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Original Research Article

Monitoring of adverse drug reactions caused by methotrexate at the dermatology department of a tertiary care centre

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ABSTRACT

Background: Dermatologists are using antineoplastic agent methotrexate for more than six decades for various skin diseases. Methotrexate is a dihydrofolate reductase inhibitor and has cytotoxic**,** anti-inflammatory and steroid sparing effect. However, long term use of methotrexate raises a concern about its safety. Careful monitoring of patients on methotrexate therapy can either minimize or prevent the adverse effects. The aim of the study was to evaluate the adverse drug reactions caused by methotrexate therapy in the treatment of dermotological diseases.
Methods: Observational clinical study done in 56 patients with skin diseases, who were on methotrexate therapy. LFT, RFT, blood counts done at baseline and every 2 weeks till the end of six months. Adverse reactions were monitored and assessed using WHO-UMC scale.
Results: Among sixteen Psoriasis patients on methotrexate (max 15 mg/wk) therapy, 62.5% experienced adverse effects and the most common ADR being GI upset in 6 patients. Other common adverse effects observed were elevated liver enzymes, leucopenia, thrombocytopenia, candidiasis and elevated serum creatinine. None of the patients in our study had pulmonary toxicity, life threatening adverse effects requiring hospitalisation or secondary lymphoma. Adverse effects caused by methotrexate were dose dependent. So low dose weekly methotrexate regimen with folate supplementation in the form of folic acid or folinic acid can minimize the adverse effects.
Conclusions: Our study was successful in identifying the adverse effects caused by methotrexate when used for various skin diseases in the department of dermatology.

Keywords: Methotrexate, Reduced folate stores, Adverse effects

INTRODUCTION

Dermatologists are using antineoplastic agent methotrexate for more than six decades for various skin diseases like psoriasis, palmoplantar pustulosis, pityriasis Rubra pilaris**,** sarcoidosis, dermatomyositis, cutaneous lupus erythematosus, phemphigus, eczema, lichen planus etc. Methotrexate is a dihydrofolate reductase inhibitor and has cytotoxic**,** anti-inflammatory and steroid sparing effect.[1] However, long term use of methotrexate raises a concern about its safety. Many prospective studies have shown that toxicities of methotrexate seldom occur and rarely require drug withdrawal. Serious adverse effects are liver, lung and hematologic toxicity but with low incidence rate.[2] Careful monitoring of patients on methotrexate therapy can either minimize or prevent the adverse effects. Association between treatment response and toxicity can help the dermatologists to individualize

the therapy. The present study is done to know the occurrence of adverse effects during methotrexate therapy in dermatology department.

Aim of the study

The aim of the study was to evaluate the adverse drug reactions caused by methotrexate in the treatment of dermatological diseases.

METHODS

***Study type*:** Observational clinical study

Study design: Open label, prospective clinical study.

Study period: November 2016 to April 2017

Study sample: 56 patients with skin diseases who are on methotrexate therapy

Study place: Department of Dermatology, Venereology and Leprology, Vinayaka Missions Medical College, Karaikal, Puduchery.

Ethical considerations

Approval from Institutional Ethical Committee was obtained, before starting the clinical study. Written informed consent was obtained in local vernacular language from every patient before enrollment. Study was done in accordance with GCP guidelines.

Inclusion criteria

Inclusion criteria were age >18 years; both male and female; diagnosed with a skin manifestation that requires methotrexate therapy, willing to give informed consent

Exclusion criteria

Exclusion criteria were pregnancy, lactating women**;** drug or alcohol abuse; white blood cell count ≤ 1500/mm^3; creatinine >1.5 mg/dl; aspartate amino-transferase >2 times upper limits of normal; platelet count <100,000/mm^3; hypersensitivity to methotrexate; pleural effusion, hepatitis, HIV, TB; age >60 years or debilitated patients; concominant use of acetylsalicylic acid, barbiturates, sulfonamides, tetracylines, sulfonylureas, probenacid, penicillin, NSAIDS, trimethoprim, sulfa-methoxazole and sulfonamides.

Screening and recruitment

Fifty six patients diagnosed with skin disease and are on methotrexate therapy were included in the study after getting informed written consent. During enrollment following baseline investigations were done.

- Demographic data of patients were recorded.
- Liver function tests (SGOT, SGPT, Total Bilirubin and ALP) and renal function tests (serum creatinine, blood urea, serum potassium and sodium) were done in a random blood sample using automated analyser.
- Complete blood count including differential count was done in a random blood sample using automated analyser.
- Hepatitis serology (HCV, HBV), HIV ELISA, TB mantoux skin test, pregnancy test.

Follow up

Follow up visit was scheduled at the end of every two weeks till the end of six months. Patients were instructed to report to the outpatient department at the end of every second week with the diary to access the tolerance and along with empty strips to collect the drugs. At the end of every second week the baseline laboratory parameters like renal function test, liver function test, and blood counts were performed. Adverse drug reactions were monitored and all relevant adverse events will be recorded in a ADR reporting form and the Causality assessment of adverse drug reactions was done using WHO UMC (World Health Organisation and Uppsala Monitoring Centre) scoring system.

