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Comparison of the clinical efficacy and safety of subcutaneous versus oral methotrexate in patients with active rheumatoid arthritis

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Abstract
Background: Rheumatoid arthritis (RA) is a chronic inflammatory rheumatic disease with a prevalence of 0.5-1% and an incidence of 25-50 cases / 100,000 population (Symmons *et al*, 1994). The burden of the disease is significant (Huscher *et al*, 2006). After 5 years, one–half of RA patients have developed clinically important changes in health status (Uhlig *et al*, 1998). Thus, the socio-economic costs of RA are quite high (Zink *et al*, 2000). The overall prevalence of RA in Bangladesh is 0.6%.
Aim of the study: The aim of this study was to compare the effects of subcutaneously administered MTX with that of orally administered one and to compare changes in clinical and laboratory measures of activity of rheumatoid arthritis.
Methods and Materials: This was a randomized clinical trial to compare the efficacy and safety of SC injectable MTX in active rheumatoid arthritis patients with that of oral one. This study was conducted during the period of January 2005 to February 2007. A total of 168 patients of RA were included in this study. Fourteen patients dropped out during this study period. They failed to attend follow up after enrolment or developed toxicities. So, finally 154 patients completed the trial. The patient with RA attending rheumatology OPD in BSMMU were considered for inclusion in the study (According to American Rheumatism Association 1988 revision criteria).
Results: In analyzing the ACR response we found, ACR-20 response was achieved by 62.3% of patients in injectable group and 39.2% in oral group where P<0.01, ACR-50 response was achieved by 38.7% in injectable group and 20.3% in oral group where P<0.05 and ACR 70 response was achieved by 8% in injectable group and 2.5% in oral group where p value was >0.10 which was not statistically significant.
Conclusion: From the present study, it may be concluded that MTX is effective in controlling disease activity in rheumatoid arthritis. Subcutaneously administered MTX is more effective than that of oral form. Future trials including bigger samples and more vigorous study design will probably determine the disease controlling ability of subcutaneous MTX before considering biological agent, which are too costly.

Keywords: rheumatoid arthritis, subcutaneous methotrexate, clinical efficacy

1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory rheumatic disease with a prevalence of 0.5-1% and an incidence of 25-50 cases / 100,000 population (Symmons *et al*, 1994). The burden of the disease is significant. After 5 years, one–half of RA patients have developed clinically important changes in health status (Uhlig *et al*, 1998) [21]. Thus, the socio-economic costs of RA are quite high (Zink *et al*, 2000) [28]. The overall prevalence of RA in Bangladesh is 0.6% (Das *et al*, 2002) [2]. A variety of disease modifying anti rheumatic drugs (DMARDs) are used to control the clinical activity of RA (Zink *et al*, 2001) [29]. Methotrexate (MTX), a derivative of folic acid and aminopterin, is the most commonly used and most recommended DMARD for the treatment of RA. MTX was originally developed as folate antagonist for the treatment of cancer. The high dose is used in cancer, the mechanism of action of low-dose MTX in RA is still unknown. Several mechanism have been proposed, including inhibition of T cell proliferation due to effect of MTX on purine and pyrimidine metabolism, inhibition of transmethylation reactions required for the prevention of T cell cytotoxicity, interference with glutathione metabolism leading to alteration in recruitment of monocytes and other cells to the inflamed joint, and promotion of the release of endogenous anti-inflammatory mediator adenosine. The pharmacokinetics of MTX has been studied extensively (Jundt *et al*, 1993) [11]. Serum and synovial fluid concentration of MXT are approximately equal (Herman *et al*, 1989) [8]. Food intake reduces the peak concentration. The bioavailability of higher oral doses of MTX in adult patients with RA is higher variable and, on average, is two-thirds that of subcutaneous (SC) or intramuscular (IM) administration (Hamilton *et al*, 1997) [7]. Although it is known that parenteral administration of MTX results in better and reliable bioavailability, it remains unclear whether this results in superior clinical efficacy and safety. Some studies, however, have suggested that IM MTX showed improved clinical efficacy with fewer side effects compared with oral MTX (Rozin *et al*, 2002) [19]. In one study, 16% of patients experienced a relapse of RA after

