلوي من أكثر العوامل التي تزيد من خطر الإصابة بهذه الأعراض الجانبية (OR=7.14, p<0.05) وذلك اعتماداً على التحليل الإحصائي اللوجستي. وكانت العوامل الأخرى التي تزيد من خطر الإصابة بهذه الأعراض هي: الجنس الذكري، الجنسية غير السعودية، التدخين، استخدام الستيرويد، نقص الألبومين ومشاكل المفاصل الخارجية.

خاتمة: يعد عقار (MTX) العقار الأكثر شيوعا في علاج مرض (RA)، وأكثر الأعراض الجانبية شيوعاً هواضطراب الأمعاء والمعدة فيما يعد تضرر الرئة من أقلها شيوعاً. إن تأثير العوامل السريرية في ظهور الأعراض الجانبية لعقار (MTX) يتطلب التحكم بالمرض وذلك لأنه لا يجب اعتبار كل العوامل المساعدة أعراضاً جانبية.

Objectives: To evaluate the side effects of methotrexate (MTX) in rheumatoid arthritis (RA) patients and to evaluate the possible predisposing variables.

Methods: A retrospective analysis conducted for all patients diagnosed with RA and treated with MTX over 3-years (January 2006 to December 2008) at King Abdul-Aziz University Hospital, Jeddah, Kingdom of Saudi Arabia. Frequency of MTX side effects and the predictive variables were recorded and analyzed statistically.

Results: Out of 116 RA patients, 71 patients used MTX. The most frequent side effect was gastrointestinal (GIT) disturbance in 31%, followed by central nervous system symptoms in 18%, hepatotoxicity in 14%, stomatitis and alopecia in 10% each, macrocytosis 7%, fever, malar rash and pancytopenia in 4%, and MTX-induced lung injury with increase in the size of rheumatoid nodule in 1% of patients. By Logistic regression analysis, renal impairment was the most significant variable increasing the risk of the side effects (OR=7.14, p<0.05). Other associated variables were male-gender, non-Saudi nationality, smoking, steroids use, hypoalbuminemia, and the presence of extra-articular manifestations.

Conclusion: Methotrexate is the most commonly drug used in the treatment of RA. Gastrointestinal disturbances were the most common side effect while lung involvement was the least. The impact of each clinical variable on MTX side effects requires paying more attention on the disease management as not all variables can be considered as risk factors.

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Methotrexate (MTX) is a folate antagonist that was first introduced in 1948 as a chemotherapeutic drug in the treatment of cancer (childhood acute lymphoblastic leukemia [ALL]).[1] It was approved by the USA-Food and Drug Administration (FDA) as a rheumatoid arthritis (RA) treatment in 1988.[2] The probability of a patient developing any clinically significant side effect over 5-years period was estimated to be 35%.[3] Common side effects include gastrointestinal (GI) symptoms (nausea, vomiting, and diarrhea), anemia, neutropenia, stomatitis, alopecia, dermatitis, malignancies (particularly lymphoma), and increases in the sizes of pre-existing rheumatoid nodules.[4] A small percentage of patients may develop potentially life-threatening side effects (1.7%), including hepatotoxicity, lung injury, and myelosuppression.[5] It was suggested that these side effects could be reduced (especially GI symptoms and hepatotoxicity) without changing the efficacy of MTX by supplementation with folic acid (dose range of 5-27.5 mg/week).[6] The revised American College of Rheumatology (ACR) recommendation in 2009[7] for the evaluation and monitoring of patients on MTX treatment includes baseline complete blood cell counts (CBC), serum creatinine analysis, liver function tests (LFT) (includes: alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, albumin, bilirubin]), hepatitis B, hepatitis C, and HIV serology, chest x-ray (obtained within the previous year), and a pregnancy test for women. Follow-up, initially every 4-6 weeks (CBC, creatinine, and AST) until the optimum dose is achieved, after then follow-ups are continued every 3 months. There have been suggested risk factors that may predict the possibility of developing MTX toxicities. They include high body mass index (BMI), female gender, use of non-steroidal anti-inflammatory drugs (NSAIDs), prior GI events, creatinine clearance <50 ml/min, abnormal LFT, high dosage of MTX, and the absence of folic acid supplementation.[8] The aim of our study is to evaluate MTX side effects in a well-defined hospital-based population of RA patients at a tertiary center and to determine the relationship between clinical variables and the possibility for developing side effects.

