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EVALUATION OF EFFICACY AND SAFETY OF METHOTREXATE IN RHEUMATOID ARTHRITIS PATIENTS

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ABSTRACT

Objective: To study efficacy and safety of methotrexate treatment alone prescribed in treatment of Rheumatoid arthritis. **Methods:** In prospective observational study, 38 patients with active Rheumatoid Arthritis (RA) were randomized to methotrexate (dose 15mg/week). After 8 weeks of treatment period, safety and efficacy parameters were observed in all the patients. The primary efficacy parameters were C reactive protein (CRP), Erythrocyte Sedimentation Rate (ESR), tender and swollen joint count, and subject assessment of pain, Subject and *Physician global assessment of disease activity*, Health assessment questionnaire and secondary efficacy parameters were Morning stiffness and rheumatoid Factor. American College of Rheumatology (ACR) core data set was also used to assess the disease activity measure in RA.[10] **Result:** All primary efficacy parameters for all the 38 patients showed significant ($P<0.05$) improvement after 8 weeks of treatment and also for secondary parameters except for Rheumatoid Factor ($P=0.342$). The common adverse event occurred were nausea, gastric acidity, fever, headache and gastric irritation. **Conclusion:** Methotrexate (15mg/week) is an effective drug in treatment for rheumatoid arthritis and has an acceptable toxicity profile.

KEYWORDS: Rheumatoid Arthritis, Methotrexate, American College of Rheumatology (ACR), Subject and Physician global assessment of disease activity.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by joint swelling, joint tenderness, and destruction of synovial joints, leading to severe disability and premature mortality.[1] It can also be defined as Rheumatoid arthritis (RA) is a systemic autoimmune disorder characterized by a chronic polyarticular synovial inflammation that may lead to irreversible joints damage with disability and deformity.[2] The cause of Rheumatoid Arthritis is unknown but its progression can be slowed or stopped with Diseases Modifying Anti-rheumatic Drugs (DMARDs).[2] Diseases Modifying Anti-rheumatic Drugs (DMARDs) alleviate the symptoms of RA and have the potential to slow or stop disease progression.[3] DMARDs are classified into two types; conventional and biologic DMARDS.[3] Methotrexate (MTX), is the most commonly used DMARD in Rheumatoid Arthritis.[4] It is the first line treatment strategy for RA as soon as possible after diagnosis and so Methotrexate is called the anchor drug.

The mechanism of action of Methotrexate in Rheumatoid Arthritis remains unclear.[5] It probably exerts both anti-inflammatory and immunosuppressive effects mediated partly through folate antagonism. Low dose Methotrexate is prescribed in a weekly dose, is safe and well tolerated because of its efficacy and safety. It can be used for years but limited due to toxicity profile (effect) with prolong use.[5] Low dose methotrexate is first-line therapy for the treatment of rheumatoid arthritis not responsive to non-steroidal anti-inflammatory drugs alone (American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines, 2002).[6]

MTX is an anti-folate with a chemical structure similar to that of folic acid and folinic acid. MTX inhibits a number of folate dependent metabolite steps, including a very potent inhibition of dihydrofolate reductase (DHFR) which reduces folic acid to dihydrofolic acid to tetrahydrofolic acid, thus inhibiting the synthesis of purines and pyrimidine and thereby block the proliferation of malignant cells.[5] Since MTX toxicity can be explained on the basis of folate deficiency such as GI toxicity and hepatic toxicity, by adding folic acid supplement with MTX in order to reduce this toxicity.[5]

The efficacy of Methotrexate in RA has being confirmed by many trials or studies. It has been reported that majority of Patients in the Methotrexate only group had good improvement.[6] Hence, present study was planned to evaluate efficacy and safety in RA patients.

MATERIAL AND METHODS/ METHODOLOGY

Patients.

The study was conducted at Rathi Hospital in Ahmedabad. All the patients recruited for the study had diagnosed Rheumatoid Arthritis according to American College of Rheumatology (ACR) criteria (for at least6 months). Which stated active disease as defined by the following criteria at enrolment, if they had ≥ 6 Tender Joint count and ≥ 6 swollen joint count by 28 joint count plus at least two of the following; morning stiffness ≥ 45min, Erythrocyte sedimentation rate (ESR) ≥ 28mm/h or C-reactive Protein (CRP) ≥ 2mg/dl.[7] All patients diagnosed with RA and having age more than 18 years were included in the study.

