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Clinical Evaluation of Dose Dependent Adverse Drug Reactions and Possible Risk Factors in Patients with Rheumatoid Arthritis Treated with Methotrexate

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ABSTRACT

Methotrexate is considered as the standard drug treatment for Rheumatoid arthritis. The purpose of this study is to find out the incidence of Adverse Drug Reactions (ADR), and possible risk factors in patients of rheumatoid arthritis administering methotrexate. And to determine the possibility of any new adverse drug reaction that is not well explored in previous studies. An observational follow up study designed and conducted using Naranjo scale to identify the adverse drug reactions in rheumatoid arthritis patients administering methotrexate in KIM's Hospital. The objective is to identify the dose dependent adverse drug reactions in rheumatoid arthritis patients and identify possible risk factors associated adverse drug reactions of methotrexate of methotrexate. Toxic effects may occur hours, to days to weeks after methotrexate administration and or overdose, the purpose of this study is to determine the relation between the dose and the occurrence of adverse drug reaction of methotrexate. During the study period clinically relevant adverse drug reaction have been presented by the patients taking methotrexate who attended hospital for their regular checkup. For example, the most commonly reported adverse drug reaction is abnormal taste for food and other less commonly presented adverse drug reaction include diarrhea, constipation, nausea, vomiting, and alopecia. In female patient's 20-49 age group reported adverse drug reaction like amenorrhea, dysmenorrhea. Methotrexate toxicity develops due to increased patient susceptibility during the treatment.

Keywords: Rheumatoid Arthritis, Methotrexate, Adverse drug reaction (ADR), Naranjo scale.

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INTRODUCTION

The Rheumatoid arthritis is a chronic progressive disease causing inflammation in the joints. RA primarily affects joints, however problems involving other organs may occur. Methotrexate is a non-biological disease modifying anti-rheumatic drug that has shown both a good control of clinical disease and a good safety. Usually adverse drug reactions (ADR'S) represents the most limiting factor during the clinical management of the disease, in particular when interactions among low dose and maximum dose of methotrexate used in the treatment of rheumatoid arthritis. This is the study of ADR's of methotrexate in Rheumatoid arthritis patients. The scale and Questionnaires used is the Naranjo scale designed by Naranjo et al.

Naranjo Scale

The Questionnaires includes:

1. Are there previous conclusive reports on this reaction?

Yes (+1) No (0) Do not know or not done (0)

2. Did the adverse event appear after the suspected drug was given?

Yes (+2) No (-1) Do not know or not done (0)

3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?

Yes (+1) No (0) Do not know or not done (0)

4. Did the adverse reaction appear when the drug was re-administered?

Yes (+2) No (-1) Do not know or not done (0)

5. Are there alternative causes that could have caused the reaction?

Yes (-1) No (+2) Do not know or not done (0)

6. Did the reaction reappear when a placebo was given?

Yes (-1) No (+1) Do not know or not done (0)

7. Was the drug detected in any body fluid in toxic concentrations?

Yes (+1) No (0) Do not know or not done (0)

8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?

Yes (+1) No (0) Do not know or not done (0)

9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?

Yes (+1) No (0) Do not know or not done (0)

Scoring

> 9 = definite ADR

5-8 = probable ADR

1-4 = possible ADR

0 = doubtful ADR

MATERIALS AND METHOD

Study design

A prospective observational follow up study

Tool

NARANJO Scale Questionnaire designed to obtain Dose dependent ADR and possible risk factors

Study Population

The study was conducted as observational follow up study in outpatient ward, Rheumatology department in KIM'S Hospital, Minister Road, Secundrabad.

Inclusion criteria

- All adult patients attending Rheumatology drug monitoring clinics during study for period of 6 months are included.
- All Rheumatoid Arthritis patients using Methotrexate.
- The Patients who are having dose dependent ADR and possible risk factors associated with toxicity are included in follow- up period between Nov 2012 to April 2013 are included

Exclusion Criteria:

- Patients below 16 years of age.
- Surgical and in patients of KIMS.
- Patients from other wards of hospital.

