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RESEARCH PAPER

Efficacy and Safety of Subcutaneous Methotrexate Compared to Oral Methotrexate Administration in Patients with Active Rheumatoid Arthritis: an Open Level Randomized Clinical Trial

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Abstract

Background: Methotrexate (MTX) is the corner stone in management of rheumatoid arthritis (RA), but its limited use as oral formulation is frequently due to gastrointestinal intolerance, variable absorption and bioavailability. Subcutaneous (SC) MTX may offer better efficacy and tolerability.

Objective: To compare the efficacy and safety of subcutaneous (SC) injection versus oral methotrexate (MTX) in patients suffering from active rheumatoid arthritis (RA).

Methods: This open labeled randomized clinical trial was conducted on 90 patients at the department of rheumatology in Bangladesh medical university (BMU) during the period from January 2013 to October 2014. In phase 1, MTX was given 10 mg orally, weekly and the dose of MTX was increased to 15 mg/week after four weeks. All patients were followed up for 8 weeks from enrollment. Six patients were excluded from 2nd page of the study due to loss of follow up and adverse event In phase 2, patients were randomized in two groups. One group received 20 mg MTX subcutaneously weekly (n=40) and the other group received the same dose of MTX orally (n=44). After another 8 weeks the dose of MTX was increased to 25 mg/week. Final follow up was given at 16 weeks after randomization. ACR20, ACR50 and ACR70 response criteria was used to see the efficacy of MTX. Safety and adverse events were also recorded.

Results: At the end of phase 1, ACR 20 response was observed in 20% patients and a significant improvement was noticed across multiple disease activity parameters ($p < 0.05$) after 8 weeks. After phase 2 follow up(16 weeks), ACR 20 & ACR 50 response were 100% & 45% , respectively in subcutaneous group and 95.5% and 29.5%, respectively, in oral group, difference was statistically significant (P value of <0.01 & <0.05). None of the patient achieved ACR70 response. The measures of disease activity (except swollen joint count) like tender joint counts, pain VAS, patient and physician global scores, HAQ, ESR, and DAS28 were significantly improved in the SC group ($p < 0.05$). Gastrointestinal upset were more in oral group like nausea occurred in 65% (SC) vs. 87% (oral), anorexia in 45% vs. 73%, and dizziness in 43% vs. 82% ($p < 0.01$). One patient discontinued oral MTX due to intolerance.

Conclusion: Subcutaneous route was safe and effective than oral methotrexate. Subcutaneous MTX may be a preferable option in patients with inadequate response or intolerance to oral MTX in patient with active RA.

Keywords: Efficacy & safety of methotrexate, oral methotrexate, subcutaneous methotrexate, rheumatoid arthritis.

Introduction

The prevalence of Rheumatoid arthritis (RA) is approximately 0.5-1%[1]. It is an autoimmune chronic inflammatory disease predominantly affects the woman[2] and some have genetic predisposition[3]. The disease burden is increased for its deforming character over the last decade, and it can be minimized by early effective treatment. In lower socio-economic countries like Bangladesh, patients cannot afford biologics and target synthetics. Methotrexate is the anchor drug for rheumatoid arthritis[5, 6] and it is cheap and widely available. But, it is not free from side effects. The most common side effects are gastrointestinal such as mucosal ulcer, nausea, loss of appetite and vomiting[7]. These

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side effects are usually common in oral MTX. Subcutaneous MTX may replace oral MTX to overcome these side effects [8]. Bioavailability of oral MTX is variable at higher doses which is approximately two thirds of the subcutaneous administration [9]. The efficacy and safety of subcutaneous MTX have been proven in different studies[10]. In some studies, remission with subcutaneous route was better in early RA.[10, 11] As MTX monotherapy has a 59% success rate with 33% remissions [12], so, that continuing MTX is important. The anti-inflammatory activity of MTX depends upon adenosine release, transmethylation reaction inhibition, uncoupling of nitric oxide synthase and accumulation of polyamines reduction. Intracellular polyglutamation is important for MTX conversion to MTX polyglutamates (MTX-PGs). The subcutaneous MTX increases bioavailability and higher MTX-PG especially the long chain[13] in RBCs. American college of rheumatology (ACR) proposed to switch to subcutaneous MTX[14] for the patient who is intolerant to oral MTX. It is a better option for those who cannot afford biologics or newer target synthetics or Biologics in lower socio-economic countries.

