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Patterns of Cytopenias Associated with Methotrexate Treated Rheumatoid Arthritis Patients

Mohsin Shakoor Malik, Amer Fakhr, Farzana Hakim*, Ahsan Amer*
Pak Emirates Military Hospital/National University of Medical Sciences (NUMS) Rawalpindi Pakistan,
*Foundation University Medical College, Islamabad Pakistan

ABSTRACT

***Objective*:** To determine the frequency of various patterns of cytopenias with Methotrexate-treated rheumatoid arthritis patients and the correlation of pancytopenia with various factors.
Study Design: Cross-sectional study.
***Place and Duration of Study*:** Rheumatology/General Medicine Department, Pak Emirates Military Hospital Rawalpindi from May 2019 to Mar 2020.
***Methodology*:** Patients with rheumatoid arthritis who were managed with Methotrexate for more than six months were included in the study. Full blood counts were performed for all the patients from the laboratory of the hospital. The frequency of monocytopenia, bi-cytopenia and pancytopenia were calculated.
***Results*:** Mean age of the study participants was 37.41±5.72 years. One hundred and sixty-eight 168(84%) patients had the presence of any cytopenia, while 32 (16%) did not show the presence of any cytopenia on full blood count. The advancing age and use of polypharmacy had a statistically significant association with cytopenias among patients with rheumatoid arthritis managed with Methotrexate (p-value <0.05).
***Conclusion*:** The presence of cytopenia emerged as a relatively common finding among rheumatoid arthritis patients managed with Methotrexate. Advanced age of the patient and patients who required more than one medication to control the symptoms of RA were found at a higher risk for developing pancytopenia while being managed with Methotrexate for rheumatoid arthritis.

Keywords: Cytopenia, Methotrexate, Rheumatoid arthritis.

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INTRODUCTION

Immune-based diseases have been diagnosed more in the last two decades, and rheumatoid arthritis has been one of the most common immunological disorders around the globe.[1] Pakistan has been no exception to this rule. With better and more accessible healthcare facilities, more patients have been diagnosed and managed with this chronic immune-based disorder.[2] Routine blood investigations, specific immunological tests and x-rays are the modalities which have been commonly adopted to support the clinical findings to make up the diagnosis of rheumatoid arthritis.3 Various simple investigations have also been important to look for the progression of the disease & adverse effects of medications used to manage RA.[4,5]

One of the commonly used cytotoxic medications to treat RA is Methotrexate. It has proved to be efficacious for patients of RA and is a preferred choice of rheumatologists worldwide.[6,7] It has certain adverse effects, which may be troublesome for the patients in the short and long term. Its effect on blood counts has been observed with great concern among all the adverse effects. It almost affects all the blood indices and needs routine monitoring, especially among high-risk cases.[8]

Epidemiological statistics show that RA has been a common immunological illness in our setup.[9,10] Multiple treatment options have been available to manage this chronic condition, but all have certain merits and demerits. Methotrexate has been a commonly used disease-modifying agent in our setup, with limited studies reporting the side effects experienced by the patients put on this agent. Therefore, we planned this study to determine the frequency of various patterns of cytopenias with Methotrexate and the association of pancytopenia with various factors among the patients of RA managed with this agent in our hospital.

METHODOLOGY

The cross-sectional study was carried out Rheumatology/General Medicine Department, Pak Emirates Military Hospital Rawalpindi from May 2019 to March 2020. Permission from the Hospital Ethics

Correspondence: Dr Mohsin Shakoor Malik, Department of Medicine H#199A, Lane 3 , Gulistan Colony, Rawalpindi-Pakistan
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Committee (via letter number A/124 EC/159/2020) was sought prior to the commencement of the study. Sample size was calculated using the WHO sample size calculator and keeping the population proportion of haematological abnormalities among patients on Methotrexate as 89%.[11]

Inclusion Criteria: Patients presenting at Outpatient Department who fulfilled the American college of rheumatology classification criteria of RA, aged 15 to 60 years and using Methotrexate as a primary disease-modifying agent for more than six months were included in this study.

Exclusion Criteria: Patients without a clear diagnosis of RA, with comorbid autoimmune disease, or those who were pregnant were excluded from the study. Patients with comorbid malignant disease of any type were also excluded at the start of the study. The study did not include patients using any illicit or psychoactive substances. Patients with any haematological disorder due to any cause other than RA or haematological or lymphoid malignancy were also excluded from the study. Patients using other medications or complementary therapies associated with cytopenias were also excluded from the study.

Non-probability consecutive sampling technique was used to gather the required sample size for this study. In addition, all the patients signed the informed consent form before enrolling in the study. About 3 ml venous blood samples were taken in EDTA potassium tubes from the patients diagnosed with RA. Full blood count was determined by using a commercial analyzer for each patient in the laboratory of our hospital. The normal value for Red blood cell count was taken as 4.32-5.72 million cells/mcL, White cell count was taken as 3,400 to 9,600 cells/mcL, and platelet count was taken as 135,000 to 317,000/mcL.[11,12] Counts less than these for each blood index was taken as cytopenia for that index.

Methotrexate was given in standard dose (Single dose: 7.5 mg orally or subcutaneously once a week, Divided dose: 2.5 mg orally every 12 hours for three doses once a week with a maximum weekly dose: 20 mg) and started as per the protocol13 with regular monitoring of the liver function tests and blood counts.