Procedure

An observational follow up study was conducted in KIM'S Hospital. This Hospital has very active Rheumatology service with a busy practice of patients attending specialized clinics for monitoring of drugs and their ADR. We included all adult patients (age more than 16 years) attending Rheumatology drug monitoring clinics during course period of study for 24 weeks. Firstly patient perform's consent forms and patient information leaf lets were designed. And a structural questionnaire (NARANJO Scale) was designed to obtain data regarding dose dependent ADR and possible risk factors. Next we obtained permission from ethical committee. To start the study we identified all the adult patients (age more than 16 years) attending the rheumatology drug monitoring clinics with rheumatoid arthritis disease being treated with Methotrexate. And each

study individual was given the information of study and took consent signature in consent forms. Data was collected through the designed patient performa's and questionnaire forms .We collected patient demographics, diagnosis and other comorbidities especially those reported to influence he risk of developing toxicity studies namely Alcohol intake , impaired renal function ,Hypo albuminuria etc. Adverse reactions were detected. The reported events were identified by using NARANJO Scale. Which is characterized into 4 categories according to the score obtained. <0-doughtful, 1-4 possible, 5-8 probable,> or = 9 definite. And the data was analyzed with application of suitable statistical tool.

RESULTS AND DISSCUSSION

Demographic data analysis

Table 1: Gender

Gender	No. of Patients	Percentage
Female	87	87%
Male	14	13%
Grand Total	111	100%

The sample population consists of 111 RA patients, among which 87 are female RA patients and 14 are male RA patients and according to the data collected there were more female patients than male. Details of age distribution in RA patients

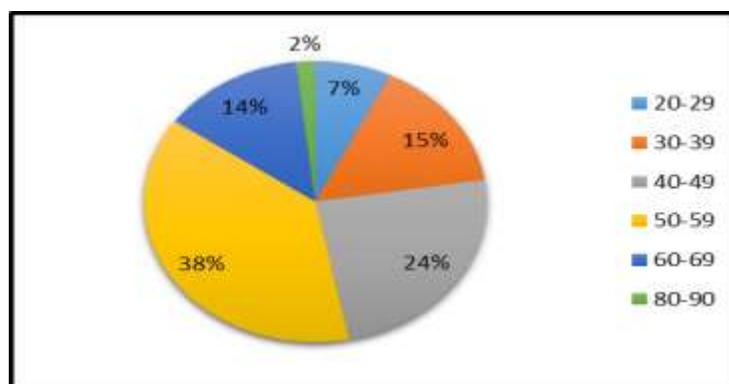


Figure 1: Details of age distribution in RA patients

The figure 1 depicts the age distribution in the study group. The highest no. of patients with RA were in the age, ranging from 50 years to 60 years in the study group.

Table 2: Details of dose of MTX given to RA patients by physician

Dose in Mg	No. of Patients
10 mg	2
15 mg	17
20 mg	44
25 mg	48
Grand Total	111

The Table-2 shows dose given to no. of patients by physician according to severity of the disease. The highest dose given is 25 mg to at least 48 patients.

Table 3: Details of dose dependent adverse drug reactions in study group

Dose in Mg	ADR		Grand Total
	Present	Absent	
10	2	0	2
15	10	7	17
20	21	23	44
25	31	17	48
Grand Total	64	47	111

Table. 3 shows the relationship between the dose and the ADR seen. As the dose is directly proportional to the occurrence of ADR. Among 48 patients taking 25 mg of drug shown some or other inconveniences with the drug. Details of ADR due to Methotrexate in Study Population