Methotrexate is an old drug with unchanged demand for the treatment of RA. The use of MTX alone or in combination in severe RA showed improvement [in] 80% cases. [17]. MTX is the anchor drug for RA treatment advocated by all past and recent guidelines [by] ACR and EULAR and MTX should be included in the first line treatment strategy.[18, 19] It is important to ensure the optimum use of MTX by its dose and duration. The most common cause of discontinuation of MTX is inadequate response and gastrointestinal side effects.[20] A study on MTX showed that the bioavailability of oral MTX is lower than that of SC MTX. [10] There is no study done in our population to see these effects. So, the aim of this study was to observe the efficacy and safety of injectable MTX in RA patient.

Materials and Methods

This is an open-label randomized clinical trial that was conducted in two phases. A total of 90 patients were enrolled in this study in the phase-1 of the study. Patients who fulfilled the American college of rheumatology (ACR) 1987 revised criteria[15] were recruited from the outpatients and inpatients department of rheumatology, Bangladesh Medical University.

Patients were eligible for enrollment if they were 18-70 years of age and presented with active disease[16] defined with the presence of at least three of the followings: (a) six or more tender joint counts, (b) three or more swollen joint count (c) ESR 28 mm or more in first hour (d) morning stiffness more than 1 hour. Systemic corticosteroids were permitted if the dosages were stable d" 10 mg for at least 2 months before enrollment. Patients treated with other DMARDs had to be discontinued for 2 weeks before enrollment. The dose of the steroid was not be changed during this study period. Patients having other rheumatologic disorders, pregnancy, lactating mother and women with child bearing potential failing to confirm adequate contraception, presence of concurrent serious medical illness e.g., chronic infection, neoplastic disease, evidence of organ damage such as serum creatinine ³ 1.5 mg /dl, SGPT (ALT) more than twice of normal value, hematological disorder including, leucocyte count d" 3,000/cu mm, platelet count d" 100,000/cu mm and change in oral steroid or administration of intra-articular injection in the last two months before enrollment or plan of elective surgery within six months were excluded from the study.

The sample size was calculated for comparison of two independent proportions. Based on previous studies, the expected ACR20 response rate was assumed to be 50% in patients receiving subcutaneous methotrexate and 20% in those receiving oral methotrexate. Considering a two-sided significance level of 5% and a study power of 85%, the required sample size was calculated using the formula for comparison of two proportions n= (Zá/2+Zâ)2[p1(1"p1)+p2(1"p2)]/(p1"p2)2 ;where p1 and p2 represent the anticipated proportions in the two groups, Zá/2 corresponds to the standard normal deviate at 5% level of significance (1.96), and Zâ corresponds to the standard normal deviate at 85% power (1.04). The calculated minimum sample size was 41 participants in each group. Finally, a total of 84 patients were included in the study to ensure adequate statistical power.

The study was conducted in 2 (two) phases. In phase 1 of the study 90 patient were included who had fulfilled the inclusion criteria. All the patient was given 10 mg MTX orally. The dose of MTX was increased by 5 mg after 4 weeks. All patients were followed up at 8 weeks from enrollment, and the outcome measures were assessed to find out the tolerability of the drug and oral efficacy. Five of the patients have failed to attend regular follow up and 1(one) patient developed herpes zoster with gluteal abscess. These 6 (six) patients were not included in the second phase of the study. In phase 2, 84 patients were randomized into two groups.

Eligible patients were randomly assigned to receive either oral methotrexate or subcutaneous methotrexate in a 1:1 ratio. A computer-generated randomization sequence was prepared using block randomization with a block size of four to maintain balance between the two treatment groups. Allocation concealment was ensured using sequentially numbered opaque sealed envelopes prepared by an independent investigator. After obtaining informed consent, each participant was assigned to the treatment group according to the next envelope in sequence. The study was conducted as an open-label clinical trial.

One group received 20 mg MTX/week, orally (n=44) and the other group received the 20 mg of MTX, subcutaneously (n=40). After 8 weeks from the randomization, the dose of MTX was increased to 25 mg. So, 25 mg MTX was given to each group for 16 weeks, and the final follow-up was done for assessment of efficacy and safety.