Methods. A retrospective study was conducted at King Abdul-Aziz University Hospital, Western region of Saudi Arabia. A computerized retrieval was conducted to identify all patients with a registered diagnosis of RA who received treatment at the hospital over 3-years period between January 2006 and December 2008. Rheumatoid arthritis patients were identified according to the 1987 American College of Rheumatology (ACR) classification criteria for the diagnosis of RA.[9] Patients were excluded if they were not taking MTX. Due to the retrospective nature of the study no ethical approval was required. Permission to conduct the study was received from the Chairman of the Department of Medicine, King Abdulaziz University Hospital, Jeddah, Saudi Arabia.

Data were collected from clinical records. These data included demographic features (age in years [divided into the following groups: Group A: less than 40 years; Group B: 40-50 years, Group C: >50-60 years; and Group D: ≥60 years of age], gender, nationality, and smoking status); clinical findings (disease duration [in years]; body mass index [BMI] calculated as weight in kilograms divided by height in meters squared [patients were considered obese when their BMI was >30 kg/m^2, according to the 2000 World Health Organization (WHO) classification for obesity);[10] the presence of extra-articular manifestations of RA (ExRA);[11] activity of the disease defined as >8 tender joints (from a 68-joint count), 8 swollen joints (from a 66-joint count), erythrocyte sedimentation rate >28 mm/hour, C-reactive protein >15 mg/L[12] or if the 28 disease activity score index (DAS28) >5.1;[13] treatment in the form of concomitant use of disease-modifying antirheumatic drugs (DMARDs), aspirin, and NSAIDs; duration of MTX use (in months); and folic acid supplementation. Associated co-morbidities were diabetes mellitus (DM), defined according to the WHO definition of a fasting plasma glucose (FPG) level of ≥126 mg/dl (7.0 mmol/l),[14] hypertension (HTN), which was classified according to the WHO-International Society of HTN (WHO-ISH) guidelines of a diastolic blood pressure >90 mm Hg,[15] and pre-existing lung disease (defined as pre-existing radiographic interstitial infiltrates).[16] Laboratory parameters included complete CBC, rheumatoid factor (RF) with a set point range (0-20 IU/L), LFT ([ALT: 30-65IU/L], [AST: 15-37 IU/L], alkaline phosphatase [ALP: 34-50gm/L], albumin [34-50gm/L], bilirubin [0-17 umol/L]), baseline hepatitis B or C infection status, serum creatinine [53-115 umol/L] with calculation of creatinine clearance using the Cockcroft formula,[17] and hypoalbuminemia if serum albumin was <34 gm/L. Methotrexate side effects were recorded once a patient developed any of the following: macrocytic red blood cells, pancytopenia, gastrointestinal upset, stomatitis, macular rash (occurring on the extremities but not in the trunk), central nervous system problems (headache, fatigue, or impaired ability to concentrate), alopecia, fever with no infection, chest infections (with *Pneumocystis carinii*, fungi, or herpes zoster virus), malignancies (lymphoma), increase in the size of rheumatoid nodules, and severe hepatotoxicity (defined as an increase in ALT level more than 3 times the normal upper limit).[18] Methotrexate-induced lung injury was diagnosed based on the modified Searles and McKendry

criteria for adverse MTX pulmonary events.[19] The criteria are further divided into major and minor criteria. Definite cases were defined as the presence of major criterion one or major criteria 2 and 3 and the presence of 3 out of 5 minor criteria. Probable cases were defined as the presence of major criteria 2 and 3 and 2 out of 5 minor criteria. The collected side effects will be tested for correlation against all the retrieved clinical variables to evaluate the relationship of each variable and to measure the risk of each variable.

Data analysis was performed using the Statistical Package for Social Sciences (SPSS software, version 16). The mean and Standard Deviation were calculated for continuous variables. Student's t-test was used to compare between mean as appropriate. Proportions for categorical variables were calculated using univariate analysis Chi-square testing. Multiple logistic regression (stepwise multivariate analysis) was performed on several variables to determine the association; with a 95% confidence interval. Odds ratios (OR) were calculated to estimate the risk size for each retrieved variable. Results were considered significant if the *p*-value <0.05.

Results. One hundred and sixteen patients fulfilled the 1987 ACR classification criteria for the diagnosis of RA observed during the 3-year study period. Forty-five patients excluded as they were receiving DMARDs other than MTX. Seventy-one patients are using MTX treatment either alone or in combination with other DMARD. **Table 1** shows the demographic and clinical characteristics of RA patients on MTX. Extra-articular manifestations of RA features detected in 38 patients (54%) and 25 patients (35%) had the disease and the active form. According to our laboratory reference, RF was detected in 48 patients (68%), and renal impairment was detected in 18 patients (25 %), with mean creatinine levels of 203±76 umol/L, ranging from

Table 1 - Demographic and clinical characteristics of 71 RA patients on MTX.