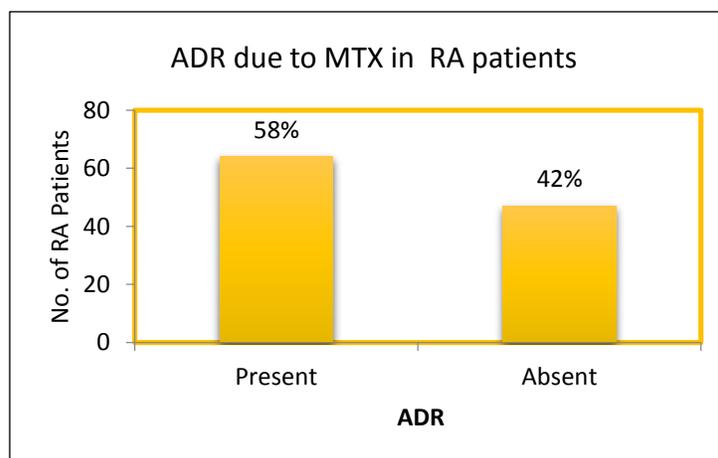


Figure 2: Details of ADR due to Methotrexate in Study Population

The Figure 2 depicts that among the total no of 111 patients, 64 patients showed one or other kind of inconveniences after taking the drug and 47 patients had no difficulties with the drug. Details of Overall ADR due to Methotrexate.

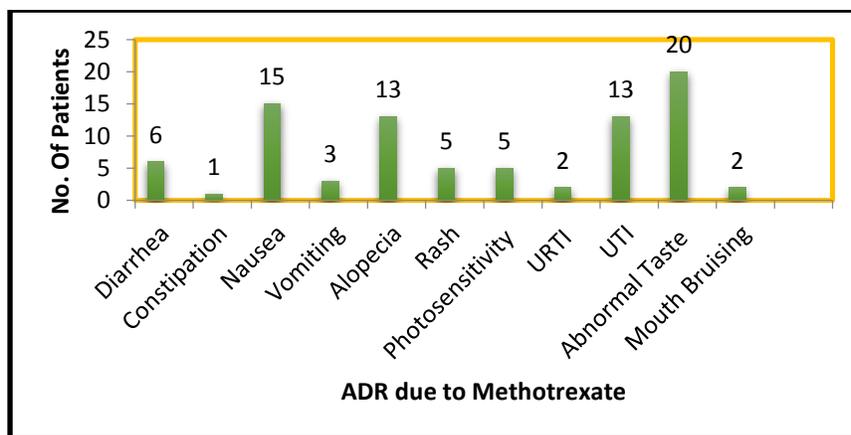


Figure 3: Details of overall ADR due to Methotrexate

The above figure shows the different ADR reported by the patients during the study. An abnormal taste of food while eating is the most common ADR reported Out of 64 patients 20 patients reported this ADR. In accordance with the Naranjo's scale's estimation of Adverse drug reactions. Abnormal taste for food is considered to be definitely methotrexate related ADR seen in 4 patients followed by nausea, diarrhea, vomiting, and alopecia seen in one patient each. The overall findings of the study concludes that methotrexate causes abnormal taste of food on long term use. The results of this study is significant and of clinical and practical importance. The results are accessed based on number of responses given by patients during the study. The questionnaire used is the standard NARANJO scale designed by Naranjo *et al*, the result obtained for patients complained of abnormal taste of for food is score 9 which corresponds to definite relation of ADR and Methotrexate.

ASSUMPTIONS

The following are the assumptions in this study

1. Patients are faithfully and accurately reporting their ADR'S
2. Patients are accurately completing their Questionnaires faithfully.

CONCLUSION

The following conclusions are made from are drawn from the analysis of data

1. Higher the dose greater the reporting of Adverse effects is observed during the study
2. Among the adverse effects reported the highly reported adverse effect of Methotrexate is Abnormal taste to the food
3. The dose related Adverse effects are as follows for 10mg -2patients reported ADR,15mg-10 Patients,20mg -21 Patients,25mg- 31 patients
4. Five ADR could be classified as definitely related to Methotrexate by NARANJO scoring method ,Abnormal taste to food, Nausea, Vomiting ,Diarrhea, Alopecia

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