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Case Study

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METHOTREXATE AND LEFLUNOMIDE INDUCED LEUKOPENIA

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ABSTRACT

Methotrexate is a folic acid antagonist which is most commonly used in chemotherapy and as an immunosuppressant in auto-immune diseases. Toxicity induced by Methotrexate depends on its dose and duration. Leflunomide is an isoxazole immuno-modulatory agent belonging to the class of disease modifying anti-rheumatic drugs. It is an inhibitor of pyrimidine synthesis and has anti- proliferative and anti-inflammatory actions. Since the use of these drugs is increasing, the possibility of cumulative toxicity of the two drugsis always a concern whenever this drug combination is prescribed. We hereby report a drug reaction (leukopenia) due to Methotrexate and Leflunomide in a 71- year-old female patient who had been prescribed Methotrexate and Leflunomide for rheumatoid arthritis.

KEYWORDS: Methotrexate, Leflunomide, Leukopenia, Rheumatoid arthritis.

INTRODUCTION

Methotrexate (MTX) is a basic drug used in most therapeutic regimens for rheumatoid arthritis worldwide. However, its use as monotherapy, or in combination with low dose corticosteroids, is often insufficient to achieve acceptable levels of activity. Therefore, various combination therapies have been tested in order to increase the efficiency of MTX. Among these, the association with Leflunomide (LEF) was found to be the most effective, with synergistic effectsin several studies.[1] Methotrexate is used at much lower doses to treat rheumatoid artheritis since 1990.[2] Leflunomide was licensed for use in rheumatoid arthritis in 1998.[3] By inhibiting several enzymes of the folic acid pathway, MTX blocks purine and pyrimidine biosynthesis, causing impaired DNA replication and cell proliferation. Tissues having high cellular turnover are more sensitive to the cytotoxic impact of Methotrexate, providing its effectiveness as a chemotherapeutic agent as well as side effects such as mucositis and cytopenias. Myelosuppression and pancytopenia are the most common haematological toxicity, which occur during treatment with low dose methotrexate. Even though the haematological toxicity is serious and potentially life-threatening, it still remains as an underestimated complication of MTX therapy.[4] Leukopenia is a reduction in the circulating white blood cell (WBC) countto < 4000/mcL causing the immune function to be generally decreased. It is characterized by:

- Neutropenia: Neutrophil count < 1500/mcL.
- Lymphocytopenia: Lymphocytes count < 1000/mcL.
- Monocytopenia: Monocyte count to < 500/mcL.[5]

CASE REPORT

A 71-year old female patient with a history of Rheumatoid arthritis (on treatment with Tab. Methotrexate and Leflunomide), SHTN and Hypothyroidism came to the OPD with complaintsof oral ulcers, cough with expectoration and decreased food intake. Her initial investigations showed decreased total count, haemoglobin and elevated CRP (Table. 1) and was initiated on Inj. Meropenem 1g TID as empirical therapy. The decision on withholding Tab. Methotrexate and Tab. Leflunomide was made in view of leukopenia. Rheumatologist suggested on holding all the DMARDs and start on Inj. Leucovorin Calcium IV 15 mg TID. Haematologist suggestion on the decreased total count was Methotrexate toxicity, hence was advised to treat with Folic acid, Folinic acid and Vitamin B12. Dermatologist suggestion in view of oral ulcers was Methotrexate induced Mucositis for which candid mouth paint, Tab. Fluconazole was advised and hence mucositis was healing. Total count was repeated again and despite the provided medication, the count was depleting and therefore Inj. Filgrastim 300 mg OD was started for 5 days and as a result, total count started increasing (TC:

8760/mcL). On 23/9/2022 Inj. Vancomycin IV was initiated for empiric treatment of MRSA infection. She received Inj. Meropenem 1g TID, Tab. Fluconazole 150 mg OD for a total duration of 7 days and Inj. Vancomycin 1g BD for 10 days.

Table. 1

PARAMETERS	ON DMARDs	FOLLOWING WITHDRAWALOF DMARDs	NORMAL RANGE
HAEMOGLOBIN	7.90 g/dl	11.7 g/dl	14 to 16g/ dl
TOTAL LEUKOCYTE COUNT	900 cells/µl	8760 cells/µl	4000 to 11,000 cells/ µl
C-REACTIVE PROTEIN	90 mg/ l	3.2 mg/l	< 10 mg/l

DISCUSSION

Methotrexate is a common disease-modifying anti-inflammatory drug used as monotherapy or in combination with other drugs and biological agents for the treatment of many autoimmune disorders.

Leflunomide (LEF) inhibits the synthesis of nucleotides in the pyrimidine pathway, along with MTX leading to reduced activity of immunocompetent cells. The concomitant use of MTX and LEF provides additional benefits, when compared to that of monotherapy.

However, this combination is risky, as there is a possibility of an additive toxicity of these drugs on liver, lung and bone marrow.[1]

Hence in patients treated with MTX, the prevalence of haematological toxicity (leukopenia, thrombocytopenia, megaloblastic anaemia and pancytopenia) is approximately estimated to be3%.[6]

Therefore when a drug is suspected to have leukopenia it should be withdrawn promptly. This judgment is clearly based on the clinical symptoms, manifestations and laboratory investigations.

CONCLUSION

Despite possible side effects of administered MTX used in autoimmune diseases, MTX is very well tolerated and its efficacy is excellent. When monitored correctly, the fatal side effects can be avoided. It is equally important that primary care physicians, haematologists and rheumatologists are aware of these complications because the majority of these serious complications can be detected on time and even prevented.

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CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

ABBREVIATIONS

MTX: Methotrexate

LEF: Leflunomide

WBC: White blood cell

OPD: Outpatient department

DMARDs: Disease-modifying antirheumatic drugs

CRP: C-reactive protein

OD: Once a day

BD: Two times a day

TID: Three times a day

IV: Intravenous

MRSA: Methicillin-resistant Staphylococcus aureus

RA: Rheumatoid arthritis

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