swiching from parenteral to oral MTX treatment (Rozin *et al*, 2002) [19]. RA mainfestalions were reported to be improved and side effects reduced by switching from oral to parenteral administration in most patients (Bingham *et al* 2003) [1]. The possibility of self-injection is a potential advantage of SC versus IM administration of MTX. Some patiients can't tolerate MTX (Kinder *et al*, 2005) [13]. This can be explained by interference of the drug with folate and homocysteine metabolism (Hornung *et al*, 2004) [9]. Low dose folic acid supplementation has been shown to prevent or diminish the influence of MTX on folic status and has demonstrated a protective effect on MTX-induced liver toxicity (Van *et al*, 2001) [22]. However, there is limited evidence that the addition of folic acid decreases the efficacy of MTX (Khanna *et al*, 2005). It has recently been proposed that 5 mg of folic acid, to be taken orally on the day following MTX administration, should routinely be prescribed for all patients receiving this drug for the treatment of RA (Whittle *et al*, 2004) but this approach necessarily been adopted worldwide. Taken together, there is strong evidence that MTX is the standard DMARD therapy for patient with RA. However, it is not clear which rout of administration is the best. The aim of the present study was to directly compare the clinical efficacy and safety of SC versus oral administration of MTX in patients with active RA.

2. Objectives

General objective

- To compare the effects of subcutaneously administered MTX with that of orally administered one.

Specific Objectives

- To compare changes in clinical and laboratory measures of activity of rheumatoid arthritis patients treated with subcutaneously administered MTX with those in patients treated with orally administered MTX.

3. Methodology and Materials

This was a randomized clinical trial to compare the efficacy and safety of SC injectable MTX in active rheumatoid arthritis patients with that of oral one. This study was conducted during the period of January 2005 to February 2007 in Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh. A total of 168 patients of RA were included in this study. Fourteen patients dropped out during this study period. They failed to attend follow up after enrolment or developed toxicities. So, 154 patients completed the trial. The patient with RA attending rheumatology OPD in BSMMU was considered for inclusion in the study (according to American Rheumatism Association 1988 revision criteria). After history taking, physical examination and obtaining consent with laboratory investigation patients who fulfilled the criteria of active RA as defined by ACR were selected for the study.

Inclusion criteria

- Patient must fulfill the ACR 1988 revised criteria
- The disease should be active
- Age-18-70 years
- Receiving of up two intra articular steroid injections were accepted except for the last two months

Exclusion criteria

- Age of the patients-less than 18 years
- Presence of other rheumatological disorders
- Pregnancy, lactating mother and women with child bearing potential
- Evidence of organ damage
- Renal – serum creatinine > 1.5 mg/dl
- Lung – Forced vital capacity (FVC) < 40% of predicted value
- Liver – SGPT (ALT) more than twice of normal value

All the patients were given an explanation of the study and information consent was taken verbally before entry into the study. Necessary patient data were collected through pre designed questioner. All the findings and data were displayed in several tables and or figures of Microsoft Excel.

4. Results

Total number of patients was 154 of which 120 were female and 34 were male. Female to Male relation was 3:5:1. The range of patient's age was 18 to 65 years and mean age was 44.9±11.9 years. Mean duration of disease was 5.6±5.3 years. Seventy-seven present of patient were rheumatoid factor positive and 44% were Rose Waaler test positive. Among 39% of patient there were positive family histories of rheumatological diseases. Seventy-eight present of patients did not get any disease modifying anti-rheumatic drugs (DMARDs) before this trial. 13 % patients were treated with steroid. After eight weeks (10mg/weeks and 15mg/weeks for next 4 weeks) of oral MTX treatment, there was some improvement as evidenced by reduction in the number of tender and swollen joint counts, HAQ score, morning stiffness, Patient's and Physician's global assessment of disease activity score and ESR (Table II). In Figure the comparison between the American College of Rheumatology (ACR) scores of second and third follow up visits were displayed. In third visit 54.5%, 14.3% and 1.9% patients achieve ACR 20, ACR 50 and ACR 70 scores respectively whereas that were achieved by 20.1%, 1.9% and 0% during the second visit respectively. In this study the male-female ratio was 1:5.3 in injectable group and 1:2.6 in oral group. Most patients were rheumatoid factor positive in both groups of patient. Sixty of seventy-five patients of injectable MTX group was rheumatoid factor positive (80%). In oral group fifty nine of seventy-nine patients were rheumatoid factor positive. The value of positive Rose Waler test was 49.3% and 39.2% in injectable and oral groups respectively. At a glance the baseline characteristics of patients in injectable and oral MTX groups after randomized has been disseminated in the Table III. In this study there was greater reduction of tender joint counts, swollen joint counts, morning stiffness, health assessment questionnaire, pain (visual analogue scale), Patient's and physician's global assessment of disease activity and erythrocyte sedimentation rate in patients received injectable methotrexate groups compared to oral groups. In analyzing the ACR response we found, ACR-20 response was achieved by 62.3% of patients in injectable group and 39.2% in oral group where $P<0.01$, ACR-50 response was achieved by 38.7% in injectable group and 20.3% in oral group where $P<0.05$ and ACR 70 response was achieved by 8% in injectable group and 2.5% in oral group where p value was >0.10 which was not statistically significant. In Table VI the comparison of improvement of the patients at different visits with baseline were displayed.

