Original Articles

Responsiveness of Outcome Measures in Juvenile Idiopathic Arthritis Patients Treated with Methotrexate

MOHAMMAD IMNUL ISLAM[1], MAHMUDA HOSSAIN[1], MANIK KUMAR TALUKDER[2], JESMIN ARA BEGUM[3], SHAHANA A RAHMAN[4]

Abstract

Objective: To investigate the responsiveness of disease activity measures in juvenile idiopathic arthritis (JIA) patients treated with methotrexate (MTX) using the Standardized response median (SRM) and the effect size (ES).

Design: Prospective observational study. Duration of the study was from June 2005 to December 2007.

Setting: This study was carried out in the department of Paediatrics, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh.

Participants: A total of 58 consecutive patients were enrolled in the study but 40 patients completed their regular follow-up. All patients received MTX orally along with non-steroidal anti-inflammatory drugs (NSAID) and/or steroid.

Results: The subjective variables including physician's and parent's global assessment were most responsive instrument. Among the articular variables, number of joints with limited range of motion was the most responsive. Functional ability was the lowest responsive.

Conclusion: While SRM and ES had been used to evaluate the responsiveness, the physician's and parent's global assessment and number of joints with limited range of motion were the most responsive outcome measure in the therapeutic response in JIA patients.

***keywords:** Standardized response median (SRM), effect size (ES), responsiveness.*

Introduction

Juvenile Idiopathic Arthritis (JIA) is the most common form of chronic arthritis in children and an important cause of both the short term and long term morbidities. JIA is the new terminology proposed by International League of Associations of Rheumatologists (ILAR)[1]. Management of JIA is rapidly changing as the need for more effective treatment is regularly documented by different studies[2]. For providing a more standardized approach in choosing the end points for clinical trials in juvenile idiopathic arthritis (JIA) patients, a core set of outcome variables had been developed.

A preliminary definition of improvement (PDI) was also formulated through an international effort[3]. These recommendations were formed after review of evidence from the literature and previous trials that specific measures meet required criteria for evaluative instruments including validity, reliability and responsiveness[4]. Among the validity criteria, responsiveness of the instruments used is of particular importance in planning clinical trials[5]. According to Ruperto et al, responsiveness of a clinical measure is defined as the ability to detect a clinically meaningful change, such as a change that clinicians or patients think is discernible and important[6]. To assess the responsiveness, the more commonly used measures are the standardized response median (SRM) and the effect size (ES)[6]. This study was designed to investigate the responsiveness of disease activity measures in juvenile idiopathic arthritis (JIA) patients

1. Paediatrician, BSMMU, Dhaka
2. MD (Paediatrics) Student, BSMMU, Dhaka
3. Associate Professor, Dept of Physiology, Ibrahim Medical College, Dhaka
4. Professor of Paediatrics, BSMMU, Dhaka
Correspondence: Dr. Mohammad Imnul Islam

treated with methotrexate (MTX) using the standardized response median (SRM) and the effect size (ES).

Materials and Methods

It was a prospective observational study. This study was carried out in the department of Paediatrics, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh during the period of June 2005 to December 2007. Patients attending the paediatric rheumatology follow-up clinic, BSMMU were enrolled in this study. For enrollment in the study patients had to have diagnosis of JIA according to the International League Against Rheumatism (ILAR) criteria[7]. JIA patients aged more than 5 years were included in the study. Patients having gross deformities, contractures and patients who were getting disease modifying agents and steroids were excluded from the study.

A total of 58 consecutive patients were enrolled in the study but 40 patients completed their regular follow-up. Informed consent was taken from all the parents or attendant before enrollment in the study. Permission was taken from ethical committee of the institution prior to start of this study.

Data were collected using standardized questionnaire containing all the core set of outcome variables. Disease activity measure was assessed at the time of diagnosis as a baseline and after six months of treatment. All patients received methotrexate (MTX) orally at a dose of 10 mg/m^2/wk as single dose. Non-steroidal anti-inflammatory drugs (NSAID) was also given along with MTX in oligoarticular and enthesitis related arthritis (ERA) patients. Prednisolone was prescribed to the polyarticular and systemic onset patients at a dose of 0.5 mg to 1 mg/kg/day for 2 to 4 weeks and then tapered off in next 4 to 8 weeks.

