Original Article

Hematological Abnormalities with Low Dose Methotrexate in Rheumatoid Arthritis Patients

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ABSTRACT

Objective: Methotrexate is the most commonly used DMARD by the physicians in Pakistan. It is very effective in arresting the disease process and preventing joint damage. Prolong use of methotrexate may cause some unwanted effects including hematological abnormalities which may be a cause of extra concern for the physicians and patients as well.

Study Design: Descriptive/cross sectional study.

Place and Duration of Study: This study was conducted at the Medical Units of Mardan Medical Complex (M.M.C) from January 2015 to December 2016.

Materials and Methods: Adult 112 male and female patients with rheumatoid arthritis were enrolled in the study. American college of rheumatology (ACR) / European league against rheumatism (EULAR) diagnostic criteria was used for rheumatoid arthritis. They were given 7.5 mg of methotrexate once weekly and were followed for six months with regular monthly full blood count.

Results: Out of 112 patients 23 were males and 89 were females. They age of patients ranged from 21 to 60 years. Mean age of the study population was 36.66 years. Anemia was found in six patients (5.4%), leucopenia was found in four patients (3.6%), thrombocytopenia was found in three patients (2.7%) and pancytopenia was found in only one patient (0.9%).

Conclusion: Hematological abnormalities is a common side effect of low dose methotrexate and these patients require regular monitoring of blood count for detecting and treatment of these abnormalities.

Key Words: Methotrexate, Hematological abnormalities, rheumatoid arthritis (RA).

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INTRODUCTION

RA is an autoimmune systemic disorder characterized by chronic polyarticular synovitis due to release of different cytokines leading to irreversible joint damage[1]. Since MTX in low doses is less toxic, cost low and is highly effective so it is mostly preferred DMARD by the clinicians for rheumatoid arthtritis[2, 3]. Half life of MTX is 7-10 hrs, it is mainly metabolized in the liver and excreted by the kidneys[4,5]. The rate of discontinuation of MTX in RA due to toxicity has been found from 10-37%[1,6]. Few retrospective studies have shown the rate of thrombocytopenia around 4.1% and pancytopenia around 0.96-1.4%[1].

Since rheumatoid arthritis is an autoimmune disorder and methotrexate is an immunosuppressive agent so it is preferred in rheumatoid arthtritis[7]. Methotrexate is usually given in low doses to patients with rheumatoid arthtritis.

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G,I.T complications are more commonly encountered side effects while stomatitis, hepatotoxicity, skin rashes, pulmonary and hematological toxicity are less common side effects with low dose methotrexate in rheumatoid arthtritis patients[8]. 3% of the methotrexate treated rheumatoid arthritis patients develop heamatologic toxicity[9]. Pancytopenia is rare but its occurrence is increased with co-administration of other drugs, low folate levels, hypoalbunaemia, old age, renal dysfunction, dehydration, and concomitant infection[9,10]. Pancytopenia observed with methotrexate may be acute or chronic. Acute pancytopenia due to methotrexate is secondary to allergic type of reaction and is rapid in onset while chronic pancytopenia is is more insidious in onset[11,12]. Dehydration increases the heamatologic toxicity of methotrexate particularly in elderly patients with compromised renal function[13,14]. NSAIDs reduces the renal excretion of methotrexate and contributes to its heamatological toxicity[15,16].

Methotrexate is most commonly used DMARDs by the physicians for rheumatoid arthritis in Pakistan. Though it is a very effective drug but it may cause some undesirable effects which may be distressing for the patients. Hematological abnormalities are one of the such effects which may occur with low dose methotrexate in rheumatoid arthtritis. This study is aimed to know the exact prevalence of hematological

abnormalities in these patients so that it can be identified and managed accordingly.

MATERIALS AND METHODS

This was a descriptive cross sectional study conducted at Medical units of Mardan medical complex (M.M.C) from January 2015 to December 2016. Study included 112 diagnosed adult cases of rheumatoid arthritis. American college of rheumatology (ACR)/European league against rheumatism (EULAR) diagnostic criteria was used for diagnosing rheumatoid arthritis[17.] Pancytopenia was defined as W.B.C count < 4 x 10^9/l, Hb < 11gm/dl , and platelet count < 130 x10^9 /l. To find out the frequency of low dose methotrexate induced hematological abnormalities in rheumatoid arthritis patients was the main objective of study. Ethical and research committee of the hospital was approached for the approval of study. Patients were selected by non-probability convenient sampling method after an informed verbal consent. Adult male and female patients were selected for study. At the start of study patients were thoroughly examined and routine baseline investigation were done. Only those patients were enrolled for study in whom there was no evidence of anemia, leucopenia and thrombocytopenia. Anemia was defined as Hb < 11gm/dl, leucopenia was taken as W.B.C count < 4 x 10^9 /l and thrombocytopenia was considered to be of platelet count less than 130 x 10^9 /l. Patients with renal insufficiency or hepatic abnormalities were also excluded from study. Similarly patients with major illnesses like Diabetes Mellitus, Hypertension and ischemic heart diseases were excluded. Patients already taking other disease modifying anti rheumatic drugs were included only with a normal blood count. Then these patients were given 7.5 mg of methotrexate weekly and were followed for six months with a regular monthly full blood count. All information was recorded on Performa for analysis using Statistical Software for Social Sciences (SPSS) version 15. Frequency and percentages were calculated for categorical variables, while mean $\pm$ SD was calculated for numerical variables. Also hematological abnormalities were stratified among age and gender to see the effect modifications. All results were presented in the form of tables and graphs.