Efficacy and Safety Parameters.

On visit at hospital Patients baseline evaluation, including demographic and clinical information were noted from the patient record file. The following efficacy parameters collected at the baseline evaluation were Tender Joint Count (TJC) and Swollen Joint Count (SJC) on 68 joints and 66 joints scale respectively, Physician and Patients Global Assessment Of Disease Activity, Subject assessment of pain (SAP) on VAS scale of 0 (no pain) to 10 (severe pain), Duration of Morning Stiffness value of Westergren ESR, CRP and Rheumatoid Factor (RF). Functional disability was measured with a Health Assessment Questionnaire (HAQ) that rated the patient's ability to perform daily activities from 0 (without difficulty) to 3 (unable to perform task).[8]

The Safety parameters included laboratory test consisting of Haematological measurements, determination of Blood Chemistry were performed during the visit and their result for Hemoglobin, Alanine aminotransferase (ALT) levels and Aspartate aminotransferase (AST) levels greater than three times the normal upper limit were noted down.[9] All the adverse event reported by the patients or observed by the physician were noted down in our Case Record Form (CRF) from the patient's record file.

Clinical Response.

Clinical assessment of RA activity was obtained after treatment, at 8 weeks from the base line data i.e the day the patient visited the hospital. Following primary efficacy parameters such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), tender and swollen joint count and subject assessment of pain (SAP), Subject global assessment of disease activity (SGADA) and Physician global assessment of disease activity *(PGADA) (Using 0-10cm VAS scale)and* Health assessment questionnaire (HAQ) and secondary efficacy parameters, Morning Stiffness (MS) and rheumatoid factor (RF)[10] were assessed.

In our study patient's clinical response to therapy was also assessed using the American College of Rheumatology (ACR) core data set of 7 disease activity measures for rheumatoid arthritis (RA). American College of Rheumatology (ACR) definition of 20% improvement (ACR 20) indicating, a decrease of at least 20 percent in the number of tender joints and a decrease of at least 20 percent in the number of swollen joints, along with a 20 percent improvement in **three** of the following: the subject's global assessment of disease status (SGADA), the subject's assessment of pain (SAP), the health assessment questionnaire (HAQ) estimate of disability and the physician's global assessment of disease status (PGADA), all of which were assessed with the use of visual-analogue scales (range, 0 to 10 cm, with higher scores indicating poorer status or more severe pain); and also the erythrocyte sedimentation rate or serum C-reactive protein concentration were recorded. The percentages of patients with an improvement of 50 percent (ACR 50) and 70 percent (ACR 70), accordingto the ACR criteria, were assessed in a similar manner.[10]

Study Design/ Protocol Design.

This was a prospective observation study conducted from August 2013 to December 2013, at The Rathi Hospital Ahmedabad, following approval by the Institutional Ethical Committee of the same hospital. A 38 patients were enrolled during the time duration of the study as mentioned above and were randomized to methotrexate (dose 15mg/week)'.

Statistical Analysis

Statistical Package for Social Science (SPSS) version 20 was used to derive statistical conclusion. Numerical values, frequency, mean and Standard Deviation (SD) was used in result. Our data showed skewed distribution and so non-parametric test was applied. Wilks Shapiro test was applied to check the normality. Wilcoxon test was used for within the group comparison and Mann Whitney test was applied for between group comparisons. $P<0.05$ was considered as significant in our study.

RESULT

Patient's Demographic characteristics

A total of 38 subjects were enrolled in the study. They were randomized and treated, 38 subjects received MTX 15mg tabled orally alone once a week. Demographical characteristics of all the patients in both the groups are shown in table 1.

Table 1: Demographic Characteristics of Patients

Sr No	Characteristics	Number of patients (N=38) n, %
1	Age Distribution (mean± SD)	46.26 ± 10.21
	28 -32 No (%)	6 (15.8)
	33 - 37	2 (5.3)
	38 - 42	4 (10.5)
	43 - 47	7 (18.4)
	48 - 52	9 (23.7)
	53 - 57	6 (15.8)
	58 - 62	1 (2.6)
	63 - 67	3 (7.9)
2	Sex	
	Female No (%)	30 (78.9)
	Male No (%)	8 (21.1)
3	ACR Functional Class No (%)	
	I	20 (52.6)
	II	17 (44.7)
	III	1 (2.6)
4	Duration Of RA in Years No (%)	
	1-3	15 (39.5)
	3-6	23 (60.5)
	>6	0
5	Co-morbidities	
	Hypertension	6 (15.8)
	DM (Diabetes Mellitus)	0
	Thyroid	1 (2.6)

Age Group

Out of 38 patients the mean age was found to be 46.3 ± 10.2 years. The highest number of patients was falling in age group 48-52 years as it is shown in table 1 and figure 1.

