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Original Article

Effect of low dose Methotrexate in newly diagnosed Rheumatoid arthritis case

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Abstract:

Rheumatoid arthritis is a painful debilitating joint disease with the proliferation of the synovium and progressive erosion of cartilage and bone. Methotrexate (MTX) has been used for the treatment of Rheumatoid Arthritis (RA) for about 3 decades. It is most effective and commonly used Disease Modifying Antirheumatic Drugs (DMARDS) because it improves symptoms, signs, disease activity and functions. This study was done from January 2016 to December 2016 for a period of 1 year under Physical Medicine and Rehabilitation department, Jalalabad Ragib-Rabeya Medical College (JRRMC), Sylhet. Here we treated the patients with low dose methotrexate. Study was done to see the effect of low dose MTX in newly diagnosed RA patients by clinical examination and DAS 28. DAS stands for disease activity score and 28 joints that are examined in this assessment. The result concluded low dose MTX improves the symptoms, signs, disease activity and functions of the patients.

Keywords: *Rheumatoid arthritis, Methotrexate, DAS 28.*

INTRODUCTION:

Rheumatoid Arthritis is a systemic autoimmune disorder characterized by a chronic polyarticular synovial inflammation because of increased release of cytokines that may lead to irreversible joint damage [1].

Its prevalence approximately 0.5 to 1 % [2]. It usually involves middle aged population, female being affected more than male. The disease directly affects physical function and mobility and results in substantial short-term and long-term morbidity. Incidence of RA in United Kingdom (UK) is 1.16 % in women and 0.44 % in Man[3]. In early phase of the disease joints are prone to damage due to repeated synovial inflammation thus the early introduction of effective treatment may inhibit the inflammatory and destructive particular damage. Initiation of DMARDS MTX therapy within the first 3 months of the onset of the disease is now standard care for rheumatoid arthritis [4]. Efficacy, safety profile, low cost and decades of clinical experience makes MTX the mainstay of treatment for RA [5].

MTX was first introduced in 1948 as an antitumor agent. From mid 1980s MTX used as the DMARD after clinical trials proved its efficacy in RA[6].It interferes with an enzyme important to DNA replication and inhibits cell reproduction that's why it is called “immunosuppressive” drug. MTX is also referred as a “disease modifying antirheumatic drugs or DMARD” as it can modify the course of the incurable disease. It inhibits the formation of polyamines that reduce production of rheumatoid factor and increase adenosine concentration and reduce cytokines [7].

Rapid clinical remission and short term effect on the acute phase reactants, as seen with low dose MTX administration in most patients with RA as well as the first flare of disease after drug discontinuation, suggest that mechanism of action of low dose MTX might be more anti-inflammatory then antiproliferative [8].

MTX is prescribed worldwide to at least 5,00,000 patients with RA. Doses between 7.5 to 15 mg weekly relieves pain, reduce number of tender and swollen joints and improve functions[9]. Recent update shows methotrexate prolong lifespan of patient who can tolerate the drug and have beneficial effects on cardiovascular mortality. RA with low dose MTX has been studied for over 25 years with very few clinically relevant adverse elements[10].

Materials and Methods:

This experimental study was conducted at the outpatient department of Physical Medicine and Rehabilitation, Jalalabad Ragib-Rabeya Medical College Sylhet from January 2016 to December 2016. In 2016, total 274 patients of Rheumatoid Arthritis were attended OPD of Physical

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Medicine and Rehabilitation at Jalalabad Ragib-Rabeya Medical College Sylhet. Among them 55 patients were newly diagnosed cases. Proper history was taken. Clinical examinations and baseline investigations were done to detect the cases after discussion of the nature of study. Patients were recruited according to inclusions and exclusions criteria. Informed written consent was taken. Newly diagnosed cases without having any Disease Modifying Anti Rheumatic Drugs (DMARD's) were selected for the study. Known cases of renal, hepatic, cardiac impairment, pregnancy were excluded from the study. Patients were prescribed low dose methotrexate 5-10mg/ week. Folate supplementation in the form of folic acid was also given to all patients. 7 patients were dropped out form the study. Patients were followed up every 4 weeks interval up to 12 weeks. During follow up patients were assessed by DAS 28 scoring. All the data were recorded in prescribed data sheets and expressed in percentages.

RESULTS:

A total 55 cases of newly diagnosed RA patients were selected for the study in the outpatient department of Physical Medicine and Rehabilitation, JRRMCH, Sylhet from January 2016 to December 2016. Table I represents age and sex distribution of the patients. 10 were male and 45 were female. Majority of the patient were in age group 31-40 years with female: male =5: 1

Table I

Age group	Male	Female
21-30	01	05
31-40	04	15
41-50	03	12
51-60	01	18
>60	01	05
Total	10	45

Table II represent response of acute phase reactant (APR). 81.82 % had high APR before treatment and 33.33 % had low APR after treatment with MTX.