Variable	Number (%)
Gender	
Male	15 (21)
Female	56 (78)
Nationality	
Saudi	43 (61)
Non-Saudi	28 (39)
Age mean± SD (years)	47.6 ± 12.9
<40	19 (27)
40-50	26 (37)
>50 - 60	10 (14)
>60	16 (23)
Disease Duration (years)	
<1	6 (9)
1-5	8 (11)
>5-10	20 (28)
>10	37 (52)
Obesity	24(34)
Smoking	6 (8)
Co-morbid illness	
Diabetes mellitus	25 (35)
Hypertension	36 (51)
Renal impairment	18 (25)
Methotrexate	
Treatment duration mean ± SD (months)	26.8 ± 12.9
Dose mean ± SD (mg/week)	10 ± 4
Discontinue treatment	12 (17)
Combination	
Other DMARDs	53 (75)
Anti-TNF	1 (1)
NSAIDs (Including Aspirin)	50 (70)
Chronic Steroid Use	5 (7)
Folic acid Use	71 (100)
Rheumatoid factor (positive)	48 (68)
Hypoalbuminemia	18 (25)
LFT abnormalities	10 (14)

MTX - Methotrexate, DMARDs - Disease Modifying antirheumatic agents, NSAIDs - Non steroidal antiinflammatoryu drugs, RA - rheumatoid arthritis, TNF - tumor necrosis factor

Table 2 - Methotrexate associated side effects in 71 patients with RA (more than one side effect may exist in a patient).

Side Effects	Number of patients (%)
Gastrointestinal upset	22 (31.0)
Central nervous system symptoms	13 (18.3)
Abnormal Liver function test	10 (14.1)
Stomatitis	7 (9.9)
Alopecia	7 (9.9)
Macrocytic red blood cells picture	5 (7.0)
Fever with no infection	3 (4.2)
Macular rash	3 (4.2)
Pancytopenia	3 (4.2)
Malignancies (Lymphoma)	3 (4.2)
Increase the size of rheumatoid nodule	1 (1.4)
Chest infections: Fungi	1 (1.4)
MTX lung injury	1 (1.4)
Chest Involvement (n=11)	
Shortness Of breath	9 (81.8)*
Shortness Of breath duration < 8weeks	2 (18.2)*
Shortness Of breath duration < 8weeks	7 (63.6)*
Non productive cough	8 (72.7)*
Previous lung disease-lung fibrosis	5 (45.4)*
Previous lung disease-bronchiactasis	5 (45.4)*
O2 saturation <90%	6 (55.5)*
O2 saturation >90%	5 (45.4)*
WBC >15,000 per mm^3	3 (27.3)*
WBC <15000 per mm^3	8 (72.7)*

MTX - Methotrexate,
*Percentage calculated out of 11 cases suspected with chest involvement.

Table 3 - Summary of clinical variables affecting Methotrexate side effects using Chi-square test (χ^2).

Risk factor	N (%)	*P*-value	OR	95% CI
Age >60	16 (22.5)	0.52	1.57	(0.45 - 4.8)
Disease duration >10 years	37 (52.1)	0.34	0.63	(0.23 - 1.6)
Male	15	0.027*	5.24	(1.08 - 25.4)
Nationality (n=71)				
Saudi	43 (61)	0.068	0.38	(0.13 - 1.07)
Non-Saudi	28 (39)	0.068	2.61	(0.92 - 7.41)
Obesity	24 (34)	0.65	0.79	(0.29 - 2.13)
Smoking	6 (8)	0.26	3.33	(0.36 - 22.48)
Co-morbid illness				
Diabetes mellitus	25 (34)	0.44	1.4	(0.53 - 4.1)
Hypertension	36 (50)	0.88	0.9	(0.35 - 2.4)
Renal impairment	18 (25)	0.006*	7.14	(1.63 - 30.33)
Methotrexate				
Discounted treatment	12 (17)	0.31	1.26	(0.85 - 1.8)
Combination				
NSAIDs	50 (70)	0.59	0.75	(0.25 - 2.14)
Other DMARDs	53 (74)	0.51	1.43	(0.48 - 4.2)
Steroid	11 (7)	0.14	3.21	(0.71 - 146.2)
Rheumatoid factor (positive)	48 (68)	0.69	0.81	(0.36 - 2.29)
Hypoalbuminemia	18 (25)	0.11	2.68	(0.78 - 8.76)
LFT abnormalities	10 (14)	0.91	0.91	(0.23 - 3.61)