ACR Outcome measures:

All the six ACR core set variables[8] were assessed in the study which included:

1) Physician's global assessment of disease activity on a 10 cm horizontal visual analog scale.
2) Parents or patients global assessment of disease activity by the same scale.
3) Patient's assessment of physical function assessed by bengali version of childhood health assessment questionnaire (CHAQ-B).
4) Number of joints with active arthritis.
5) Number of joints with limited range of motion
6) Acute phase reactant – erythrocyte sedimentation rate (ESR)

Global assessment of disease activity by physician and patient /parent was done by using Visual analog scale (VAS). A 0-10 cm horizontal scale was taken to represent the status of global assessment of disease activity. The line started at zero which indicated absent disease activity and the extreme end of the line was at 10 cm indicating maximum (100%) activity of the disease[9]. Functional assessment was done by using bengali version of childhood health assessment questionnaire (CHAQ-B). Bengali version of CHAQ was previously validated and compared with original and different modified CHAQ prior to this study and it was found reliable[10]. CHAQ scores range from 0 - 3 with 0 representing the best functional ability and 3 being the worst[11]. All assessment was done by the same investigator. Disease activity assessed by ACR core set outcome measures at baseline and final follow up at 6 months was compared.

Statistics: In this study outcome variables were not normally distributed. So, non-parametric methods had been used for assessing the responsiveness. According to parametric statistics, the standardized response mean (SRM) is the mean change in the score from base line to the follow-up visit divided by the standard deviation of this change. The effect size (ES) is the mean change in score divided by standard deviation of baseline score. When non-parametric statistics are used, the mean is changed to median and the standard deviation is changed to three-quarters of the interquartile range. Therefore, highest SRM and ES values indicate greater responsiveness[12]. Data were analyzed using software SPSS 10 for windows and Excel 5.0 (Microsoft corporation).

Results

A total of 40 children with JIA, 29 boys and 11 girls completed six months treatment and follow-up. The age at presentation of JIA ranged from 7 to 16 years. Disease duration at the beginning of MTX therapy ranged from 6 weeks to 60 months. The disease subtypes were polyarthritis in 18(45%) patients (2 rheumatoid factor positive), oligoarthritis in 11(27.5%) patients, systemic onset arthritis in 5 (12.5%) patients and enthesitis related arthritis in 6 (15%) patients.

Table -I shows the median baseline value, the median changes at 6 months and the standardized response mean (SRM) and the effect size (ES) of each outcome variables. Subjective variables including both physician's and patient/parent global assessment of overall well being shows that SRM was above 3. Among the SRM of articular variables, number of joints

Table-I

Baseline values, changes, effect sizes (ES) and standardized response medians (SRM) of outcome measures (n=40)

Outcome variables	Median baseline value	Median change at 6 months	Effect size (ES)	Standardized response median (SRM)
Subjective variables				
Physician's global assessment	10	-9	0	4
Patient/guardian global assessment	10	- 9	0	3.2
Articular variables				
Number of joints with active arthritis	4.5	- 4	1.33	1.12
Number of joints with limited range of motion	3	- 2.5	1.67	3.33
Functional ability	1.88	-1.5	0.9	0.33
Laboratory variables ESR (mm/h)	107.5	- 70	2.3	1.75

with active arthritis was 1.12, while number of joints with limited range of motion was 3.33. SRM of laboratory variables (ESR) was 1.75. Functional ability (CHAQ) provided the lowest SRM value (0.33). In this table it is shown that value of ES of subjective variable were 0 (low). ES was higher among the articular variables and it was found highest in laboratory variable (ESR).

Discussion

Among the sensitivity statistics measures to assess the responsiveness, the more commonly used measures are the standardized response mean (SRM) and effect size (ES). This study investigated the responsiveness of outcome measures in JIA patients treated with MTX using SRM and ES. The results of our analysis indicated that articular and subjective variables were better responsive. Laboratory variables (ESR) showed intermediate responsiveness. Functional ability (CHAQ) was least responsive (Table-1). Responsiveness of outcome measure had

rarely been investigated in JIA. Ravelli et al in their study found that subjective variables of the disease activity, either by the physician's or parent's, were the most responsive measures, whereas functional ability had the lowest responsiveness[12]. Their study population included only polyarticular JIA patients. In another study of JIA patients with oligoarthritis done by Ruperto et al, the physician's global and articular variables showed maximum responsiveness, whereas functional ability measured by CHAQ was the least responsive[6]. A similar study which included both polyarthritis and oligoarthritis JIA patients showed that articular variables and ESR had greater responsiveness[13]. They also showed that among the subjective variables the physician's assessment was the most responsive and assessment by the parent's was the lowest one[13]. Our study also found similar results: physician's global assessment being the highest responsive and parent's/ patient's being lower than physicians (Table-1). Similar results had been reported in adult patients with rheumatoid arthritis[14].

Most of the studies done to investigate the responsiveness of outcome measures in JIA patients found that the functional ability measured by CHAQ was least responsive[6,12,13]. Our study also found similar results.

Health status measures had been shown to be sensitive to change over long duration in clinical trials and observational studies in adult rheumatoid arthritis (RA)[15]. The low performance of the CHAQ should be considered with caution in this study because in our study sample size was small (only 40 sample) and duration was only 6 months.

