FREQUENCY OF METHOTREXATE INTOLERANCE IN JUVENILE IDIOPATHIC ARTHRITIS PATIENTS (JIA): AN EXPERIENCE USING METHOTREXATE INTOLERANCE SEVERITY SCORE (MISS)

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ABSTRACT

Objective: To determine frequency of methotrexate (MTX) intolerance using Methotrexate Intolerance Severity Score (MISS) in patients with Juvenile Idiopathic Arthritis (JIA).

Study Design: Descriptive study.

Place and Duration: Rheumatology Department of Pakistan Institute of Medical Sciences Islamabad from July 2011 to May 2012.

Patients and Methods: Patients of either sex, less than 16 years of age, visiting the Rheumatology outpatient department with JIA were included by non probability purposive sampling. All patients were prescribed MTX in an oral dose of 0.5mg/kg body weight per week for three months. MISS was applied. MISS is a 4 item questionnaire, inquiring about abdominal ache, nausea, vomiting and behavioral symptoms while taking MTX. For every question the patient is given a score. A score of 0 means no complaints, 1 point means mild, 2 point means moderate and 3 points means severe. The minimum possible total score on MISS is 0 point and a maximum is 36 points. A cutoff score of 6 or above was taken as intolerance as judged by the team.

Results: A total of 100 patients/parents completed the MISS questionnaire. Forty percent patients showed MTX intolerance and nausea, abdominal pain, vomiting and behavioral symptoms were observed in majority of the patients.

Conclusion: MISS questionnaire was found simple to administer. Forty percent patients were found intolerant.

keywords: Juvenile Idiopathic Arthritis, Methotrexate, Methotrexate Intolerance Severity Score.

INTRODUCTION

Juvenile Idiopathic Arthritis (JIA) comprises of a group of disorders which involve chronic arthritis of unknown etiology with an onset before sixteen years of age. JIA is known to be the most common cause of rheumatic disease and acquired debility in children[1,2]. The International League of Associations for Rheumatology have developed classification system for arthritis in children and provided 7 subcategories of JIA. These sub categories include: Systemic arthritis, Oligoarthritis, Polyarthritis (RA factor positive, RA factor negative), Psoriatic arthritis, Enthesitis related arthritis and Undifferentiated arthritis[3]. Diagnosis of JIA is almost always clinical and laboratory investigations which include complete blood picture, erythrocyte sedimentation rate, C reactive proteins and others are used for confirmation and to rule out other possible causes of childhood arthritis.

Aim of treatment is to relieve pain, maintain normal growth, muscle strength, joint function and prevent joint deformity and damage. Methotrexate (MTX) has been used for more than 20 years in the management of JIA patients. It is now considered the first line Disease Modifying Antirheumatic Drug (DMARDs) for the treatment of JIA[1]. Weekly administration of MTX is recommended initially either alone or with a supplementation with steroid therapy[4]. Review of literature suggests that it is a relatively safe drug and early treatment with MTX can induce disease remission in more than 70% of patients[5,6]. Serious adverse effects of MTX are less likely but the commonly encountered ones are related to the gastrointestinal tract including nausea, vomiting, abdominal pain and diarrhea. These adverse effects are minimized by regular use of folic acid supplements. Despite such supplementations, JIA patients may still experience them, sometimes to an extent that

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the thought of taking MTX may make them vomit, cry or become restless[7,8,9]. Since JIA treatment and management is on long term basis the occurrence of these disturbing adverse effects can affect the patient compliance to treatment. Non compliance can affect the treatment outcome; therefore early detection of such patients can help in timely alternation in treatment plans and prevent JIA progression. With this background, MTX intolerance was identified in JIA patients attending the rheumatology service, using an internationally recognized MTX Intolerance Severity Score (MISS) questionnaire[10].

PATIENTS AND METHODS

This descriptive study was conducted at the Department of Rheumatology, Pakistan Institute of Medical Sciences (PIMS) Islamabad, from July 2011 to April 2012. The study protocol was approved by the medical ethical committee of the hospital. Non probability purposive sampling was done. Patients of either sex, less than 16 years of age, visiting the Rheumatology outpatient department between 2011 and 2012 with the diagnosis of JIA (all subcategories) were enrolled. The diagnosis of JIA was made according to the criteria laid down by International League of Associations for Rheumatology. All patients enrolled in the study were prescribed MTX in an oral dose of 0.5mg/kg body weight per week. Patients were also prescribed folic acid 5 mg per week as the standard protocol followed at the Rheumatology clinic. Every patient was followed up monthly for three months. MISS questionnaire was applied after 3 months of MTX intake. Patients with a history of non compliance to other treatments in the past and those receiving concomitant treatment were excluded. Informed consent was taken from all patients or parents. Relevant history was recorded. Demographic data including age, gender, type and duration of JIA was also obtained.

The MISS questionnaire which was used in JIA patients to identify the presence of MTX intolerance is a recently developed and validated tool supported by American College of Rheumatology and published in 2011[10]. MISS has been shown to be short and easy to be completed by patients or parents, easy to interpret by physicians and contains all relevant aspects of MTX intolerance. Permission to use the MISS questionnaire for this study was taken from the corresponding author and research team of University Medical Center Utrecht, Wilhelmina Children's Hospital, Netherland. MISS is a 4 item questionnaire comprising of 3 questions each for abdominal ache and nausea, 2 questions regarding vomiting, and 4 questions about behavioral symptoms while taking MTX. Gastrointestinal adverse effects and behavioral symptoms occurring after MTX intake, before MTX intake (anticipatory symptoms), and/or when thinking of taking MTX (associative symptoms) are included in MISS questionnaire. For every question in each of the 4 domains patient or parent could score on Likert scale with score 0 (no complaints), 1 point (mild), 2 points (moderate), or 3 points (severe). The minimum possible score on MISS is 0 point and a maximum is 36 points. A cutoff score of 6 or above in present study was considered as intolerance[10]. During the study period, a total of 117 JIA patients were found eligible and enrolled. Thirteen patients failed to come for follow up visits and 4 patients dropped out because of poor treatment compliance. These 17 patients were therefore excluded from the study. A total of 100 patients/parents completed this study. MISS Questionnaire was concise and comprehensive making the data collection less cumbersome.

