"SAFETY PROFILE OF METHOTREXATE IN PATIENTS WITH RHEUMATOID ARTHRITIS"

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Dr. ARATHI DARSHAN
MD, FICP
Professor and Head,
Department of General Medicine,
J. N. Medical College,
Nehru Nagar, Belagavi
Date : 14.12.21
Place : Belagavi

Dr. (Mrs.) N.S. MAHANTSHETTI
MD, DCH
Principal,
J. N. Medical College,
Nehru Nagar, Belagavi

Date : 14/12/21
Place : Belagavi

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Nehru Nagar, Belagavi- 590 010, Karnataka, INDIA

0831 - 2471350 0831 - 2470759 www.jnmc.edu principal@jnmc.edu

Ref No: MDC/PG/ Date: 15-11-2021

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Dr. (Mrs.) N.S. Mahantashetti.
Chairperson-Antiplagiarism Committee &
Principal,
J. N. Medical College, Belagavi.

To,
Reg. No. BG0119006.
Postgraduate Student,
2019-20 Batch,
Department of General Medicine,
J. N. Medical College, Belagavi.

ABSTRACT

TITLE: "SAFETY PROFILE OF METHOTREXATE IN PATIENTS WITH RHEUMATOID ARTHRITIS"

Background: Methotrexate (MTX) is recommended as first-line therapy in patients with active RA as monotherapy or in combination with other disease-modifying anti-rheumatic drugs (DMARDs). Despite being considered a safe drug, some toxicities of MTX are inevitable and patients are stopping further treatment with MTX for the same.

Objective: To evaluate the safety profile of Methotrexate in patients with Rheumatoid Arthritis (RA).

Methods: Between 1st January 2020 to 31st December 2020, 117 patients diagnosed with RA and under methotrexate treatment at least for six months as monotherapy or in combination with other DMARDs were included in this cross-sectional study. Patient demographics, disease and treatment characteristics, side effects, and blood and laboratory markers specific to RA.

Results: The study consisted of predominantly females (85.5%), and the mean age of patients was 47.92±13.398 years. Mean disease duration and treatment duration were 4.19±4.28 years and 2.63±2.78 years, respectively. Around 98.3% of patients received MTX as a combination therapy, 70.1% received the optimal dose (≥12.5mg) of MTX, and 88.9% received an oral form of MTX. Patient-reported side effects were reported in 47% of patients. Apart from common reported minor side effects such as fatigue (17.1%), nausea (16.2%), anorexia (11.1%), stomatitis/oral ulcers (10.3%), epigastric burning (8.5%), hair fall (3.4%), and vomiting in 0.9% of patients, no serious or life-threatening side effects were reported. In this study, 64.1% patients were anemic, 1.7% patients had leukopenia, 4.3% patients had thrombocytopenia and 13.7% patients had elevated transaminases levels.

Demographic and clinical factors including age (p=0.774), gender (p=0.058), disease activity (p=0.220), duration of treatment (p=0.079), MTX dose (p=0.321), type of treatment i.e. MTX monotherapy or in combination therapy with other DMARDs (p=0.610), MTX form i.e. oral or subcutaneous (p=0.600) were not associated with side effects. Similarly, no significant association between side effects and type of treatment (p=0.686), a dose of MTX (p= 0.725) was observed. Hence, this study proposes that our group of study population tolerated methotrexate well without any life-threatening side-effects.

Conclusion: MTX is a reasonably safe drug; use of methotrexate in combination with other DMARDs is safe and should be encouraged as first line treatment of RA on routine basis. However**,** periodic blood and laboratory monitoring along with patient follow-ups are essential to detect toxicities as early as possible.

LIST OF ABBREVIATIONS

GLOSSARY	ABBREVIATIONS
RA	Rheumatoid Arthritis
DMARDs	Disease modifying anti-rheumatic drugs
NSAIDs	Non-steroidal anti-inflammatory drugs
MTX	Methotrexate
TNF	Tumor Necrosis Factor
ACPA	Anti-cyclic Citrullinated Peptide Antibody
RF	Rheumatoid Factor
ESR	Erythrocyte Sedimentation Rate
CRP	c-Reactive Protein
HLA	Human Leukocyte Antigen
HCQ	Hydroxychloroquine
ACR	American College of Rheumatology
EULAR	European League Against Rheumatism
CDAI	Clinical Disease Activity Index
csDMARDs	Conventional synthetic Disease modifying anti-rheumatic drugs
EAMs	Extraarticular manifestations
COX-2	Cyclo-oxygenase-2
ALT	Alanine Transaminase
AEs	Adverse Effects
DAS28CRP	Disease Activity Score
G-CSF	Granulocyte-Colony stimulating factor