Laboratory variables (ESR) showed intermediate responsiveness in our analysis. Previous studies in adult RA differed greatly in their estimation of the relative responsiveness of the ESR; in some studies it was reported to be one of the high responsive measure[16], while in other, its responsiveness was relatively poor[17].

To assess responsiveness, we used a sensitivity statistics by measuring both the SRM and the ES. Although statistically similar, the ES and the SRM may give different results depending on the differences in relative magnitude between baseline and change score interquartile range, as the median change is fixed for both the methods[12]. Among the subjective variables, both physician's and patient's global assessment, median baseline value was high as because most of the patients enrolled in this study had severe disease. Mild or moderate cases were only a few. After therapy there was marked improvement found in the both physician's and patient's global assessment. So, the numerical results showed that the ES was 0 (zero). As explained above, it could be due to high median baseline values. Also may be for non-parametric value of this study, the SRM values for responsiveness were found consistant, whereas the ES was inconsistent.

Conclusion

While standardized response mean (SRM) and effect size (ES) had been used to evaluate the responsiveness, the results of our study concluded that articular and subjective variables showed better responsiveness in JIA patients treated with methotrexate. Functional ability showed the lowest responsiveness. The responsiveness of disease activity measures in JIA patients should be further investigated in long duration study enrolling higher number of cases.

References

1.   Jennifer EW, Norman TI. Juvenile Idiopathic Arthritis. Pediatr Clin N Am 2005; 52: 413-42.

2.   Wallace CA. Current management of idiopathic arthritis. Best Pract Res Clin Rheumatol 2006; 20: 279-300.

3.   Giannini EH, Ruperto N , Ravelli A, Lovell DJ, Felson DT, Martini A. Preliminary definition of improvement in Juvenile Arthritis. Arthritis Rheum 1997; 40: 1202-09.

4.   Fortin PR, Stucki G, Katz JN. Measuring relevant change: an emerging challenge in rheumatologic clinical trials. Arthritis Rheum 1995; 38:1027-30.

5.   Guyatt G, Walter S, Norman J. Measuring change over time: assessing the usefulness of evaluative instruments. J Chron Dis1987; 40: 171-78.

6.   Ruperto N, Ravell, A, Viola S, Corsi B, Martini A, Falcini F, et al. Responsiveness of outcome measures in juvenile chronic arthritis. Rheumatology 1999; 38: 176-80.

7.   Michael H, Taunton RS. Classification of childhood arthritis. Best Pract Res Clin Rheumatol 2002; 16: 379-96.

8.   Felson DT, Anderson JJ, Boers M, Bombardier C, Chernoff M, Fried B, et al. The American College of Rheumatology prelininary core set of disease activity measures for rheumatoid arthritis clinical trials. Arthritis Rheum 1993; 36: 729-40.

9.   Daniel JM, William JK. Arthritis and Allied condition. In: John HK, Paul AD, editors. Rheumatology. 2nd ed. Philadelphia: W.B. Saunders; 1995. P. 215-82.

10. Hossain M. Modification and Bengali translation of Childhood Health Assessment Questionnaire (CHAQ) for assessing the outcome measure in Juvenile Idiopathic Arthritis patients [Thesis]. Bangladesh: Bangabandhu Sheikh Mujib Medical University; 2006.

11. Ravelli A, Viola S, Ruperto N, Corsi B, Martini A. Correlation between conventional disease activity measure in Juvenile chronic arthritis. Ann Rheum Dis 1997; 56: 197-200.

12. Ravelli A, Ruperto N, Martini A, Viola S, Migliavacca D, Pistorio A, et al. Responsiveness of clinical measures in children with oligoarticular juvenile chronic arthritis. J Rheumatol 1999; 26: 1827-30.

13. Tatiana B Brasil, Virginia P L Ferriani, Claudia S M Machado. Health related quality of life survey about children and adolescents with Juvenile idiopathic arthritis. J Pediatr 2003; 79: 63-68.

14. Ward MM. Clinical measures in rheumatoid arthritis: which are most useful in assessing patients? J Rheumatol 1994; 21: 17-22.

15. Anderson JJ, Felson DT, Meenan RF, William HJ. Which traditional measures should be used in rheumatoid arthritis clinical trials? Arthritis Rheum 1989; 32: 1568-80.

16. Van der Heide A, Jacobs JWG, Dianant HJ, Bijlsma JWJ. The impact of endpoint measures rheumatoid arthritis clinical trials. Semin Athritis Rheum 1992; 21: 287-94.

17. Anderson JJ, Felson DT, Meenan RF. Sensitivity of a health status measure to short - term clinical changes in arthritis. Arthritis Rheum 1989; 34: 844-50.