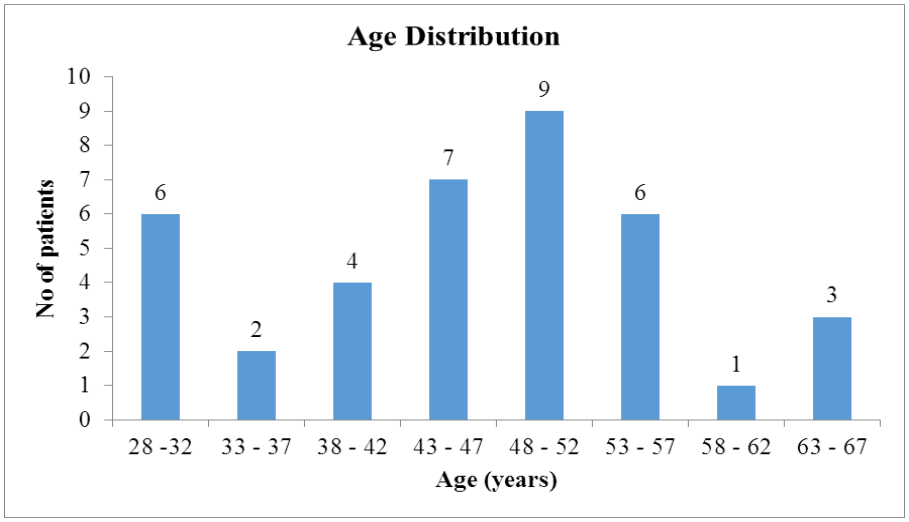

FIG 1: Age wise distribution of the patients

Gender

Approximately 79% of female were suffering from rheumatoid Arthritis as shown in table 1.

According to ACR Functional status Class.

ACR Classification Criteria of Functional Status in Rheumatoid Arthritis[17]

Class I:	Completely able to perform usual activities of daily living (self-care, vocational, and avocational)*
Class II:	Able to perform usual self-care and vocational activities, but limited in avocational activities
Class III:	Able to perform usual self-care activities, but limited in vocational and avocational activities
Class IV:	Limited ability to perform usual self-care, vocational, and avocational activities

*Self-care activities include dressing, feeding, bathing, grooming and toileting. Avocational (recreational and/or leisure) and vocational (work, school, homemaking) activities are patient-desired and age- and sex-specific.

Approximately 53% of patients were falling under ACR Function class I as per ACR functional classification as shown in table 1 and figure 3.

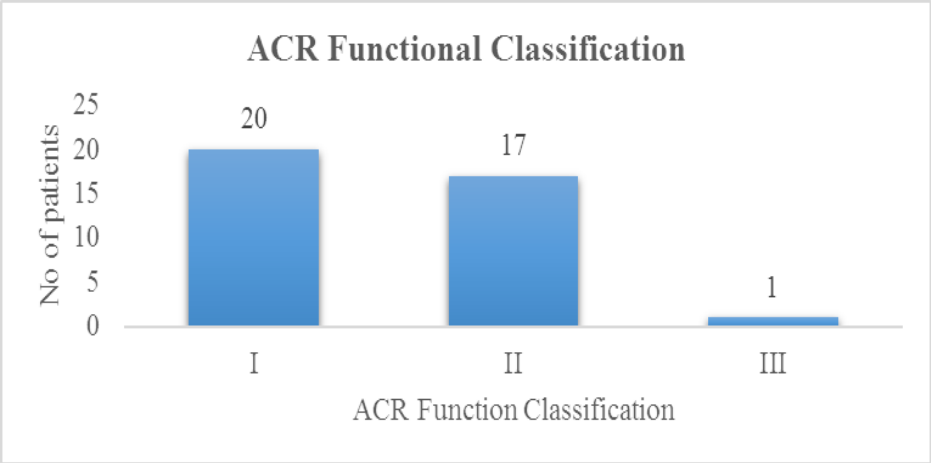

Fig 3: ACR Functional wise Classification of the patients.