Both clinical and laboratory outcome measures were recorded in the RA clinic in the outpatient of department of rheumatology as per schedule in both phase of the study. In both groups, 1(one) relative was registered to monitor the medication and either patient or 1(one) relative were trained to give subcuteneous methotrexate at home. Beside regular clinic follow up patient were contacted for any adverse effects over telephone time to time. Meticulous history taking, physical examination, and laboratory investigations, total tender and swollen joint count, patients' and physicians' global assessment, and health assessment questionnaire were recorded during every visit during each follow up. The baseline laboratory investigations, like complete blood count (CBC), urine

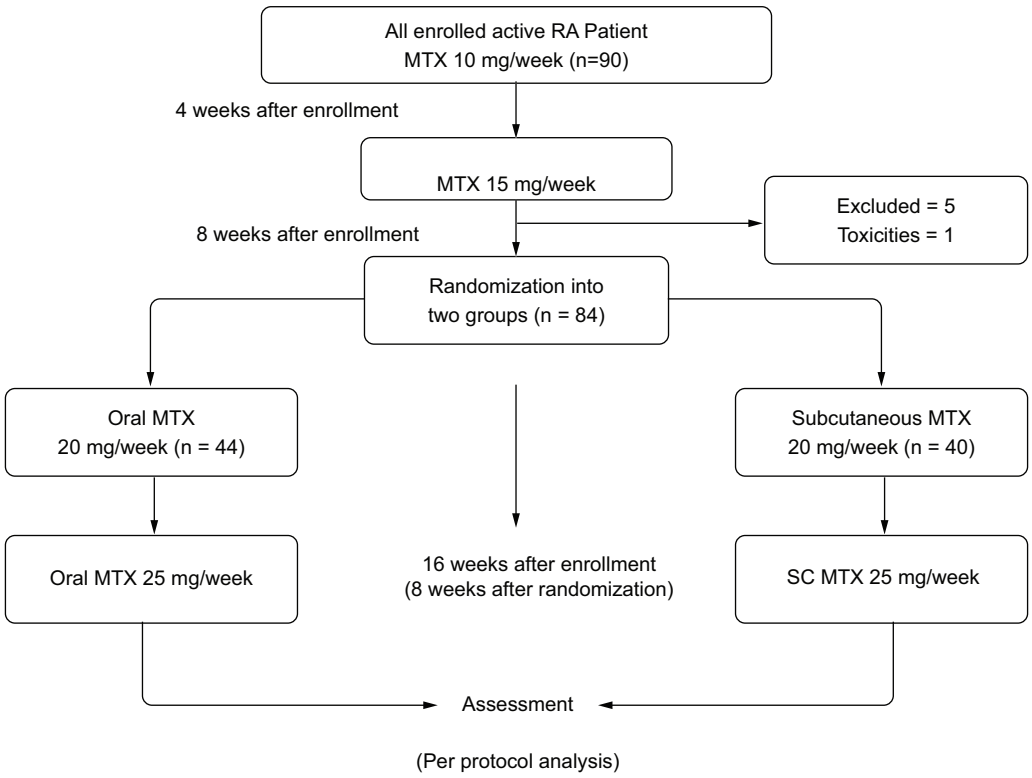

Figure 1: Flow chart for study procedure

for routine examination, SGPT, serum creatinine, rheumatoid factor, Rose-Waaler test, and C-reactive protein (CRP) were done in each visit. In some of the patient needed more detailed investigations e.g.- blood sugar, electrocardiogram(ECG), X-ray chest P/A view, computed tomography (CT) scan of chest where indicated. Patients were withdrawn temporarily from the study, if WBC count was reduced but >3,000/ cu mm, neutrophils count was < 2000/cu mm and platelet count was <150000/cu mm, SGPT was > 2 times the upper limit of normal, serum creatinine levels was > 25% over baseline levels. The patients were permanently withdrawn from the study if WBC d" 3,000/ cu mm, neutrophil d" 2,00/cu mm, platelet count d" 100,000/cu mm, SGPT ³ 3 times the upper limit of normal, serum creatinine ³ 50% rise over base line. The clinical parameters for evaluation were; tender joint count(TJC) and swollen joint count(SJC), pain assessed by VAS 0 -10 cm, patient's global assessment of disease activity score on 0-10 scale, physician's global assessment of disease activity score on 0-10 scale and Bengali HAQ (0-3).