Table II

Acute phase reactant	Before treatment n=55	After treatment n =48
High	81.82 %	---
Low	---	33.33 %

Table III represent pre and post treatment response of MTX on joints before and after treatment. 70.91 % had swollen joints and 89.09 % had tender joints before treatment (n=55). After treatment it reduced to 10.42 % swollen joints and 52.08 % tender joints (n=48).

Table III

Involved joints	Before treatment n=55		After treatment n=48	
	Number of cases	Percentage %	Number of cases	Percentage %
Swollen joint	39	70.91	5	10.42 %
Tender joint	49	89.09	25	52.08 %

Table IV shows rheumatoid factor positive in 83.64% (46) cases and Anti CCP (anti citrulinated pyrophosphate) positive in 26.64% (13) cases.

Table IV

Sero positivity	Number of cases	Percentage
Rheumatoid factor	46	83.64 %
Anti CCP	13	26.64 %

Table V represent pre and post treatment disease activity. At 0 week, 54.55% patients were in high disease activity (DAS 28 >5.1), 43.64% patients were in moderate disease activity (DAS 28 between 3.2-5.1) and 1.82% patients were in low disease activity (DAS 28 <3.2). AT 4th week, 18.75 % were in high disease activity, 68.75 % were in moderate disease activity and 12.50 % were in low disease activity. At 8th week, 68.75 % were in moderate disease activity and 31.25 % were in low disease activity. At 12th weeks, 60.42 % were in moderate disease activity and 39.58 % were in low disease activity.

Table V

Progress of disease activity	0 week (n=55)		4th week (n=48)		8th week (n=48)		12th week (n=48)	
	Number of cases	Percentage %	Number of cases	Percentage %	Number of cases	Percentage %	Number of cases	Percentage %
High disease activity DAS 28->5.1	30	54.55 %	09	18.75 %	---	---	---	---
Moderate disease activity DAS 28 ≥ 3.2-5.1	24	43.64 %	33	68.75 %	33	68.75 %	29	60.42 %
Low disease activity DAS 28 ≤ 3.2	01	1.82 %	06	12.50 %	15	12.50 %	19	39.58 %

DISCUSSION:

In Rheumatoid Arthritis joints are usually involved at the early stage of the disease. Thus the early introduction of effective treatment can inhibit the inflammatory and destructive mechanism. MTX is the preferred treatment for most of the patients of rheumatoid arthritis. Recent studies have shown an increased use of MTX from 5 to 90 % in Finland and from 25 to 90 % in the USA [11].

Our study had done to see the effect of low dose methotrexate in Rheumatoid arthritis patients and results showed improvement of symptoms and signs and functions. In 2009 Braun et al showed MTX improved signs, symptoms, disease activity and functions to a similar degree as the TNF alpha blockers in monotherapy [12].

Hurst et al, performed a study on 1160 patients of rheumatoid arthritis who was treated with DMARD- methotrexate, hydroxychloroquine, and injectable gold. Methotrexate the most effective DMARD among three because of the length of therapeutic segment [13].

Handy et al, examined small group of patients and commented who received MTX showed rapid and greater improvement [14].

In this study before treatment high ESR were found in 81.82% cases. But it reduced to 33.33 % after treated with MTX. Segal et al, performed a study where ESR & CRP measured after administration of MTX and showed decrease level of ESR and CRP indicates rapid clinical effect of drug in RA [15].

Here in this study we prescribe MTX at a dose 5-25 mg every weekly. Willkens et al, performed a study on 32 patients of RA with low dose MTX range 7.5 to 10 mg weekly and showed improvement in 75 % patients [16].

Hoffmeister et al, showed improvement of 45 of the 78 (58 %) RA patients within 4 weeks after treatment with MTX [17]. Michael et al showed response of RA among twenty nine patients. 11of them had major clinical improvement and 14 had moderate improvement. But when the dose of MTX reduced below 10mg every week or when discontinued, a flare of arthritis occurred in more than 80 % of the patients [18].

In this study response of MTX on joints showed 70.91 % had swollen joints and 89.09 % had tender joints before treatment. After treatment with MTX it decreases to 10.42 % swollen joints and 52.08 % tender joints.

Weinblatt et al, performed a randomized trial on 133 patients of RA with oral MTX. After two years of therapy he found marked improvement in acute phase reactant, joint pain, tenderness index and joint swelling Index [19].

In this study before treatment 55.55 % with high disease activity (DAS 28 > 5.1). After 12th week of treatment with MTX 39.58 % presented as low disease activity (DAS 28 < 3.2).

Sanmarti et al performed a study on 60 patients, of early RA who treated with MTX. Result concluded that there where reduction in disease activity during one year follow up. DAS was 5.8± 0.8 (high disease activity) at early and 3.9 ± 1.3 (moderate disease activity) at one year later [20].