Duration of Rheumatoid Arthritis (RA)

There were approximately 61% of patients who had rheumatoid arthritis for 3 to 6 years as shown in Table 1 and figure 4.

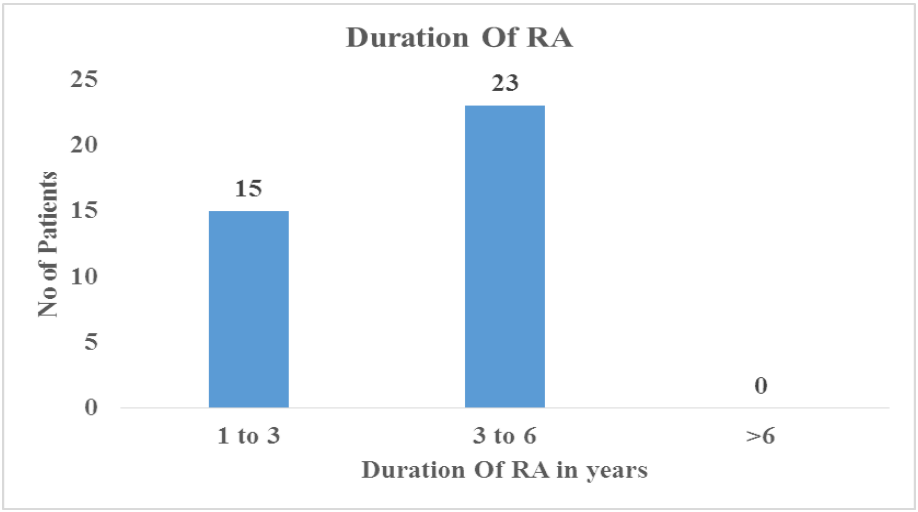

Fig 4 Distribution of patients according to Duration of RA

Associated Co-Morbidities in both the Groups.

Hypertension was the most frequent associated co-morbidity among all the patients as shown in table 1 and figure 5.

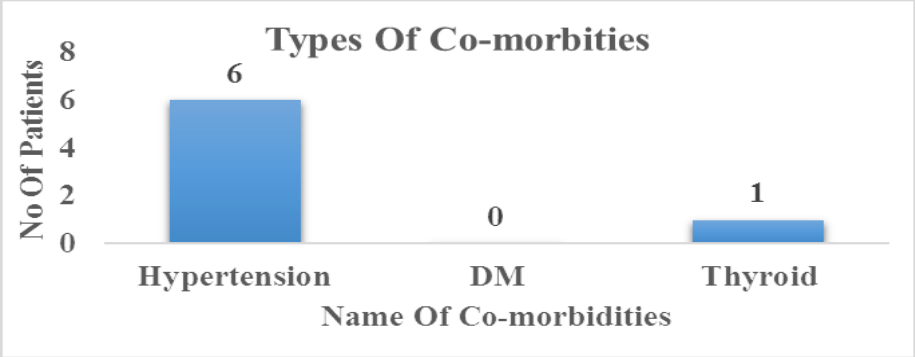

Fig 5: Co-morbidities seen in the patient

Clinical Efficacy

All primary efficacy parameters showed significant (P<0.05) improvement after receiving treatment as shown in table 2 and figure 6. All the primary efficacy parameters were similar to ACR core set criteria for improvement.

Table 2: Primary Clinical efficacy parameters measured in patients.

Sr. No	Parameters	Baseline Data (mean ± SD)	After Treatment (mean ± SD)	Δ	P value
1	**CRP**	34.69 ± 34.2	20.96 ± 22.1	13.73	0.001
2	**ESR**	60.50 ± 23.3	50.37 ± 23.0	10.13	<0.001
3	**TJC**	19.55 ± 4.0	14.97 ± 3.8	4.58	<0.001
4	**SJC**	10.61 ± 2.2	8.21 ± 2.0	2.39	<0.001
5	**SAP**	7.13 ± 1.2	5.96 ± 1.3	1.18	<0.001
6	**SGADA**	13.51 ± 18.8	11.75 ± 17.9	1.76	<0.001
7	**PGADA**	15.25 ± 21.8	12.23 ± 16.9	3.02	<0.001
8	**SAPF**	1.38 ± 0.3	1.13 ± 0.3	0.25	<0.001

ΔValue = Baseline value - after treatment value.