The each follow up include above mentioned clinical and biochemical parameters. The efficacy was measured by ACR response criteria and DAS28 score. Improvement in rheumatoid arthritis was determined by ACR 20 and ACR 50 criteria.[3,16] In ACR 20 criteria required 20% improvement, Which includes 1) 20% decrease in tender joint count, 2) 20% decrease in swollen joint count, 3) 20% decrease in three of the following five categories (a) patient's assessment of pain(VAS,0-10) (b) patient's global assessment of disease activity (c) physician's global assessment of disease activity (d) patients assessed disability (HAQ DI) (e) acute phase reactant (ESR and/or CRP). The same way was the tool for calculation for ACR 50 and ACR70 but 50% and 70%, respectively, improvement criteria were required. The DAS28 score was also compared between two groups to see the efficacy of MTX, which measures the activity of rheumatoid arthritis (RA) by evaluating 28 specific joints for tenderness and swelling, along with blood inflammation markers (ESR or CRP) and patient global assessment. Scores typically range from 0 to 9.4, with lower scores indicating better control.[31] Tolerability was also assessed for both SC and oral MTX at base line of the study and during each follow up period. Statistical analysis was done by using IBM SPSS Statistics for Windows, Version 22.0. Mean of all quantitative variables were measured. Comparison of quantitative variables among the group and in between groups was measured by Paired t- test. P value of less than 0.05 was considered as significant. Per protocol analysis was applied for assessing the efficacy of MTX.

Results

A total of 90 patients were enrolled in this study in the phase-1 of the study. A total 6(six) patient were dropped as 5(five) of the patients have failed to attend regular follow up and 1(one) patient developed herpes zoster with gluteal abscess. So, finally 84 participnt were included for analysis. The mean age of all subjects was 40.8 ±12.1 years. Female to male ratio was 13:1. All patients were naive to DMARDS, steroids (Table I).

The disease activity was very high at the base line (DAS28 ESR-7.4±5.0). There was a statistically significant improvement all parameter of disease activity ($p<0.05$) except swollen joint count ($p=0.059$) and DAS 28ESR score($p=0.231$) after 15 mg oral MTX therapy for 8 weeks. The comparative value of parameters at base line versus after 8 weeks of oral MTX therapy were; tender joint count (28.26 ± 10.96 vs. 20.61 ± 9.37, $p=0.001$), swollen joint count(5.95 ± 5.83 vs. 4.35 ± 5.04,$p=0.059$), morning stiffness in hours(2.52 ± 0.60 vs1.67 ± 0.57,$p=0.001$), pain visual analogue scale(6.02 ± 1.11 vs4.32 ± 0.92, $p=0.001$) , patient's global assessment of disease activity(5.95 ± 1.13 vs4.28 ± 0.92, $p=0.001$), physicians global assessment of disease activity(5.79 ± 1.23 vs. 4.08 ± 1.13, $p=0.001$), Erythrocyte Sedimentation Rate(73.57 ± 28.07 vs. 61.68 ± 26.8 , $p=0.006$), HAQ DI(2.1±0.3vs 1.9±0.2, $p=0.000$), DAS28 ESR(7.4±5.0 vs. 6.5±4.7, $p=0.231$) (table-II).

Table I: Baseline demographic and clinical characteristics of the study patients at enrollment (N=84) characteristics

Demographic characteristics	Mean ± ?SD	n (%)
Age in year	40.8 (±12.1)	
Sex		
Male		6 (7.1)
Female		78 (92.9)

After completion of 8 weeks of treatment with MTX 10mg/week ACR 20 response was observed in 20% patients. But, significant reduction of DAS28 score was not achieved after oral 15 mg MTX (Table II).

At the end of phase 1, Most of the patients tolerated MTX 10 mg/week with few side effects like nausea (95.5%, dizziness (88.09%), headache (67.9%), weakness (44.4%), vomiting (22.61%), abdominal pain (8.33%), and oral ulcer (2.3%) (Table III). All these adverse effects were very transient and were managed conservatively.

At the end of 8 weeks of phase I, six patients dropped out from the study. The remaining patients (n=84) were randomized into subcutaneous MTX group (n=40) and oral MTX group (n=44). In the injectable group (n=40), the mean age was 44.78±10.18 years. The mean duration of disease was 4.9yrs (± 5.9). In the oral group (n=44), the average age was 46.82±12.91 years. The average duration of disease was 3.5yrs (±3.9). The differences between the values of the baseline characteristics of both oral and injectable groups were not statistically significant at baseline (Table IV).