RESULTS

Out of 112 diagnosed cases of RA, 23 (20.5%) were males and 89 (79.5%) were females. Age range was from 21 to 60 years with mean age of 36.66 years. Mean hemoglobin was 13.11, mean total leukocyte count (T.L.C) was 6733.8750 and mean platelet count was 296053.5714. Age and smoking were two other parameters included in the study but they bear no significant association with the hematological abnormalities (p-value > 0.05). Similarly gender and body weight has no significant association with hematological abnormalities, (p-value > 0.05).

Percentages and means of the study population and different hematological parameters are given in tables, and most of these changes were observed mainly in the last two months of follow up except pancytopenia which was observed early in the first month of the study.

Table No. 1: Age and Gender of Patients.

Gender of patient	No of patients	% of total n	Min	Max	Mean	Std. Deviation of age
Male	23	20.5%	30	58	43.7826	9.94511
Female	89	79.5%	21	60	34.8315	8.96488
Total	112	100.0%	21	60	36.6696	9.82403

Table No. 2: Hematological Parameters

Para-meters	No of patients	Mean	Std. Devia-tion	Mini	Max
Heamo-globin	112	13. 1161	1.863 57	9	17
Total white cell count	112	6733. 8750	1904.9 9553	3000	10000
Platelets count	112	29605 3.5714	86442. 61199	90000	450000

Table No. 3: Hematological Abnormalities

Abnormality	No. of patients	% of patients
Anemia	6	5.4%
Leucopenia	4	3.6%
Thrombocytopenia	3	2.7%
Pancytopenia	1	0.9%

DISCUSSION

Adverse drug reactions during the treatment of rheumatoid arthritis with DMARDs can lead to significant morbidity and mortality. It is estimated that between 3% and **11%** of hospital admissions can be attributed to these drug side effects. Any drug can conceivably have a toxic or undesired effect. However, a substantial portion of undesirable drug reactions may be preventable and treatable if detected early.

Pancytopenia a rare but potentially fatal complication of methotrexate therapy, may occur acutely within one to two months of starting methotrexate and is not dependent on dose and route of administration. Acute pancytopenia is due to an allergic type of reaction and is rarely avoidable, more commonly it occurs late as a cumulative effect[11, 12]. In our study we were encounter with a single patient who developed pancytopenia acutely.

Methotrexate is inhibitor of enzyme dihydrofolate reductase leading to decrease production of thymidylate and DNA. Tissues undergoing rapid cellular turnover

with a high fraction of cells in S phase cycle (oral mucosa, G.I tract , bone marrow cells and testicular tissue) are more susceptible to its cytocidal effect. Low levels of intracellular folates have been found in hepatocytes and peripheral blood lymphocytes of RA patients treated with MTX [18,19]. Folate supplementation have been found to be beneficial in reducing hepatotoxicity , mucosal and G .I side effects[20], but up till now no studies have shown beneficial role of folic acid supplementation on MTX induced heamatological abnormalities . This also occurs in our study as all our patients were receiving folic acid supplementation. Stomatitis precede or accompany pancytopenia and may be taken as a warning sign[21]. Patients with mucositis and neutropenia have four times higher risk of septicemia than individuals without mucositis[22]. These ulcers not only provide route of entry for endogenous oral flora but are also favorable site for secondary infections. Our single patient with pancytopenia did not develop oral lesions it may be due to fact that he developed pancytopenia acutely.

Hematological toxicity with low dose MTX occurs in 2-4% of cases[23]. Our study correlates with these findings. Renal impairment or reduced renal blood flow as it occurs with NSAIDs increases the frequency of hematological toxicity[24]. Therefore MTX is contraindicated in any patients with a GFR less than 30 ml/min[25]. Though we did not included patients with renal impairment in our study but NSAIDs may interfere with the study results as almost all of the patients were on NSAIDs for symptomatic control of pain which need further studies on large scale to confirm this relation.

Edelman etal in his study reported age as a major contributor for MTX induced hematological toxicity through an unknown mechanism[26]. In our study age was found to be insignificant risk factor (p value > 0.05). We follow our patients for only six months, it may be due to prolong duration of treatment with MTX in elderly patients that may cause hematological abnormalities which needs further workup. The main limitation in our study was simultaneous use of other DMARDs by our patients as well and that may have an effect on hematopoietic system along with methotrexate in rheumatoid arthritis patients.

According to pharmacokinetics of methotrexate, the drug and its metabolite is highly plasma proteins bound, hypoalbumenemia will lead to high level of free methotrexate and consequently high risk of myelosuppression. This may be a contributing factor to myelosuppression in our study as rheumatoid arthritis patients consumes high level of albumin at site of inflammation leading to hypoalbumenemia, once hematological abnormalities occur discontinuation of the drug is the only option but the use of G-CSF and methylprednisolone are also beneficial.[27]

CONCLUSION

Methotrexate induced hematological abnormalities are relatively common and it may be a cause of increasing concern for the physicians and patients as well. Fortunately life threatening pancytopenia is rare. Certain factors such as advance age, renal dysfunction and interaction of methotrexate with certain drugs increases the chances of pancytopenia. So it is advisable to exercise extreme care in the use of methotrexate specially in the presence of associated risk factors causing pancytopenia, by regular monitoring of blood count. Prompt discontinuation of methotrexate with development of hematologic toxicity is the only solution.

Author's Contribution:

Concept & Design of Study:	Muhammad Abbas
Drafting:	Muhammad Khalid
Data Analysis:	Sajjad Ali
Revisiting Critically:	Amir Khan
Final Approval of version:	Amir Khan

Conflict of Interest: The study has no conflict of interest to declare by any author.

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