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INTRODUCTION

Rheumatoid arthritis (RA) is among the major systemic autoimmune diseases with a prevalence of 0.4% to 1.3% worldwide and 0.28% to 0.7% in India.[1,2] RA is predominantly seen in females with a 2-3 times higher frequency than men and is characterized by symmetric bilateral involvement of joints associated with pain and swelling. Although the initial disease is associated with mild symptoms and fewer joint involvement, severity increases with the progression of the disease, characterized by inflammation of multiple joints with extraarticular symptoms. If untreated, the inflammation of the synovial tissue can lead to permanent structural damage characterized by joint destruction, bone erosion, eventually leading to long-term disability and impaired quality of life.[3]

Early diagnosis and treatment initiation within five months is paramount as it helps substantially reduce the progression of joint changes and prevents irreversible damage to the joints. Different drug classes such as corticosteroids, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), and Disease-Modifying Anti Rheumatic Drugs (DMARDs), are being used to treat RA. In India, >75% of patients with RA are prescribed DMARDs as the first line of treatment.[3] Among these, Methotrexate (MTX) is used as the first-line therapy drug in RA patients around the world, unless otherwise contraindicated or not tolerated by the patient.[4] Initial treatment with either MTX or a combination of MTX and glucocorticoid followed by sequential application of target therapies, including biologics, has shown significant improvement in disease outcome.[5]

MTX, an anti-metabolite drug, is an analog of folic acid interferes with dihydrofolate reductase enzyme activity, thereby preventing the synthesis of nucleotide and purine metabolism. These increase the production and release of adenosine, having anti-inflammatory properties.[1] Although methotrexate benefits many RA patients and is

widely used due to its perceived efficacy, acceptable safety profile, and low cost, it is associated with side effects including hair loss, stomatitis, nausea, bone marrow toxicity, secondary infections, and hepatotoxicity.[6] The incidence of side effects has resulted in uncertainties among physicians while prescribing MTX in RA patients.

Usage of methotrexate under the recommended optimal weekly dose of up to 25mg is generally considered safe. While the safety profile of MTX under these circumstances is generally considered good, toxicities have been reported in the elderly population.[7] Moreover, studies determining the safety profile of MTX in the Indian population especially, in the regions of Karnataka, are limited. Hence, the present study was carried out to determine the incidence of patient reported side effects of MTX in RA patients in this part of Karnataka.

REVIEW OF LITERATURE

EPIDEMIOLOGY OF RA

RA is a systemic, autoimmune, inflammatory disorder of joints with a global prevalence of 0.5-1%.[8] Most often seen in older individuals in the fourth and fifth decades of life; women are twice at risk than men. Presence of destructive polyarthritis is the hallmark of disease which negatively impacts the day-to-day activities at personal and professional front, thereby decreasing the quality of life. RA is classified into seropositive and seronegative disease, depending on Rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (ACPAs) positivity.[9] McGonagle et al.[10] (2018) proposed a mechanistic immunological based classification of rheumatoid arthritis. Based on this, the disease is classified as

- Monogenic auto-inflammatory disease
- Polygenic auto-inflammatory disease
- Mixed pattern disorder
- Polygenic autoimmune disease
- Monogenic autoimmune disease

ETIOPATHOGENESIS

Along with genetic factors, increased prevalence of RA is observed within families, with a familial risk of RA development of approximately 50%. Risk factors of RA development are as follows:[9,11,12]

Genetic factors:

- Major histocompatibility regions encoding HLA proteins at position 70 and 71 (HLA DRB1 alleles)
- Protein tyrosine phosphatase, non-receptor type 22 (PTPN22)
- Interleukin-6 receptor
- TNF receptor associated factor-1 (TRAF1/C5)
- Signal transducer and activator of transcription 4 (STAT4)
- Peptidyl arginine deiminase 4 (PADI4)
- Fc gamma receptor (FCGR)
- CD40
- CC chemokine ligand 21 (CCL21)
- CC chemokine receptor 6 (CCR6)

Epigenetic factors

- DNA methylation changes in the genome of fibroblast-like synoviocytes (FLS)

Environmental factors

- Female sex (early menopause, polycystic ovary syndrome and preeclampsia)
- Smoking
- Occupational dust
- Air pollution
- Dietary factors including excessive intake of sugar, sodium, protein and iron
- Obesity
- Low Vitamin D levels
- Microorganisms including *Proteus* and *Escherichia* species.