Table 1: Baseline characteristics of patients (N=154)

Variable	Mean ± SD	n (%)
Age in year	44.9 ± 11.9	
Duration in year	5.6 ± 5.3	
Sex		
Male		34 (22.1)
Female		120 (77.9)
Several Scores/Parameter		
Tender Joint Count	50.2 ± 14.1	
Swollen Joint Count	22.4 ± 12.1	
Health Assessment Questionnaire (HAQ) score	2.1±0.6	
Morning Stiffness (Hours)	2.1 ± 1.5	
Pain (Visual Analogue Scale) (0-10)	6.7±1.6	
Patient's Global Assessment of Disease Activity (0-10 cm scale)	6.6±1.5	
Physician's Global Assessment of Disease Activity (0-10 cm scale)	5.7±1.5	
Erythrocyte Sedimentation Rate (ESR)	69.5±29.1	
Rheumatoid factor (RA) test		
Negative		35 (22.7)
Positive		119 (77.3)
Rose Waler Test		
Negative		86 (55.8)
Positive		68 (44.2)
Family History of disease		
Yes		60 (39.0)
No		94 (61.0)
Drug history of DMARDs		
Yes		34 (21.9)
No		120 (78.1)
Treatment with steroid		
Yes		20 (13.0)
No		134 (87.0)

Values are Mean±SD; DMARD=disease modifying antirheumatic drug

Table 2: Comparison of baseline characteristics with 3rd follow up (N=154)

Variable	Baseline	Third visit
Tender Joint Count	50.2±14.1	33.9±16.6
Swollen Joint Count	22.4±12.1	11.9±9.6
Health Assessment Questionnaire (HAQ) score	2.1±0.6	1.4±0.6
Morning Stiffness (hours)	2.1±1.5	0.8±0.7
Pain (Visual Analogue Scale, 0-10cm)	6.7±1.6	4.3±1.7
Patient's Global assessment of disease activity (0-10cm scale)	6.6±1.5	4.3±1.6
Physician's Global assessment of disease activity (0-10cm scale)	5.7±1.5	3.6±1.4
Erythrocyte Sedimentation Rate (ESR) mm in 1st hour	69.5±29.1	54.2±28.2

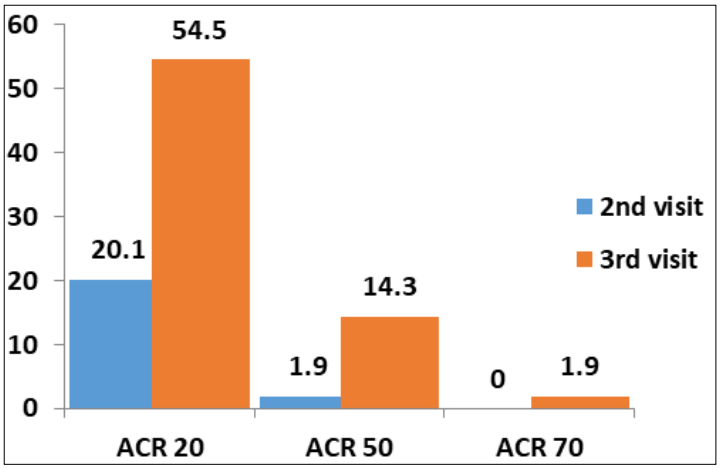

Fig 1: Comparison of American College of Rheumatology (ACR) responses at second and third follow up visit