LFT - Liver function test, NSAIDs: non-steroidal anti-inflammatory drugs, DMARDs: Disease modifying antirheumatic agents, OR - odds ratio, CI - confidence interval

124-341 umol/L. Hypoalbuminemia detected in 18 patients. Associated co-morbidities were DM, HTN, and pre-existing lung disease. One patient (1.4%) was hepatitis-B-positive, and one patient (1.4%) was hepatitis-C-positive. Methotrexate side effects were also documented in **Table 2**. Abnormal LFT was detected in 10/71 patients (14%); 4/71 patients (8.4%) were considered to have severe hepatotoxicity, while 6/71 (13%) had minor elevation in their LFT level. In patients with severe hepatotoxicity, the mean ± SD elevation in liver enzyme levels was 97.9±197.2 umol/L for AST (ranging from 40-944 umol/L) and 51.9±35.3 umol/L for ALT (ranging from 40-260 umol/L). Two patients (2.8%) where infected with hepatitis B virus while 3 patients (4.2%) where infected with C virus. Nine out of the 10 patients with abnormal LFT had underlying chronic liver disease in the form of : 1 (1.4%) liver cirrhosis, 3 (4.2%) with fatty infiltration of the liver and 5 patients (7%) with other chronic liver diseases. Radiological observation of underlying lung disease was documented in 11/71 patients (15.3%) in the form of bronchial asthma, chronic obstructive pulmonary disease (COPD), bronchiactasis and pulmonary fibrosis, and only one patient had MTX-related pulmonary toxicity. This single patient had the following MTX-induced lung injury risk factors: female-gender, BMI >30, on NSAIDs, RF-positive, HTN, and pre-existing lung disease in the form of bronchiactasis, confirmed by chest CT scan. The patient received 10 mg/week MTX for a period of 6 months, but did not have DM, renal impairment, or hypoalbuminemia.

The clinical variables available for retrieval were 20 including: patient's age, gender, nationality, disease duration, MTX treatment duration, total MTX dose, ASA use, NSAIDs use, steroid past usage, steroid current usage, other DMARDs use, anti-tumor necrosis factor use, rheumatoid factor, hypoalbuminemia, renal impairment, liver function abnormalities, DM, HTN, obesity, and smoking. The most significant predictor (p<0.05) for MTX side effects by chi-square testing were male gender (OR=5.24) and renal impairment (OR=7.14). Other associated variables according to the value of the OR, which was not statistically significant: non-Saudi nationality (OR=5.24), smoking (OR=3.33), steroids use (OR=3.21), hypoalbuminemia (OR=2.68), and the presence of ExRA (OR=2.38). On logistic regression analysis by stepwise method, renal impairment was the only significant predictor (B-coefficient= 0.32, OR=2.8, p<0.05, 95% CI=0.11-0.61). There was no statistical significance association between the side effects and the total dose as well as treatment duration. **Table 3** summarizes the statistically significant anticipated variables with clear relationship with MTX side effects.

