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Research Article

Frequency of methotrexate intolerance in rheumatoid arthritis patients presented to department of rheumatology PIMS hospital Islamabad

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ABSTRACT

Introduction: Rheumatoid arthritis is systemic inflammatory disease having articular and extra articular manifestations. Methotrexate (MTX) is one of the synthetic diseases modifying anti rheumatic drug (DMARD) and is considered the first choice for rheumatoid arthritis (RA) patients. **Aims and objectives:** The purpose of the study is to find out frequency of methotrexate related gastrointestinal (GI) symptoms so called intolerance.GI symptoms are the most common side effect leading discontinuation of the drug. **Methodology of the study:** This cross sectional study was conducted at department of rheumatology PIMS hospital Islamabad during March 2018 to December 2018 with the permission of ethical committee of hospital. There were 250 patients who were selected for this descriptive study. All patient who were using methotrexate for more than 6 month were included in the study. All patients were treated with MTX for at least 6 months and received weekly folic acid (5 to 15 mg). Patients' data on disease activity, MTX dose and route of administration, co-medication, history of peptic ulcers and smoking was collected. **Results:** There were total 250 patients which included in this study. The data were collected from both genders. The mean age of patients was 42.5 years and the majority of the patients were female. Out of 250 there were 160 female and 90 male patients. Total number of intolerant patients were 72. Among intolerant 60 were female and 12 were male. There were 30 patients having symptoms before Methotrxate dose, 65 Patients having symptoms after dose and 15 having symptoms when think of Methotrexate. **Conclusion:** It is concluded that the well-known MTX-induced gastrointestinal symptoms upon MTX administration. In addition to known gastrointestinal symptoms including abdominal pain, nausea, vomiting after MTX therapy, anticipatory and associative features which are believed to be conditioned phenomenon could hamper MTX compliance.

Key words:Methotrxate, Rheumatoid arthritis, Inflammatory, Disease.

INTRODUCTION

Rheumatoid arthritis is systemic inflammatory disease having articular and extra articular manifestations. Methotrexate (MTX) is one of the synthetic diseases modifying anti rheumatic drug (DMARD) and is considered the first choice for rheumatoid arthritis (RA) patients. In RA and

PsA treatment, methotrexate (MTX) is the first-choice disease-modifying anti-rheumatic drug (DMARD) due to low costs, efficacy and an acceptable safety profile. Serious adverse effects such as pulmonary toxicity, hepatotoxicity and bone marrow suppression are rare or transient if MTX is stopped. In contrast, gastrointestinal adverse effects are common, affecting as many as 66% of patients. Due to these adverse effects, up to 12% of RA and PsA patients discontinue MTX after 6 months to 2 years of treatment. The main goal of treatment for Rheumatoid arthritis patients is remission/or minimal disease activity to have better quality of life[1].Methotraxte should be started after diagnosis of rheumatoid arthritis until and unless contraindicated. The therapeutic effects of methotrexate and others DMARD are acquired after weeks to months[2].It are recommended that MTX should be started before other DMARDS[3].

In 1951, Gubner found that MTX was effective for RA and psoriatic arthritis[4].MTX acts by antagonizing many folate enzyme like dihydrofolate reductase, amin imidazole ribonucleotide transfarmylase(ATIC) and thymidylate synthase (TSER)MTX has disadvantages and can cause toxic effect in RA patients[5-6]. Polymorphism in methylenetetrahydrofolate reductase (MTHFR), C677T, is associated with MTX toxicity and polymorphism in folate and synchronized use of folate and can reduce toxicity[7, 8,9,10].

MTX intolerance is one of the common causes of discontinuation of this drug. Pulmonary toxicity,hepatic toxicity and bone marrow suppression are rare side effects of MTX and are mostly reversible if the dug is discontinued[11]. Gastrointestinal side effect like nausea, vomiting, abdominal pain and behavioral symptoms like irritability and restlessness are common and leads to discontinuation of the drug in upto12% RA and psoriatic arthritis patients[11,12,13,14] .In JIA 50% have GI Symptoms when they take the drug ,before taking the dose and even thinking of the drug[15].