Table 3: Baseline characteristics of patients in injectable and oral MTX groups after randomized

Parameters	Injectable (n=75)	Oral (n=79)
Age	45.7±11.5	44.1±12.3
Sex-M: F	12:63	12:57

	01:5.3	01:4.74
Tender Joint Count	36.5±15.9	31.5±17.1
Swollen Joint Count	12.9±10.1	10.9±9
Monitoring Stiffness (Hours)	0.8±0.8	0.8±0.6
Health Assessment Questionnaire	1.44±0.51	1.41±0.63
Pain (Visual Analogue Scale)	4.2±1.8	4.4±1.7
Patient's Global Assessment of Disease Activity	41.±1.6	4.4±1.6
Physician's Global Assessment of Disease Activity	3.4±1.3	3.8±1.5
ESR (mm) in 1st hour	48.1±25.8	59.9±29.3
Rheumatoid Factor- Positive: Negative	650:15:00	59:20:00
Rose Waler- Positive:Negative	37:38:00	31:48:00

Table 4: Comparison of improvement among patient between third and final visit by two groups (N=154)

Parameters	Injectable			Oral		
	3rd visit	Final Visit	Reduction	3rd visit	Final Visit	Reduction
Tender Joint Count	36.5±15.9	18.5±11.5	17.9.5±15.8	31.5±17.1	24.6±15.5	6.9±15.7
Swollen Joint Count	12.9±10.1	4.5±4.6	8.4±9.5	10.9±9	7.2±8.5	3.7±8.4
Morning Stiffness (Hours)	0.8±0.8	0.4±0.8	0.4±1.07	0.8±0.6	0.6±0.7	0.17±0.77
HAQ	1.45±0.51	0.89±0.48	0.55±0.52	1.41±0.63	1.05±0.65	0.36±0.52
Pain (VAS	4.2±1.8	2.2±1.5	1.97±2.0	4.4±1.7	3.4±1.7	1.05±1.85
PGADA	4.1±1.6	2±1.5	2.12±1.9	4.4±1.6	3.4±1.7	1.1±1.9
PhGADA	3.4±1.3	1.7±1.4	1.75±1.8	3.8±1.5	2.8±1.6	1.03±1.7
ESR (mm/hr)	48.1±25.8	29.1±16.5	19.0±30.4	59.9±29.3	42±26.6	17.8±26.7

* All values are the Mean±SD
*Visual analogue Scale (VAS) for pain ranges from 0=no pain to 10=extreme pain
*Patients (PGADA) and physician's (PhGADA) global assessment of disease activity range from 0=no disease activity to 10= extreme disease activity
*HAQ: Health Assessment Questionnaire (0-3) =no difficulty to 3=unable to perform activity

Table 5: ACR response at final visit: Comparison of oral and injectable MTX group (N=154)

ACR response		Inject	Oral	Total	p-value
		n (%)	n (%)	n (%)	
ACR 20	Yes	46(62.3)	31(39.2)	77(50.0)	P<0.01
	No	29(38.3)	48(60.8)	77(50.0)	
ACR 50	Yes	29(38.7)	16(20.3)	45(29.2)	P<0.05
	No	46(61.3)	63(79.7)	109(70.8)	
ACR 70	Yes	6(8.0)	2(2.5)	8(5.2)	P>0.10
	No	69(92.0)	77(97.5)	146(94.8	
Total		75(100.0)	79(100.0)	154(100.0)	

Table 6: Comparison of improvement at different visits with baseline (N=154)