Disease activity and quality of life was significantly improved at 16 weeks of follow up visit. There was a statistically significant improvement of all parameter in injectable MTX group compared to oral group($p<0.05$). The tender joint count was 15±8.34 vs 8.4±4.13($p<0.00$), swollen joint count was 2.82 ± 3.67 vs 1.53 ± 2.08($p<o.054$), morning stiffness in hours 0.52±0.59 vs 0.3±0.47 ($p<0.064$), pain by visual analogue scale was 3.00±0.96 vs 2.5±0.91($p<0.017$), patient's global assessment of disease activity was 3.05±0.89 vs2.47±0.86($p<0.003$), physician's global assessment of disease activity was 2.84±1.05 vs1.88±0.97($p<0.000$), erythrocyte sedimentation rate was 49.57±17.57vs34.68±14.75 ($p<0.000$), HAQ was 1.4±0.2 vs 1.1±0.15 ($p<0.000$), DAS28 score was 5.8±1.7vs 4.5±1.2 ($p<0.000$), oral versus injectable MTX ,respectively (Table VI).

ACR 20 response was achieved by 100% of patients in injectable group and 95.5% in oral group ($P < 0.01$), ACR 50 response was achieved by 57.5% in injectable group and 29.54% in oral group ($P < 0.05$) . The ACR 70 response was achieved by none of the patient in both injectable and in oral group (Table VII).

Frequently observed adverse events in injectable group were nausea 26 (65%), anorexia 18 (45%), dizziness 17 (43%), headache 12 (30%). In oral group most frequently observed adverse events were nausea 39 (87%), anorexia 32 (73%), dizziness 36 (82%), headache 19 (43%). Nausea, anorexia and dizziness were observed more in oral group compared injectable MTX and their differences were statistically significant($p< 0.05\%$) (Table VIII).

Discussion

This open-label randomized clinical trial was conducted to determine whether the efficacy and safety of parenteral methotrexate (MTX) differs from

Table II: Comparison of disease status at baseline and at the end of 8 weeks after oral MTX (N =84)

Parameters	Baseline Mean±SD	After 8 weeks Mean±SD	Reduction	*p-value
Tender Joint Count	28.26±10.96	20.61 ± 9.37	7.65±1.59	0.001
Swollen Joint Count	5.95±5.83	4.35 ± 5.04	1.6±0.79	0.059
Morning Stiffness (Hours)	2.52±0.60	1.67 ± 0.57	0.95±0.03	0.001
Pain (Visual Analogue Scale)	6.02±1.11	4.32 ± 0.92	1.70±0.19	0.001
Patient's Global Assessment of Disease Activity	5.95±1.13	4.28 ± 0.95	1.67±0.18	0.001
Physicians Global Assessment of Disease Activity	5.79±1.23	4.08 ± 1.13	1.71±0.10	0.001
Erythrocyte Sedimentation Rate	73.57±28.07	61.68±26.8	11.89±1.27	0.00
HAQ DI	2.1±0.3	1.9±0.2	0.2±0.1	0.000
DAS28 ESR	7.4±5.0	6.5±4.7	0.9±0.3	0.231

*t test was done to measure the level of significance. Values are the mean ± SD (SD = Standard Deviation)

Table III: Adverse effects in phase 1 after treating with oral MTX (N= 84)

Adverse effects	Frequency (n)	Percentage (%)
Nausea	80	95.23%
dizziness	74	88.09%
Headache	57	67.9%
Weakness	34	44.4%
Vomiting	19	22.61%
Abdominal pain	7	8.33%
Oral ulcer	2	2.3%

Table IV: Baseline demographic and clinical characteristics of patients in injectable and oral group at randomization (N=84)

Demographic characteristics	Oral (%) (n=44)	Injectable (%) (n=40)	*p-value
Age in year	46.82 ± 12.91	44.78 ± 10.18	0.426
Sex			0.015#
Male	6 (13.6)	0 (0.0)	
Female	38 (86.4)	40 (100.0)	
Clinical characteristics			
Tender Joint Count	29.91±11.38	26.45 ±10.33	0.150
Swollen Joint Count	7.18 ± 6.89	4.60 ± 4.08	0.042
Morning Stiffness (Hours)	2.52 ± 0.505	2.53 ± 0.506	0.984
Pain (Visual Analogue Scale)	6.20 ± 1.07	5.83 ± 1.13	0.118
Patient's Global Assessment of Disease Activity	6.20 ± 1.07	5.66 ± 1.15	0.028
Physician's Global Assessment of Disease Activity	5.91 ± 1.22	5.65 ± 1.25	0.339
Erythrocyte Sedimentation Rate	80.18 ± 25.60	66.30 ± 29.15	0.023
HAQ	2.2±0.35	2.1±0.3	0.048
DAS28 ESR	7.6±5.0	7.1±4.9	0.645