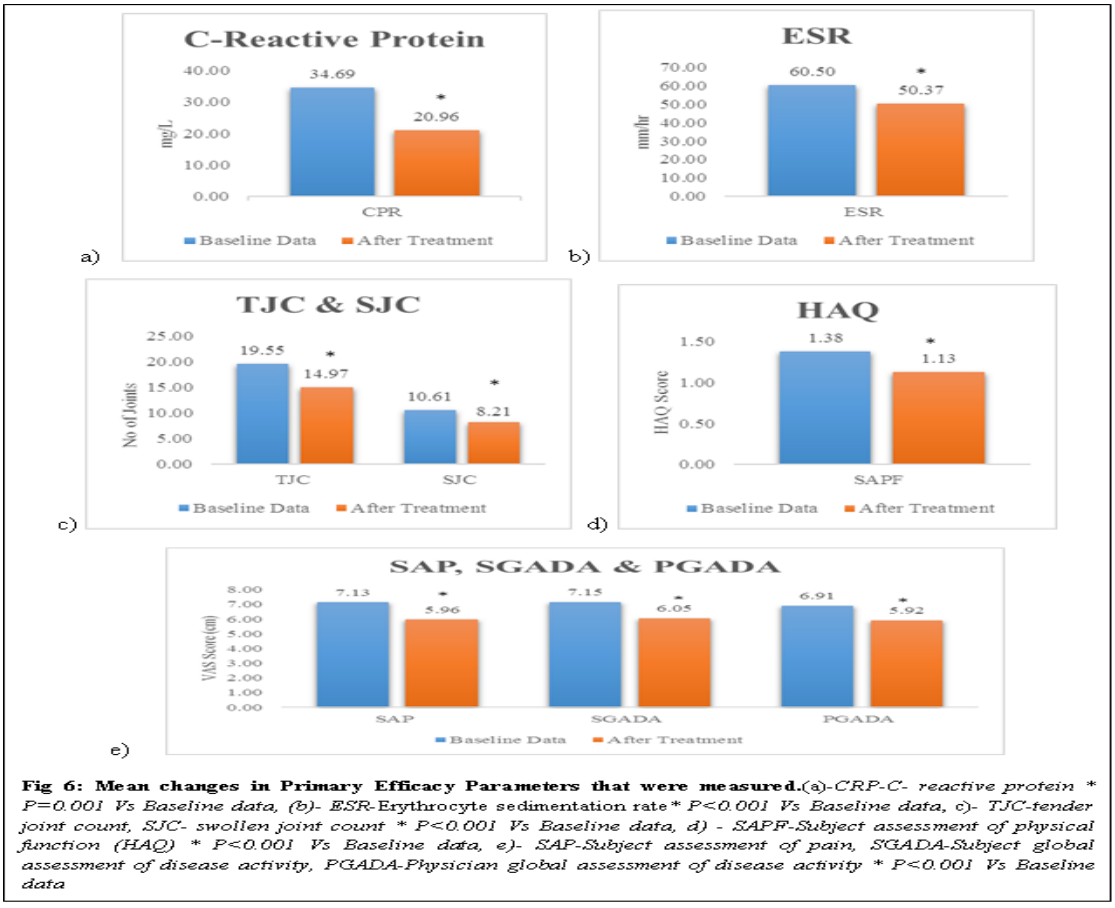

Fig 6: Mean changes in Primary Efficacy Parameters that were measured.(a)-*CRP-C- reactive protein * P=0.001 Vs Baseline data, (b)- ESR-*Erythrocyte sedimentation rate** P<0.001 Vs Baseline data, c)- TJC-tender joint count, SJC- swollen joint count * P<0.001 Vs Baseline data, d) - SAPF-Subject assessment of physical function (HAQ) * P<0.001 Vs Baseline data, e)- SAP-Subject assessment of pain, SGADA-Subject global assessment of disease activity, PGADA-Physician global assessment of disease activity * P<0.001 Vs Baseline data*

The difference in the secondary clinical efficacy parameters Rheumatoid Factor (RF) and Morning Stiffness (MS) are shown in table 3 and figure-7. There was significant improvement ($p < 0.05$) in morning stiffness (MS) after treatment. While there was no significant improvement ($p=0.342$) in Rheumatoid Factor (RF) after treatment.