Statistical analysis

Statistical analysis was performed with the help of statistical package SPSS (Statistical package analysis package for the social sciences) version 11.0.1

- Baseline characteristics of the study patients were tabulated by descriptive statistics (mean)
- The adverse drug reactions were tabulated and expressed in percentage and p value <0.05 is significant

Patient disposition

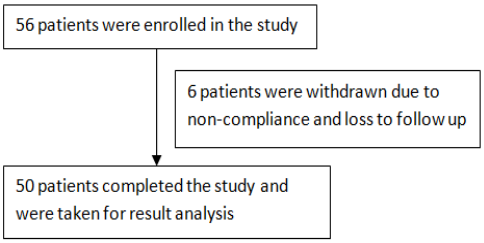

Figure 1: Patient disposition.

RESULTS

In our study most of the patients were in the age group 40-50 years (Table 1). None of the study patients had abnormal baseline values (Table 2). In our study methotrexate was commonly prescribed for psoriasis followed by eczema, lichen planus, cutaneous lupus erythematosus, pityriais rubra pilaris, vesiculobullous

diseases and cutaneous sarcoid with the maximum dosage of 15 mg/kg, 15mg/kg, 12.5mg/kg, 25 mg/kg, 25mg/kg, 17.5mg/kg and 25 mg/kg respectively (Table 3). In two psoriasis patient's methotrexate was withdrawn due to thrombocytopenia in one patient and elevated liver enzyme in another patient (Table 3). In three eczema patients methotrexate was withdrawn due to elevated liver enzymes in two patients and elevated creatinine in one patient (Table 3). Likewise in one lichen planus patient methotrexate was withdrawn due to severe anemia (Table 3). GI upset was the most among side effects observed among patients with psoriasis (Table 4), cutaneous lupus erythematosus (Table 7), vesiculobullous diseases (Table 9) and cutaneous sarcoid (Table 10). Elevated liver enzymes was the most common adverse effects observed in patients with eczema (Table 5), lichen planus (Table 6) and pityriasis rubra pilaris (Table 8).

Table 1: Baseline demographic characteristics.

Demographic characters	Number of patients (n=50)
Age in years	
30-40	14
40-50	19
50-60	17
Sex	
Male	29
Female	21

Table 2: Baseline investigations.

Lab parameters	Baseline mean
SGOT(IU/L)	36.18
SGPT(IU/L)	30.10
Total Bilirubin (mg%)	0.62
ALP(IU/L)	68.02
WBC count	1300
Platelet count	1,10,000
Blood urea	22.21
Serum creatinine	0.73
Serum sodium	136.08
Serum potassium	3.95

Table 3: Skin diseases prescribed with methotrexate therapy showing percentage of patients with ADR and percentage of patients requiring methotrexate withdrawal.

Skin disease	No. of patients	Percentage of patients getting max dose of methotrexate (mg/wk)	Percentage of patients experiencing adverse events (%)	Percentage of patients requiring withdrawal of drug due to ADR (%)
Psoriasis	16	81.25 (15)	62.5	12.5
Eczema	12	16.7 (15)	41.7	25
Lichen Planus	10	50 (12.5)	50	10
Cutaneous lupus erythematosus	4	50 (25)	50	Nil
Pityriasis rubra pilaris	4	25 (25)	50	Nil
Vesiculobullous diseases	2	100 (17.5)	50	Nil
Cutaneous sarcoid	2	50 (25)	100	Nil

Table 4: ADR in psoriasis patients.

Most common ADR among psoriasis patients	Causality	P value
GI upset (6 patients)	Probable	-
Elevated liver enzymes (2 patients)	Probable	<0.05*
Leukopenia (1 patient)	Probable	<0.05*
Thrombocytopenia (1 patient)	Probable	<0.05*

*p value <0.05 is significant

Table 5: ADR in eczema.

Most common ADR among eczema patients	Causality	P value
Elevated liver enzymes (3 patients)	Probable	<0.05*
GI upset (2 patients)	Probable	-
Raised serum creatinine (1 patient)	Probable	<0.05*

*p value <0.05 is significant.

Table 6: ADR in lichen planus.

Most common ADR among lichen planus patients	Causality	P value
Elevated liver enzymes (2 patients)	Probable	<0.05*
GI upset (1 patients)	Probable	-
Anemia (1 patients)	Probable	<0.05*
Candiasis (1 patient)	Possible	-

*p value < 0.05 is significant.

Table 7: ADR in cutaneous lupus erythematosus patients.

Most common ADR among cutaneous lupus erythematosus patients	Causality	P value
GI upset (1 patient)	Probable	-
Bruising (1 patient)	Possible	-

Table 8: ADR in pityriasis rubra pilaris patients.

Most common ADR among pityriasis rubra pilaris patients	Causality	P value
Elevated liver enzymes (2 patients)	Possible	<0.05*

*p value < 0.05 is significant. Both the patients received concomitant oral retinoid therapy which may also contribute to hepatotoxicity.

Table 9: ADR in vesiculobullous patients.