Discussion. Rheumatoid arthritis is a chronic heterogeneous disorder characterized by periods of remission and relapse. Methotrexate is an anchor DMARD used in the treatment of RA. The drug has been proven to reduce pain, prevent deformities, and promote a good quality of life[20] in RA and other inflammatory disorders as sero-negative arthritis, myositis, systemic sclerosis, vasculitis, Crohn's disease, and Felty's syndrome.[21] For inflammatory disorders, the therapeutic dose of MTX is low (a low-dose therapy is a weekly pulse of 7.5-25 mg/week), in cancer treatment, however, the dose is higher (a weekly cyclic 1 gram or more/m^2).[22] According to the American College of Rheumatology (ACR), noticeable improvement in arthritis and other rheumatic disease symptoms is observed 3-6 weeks after starting MTX treatment. It may take up to 12 weeks for some patients to notice the full benefit of the drug.[8] If a patient develops myelosuppression either due to MTX side effects or as an interaction with other drugs, it may be corrected by stopping the drug and folinic acid supplementation (dose of 2.5-5 mg once weekly) 8-12 hours after MTX administration, as it interferes with the action of MTX.[23] In our study, we observed that 31% of our patients developed GI symptoms, which is similar to the updated systematic review in 2009.[24] Out of the 7 patients who developed stomatitis, one was taking the drug incorrectly, namely, 7.5-mg daily rather than weekly, due to a misunderstanding. The frequency of MTX was changed to the correct weekly form, and the folic acid dose was increased. Subsequent follow-up showed resolution of symptoms after 6 weeks. The rest of the patients with stomatitis responded to a higher dose of folic acid. The incidence of hepatotoxicity increased if the patient was taking another hepatotoxic medication such as Leflunomide, pre-existing viral hepatitis, DM, alcohol consumption.[25] In 4 of our patients (6%) with severe hepatotoxicity, all had associated DM, but none had hepatitis B or C infections, and none were on concomitant Leflunomide treatment. It is not known whether hepatotoxicity is related to MTX side effects or to the fatty infiltration of the liver, which is a well-known association with this common endocrine disorder that has been documented previously.[26] The rest of the patients (8%, 6/71) with abnormal LFT continued their treatment, and subsequent guideline-directed LFT assessments were within normal limits. Despite previous studies on the relationship between alcohol intake and hepatotoxicity, we could not include alcohol intake as one of the variables during data collection, due to the retrospective methodology of our study. Hypoalbuminemia detected in 18 (25%) and 10 had abnormal LFT (18%). Only one patient had hypo-albumenia with abnormal LFT and non-active disease, which may reflect the true MTX, associated side effects as hepatotoxicity. Concerning the other serious complication of MTX treatment, only one patient was documented as MTX-induced lung injury. In 1995, Golden e al[16] suggested that pre-existing interstitial pneumonia (IP) is a predisposing factor for RA patients to develop an MTX-induced lung injury.[16] Moreover, Alarcón et al[27] in 1997, listed additional risk factors for MTX-induced lung injury, such as an age of >60 years, DM, previous use of DMARDs, and hypoalbuminemia.[27] Neither DMARD use nor hypoalbumenia was investigated, as they did not fit patient characteristics. The patient's condition was managed by stopping the drug and administering steroids, after which the symptoms improved within 2 weeks. Of the other 10 patients who had respiratory involvement documented by chest CT scan, 5 had lung fibrosis that could be related to the pleuropulmonary manifestation of RA, and 5 had bronchiactasis that could be related to previous or repeated lung infections, such as tuberculosis. In the 3 patients who were thought to have MTX-induced lung injury, their follow-up evaluation showed irreversible lung pathology, even after stopping the medication and administering steroids, which made the proposed diagnosis less likely. Seven patients (10%) suffered from alopecia, which is troublesome for young females, for whom the disease most commonly occurs. Other etiologies to be investigated, such as iron deficiency anemia, which is a common dietary problem at that age and it is reversible with iron supplementation. Central nervous system symptoms were observed in 13 patients (18%) which is higher than the reported figure (3%), which could be explained by the fact that 36% of the patients >50 years in which complain from similar symptoms.[5] Rheumatoid arthritis is associated with 2 folds increase in the malignancy risk in comparison to the general population and lymphoprolefrative disorders have been documented to occur in <1% of the patients on MTX.[28] Lymphoma occurred in 3/71 patients (4.2%) in which 2 had the disease >10 years. This could explain that the lymphoma is related to the disease itself and not the drug. The Department of Rheumatology at KAAUH has been providing 5-minute consultations by the treating physician in the clinic for every newly diagnosed RA patient to explain the following: the effect of the drug, the importance of folic acid supplementation, frequent blood monitoring, follow-up, and finally, for female patients, a recommendation to avoid becoming pregnant while on the drug. The correlations detected mathematically in **Table 3** showing that MTX side effects had other points to consider decreasing severity. Renal impairment was very interesting because it increase the risk of all MTX side effects with more than 7-folds compared to patients with normal kidney function. Although the steroid use,

smoking, non-Saudi nationality, and hypoalbuminemia had a marginal statistical insignificance, it can be reverted to sample size limitation.

A previous study was conducted at King Faisal Specialist Hospital (KFSHRC) at Riyadh, Saudi Arabia, assessing the efficacy and safety of MTX in 18 patients with systemic onset juvenile RA (SO-JRA), in which none of the patients developed any toxicity.[29] Although the sample had provided a wealth of relationships, but more robust results would be reached if this analyses includes larger sample and carried out prospectively. For that, we recommend a 10-year retrospective multicenter trial in our region to identify all cases of serious complications from MTX, including MTX-induced lung injury, to compare them to a group of controls, and subsequently to identify the risk factors for developing such complications.

In conclusion, MTX is the first prescribed and commonly used DMARD for the treatment of RA, alone or in combination with other drugs. Methotrexate has a very few clinically significant side effects, which could be decreased by patient education, folic acid supplementation, and close clinical and biochemical follow-up. Even if the patient developed such side effects, other etiologies must be examined for proper management.

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