CONCLUSIONS:

Clinical course of RA is generally one of the exacerbation and remission. 40 % patients become disabled after 10 years. Although there is no cure for RA yet, a variety of treatment are available that can slow down the condition and keep the joint damage to a minimum. In this study we treated newly diagnosed RA patient with low dose MTX. Our limitations were small sample size, poor socio economic condition causes failure to perform follow up investigations, lack of consciousness to continue the drug for a longer period. Besides all these limitations we concluded our study that low dose MTX improves symptoms, signs, disease activity and functions and early intervention with DMARD's in yearly RA gives the least opportunity for attempting achieve disease remission.

References:

1. Salliot C,Van der Heijde D. Long term safety of methotrexate monotherapy in patients with RA : a systematic literature research. Ann Rheum Dis 2009; 68:1100-4.
2. Buhroo AM, Baba AN. Adverse effect of low dose methotrexate in patients with RA. IJPMR 2006; 17(2):21-5.
3. Symmons D, Tunner G, Webb R, Asten P, Barrett E, Lunt M, Scott D, Silman A. The prevalence of RA rhen United Kingdom : New estimates for a new century. Rheumatology 2002; 41(7): 793-800.
4. Nell VP, Machold KP, Eberl G. Benefits of very early referal and very early therapy with DMARD'S in patient with early RA. Rheumatology 2004; 43 : 906-14.
5. Shinde CG, Ventatesh MP, Kumar TM, Shivakumar HG. Methotrexate: a gold standard treatment of RA. J pain Palliat Care Pharma Cother 2014; 28(4) : 351-8.
6. Cronstein BN, Eberle MA, Gruber HE, Levin RI. Methotrexate inhibits neutrophil function by stimulating adenosine release frim connective tissue cell. Proc Natl Acad Sci USA 1991; 88(6) : 2441-5.
7. Swierkot J, Szechiniski J. Methotrxate in rheumatoid arthritis. Pharmacol Rep 2006; 58 : 473-92.
8. Cutolo M, Pazzorni C, Seriolo B, Straub RH. Antiinflamatory mechanisms of methitrexate in rheumatoid arthritis. Ann Rheum Dis 2001; 60 (8) : 729-35.
9. Kaltsonudis E, Papagoras C, Dross AA. Current and futurer role of methotrexate in the therapeutic armamentarium for RA. Int J Clin Rheumatol 2012; 7(2) : 179-189
10. Dross AA, Karantanas AH, Psychos D, Tsampoulas C, Moutsopoulous HM. Can treatment with methotrexate influence the radiological progression of rheumatoid arthritis? Clin Rhrumatol 1990; 9(3) : 242-5.
11. Sokka T, Pincus T. Ascendency of weekly low dose methotrexate in usual care of rheumatoid arthritis frim 1980-2004 at two sites in Finland and USA. Rheumatology 2008; 47 : 1543-7.
12. Braun J, Rau R An update on methotrexate. Curr Opin Rheumatol 2009; 21: 216-23
13. Hurst S, Kallan MJ, Wolfe FJ, Fries JF, Albert DA. Methotrexate, hydroxychloroquine, intramuscular gold in rheumatoid arthritis relative area under the curve effectiveness and sequence effects. The Journal of Rheumatology 2002; 29(8) : 1639-45.

14. Hamdy H, Mckendry RJR, Mierins E, Liver JA. low dose methotrexate copared with azathioprine in the treatment of rheumatoid arthritis. A twenty four week controlled clinical trial. Arthritis Rheum 1987; 30 : 361-8

15. Segal R, Caspi D,Tishler M, Wigler I. Short term effect of low dose methotrexate on the acute phase reaction in patient with RA. J Rheumatol 1989; 16(7) : 914-7.

16. Willkens RF, Watson MA, Paxson CS. Low dose pulse methotrexate therapy in rheumatoid arthritis. J Rheumatol 1980; 7 : 501-5.

17. Hoffmeister RT. methotrexate therapy in rheumatoid arthritis:15 years experience. Am J Med 1983; 75(6A) : 69-73.

18. Michael E, Weinblatt MD. Methotrexate in Rheumatoid Arthritis : A, Wolfe Quarter Century of Development. Trans Am Clin Climatol Assoc 2003; 124 : 16-25.

19. Weinblatt ME, Kaplan H, Germaih BF, Merriman RC, Solomon SD, Wall B, Anderson L, Block S, Small R, Wolfe F.Methotrexate in RA: effects on disease activity in a multi center prospective study. JRheumatol 1991; 18(3) : 334-8.

20. Sanmarti R, Gomez A, Ercilla G, Gratacos J, Larrosa M, Suris X, Vinas O, Salvador G, Munoz-Gomez J, Canete JD. Radiological progression in early rheumatoid arthritis after DMARD's: a one year follow up study in a clinical setting. Rheumatology 2003; 42 : 1044-49.