Visit	Injectable		Oral	
	Absolute change	% change	Absolute change	% change
Tender Joint Count				
2nd visit	-9.3±1.5	-17.9	-7.3±1.3	-15.3
3rd visit	-15.8±1.8	-30.3	-16.7±1.904	-34.7
5th visit	-33.8±1.5	-64.6	-23.6±1.789	-49.1
Swollen Joint Count				
2nd visit	-6.395±1.3	-26.9	-6.03±0.9	-28.6
3rd visit	-10.867±1.6	-45.6	-10.15±1.1	-48.2
5th visit	-19.28±1.3	-81.1	-13.8±1.4	-65.9
Health assessment Questionnaire				
2nd visit	-0.29±0.09	-13.3	-0.31±0.06	-15.7
3rd visit	-0.72±0.06	-33.3	-0.56±0.07	-28.5
5th visit	-1.27±0.07	-58.7	-0.91±0.07	-46.7
Pain (Visual Analogue Scale)				
2nd visit	-1.0±0.176	-16.6	-1.3±0.196	-19.7
3rd visit	-2.30.218	-35.7	-2.4±0.196	-35.2
5th visit	-4.2±0.202	-66.1	-3.4±0.23	-50.5
Patient's Global Assessment of Disease Activity				
2nd visit	-1.0±0.17	-16.6	-1.2±0.191	-18.9
3rd visit	-2.2±0.209	-35.8	-2.2±0.199	-33.5
5th visit	-4.4±0.206	-68.8	-3.3±0.236	-50
Physician's Global Assessment of Disease Activity				
2nd visit	-1.0±0.184	-19.1	-1.1±0.184	-20.4
3rd visit	2.1±0.19	-38.5	-1.9±0.175	-34.1

5th visit	-3.8±0.207	-69.9	-3.0±0.236	-51.6
ESR (Erythrocyte Sedimentation Rate)				
2nd visit	-13.2±3.253	-19.7	-12.7±3.101	-18.8
3rd visit	-19.5±3.768	-28.9	-11.5±3.311	-17
5th visit	-38.5±3.544	-57	-29.3±3.182	-43.4
MS (Morning Stiffness)				
2nd visit	-1.047±0.150	-49.8	-0.88±0.130	-42.4
3rd visit	-1.44±0.201	-68.8	-1.22±0.156	-58.3
5th visit	-1.89±0.183	-90.1	-1.38±0.170	-66.1