RESULTS

Data had been analyzed using SPSS version 17. Descriptive statistics were use to describe the results. Demographic data of the 100 patients is shown in Table 1. Forty out of 100 patients scored above the cut off limit of 6 and therefore labeled as intolerant. In the 40 % patients who developed MTX intolerance different advers effects were observed as shown in Table 2. It was also observed that the gastrointestinal adverse effects extended beyond one domain in majority of the patients.

DISCUSSION

In this study MTX intolerant patients were identified using MISS questionnaire. The MISS

Table-1: Demographic data of juvenile Idiopathic arthritis (JIA) patients (n=100)

Demographic variables		n (%)
Gender	Male	47 (47%)
	Female	53 (53%)
Age groups	<5 years	18 (18%)
	6-10 years	35 (35%)
	11-16 years	47 (47%)
JIA subtypes	Oligo Articular (Persistant)	45 (45%)
	Oligo Articular (Extended)	10 (10%)
	Polyarticular (RA +ve)	16 (16%)
	Polyarticular (RA -ve)	14 (14%)
	Enthesitis related	10 (10%)
	Systemic Onset	5 (5%)

questionnaire designed and validated recently, has been used in this study because of its high sensitivity and specificity and specifically because it has been designed for diagnosing MTX intolerance in JIA patients[10]. Other such scales like the Gastrointestinal Symptom Scale for Kids (GISSK) assesses other specific aspects like the gastrointestinal adverse effects in JIA patients independent of treatment[11]. The minimum possible score on MISS is 0 point and a maximum is 36, at cut off score of 6 and above, Maja et al expressed that 88% of JIA patients diagnosed as MTX intolerant according to gold standard criteria set by them could be identified as intolerant using MISS; therefore they recommended a score of 6 to be the cut off value for patients to be considered intolerant to MTX. In their study, the prevalence of MTX intolerance was as high as 50.5%[10]. In the current study same score of 6 as the cut off value was considered as intolerant. In present study 40% of JIA patients were found to be intolerant to MTX over a period of ten months. These figures are roughly the same as mentioned by Maja et al[10]. In other studies where MISS was not applied, the prevalence of MTX related adverse effects may have been under reported[12]. Failure to pick up such intolerance among these young patients results

Table-2: Methotrexate intolerance to adverse effects in each domain showing overlapping of the symptoms in same patients (n=40)

Methotrexate intolerance severity score	Intolerance n (%)
Abdominal Pain	
· After taking MTX, I have a stomach ache	20(50)
· I have a stomach ache several hours to one day before taking MTX	4(10)
· I have a stomach ache when I think of MTX	4(10)
Nausea	
· After taking MTX, I am nauseous	32(80)
· I am nauseous several hours to one day before taking MTX	20(50)
· I am nauseous when I think of MTX	24(60)
Vomiting	
· After taking MTX, I have to vomit	14(35)
· I have to vomit several hours to one day before taking MTX	3(8)
Behavioural Symptoms	
· I become restless when I have to take MTX	24(60)
· I have to cry when I have to take MTX	4(10)
· I become grumpy/irritable when I have to take MTX	20(50)
· I do not take MTX, because I dislike the side effects so much	4(10)

The values are number percentages out of total intolerant patients

in poor patient compliance and increased chances that the patient may exercise other options. Such patients are likely to give up properly supervised rheumatology guidance and resort to alternative therapies which lead to pain, disability, deformity and compromised child growth.[4, 12]

The severity of each side effect was also demonstrated with the help of MISS. Among the domain of behavioral symptoms, 60% of the

intolerant patients experienced restlessness with MTX. There was high frequency of anticipatory adverse effects particularly nausea a day before MTX intake (50%) or nausea with even the thought of taking MTX. In clinical practice these anticipatory and associative symptoms are usually not asked for, nor are apparent; therefore they may remain undetected. These symptoms if severe can affect the quality of life of patients or make them give up the proper treatment. Lack of timely identification of these symptoms may result in early termination of otherwise effective treatment[10]. These behavioral anticipatory adverse effects may appear due to stimuli like colour of the tablet etc. These stimulate higher brain centers which in turn evokes a conditioned response prior to taking the medicines[13,14]. It has been shown that these conditioned responses may be coped with by employing cognitive behavioral therapy[15].

The results of our study only shows frequency of oral MTX intolerance in JIA patients as patients on parenteral treatment were excluded. It would however be interesting to determine and compare the oral and parenteral methotrexate intolerance using this questionnaire. In addition, long term follow up of JIA patients on MTX would also determine the number of patients who would discontinue MTX due to development of its adverse effects.

Since the severity of MTX intolerance often remains undetected in clinical practice it is recommended to use MISS questionnaire in assessment of MTX intolerance and its type. Early identification of intolerant patients would help in addition of adjuvant treatment like antiemetic or psychotherapy depending upon type and severity of MTX related adverse effects.

CONCLUSION

This study demonstrated that 40% of juvenile idiopathic arthritis patients were methotrexate intolerent using MISS in a period of ten months. MISS questionnaire was found simple to administer and useful in identification of juvenile idiopathic arthritis patients who were methotrexate intolerant .

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