MTX intolerance is defined as score of ≥6 on methotrexate intolerance severity score (MISS), including at least one anticipatory, associative or behavioral symptoms. MISS was already validated for JIA and consists of four domains: abdominal pain, nausea ,vomiting and behavioral symptoms like restlessness ,irritability and refusal of drug developing in response to GI symptom[15].It assesses symptom after administration, before administration (anticipatory)and when thinking of drug(associative) and each domain on MISS questionnaire raging from zero(0) to three (3) depending on the severity of symptoms ,0 no symptoms and 3 sever symptoms[15].

Aims and objectives

The purpose of the study is to find out frequency of methotrexate related gastrointestinal (GI) symptoms so called intolerance.GI symptoms are the most common side effect leading discontinuation of the drug.

Methodology of the study

This cross sectional study was conducted at department of rheumatology PIMS hospital Islamabad during March 2018 to December 2018 with the permission of ethical committee of hospital. There were 250 patients who were selected for this descriptive study. All patient who were on oral methotrexatefor > 6 months were included in this study.

Data collection

The data were collected through a systematically developed questionnaire which include all the demographic data of patients. It include age, gender, duration,methotrexate use, dose of methotrexate, Intolerance and symptoms that lead to intolerance.

Exclusion criteria

1. Age <18 years
2. Methotrexate use <6 months

Statistical Analyses

Comparisons between the two groups were done using the t test or the chi-square, where appropriate. Data analysis was carried out using the SPSS software (Statistical Package for the

Social Sciences, version 15.0, SPSS Inc, Chicago, Ill, USA).

Results

There were total 250 patients which included in this study. The data were collected from both genders. The mean age of patients was 42.5 years and the majority of the patients were female. Out of 250 there were 160 female and 90 male patients. Total number of intolerant patients were 72. Among intolerant 60 were female and 12 were male. There were 30 patients having symptoms before Methotrxate dose, 65 Patients having symptoms after dose and 15 having symptoms when think of Methotrexate.