Most common ADR among vesiculobullous disease patients	Causality	P value
GI upset (1 patient)	Probable	-

Table 10: ADR in cutaneous sarcoid patients.

Most common ADR among cutaneous sarcoid patients	Causality	P value
GI upset (1 patient)	Probable	-
Anemia (1 patient)	Probable	<0.05*

*p value < 0.05 is significant.

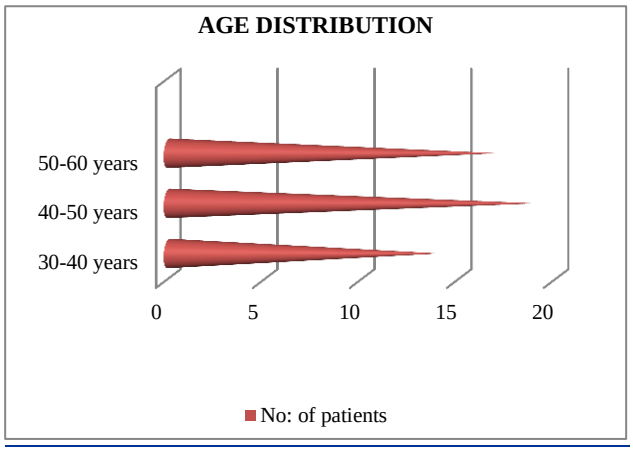

Figure 2: Age distribution.

Mean age was 51.4

DISCUSSION

Methotrexate is widely used in various dermatological conditions like psoriasis, atopic dermatitis, pityriasis rubra pilaris, pityriais lichenoides, chronic spontaneous utricaria, bullous phemphigoid, phemphigus, cutaneous lupus erythematosus etc. due to their anti–inflammatory and immunomodulatory effect and in high doses they are used as antineoplastic agent for leukemia and other cancers.[3] Benefits come within 6-8 weeks of therapy and maximum benefit seen after 5 months of therapy. Many alternative options exist and continue to emerge like new biological therapies and monoclonal antibodies for the treatment of above mentioned various dermatological conditions but methotrexate is preferred due to is proven efficacy, tolerability and affordability. Moreover safety issues of new biological therapies are currently lacking.

So proper screening for adverse effects in patients on methotrexate therapy can maximize the efficacy of methotrexate with improved compliance.

The commonest indication for methotrexate is psoriasis. Being affordable drug it is preferred for lifelong treatment of psoriasis.[4] In our study among 16 Psoriasis patients who were on methotrexate (max 15 mg/wk) therapy, 62.5% experienced adverse effects and the most common ADR being GI upset in 6 patients. A similar study conducted in 157 psoriasis patients showed 61% patients with adverse effects who were on methotrexate therapy.[5] The reason behind GI upset is centrally mediated due to intracellular accumulation of methotrexate causing folate store depletion affecting the synthesis and metabolism of neurotransmitters in the CNS.[6,7]

Two psoriasis patients in our study showed significant elevated liver enzymes. The old method of daily dosing of methotrexate was much more hepatotoxic than weekly dose regimen. One systemic review found that 28% of psoriasis patients on long term treatment developed grade 1 fibrosis on liver biopsy and the risk was dose related[8]. Many researchers have recommended aminoterminal peptide of type III procollagen as a serological marker for fibrosis and also liver biopsy in patients with consistent elevated liver enzymes.

Two other psoriasis patients had hematological adverse effects one with leucopenia and one with thrombo-cytopenia which was significant. This is due to antimetabolite and cytotoxic effects of methotrexate. Studies have shown that bone marrow depression can occur even with low dose of methotrexate.[9] Bone marrow depression is of rapid onset and more prone in patients with renal dysfunction or concomitant drugs that cause methotrexate toxicity like NSAIDS, trimethoprim etc.

Eczema is another chronic relapsing disease requiring methotrexate therapy. In our study, among 12 eczema patients 41.7% had adverse effects with the most common being elevated liver enzymes. One of the eczema patients had elevated serum creatinine which was significant. Methotrexate is excreted unchanged in kidney and renal dysfunction can be explained by toxic levels of drug, pre-existing renal disease, elderly individual, reduced folate stores with increased homocysteine causing atherothrombotic vascular disease and drug-drug interactions.[8]

One of the lichen planus patient on methotrexate therapy (12.5 mg/wk) developed opportunistic infection (candidiasis) which may be due to immunosuppressive property of methotrexate.

None of the patients in our study had pulmonary toxicity, life threatening adverse effects requiring hospitalisation or secondary lymphoma. Methotrexate adverse effects are due to reduced folate stores and they are dose dependent. So low dose weekly methotrexate regimen with folate supplementation in the form of folic acid or folinic acid can minimize the adverse effects.[10]

CONCLUSION

Our study was successful in identifying the adverse effects caused by methotrexate when used for various skin diseases in the department of dermatology. Proper screening and routine monitoring for tolerability will improve the compliance and efficacy of methotrexate.

Limitations

Single centered study with limited sample size. Genetic polymorphisms contributing to adverse effects should be studied for better tolerability.

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