5 Discussion

Methotrexate is the most widely used disease modifying anti-rheumatic drug for the treatment of rheumatoid arthritis in all over the world due to its effectiveness, disease controlling capacity, capability of providing sustained remission (Kremer *et al*, 1986) [7], weekly convenient doses and better patients compliance. But problem with this drug is that there is wide variation of absorption of oral MTX above doses of 17.5 mg/week due to absorption saturation. Absorption of MTX is more predictable by parental route (Thompson *et al*, 1984). Parental route provides higher and prolonged serum concentration than that of oral form (Freemann *et al*, 1975). Among parenteral routes, subcutaneous MTX is less painful and easier to administer in comparison to intramuscular route and results in similar absorption (Brooks *et al*, 1990). The bio-availability of subcutaneously administered MTX is more than that of oral from. So, for better efficacy of MTX at doses of 25 mg weekly or more, a change to parenteral route (subcutaneous) should be considered (Hoekstra *et al*, 2004). In the present study, we have assessed the compliance, efficacy and safety of subcutaneous MTX in active RA. In our study, the average age of patients was 44.9±11.9 years, F:M ratio was 3.5:1, mean duration of disease was 5.6±5.3 years. This value were equivalent to the values of trial done at this institute in 2000. That study revealed mean age was 44.05±14.12 years. F:M = 4:1, duration of disease was 5.53±6.33 years. But in other study done by Weinblatt *et al* 1985 revealed that mean age was 8.38±8.32 years. This discrepancy was probably due to change in the previous concept and administration of DMARD. In the present series, seventy seven percent of patients were seropositive but it was ninety five percent in the study done by Weinblatt M.E. The lower rate of seropositivity could be due to shorter duration in the present series. Prior to analysis different characteristics in both groups were compared to find out whether they had any statistically significant discrepancy. The mean age, mean duration of disease, tender and swollen joint counts, patient's and physician's global assessment of disease activity and ESR varied numerically between the two groups but differences were not statistically significant. After 132 month of MTX therapy by Weinblatt, significant improvement was noted in the number of tender joints, swollen joints, patients and physician's global assessment of ($p<0.001$) Table No-VII and better response obtained in subcutaneous MTX group. ACR 20 and ACR 50 response were 62.3% and 38.7% in the injectable group. In the oral group, the results were 39.2% and 20.3% respectively. In both groups, ACR responses were statistically significant ($p<0.001$). But no significant ACR 70 was achieved during this period – it was 8% in the injectable and 2.5% in the oral MTX group ($p>0.10$). Probably higher dose with longer duration of therapy was needed to achieve this. Side effects with methotrexate therapy occurred irrespective of the dose of MTX which is consistent with other study where side effects were noted in the first eight weeks but nausea was marked at the higher dose. Gastrointestinal side effects were most common in most studies. In my study, common side effects noted in subcutaneous and oral MTX group were nausea (66.2% Vs 83.5%), anorexia (42.6 % Vs 45.5%), Vomiting (10% Vs 15%), dyspepsia (26% Vs 48%), dizziness (41.2% 44.3%), diarrhoea (1.5 % Vs 5.1). In other two studies anorexla and nausea was 52% and 34.92% respectively (Weinstein *et al*. 1985). This variation may be due to use of limited number of cases in all studies. Adverse effects were relatively less in subcutaneous MTX group than that of oral from. The withdrawal rate was 11.5% due to MTX toxicity in the long-term prospective study of MTX for the treatment of RA (Michael *et al*, 1982) [18]. In my study this value was 5.3%. In another study 5.5% cases developed MTX induced pneumonitis but in my study, one patient developed this. This variation is due to limited number of cases in all studies and short period of follow up in the present study. One patient developed renal impairment. MTX treatment discontinued and patient was followed up. No clinically significant haematologic toxic effects were experienced. Alopecia was present in 41% of patients in injectabale MTX group and 26.6% in the oral group. Oral ulcer developed in two patients in injectable group and 3 patients in oral group. Several studies have compared the various modes of MTX administration (Kremer *et al*, 1986) [7]. Oral MTX is rapidly but incompletely absorbed approximately 15% less than intramuscular, although with large individual variability (Furst *et al* 1995). Hamilton and JM Kremer have shown that intramuscular MTX may be more effective than oral from at the dose of 17 ± 3.8 mg due to variable bioavilability (Hamiltons *et al*, 1997) [7]. This difference is due to absorption saturation in oral from. Rozin A *et al*, have revealed that the relapse in the clinical symptoms of RA may be observed after switching from intramuscular to oral administration (Rozin *et al*, 2002) [19]. A open study conducted by Bringham SJ, Buch H, *et al*, comparing oral with intramuscular MTX also showed increase efficacy with fewer adverse effects with intramuscular administration (Bringham *et al*, 2003). Lindsay G, Russel – White C have revealed that self-administration of subcutaneous MTX is more convenient than intramuscular from in the patients of RA (Lindsay *et al*, 2000). In one study, 33 patients with methotrexate therapy at the doses of 7.5 – 15 mg/week. At the end of 24 weeks, 72% had moderate to marked clinically significant improvement (Erickson *et al*, 1995). In my study, at the end of 20 weeks significant improvement occurred as evidenced by ACR response and it was more in subcutaneous injectable group. In this study, through 21.9 and 13 percent of patients had history of taking DMARDs and corticosteroid respectively we did not permit concurrent therapy with systemic corticosteroid>10mg/day and local

steroid injection but permitted the use of NSAIDs both as regular therapy and on an as needed basis. We have frequently used the term 'Improvement' rather than 'remission' since not all patients were observed for continued full improvement over a long period of time. Willkens *et al*, have shown that baseline morning stiffness declined from 122 minutes to 45.5 ±15.4 minutes after 24 weeks of MTX therapy (Willkens et at, 1992). In my study, this value was 2.1 ± 1.5 hours initially and was reduced to 0.4 ± 0.8 hours after 20 weeks of MTX treatment (P<0.001). In a study they conclude that weekly low dose MTX therapy is efficacious for refractory RA. The present study also shown there were significant reduction of pain (VAS) 4.2± 1.8 to 2.2±1.5 (P<0.001) in injectable group and 4.4±1.7 to 3.4 ± 1.7 (P<0.001) in the oral group. Tender joint count reduced from 36.5 ± 15.9 to 18.5±11.5 (P<0.001) in injectable group and 31.5±17.1 to 24.6 ± 15.5 (P<0.001) in oral group. Swollel joint count reduced from 12.9 ± 10.1 to 4.5 ± 4.6 (P<0.001) in injectable group and 10.9 ± 9 to 7.2 ± 8.5 (P<0.001) in the oral group. There were also reduction in the morning stiffness, patient's and physician's global assessment of disease activity and HAQ. A significant reduction in prednisolone and NSAIDs was achieved. Another study done by (Weinblatt ME. *Et al* 1991) with 30 patients of active RA despite therapy with 17±4 mg/week MTX. All patients were given leflunomide 10-20 mg/day. After 9 months of treatment, 57% of patients met ACR 20 response criteria and only 2 patients (6.7%) met ACR criteria for remission (Weinblatt *et al*, 1998). In my study, MTX mono therapy 25 mg/week gave 62.3% ACR 20 response in subcutaneous injectable MTX group and 39.2 % in the oral group (P<0.01). No ACR remission criteria met by any patient in my study. Probably higher does and or combination with other DMARD eg leflunomide will be needed to achieve this. 7 patients withdrew from the study. In my study, this value was less (14 out of 154). This discrepancy was due to additive toxic effect of leflunomide. A study done by Hoekstra M *et al* with 15 patients of RA to determine the bio- availability of higher dose of MTX (≥25mg/week) in RA patients. The mean bio-availability after oral MTX was 0.64 (0.21-0.96) compared to subcutaneous administration and they recommend the use of parenteral (subcutaneous) MTX at doses of ≥25 mg/week for better efficacy (Hoekstra *et al*, 2004). Determination of bio-availability of MTX was beyond the scope of this study but we found better efficacy and more patient compliance of subcutaneously administered MTX in comparison to equal dose of oral MTX.