On the other hand, HLA DRB*1301 allele is protective in RA patients with positive ACPA. Healthy dietary lifestyle with increased uptake of fruits, vegetables, fish and omega3 fatty acids, moderate alcohol consumption is considered safe with considerable reduction of RA risk. Similarly, breastfeeding, use of hormone replacement therapy and oral contraception have a protective role against RA development. Despite the knowledge on the role of individual risk factors of RA, the precise mechanism of development of RA is elusive.

Role of MHC alleles in transition of preclinical RA to symptomatic RA is addressed in previous studies.[13,14] According to Deanne et al.[15] (2014), interaction among the genetic, epigenetic and environmental factors during the preclinical stage stimulate autoimmune reaction with subsequent elevation in the circulating autoantibodies. Substantial elevations over the years will lead to development of clinical signs and symptoms. The transition from initiation of disease to development of symptomatic clinical disease occurs through a combination of multiple processes, including expansion of autoreactive T and B cells, epitome spreading, increase inflammatory reaction and related antigen production, upregulation of signaling molecules and alteration of autoantibodies. Clinical disease progression and advanced stage of the disease is characterized by increased innate and adaptive immune response, with resultant chronic inflammatory state. Within the synovium, there is substantial increase of inflammatory mediators including cytokines, chemokines and metalloproteinases, which leads to joint manifestations including bone destruction.[12,16]

CLINICAL FEATURES

RA, typically has an insidious or acute onset. Bilaterally symmetrical symptomatic polyarthritis involving joints of the hands is hallmark of the disease. The number of joints involved at baseline determines the extent and progression of disease and hence, acts as a reference for future examinations. Early morning stiffness that lasts for at least an hour is the key deterministic feature of RA. The associated signs and symptoms include fever, tiredness, malaise and weight loss. Presence of Rheumatoid nodules, especially in the elbow region is indicative of advanced disease. Elderly patient often presents with prominent stiffness and pain in the limb girdle rather than peripheral arthritis known as polymyalgia presentation. Another atypical variant is known as palindromic rheumatism, wherein the patients experience regular joint pain and stiffness of at least one joint lasting for hours to days.[17] The sequential events in RA included pannus formation, synovial hyperplasia, joint malformation, and cartilage and bone erosion. This further leads to difficulty in physical function and mobility with resultant short-and long-term morbidity and decreased quality of life.[18]

Although RA is predominantly an articular disease, extraarticular involvement is not uncommon, are reported in at least 50% of RA patients. Based on the Malmö criteria, extraarticular manifestations (EAMs) can be classified into severe and non-severe EAMs. Table 1 summarizes the most common EAMs associated with RA.[19]

Table 1: Extraarticular manifestations associated with Rheumatoid arthritis

Tissue or organ	Non-severe EAM	Severe EAM
Skin	Nodules, Raynaud's phenomenon	Petechiae, purpura, ulcers and gangrene
Respiratory system	Bronchiolitis obliterans, pneumonia	Pleuritis, interstitial lung disease
Heart	Valvular heart disease, Myocarditis, Arrhythmias	Pericarditis, coronary vasculitis and aortitis
Nervous system	-	Mono/polyneuritis multiplex, Central nervous system vasculitis
Eyes	Sicca syndrome, Secondary Sjogren's syndrome	Episcleritis or scleritis, Retinal vasculitis
Hematology	-	Felty's syndrome
Renal system	-	Glomerulonephritis, Interstitial nephritis, Amyloid deposition
Musculoskeletal system	-	Osteoporotic changes, tendon and ligament rupture

DIAGNOSIS

Since there is no exact definition of RA and a pathognomic test, the diagnosis is based on the clinical presentation and laboratory investigations. RA must be suspected in patients presenting with symmetrical joint involvement, persistent pain and swelling of ≥3 joints, and/or morning stiffness lasting for ≥ 30 minutes.[20] Radiographic examination of the involved joints should be performed to evaluate joint erosions.[4]. Presence of anti-CCP antibody (ACPA) is a strong diagnostic indicator of RA, while elevated ESR and CRP levels assist in measuring the severity of inflammation. Positive RF is noted in about 5% of the normal population, hence mere presence of RF cannot be considered as a criterion for the diagnosis. RA must be differentiated from other inflammatory disorders including psoriatic arthropathy and osteoarthritis. According to the guidelines of 2010 ACR/EULAR classification criteria for RA, patients who have

≥1 joint with definite swelling of joint and synovitis with other diagnosis ruled out should be suspected to have RA.[21] Based on the classification criteria summarized in table 2, patient with total score of at least 6 of 10 can be classified as RA.