*t test was done to measure the level of significance. Values are the mean ± SD, SD = Standard

Table V: Comparison between oral group and injectable group at the end of 16 weeks (N=84)

	Final visit			
	Oral group (n=44) (Mean ± SD)	Injectable group (n=40) (Mean ± SD)	Difference between two groups	*p-value
Tender Joint Count	15±8.34	8.4±4.13	6.6±4.21	0.000
Swollen Joint Count	2.82 ± 3.67	1.53 ± 2.08	1.29±1.59	0.054
Morning Stiffness (Hours)	0.52±0.59	0.3±0.47	0.49±0.12	0.064
Pain (Visual Analogue Scale)	3.00±0.96	2.5±0.91	0.50±0.05	0.017
Patient's Global Assessment of Disease Activity	3.05±0.89	2.47±0.86	0.58±0.03	0.003
Physician's Global Assessment of Disease Activity	2.84±1.05	1.88±0.97	0.96±0.08	0.000
Erythrocyte Sedimentation Rate	49.57±17.57	34.68±14.75	14.89±2.82	0.000
HAQ	1.4±0.2	1.1±0.15	0.3±0.05	0.000
DAS28 ESR	5.8±1.7	4.5±1.2	1.3±0.5	0.000

*t test was done to measure the level of significance. Values are the mean ± SD (SD = Standard Deviation)
#Chi square test

Table VIII: ACR response at the end of 16 weeks (final visit)

Parameters	Oral (n=44) n (%)	Injectable (n=40) n (%)	Total n (%)	p value
ACR20	42 (95.5)	40 (100.0)	82 (97.6)	<0.01
ACR50	13 (29.5)	18 (45.0)	31 (36.9)	<0.05
ACR70	0 (0.0)	0 (0.0)	0 (0.0)	

*Chi square test, ACR = American College of Rheumatology

Table VIII: Comparison of adverse effects between Injectable and oral MTX group in phase 2 (N=84)

Category label	Injectable group n = 40	Oral group n = 44	P-Value*
Nausea	26 (65%)	39 (87%)	0.009
Anorexia	18 (45%)	32 (73%)	0.009
Dizziness	17 (43%)	36 (82%)	0.000
Headache	12 (30%)	19 (43%)	0.211

*Chi-Square test

oral administration in patients with rheumatoid arthritis (RA). The study was done in 2(two) phases, the initial phase-1(N=90) included administration of oral MTX to observe its efficacy, tolerability and drug adherence. Six patients were excluded after the initial run in period of 8 weeks (phase-1). Then 84 patients were randomized into two groups: oral group (n=44) and injectable MTX group (n=40). In the injectable group (n=40), the average age was 44.78±10.18 years. The average duration of disease was 4.9yrs (± 5.9). 62.5 percent patients were seropositive. In the oral group (n=44), the average age was 46.82±12.91 years. The average duration of disease was 3.5yrs (±3.9). During the initial 8-week of phase 1 period, the MTX dose was escalated to 15 mg orally after the first four weeks, which is consistent with common RA dosing strategies. At the end of 8 weeks following enrollment, significant improvement was noted across all clinical outcome measures with oral MTX. Though there was few adverse event in phase-1 but were managed conservatively only 1 patient had to discontinue due to toxicity. In phase-2 of the study, subcutaneous MTX group showed significant improvement ACR 20 and ACR 50 response criteria compared to oral MTX with a less gastrointestinal and other adverse effect profile. But neither group achieved ACR70 response criteria.

In phase-1 of the study, gastrointestinal (GI) adverse effects were frequently reported, with nausea (95.23%), vomiting (22.61%), and abdominal pain (8.33%) being the most common. Similar gastrointestinal intolerance has been documented in previous work, including Braun et al., who reported GI side effects in 75% of patients receiving MTX therapy.[20,21] Other studies have also demonstrated a high rate of gastrointestinal reactions associated with oral MTX administration.[22,23]

Additional adverse effects observed in this phase-1 cohort included dizziness (88.09%), headache (67.9%), weakness (44.4%), and oral ulcers (2.3%). Despite these events, most patients tolerated MTX well, with only one patient discontinuing therapy due to severe gastrointestinal intolerance. Overall, six patients discontinued from the study: one due to toxicities (gluteal abscess and herpes zoster), and five due to irregular follow-up. This pattern is comparable to the findings of Braun et al., who reported dropout in three patients—one due to a gluteal abscess associated with herpes zoster infection, and two due to loss to follow-up.[19] The adverse event profile observed in this study aligns closely with previously published evidence and underscores the well-recognized limitations of oral MTX, especially gastrointestinal intolerance. These findings further support the clinical rationale for considering parenteral MTX in patients who experience significant side effects or inadequate response with oral formulations.