6. Limitations of the study

The limitation of this study is that firstly, this trial was conducted in the tertiary center. So,patients usually having of severe disease, receiving multiple drugs irregularly often with steroid. Secondly, patients of nearby area with good communication having ability to attend the trial regularly were enrolled. Thus, patients from distal area and having financial constrains were excluded. Thirdly, interruption in the availability of injectable MTX was another remarkable limitation. Lastly, strict strength in the protocol was interrupted possibly due to poor acknowledgement of protocol and financial constraints.

7. Conclusion and recommendations

From the present study, it may be concluded that MTX is effective in controlling disease activity in rheumatoid arthritis. Subcutaneously administered MTX is more effective than that of oral form. Future trials including bigger samples and more vigorous study design will probably determine the disease controlling ability of subcutaneous MTX before considering biological agent (eg, rituximab), which are too costly. A long-term study with larger samples has to be carried out with injectable MTX for the treatment of RA to conclude its exact effectiveness.

8. References

1. Bingham-SJ, Buch *et al*. Parenteral methotrexate should be given before biological therapy. Rheumatology. 2003; 42:1009-10
2. Das Bhusan Bidhu. Prevalence of Rheumatic disorders in an urban population of Dhaka city, MD thesis, Dept. of Medicine, BSMMU, Dhaka, Bangladesh, 2002.
3. Erickson AR, vogeigesang SA; usefulness the American College Rheumatology recommendation for liver biopsy in methotrexate treated rheumatoid arthritis patient.
4. Arthritis Rheum, 1995, 38:115.
5. Freeman–Narrod M, Gerstley BJ, Engstrom PF. Comparison of serum concentration of methotrexate after various roules of administration. Cancer. 1975; 36:1619-24.
6. Furst DE. Practical clinical pharmacology and drug interactions of low dose methotrexate therapy in rheumatoid arthritis. Br J Rheumatol. 1995; 34:20-50.
7. Hamilton RA, Kremer JM. Why intramuscular methotrexate may be more efficacious than oral dosing in patients with rheumatoid arthritis. Br J Rheumatol. 1997; 36:86-90.
8. Herman RA, veng-Pederson P, Hoffman J, Kocknke R, Furst DE, Pharmacokinetics of low dose methotrexate in rheumatoid arthritis patients. J pharn Sci. 1989; 78:165-71.
9. Hornung N, Ellingsen T, Stengaard – Pedersen K. Poulsen JH. Folate homocysteine, and cobalamin status in patients with rheumatoid arthritis treated with methotrexate, and the effect of low dose folic acid supplement. J rheumatol. 2004; 31:2374-81.
10. Hoeckstra M, Haagsma C, Neef C, Proost J, Knuif A, Van de Laar M, *et al*. Bioavaliablity of higher dose of methotrexate comparing oral subcutaneous administration in patients with RA. J Rheumatol. 2004; 31(4):645-8.
11. Jundt JW, Browne BA, Fiocco GP, Steele AD, Mock D. A comparison of low dose methotrexate bioavailability: oral solution, oral tablet, subcutaneous and intra-muscular dosing. J Rheumatol. 1993; 20:1845-9.
12. Khanna D. park GS Paulus HE. Simpson K M. Elashoff D. Cohen SB. *Et al*. Reduction of the efficacy of methotrexate by the use of folic acid: post hoc analysis from two randomized controlled studies. Arthritis Rheum. 2005; 52:3030-8.
13. Kinder AJ. Hassel AB. Brand J. Brownfield A. Grove M. Shadforth MF. The treatment of inflammatory arthritis with methotrexate in clinical practice: treatment duration and incidence of adverse drug reactions. Rheumatology (Oxford) 2005:44:61-6.
14. Kingdom. Br J Rheumatol. 1994; 33:735-9.
15. Thomson RN, Watts C, Edelman J, Russel AS. A controlled to centre trial of parenteral methotrexate