Table 2: Classification criteria for RA score

Criteria	Score
Joint involvement	
One large joint	0
2-10 large joints	1
1-3 small joints (with or without involvement of large joints)	2
4- 10 small joints (with or without involvement of large joints)	3
> 10 joints (at least one small joint)	5
Serology (at least one test result is needed for classification)	
Negative RF and negative ACPA	0
Low-positive RF or low-positive ACPA	2
High-positive RF or high-positive ACPA	3
Acute phase reactants (at least one test result is needed for classification)	0
Normal CRP and normal ESR	1
Abnormal CRP or abnormal ESR	
Duration of symptoms	
< 6 weeks	0
≥ 6 weeks	1

MANAGEMENT

Earliest evidence of management of RA is dated back to 1950s with the introduction of glucocorticoid therapy for Rheumatoid arthritis to reduce inflammation.[22] Following this, methotrexate introduced to the management protocol in 1980s and 1990s, and is still widely being used.[23] Recently, treat-to target approach had been recommended to induce remission and decrease disease activity. Many biologic therapies have been introduced classified as disease modifying drugs to achieve the treatment goal.

Currently, the primary goals of treatment include:

- Symptomatic management with focus on reduction of pain and other disease related symptoms.
- Control the disease activity, halt the progression of disease and attain disease free state
- Reduce or eliminate the damages caused by arthritis

As recommended by the American college of Rheumatology updated guidelines, till date, Methotrexate is still recommended as the first line of treatment of RA, unless otherwise contraindicated. It is generally prescribed at an initial dose 7.5 mg/week and rapidly escalated to 25 mg/week.[24] Methotrexate is not recommended in patients with increased risk of hepatotoxicity. Folic acid supplementation is advised to combat adverse effects. In such cases, DMARDs are considered as first line of treatment. Furthermore, glucocorticoids (prednisolone 5-10mg) are added as an adjunct for a short duration to enhance the effect of DMARDs. Verschueren et al.[25] (2015) suggested that a combination of methotrexate and glucocorticoids for 16 weeks was effective in disease remission. Etanercept and methotrexate combination resulted decreased disease activity and functional disability than MTX monotherapy. Moreover, it stopped the radiographic progression of disease.[26] Thus, in patients not responding to Methotrexate, combination therapy is advised. Figure 1 summarizes the treatment recommendations.

Other adjuvant therapies

- NSAIDs and cyclo-oxygenase-2 (COX-2) inhibitors are generally prescribed to reduce the pain. However, are not advised for long term due to significant potential gastrointestinal, renal and cardiovascular toxicities. In elderly patients

>65 years old and those with history of peptic ulcer disease, proton pump inhibitor is advised to prevent gastrointestinal bleeding.[17]

- Omega-3 fatty acid supplementation is also proven effective
- Physiotherapy, splinting and occupational therapy are also advised to aid in better functioning.[27]