Table 01: Age distribution of RA patients

Age (years)	Number of patients
20 to 35	70
36 to 50	100
51 to 65	80

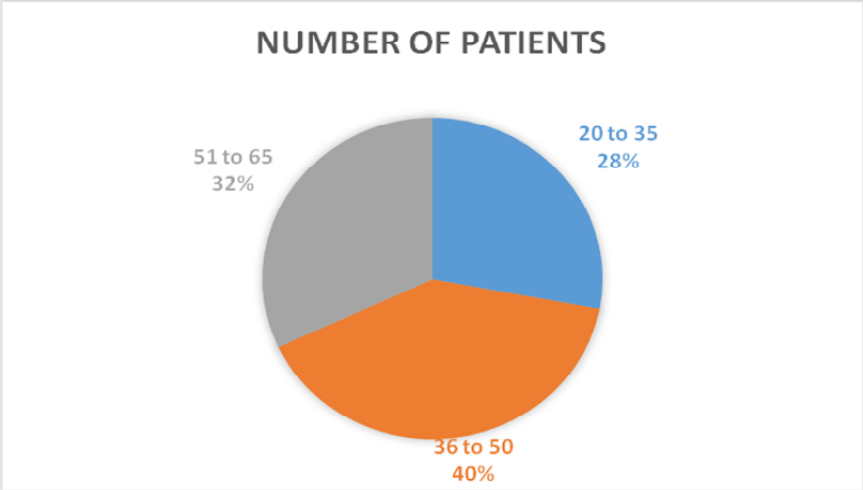


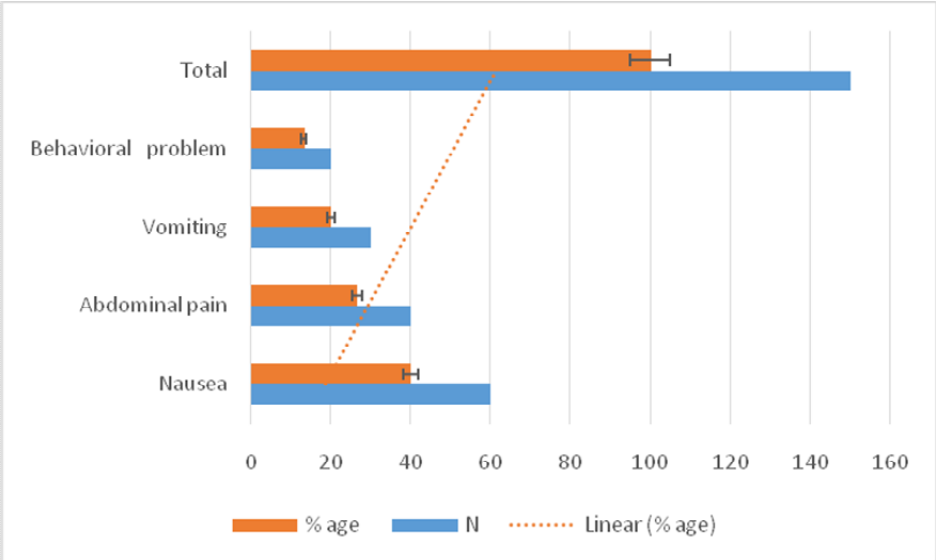
Table 2: ANOVA for the selected intolerant patients

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	7.487a	2	.024
Likelihood ratio	9.147	2	.010
Linear-by-linear association	.256	1	.613
N of valid cases	150		

Out of which 40 % of patients suffering from nausea, 26.6% (abdominal pain), 20% (vomiting) and 13.3% (behavioral problem).

Table 03: Methotrexate intolerance in patients with rheumatoid arthritis

Symptoms	N	% age
Nausea	60	40
Abdominal pain	40	26.6
Vomiting	30	20
Behavioral problem	20	13.3
Total	150	100



DISCUSSION

We showed that besides the well-known MTX-induced gastrointestinal symptoms upon MTX administration, RA patients also had anticipatory and associative gastrointestinal and behavioural symptoms before MTX administration, collectively termed MTX intolerance[16]. Studies in RA have found similar occurrence rates compared to our study; nausea was the most prevalent symptom, occurring in 14.4 to 28.0% compared to 32.0% in our cohort, followed by abdominal pain in 9.7 to 10.6% compared to 11.3% in our cohort and vomiting in 3.4% compared to 6.5% in our cohort[17]. Of note is that comparisons were made between symptoms occurring only after MTX, as it is likely that previous studies took solely these symptoms into account (not the pre-treatment symptoms)[18].

Besides the observed association between parenteral MTX and MTX intolerance, age was also associated with MTX intolerance, namely older patients (>65 years) were less likely to have MTX intolerance than younger patients (≤65 years)[19]. In previous studies, neither younger nor older age (>65 years) was associated with occurrence of MTX-related gastrointestinal and other side effects. Validation studies are required to determine whether younger age is a risk factor for MTX intolerance[20].

Anticipatory and associative gastrointestinal symptoms could have a negative impact on patients' quality of life and impede the use of MTX. Nevertheless, these symptoms are clinically not very evident[21]. Consequently, they cannot be easily detected by physician assessment only, but can be detected using the MISS. Therefore, using the MISS is advantageous as it allows early detection of symptoms[22]. This could create a window of opportunity for timely treatment of MTX intolerance, as well as for early treatment of emerging physical symptoms, which could prevent the development of conditioned responses and therefore MTX intolerance. Similar to JIA, treatment of (physical) symptoms could include lowering the MTX dose, switching to parenteral MTX or starting behavioural therapy or anti-emetics[23].

CONCLUSION

It is concluded that the well-known MTX-induced gastrointestinal symptoms upon is common side effect of MTX.GI symptoms are the most common reason for discontinuation of the MTX.In addition to known gastrointestinal symptoms including abdominal pain, nausea, vomiting after MTX dose, anticipatory and associative features which are believed to be conditioned phenomenon could hamper MTX compliance. Timely intervention like change of

route, folic acid, antiemetic, behavioural therapy can prevent the MTX incompliance and provide a smooth path for an otherwise effective DMARD for RA.

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