Table 3: Change in Secondary efficacy parameters

SR NO	Parameters	Baseline Data	After treatment	Δ	P value
1	MS	70.66 ± 10.5	58.82 ± 10.8	11.84	<0.001
2	RF	121.71 ± 101.4	127.18 ± 162.3	-5.47	0.342

Safety

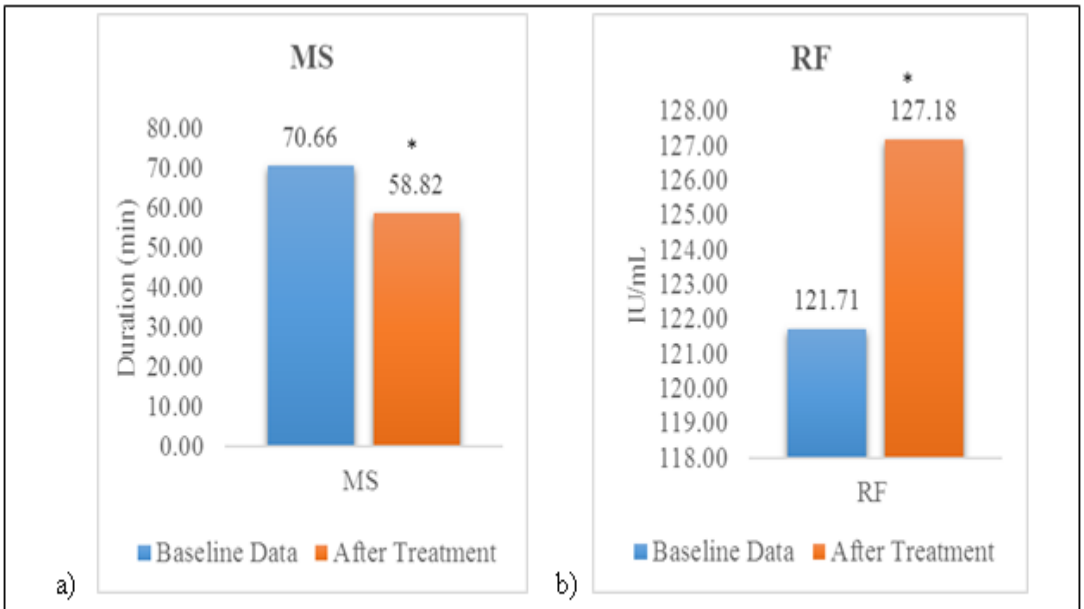

FIG 7: Mean changes for Secondary efficacy parameters. a)- MS-Morning Stiffness* *P<0.001 Vs Baseline data*, b)- Rheumatoid Factor (RF)* *P=0.342 Vs Baseline data*.

Liver function test, Hematological test and other result were observed. For liver function test ALT and AST enzymes were considered to abnormal when their level rises 3 times the upper limit of normal but in both the groups ALT and AST levels were within the normal range (for all the patients after treatment) no abnormality was seen.[9]

The common adverse events that occurred during the treatment were nausea, gastric acidity, gastric irritation, fever and headache as shown in table 4. The adverse events were seen in 8 (21.1%) subjects.

Table 4: Adverse events that occurred during the treatment

Sr No	Adverse Event	Group-I (N=38) n (%)
1	Nausea	2 (5.3)
2	Gastric Acidity	1 (2.7)
4	Fever	1 (2.7)
5	Headache	1 (2.7)
6	Nausea & Gastric Acidity	2 (5.3)
7	Nausea & Gastric irritation	1 (2.7)
	Total	8 (21.1)

n= Number of patients.