Both the treatment group has showed discernable improvement in term of ACR response criteria but magnitude of response was higher injectable MTX group. The ACR 20 response was achieved by all of patients in injectable group compared to 95.5% in oral MTX group which suggest that both route were effective for clinical improvement. This is consistent with the other studies that early or active rheumatoid arthritis responds to DMARDS with a lower percentage of improvement.[28]

But a notable response difference was found in ACR 50 criteria. The injectable group achieved ACR 50 response in 45% compared to 29.5% in oral group with a statistically significant difference. This is indicating subcutaneous route was more effective the oral MTX in controlling the disease activity. The factors that may have contributed to this may due to increased bioavailability of injectable formulation, less variable absorption and increased drug adherence due less gastro-intestinal irritations. The same kind of superior efficacy was observed for injectable MTX in other studies in case of moderate to severe RA.[20, 29]

Whereas , none of the patients in both group achieved an ACR 70 response. Achievement of ACR 70 in routine

clinical practice is often lower than in randomized controlled trials, especially in patients with long-standing disease, comorbid conditions, or suboptimal dosing.[30] It is possible that the duration of follow-up, baseline disease activity, or medication dose in this study may not have been sufficient to achieve the highest response threshold.

The frequently observed adverse events in phase 2; in injectable group were nausea, anorexia, dizziness, headache. In oral group most frequently observed adverse events were nausea, anorexia, dizziness, and headache. The adverse event was significantly higher in oral group. Observations from different studies suggest that initiation of MTX therapy by the SC route is superior to initiation of MTX therapy by the oral route and well tolerated. [23-25] The previous studies have already suggested that in patients with poor compliance, inadequate effectiveness and gastrointestinal side effects of MTX, a switch from the oral administration to IM or SC administration should be considered.[25] The patients have been shown to benefit from parenteral administration of MTX, particularly with regard to the number of gastrointestinal AEs.[26]

Investigators in Canada and the UK have shown that changing from oral to parenteral administration of MTX in patients with an inadequate response is also advantageous for cost-effectiveness reasons, since subsequent therapy with biologic agents can be avoided or delayed.[26] Nevertheless, patients who are unresponsive to MTX are suitable candidates for therapy with biologic agents.[27] The cost of oral versus SC administration of MTX differs from country to country, and no direct socioeconomic comparison has yet been published. One recent study showed that SC MTX therapy was begun at the widely used starting dosage of 15 mg/week, ACR 20 response rates as high as 80% were achievable. They also suggest that initiation of MTX therapy by the SC route, using a possible dosage of 15 mg/week for a period of at least 24 weeks (including a possible dosage increase) is superior to initiation of MTX therapy by the oral route, since the ACR 20 response rate of 60% which is typically obtained with oral MTX was increased to 78% in patients taking SC MTX.[20]

This study had several limitations. Most likely more severe form of RA patients were enrolled as this study was conducted in a tertiary care hospital of Bangladesh. Most of them received diverse medications including steroid and also provided poor records of past medications. Enrolled patient were mostly from nearby area of the center. Lack of overcoming the investigator biasness was another limitation of this study. Laboratory tests were done from different center of different standards.

One of the strengths of this study was a well-defined protocol where patient had a phase-1 for run in period to check the tolerability and adherence of the patient then they were randomized. Patient randomization was done following the random number table. Finally, the dropout rate was markedly low. There was no drop out in phase 2.

Conclusions

During the study it is evident that parenteral administration of MTX is superior to oral MTX in respect of efficacy, adverse effects and toxicities encountered by the treated patients. As the study is carried out among a small group of patients, further broad based study is required for a definite conclusive inference on the issue. Future trials including bigger samples, long term and more vigorous study design will probably determine the disease controlling ability of subcutaneous MTX and its tolerability before considering biological agent, which are too costly.

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