Statistical Package for Social Sciences (SPSS) version 23.0 was used for the data analysis. Frequency and percentage were calculated for the qualitative variables while, mean and standard deviation were calculated for the age of the patients and duration of illness. Pearson chi-square test was used to see the association between the age, gender, polypharmacy and duration of Methotrexate use with pancytopenia. The *p*-value less than or equal to 0.05 was considered significant for this study.

RESULTS

Two hundred patients with rheumatoid arthritis who had been using Methotrexate for more than six months were recruited in the study. The mean age of the study participants was 37.41±5.72 years. The mean duration of Methotrexate use among the study participants was 12.6±3.577 months (Table-I). 168(84%) patients had the presence of any cytopenia, while 32 (16%) did not show the presence of any kind of cytopenia on full blood count. 15(7.5%) had monocytopenia, 9(4.5%) had bi-cytopenia, and 8(4%) had pancytopenia. As shown in Table-II, advancing age (*p*-value-0.016) and use of polypharmacy (*p*-value-0.011) had a statistically significant association with the presence of pancytopenia among the patients who have rheumatoid arthritis managed with Methotrexate.

Table-I: Characteristics of Patients with Rheumatoid Arthritis (n=200)

Study Parameters	n (%)
Age (years)	
Mean±SD	37.41±5.72 years
Range (min-max)	15 years-57years
Mean duration of Methotrexate use (months)	12.6±3.577 months
Gender	
Male	55(27.5%)
Female	145(72.5%)
Patterns of Cytopenias	
Monocytopenia	15(7.5%)
Bi-cytopenia	09(4.5%)
Pancytopenia	08(4%)
Use of Polypharmacy	
No	114(57%)
Yes	86(43%)

Table-II: Relationship of Various Factors with the Presence of Pancytopenia (n=200)

Socio-Demographic Factors	No Cytopenia	Mono or Bi-cytopenia	Pancytopenia	*p*-value
Age				
<40 years	109(64.9%)	09(37.5%)	03(37.5%)	0.016
>40 years	59(35.1%)	15(62.5%)	05(62.5%)	
Gender				
Female	120(71.4%)	18(75%)	07(87.5%)	0.541
Male	48(28.6%)	06(25%)	01(12.5%)	
Duration of Methotrexate use				
<12 months	74(44.1%)	06(25%)	05(62.5%)	0.098
>12 months	94(55.9%)	18(75%)	03(37.5%)	
Polypharmacy				
No	102(60.7%)	11(45.8%)	01(87.5%)	0.011
Yes	66(39.3%)	13(54.2%)	07(12.5%)	

DISCUSSION

Adequate knowledge of adverse effects is necessary for clinicians to prescribe any medication. However, it gets more important when cytotoxic drugs are prescribed for the long-term management of any clinical condition. The main problem in our part of the world is that a limited number of rheumatologists and immunologists have been trained, and these specialities are at a toddler stage. Therefore, general practitioners or medical specialists are more often prescribing drugs for rheumatoid arthritis. Methotrexate has been one of the most common drugs in this regard, and limited data exist for our population concerning its common side effects.[14] We planned this study to determine the frequency of various patterns of cytopenias with Methotrexate treated Rheumatoid arthritis patients and the correlation of pancytopenia with various factors at our teaching hospital.

There is a complex mechanism and more than one pathway by which Methotrexate could lead to different types of cytopenias. For example, Sosin *et al*. and Grove et al. highlighted different cases and pathways that may be responsible for bone marrow suppression and lead to low blood cell counts. They may be red blood cells, white blood cells or platelets.[15,16] Mameli *et al*. targeted elderly patients of RA managed with Methotrexate to look for the risk factors for cytopenias among these patients. They concluded that low albumin levels and sepsis emerged as risk factors for cytopenias among the target population.[17] Patsiornik *et al*. in 2009 published an interesting case of an eighty-two-year-old patient of RA developing pancytopenia on a low dose of Methotrexate. MTX was discontinued, the patient was placed on neutropenic precautions and was treated with blood and platelets transfusions, folic acid and G-CSF. Patient was discharged on day-14 with normal hematologic parameters.[18] Presence of complications in an old age patient strengthened our results as advancing age was significantly correlated with pancytopenia in our study. However, more research is needed to establish the exact association and make separate guidelines for the elderly regarding using Methotrexate if required.

STUDY LIMITATIONS

We could not establish that the decline in cell counts was due to the use of Methotrexate. Instead, it could be an underlying immune-based disease process of RA, affecting cell counts. More studies with a better design may generate reliable results regarding this major adverse effect of Methotrexate.

CONCLUSION

The presence of cytopenia emerged as a relatively common finding among rheumatoid arthritis patients managed with methotrexate. In addition, the advanced age of the patient and patients who required more than one medication to control the symptoms of RA were found at a higher risk for developing pancytopenia while being managed with methotrexate for rheumatoid arthritis.

Conflict of Interest: None.

Author's Contribution

Following authors have made substantial contributions to the manuscript as under:

MSM & AF: Concept, data acquisition, data analysis, critical review, approval of the final version to be published.

FH & AA: Study design, drafting the manuscript, data interpretation , approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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