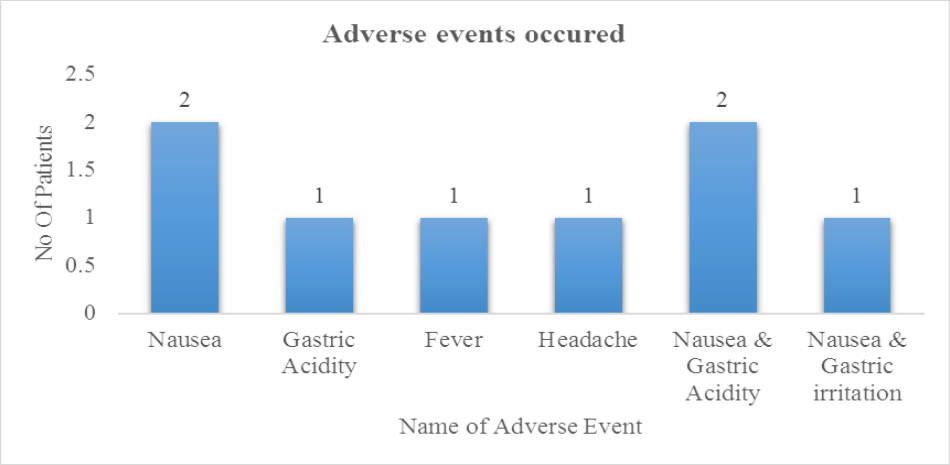

Fig 8: Adverse events that occurred during the treatment.

RESULT AS PER American College of Rheumatology (ACR)

The American College of Rheumatology (ACR) core data set of 7 disease activity measures for rheumatoid arthritis (RA) (hereinafter referred to as the "Core Data Set"), used to assess outcomes in clinical trials of treatments for RA. The Core Data Set includes 3 assessor derived measures—tender joint count, swollen joint count and physician global assessment; 1 laboratory test—erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) level; and 3 patient self-report questionnaire measures—functional disability, pain and patient global assessment.[10] The Core Data Set also includes a radiograph for study conducted. Improvement of at least 20% in both tender and swollen joint counts as well as in 3 of the 5 additional measures is designated the ACR preliminary definition of improvement and known as the ACR 20% response criteria (ACR20).[10]

Clinical efficacy Parameters

Overall patient clinical response to therapy was also assessed by ACR criteria. To be considered an ACR 20% responder/ improvement, a subject had to have a ≥20% improvement in tender and swollen joint count and in at least three of the following five criteria: patient global assessment, physician global assessment and pain intensity, HAQ, CRP or ESR. The same criteria's applies for the ACR 50 and ACR 70 improvement.[10]

In total 22 (57.89) patients out of 38 showed improvement as per the American College of Rheumatology (ACR) core set criteria. 4 (11%) of patients did not show improvement after treatment while 19 (50%) of patients showed ACR 20 percent response after treatment duration for 2 months. The details of number of patients and their percentage showing ACR 20 and ACR 50 percent improvement is shown in table 5.

Table 5:- Patients showing improvement according to American College of Rheumatology (ACR) criteria.

Sr No	ACR Improvement	No Of Patients (%)
1	No improvement	4 (10.5)
2	<ACR 20	12 (31.6)
3	ACR 20	19 (50)
4	ACR 50	3 (7.9)
Total		38

DISCUSSION

This prospective observation study was carried out at private hospital to evaluate efficacy and safety of Methotrexate for the management of rheumatoid arthritis (RA). The patients received Methotrexate by oral route 15mg. Patients were randomly allotted the treatment as per the study criteria. Our study aim was to evaluate the clinical response in terms of efficacy and safety of the patients with methotrexate treatment. As per result of the study, Methotrexate treatment resulted in better improvement in signs and symptoms of rheumatoid arthritis except for RF and decreased the function of patients as measured by clinical efficacy parameters. The RF showed non-significant improvement may be due to high variance (after treatment) and small sample size. Our study included primary clinical efficacy parameters like C- reactive protein (CRP), Erythrocyte sedimentation rate (ESR), tender joint count (TJC), swollen joint count (SJC), physician global assessment (PGADA), subject global assessment of disease activity (SGADA) and subject assessment of Pain (SAP) and health assessment questionnaire (HAQ) and the secondary clinical efficacy parameters like Morning stiffness (MS) and Rheumatoid Factor (RF). Even though it was generally excepted that 2 years of treatment is required to demonstrate prevention of functional disability[15], Our study result suggested Methotrexate showing significant improvement in function disability. Due to fix period of our study it couldn't be possible to examine progression of the damage to articular structure. Some of the finding reported that damage to articular structure can be

examined by X-ray.[8] Similarly a study by P Emery et al concluded that a significant improvement in the selected primary efficacy parameters was observed in both Leflunomide and methotrexate group. In our study the findings are parallel to P Emery et al study.[11] In our study the secondary efficacy parameters which included Morning stiffness (MS) and rheumatoid factor (RF), which shows significant improvement except rheumatoid factor (RF) (P=0.342).