therapy for refractory rheumatoid arthritis. J Rheumatol. 1984; 11(6):760-63.
16. Kremer JM, Lee JK. The Safety and efficacy of the use of methotrexate in the long-term therapy for rheumatoid arthritis. Arth & Rheum, 1986, 822-32.
17. Lindsay G, Russel- White C, Sandhu S, Livingstone J. Self-administration of subacutaneous methotrexate: a survey of patients benefit and convenience. Rheumatology. 2000; 39(suppl):85.
18. Michaels RM, Nashel DJ, Leonard A, Silwinski AJ, Weekly intravenous methotrexate in the treatment of rheumatoid arthritis. Arthritis & Rheum. 1982; 25:339-41.
19. Rozin A, Schapira D, Balbbin- Gurman, *et al*. Relapse of rheumatoid arththritis after substitution of oral for parenteral administration of methotrexate. Ann Rheum Dis. 2002; 61:756-7.
20. Symmos DP, Barrett EM, Blackhead CR, Scot DG, Silman AJ. The incidence of rheumatoid arthritis in the United
21. Uhlig T, Kvien TK, Glennas A, Smedstad LM, Forre O. The incidence and severity of rheumatoid arthritis: results from a county register in Oslo, Norway. J Rheumatol. 1998; 25:1078-84.
22. Van Ede AE. Laan RE, Rood MJ. Huizinga TW. van de Laar MA. van Denderen CJ. *Et al*. Effect of folic or methotrexate in rheumatoid tation on the toxicity and efficacy of methotrexate in rheumatoid arthritis: a forty-eight-week, multicener, randomized, double-blind, placebo-controlled study. Arthritis: Rheum. 2001; 44:1515-24.
23. Weinblatt ME, Coblyn JS, Fox DA, Frasser PA, *et al*. Efficacy of low dose methotrexate in rheumatoid arthritis. N Engl J Med. 1985; 312:818-22.
24. Weinstein A, Marlowes, Korns, Faronhar F. Low dose methrotrexate in the treatment of rheumatoid arthritis. Long term observation. Am J med. 1985; 79:331-37.
25. Weinblatt ME, Kaplan H, Germain BF, *et al*. Methotrexate in Rheumatoid Arthritis; Effects of disease activity in a multicenter prospective study. J Rheumatol. 1991; 18:334-38.
26. Weinblatt ME, Maler AL, Frasser PA, Colyn JS. Long term prospective study of methotrexate i rheumatoid arthritis. Conclusions after 132 months of therapy. J Rheumatol. 1998; 25:328-42.
27. Willkens RF, Urowitz MB, Stablein DM *et al*. Comparison of azathioprine, methotrexate and combination of both in the treatment of rheumatoid arthritis. Arthritis & Rheum. 1992; 35:849-56.
28. Zink A, Braun J, Listing J, Wollenhaupt J, and the German Collaborative Arthritis Centers. Disability and handicap in rheumatoid arthritis and ankylosing spondylitis---- results from the German rheumatological database. J Rheumatol. 2000; 27:613-22
29. Zink A, Listing J, Niewerth M, Zeidler H. for the German Collaborative Arthritis Centers. The national database pf the German Collaborative Arthritis centers. II. Treatment of patients with rheumatoid arthritis. Ann Rheum Dis. 2001; 60:207-13.