We have selected primary and secondary clinical efficacy parameter's based on ACR core set criteria for improvement as well as our study objective. The study by P emery et al reported a significant improvement in Morning stiffness and rheumatoid factor.[11] According to our observation certain factors may alter the result which included limit range of sample size, study duration and patients disease condition. The wide variation in sample that may have nullified the negative result.

According to Peter et al study reported significant (P<0.05) improvement in efficacy parameters were almost similar to our study. Peter et al study reported that signs and symptoms of RA decreased in more patients in the groups that received infliximab plus Methotrexate than in the group that received methotrexate alone as judge by the percentage wit ACR 20, ACR 50 and ACR 70 responses.[8]

In our study the time interval was 8 weeks interval. However baseline data recorded at time of 1st visit and after 8weeks of treatment again results were observed. Study by peter et al, have included result at the end of 54 weeks of treatment.[10] Now the result of serum Rheumatoid Factor value shows significant improvement in infliximab + Methotrexate whereas Methotrexate alone had no significant effect, so this findings are opposite compared to our study, so the reason could be of sample size and longer study period.

All the patients shows significant (P<0.05) improvement in primary clinical efficacy parameters after treatment. While for the secondary clinical efficacy parameters, there was significant (P<0.05) improvement in Morning stiffness and no significant (P=0.342) in rheumatoid factor value after treatment.

Another study by Rahman et al[12] on infliximab dose escalation in patients with rheumatoid arthritis reported that 26% of patients in Group 1 (placebo plus MTX), 58% of patients in group 2 (3mg/kg plus MTX) and 61% of patients in group 3 (10mg/kg plus MTX) achieved an ACR 20 response at week 22.[12] While in our study 50% of patients in Methotrexate treated group achieved an ACR 20 response after treatment.

Safety

In present study all the patients in our study had no any abnormality in liver enzyme ALT & AST. Plasma liver enzyme ≥ 3 times the upper limit of normal was considered as abnormal.[9] As compared with P emery et al, 16.3% treated with methotrexate for 1 year resulted in elevation of plasma liver enzyme.[11] P Emery et al study protocol, mentioned that folate supplement was not mandatory in Methotrexate taking patients, while in our study it was mandatory to prescribe folic acid supplement along with methotrexate treatment, this may be the reason that may decrease the plasma liver enzyme up to the normal level (side effect of Methotrexate). In our study dose of MTX was constant 15mg per week and folic acid was compulsory for all the patients with Methotrexate treatment. A study carried out by Morgan et al[13] and Hoekstra et al[14] reported that folate supplementation lowers the rate of hepatotoxicity.

A similar study by Peter et al where certain adverse events tended to occur more frequently in the group that received infliximab + methotrexate than the group that received methotrexate alone, including upper respiratory tract infection (34% vs 22%), sinusitis (17% vs 6%) and headache (26% vs 16%). Cancer developed in 5 infliximab treated patients.[8] In our study only 8 (21.1) patients were suffered from unwanted side effects treated with Methotrexate.

Through all the efforts were made to make this study very scientific and objective, it could be suffering from some of the inherent limitations. They are first the Sample size, is very small for the study to produce effective result and give confirmative conclusion on the treated drug. Second the study was carried out short period of five months only and the third limitation was due to shorter duration of study and high cost of detection, it was not possible to conduct certain tests (such as X-rays) for detection of progression of joint damage.

CONCLUSION

However, despite the above limitation the study showed that, firstly we can conclude the outcome of Methotrexate that may give platform for larger scale study and that may also support the newer treatment guidelines. Secondly if parenteral Methotrexate by IM route is giving alternative to oral route methotrexate it can reduce all the Gastric toxicity. Thirdly it has provided baseline data for comparing with other similar studies at the level of state, country and the world and also for future studies of similar nature.

Abbreviation: Rheumatoid arthritis (RA), Methotrexate (MTX), American College of Rheumatology (ACR), C - reactive protein (CRP), Erythrocyte Sedimentation Rate (ESR), tender joint count (TJC), swollen joint count (SJC), Subject Assessment of Pain (SAP), Subject global assessment of disease activity(SGADA) and Physician global assessment of disease activity (PGADA), Health assessment questionnaire (HAQ), Subject assessment of physical function (SAPF), Morning stiffness (MS) and Rheumatoid Factor (RF).

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