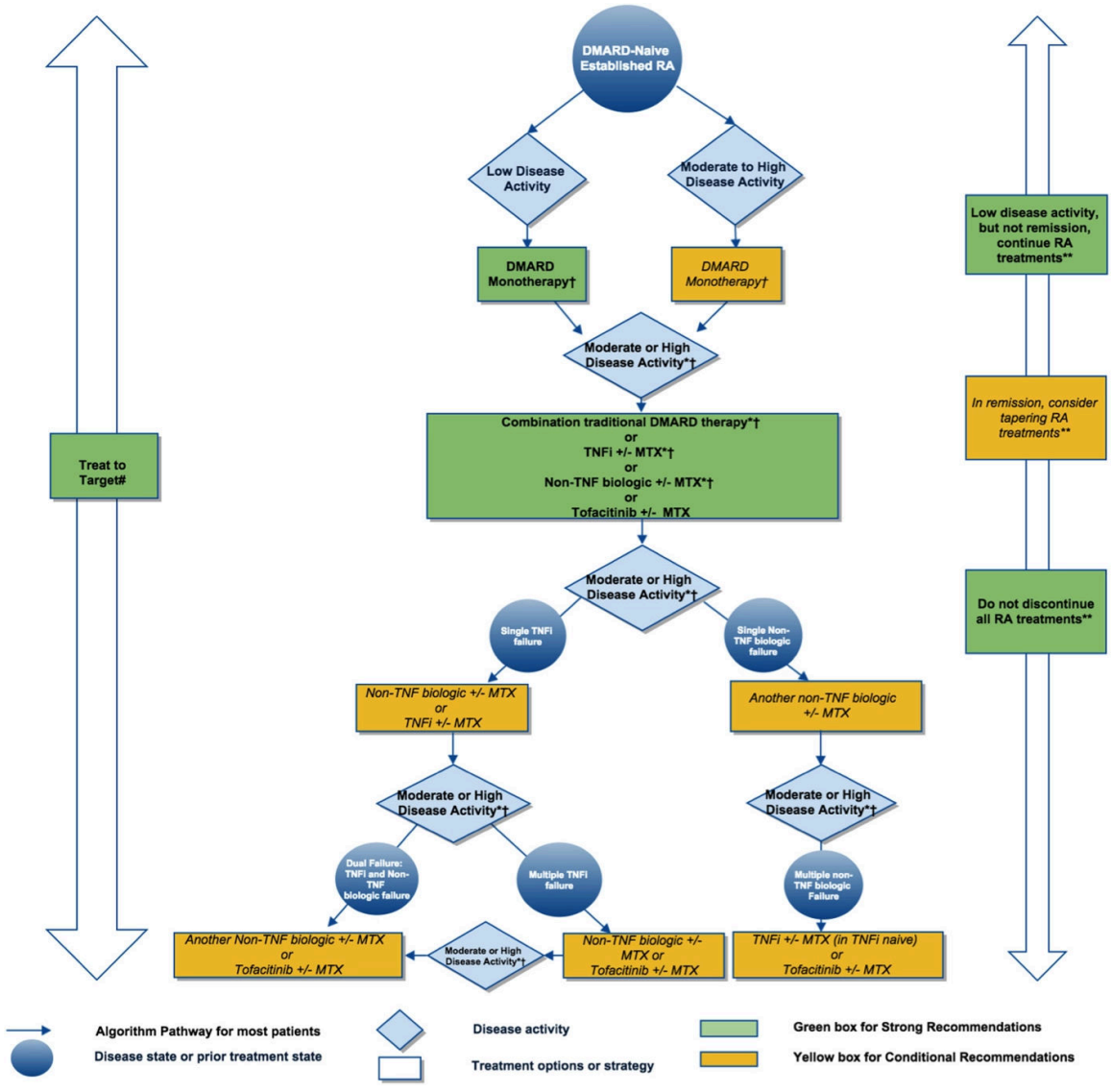


Figure 1: 2015 ACR Recommendations for management of RA[28]

DISEASE MODIFYING ANTIRHEUMATIC DRUGS

DMARDs are beneficial for reducing the rate of erosive changes and preventing irreversible damage of the joints. Currently used DMARDs include Methotrexate (MTX), Hydroxychloroquine (HCQ), Leflunomide (LEF) and Sulfasalazine (SSZ). Available DMARDs are listed in Table 3.[27,29]

Table 3: Currently available Disease modifying anti-rheumatic drugs

Drug	Mechanism for rheumatoid arthritis	Adverse effects	Typical dosage
Nonbiologic† Methotrexate	Inhibits dihydrofolate reductase	Liver effects, teratogenesis, hair loss, oral ulcers	Up to 25 mg/week orally or SC
Leflunomide (Arava)	Inhibits pyrimidine synthesis	Liver effects, gastrointestinal effects, teratogenesis	10-20 mg/week orally
Hydroxychloro-quine (Plaquenil)	Antimalarial, blocks toll-like receptors	Rare ocular toxicity	200-400 mg/day
Sulfasalazine (Azulfidine)	Folate depletion, other mechanisms unknown	Anemia in glucose-6-phosphate dehydrogenase deficiency, gastrointestinal effects	500-1,500mg BD
Biologic Anti-TNF agents Adalimumab (Humira)	Anti-TNF-α	TB, opportunistic infection	40 mg SC, twice a month
Certolizumab pegol (Cimzia)	Anti-TNF-α, pegylated	TB, opportunistic infection	400 mg/month SC
Golimumab (Simponi)	Anti-TNF-α	TB, opportunistic infection	100 mg/month
Infliximab (Remicade)	Anti-TNF-α	TB, opportunistic infection, infusion reaction	3-5mg/kg IV every six to eight weeks
Other biologic agents Abatacept (Orencia)	Costimulator blocker, cytotoxic T lymphocyte antigen 4	Opportunistic infection	125mg/week, SC or 500-1,000mg/month IV

Anakinra (Kineret)	Anti-interleukin-1 receptor blocker	Opportunistic infection, injection site pain	100 mg subcutaneously daily
Rituximab (Rituxan)	Anti-CD20, eliminates B cells	Infusion reaction, opportunistic infection, progressive multifocal leukoencephalopathy	1,000mg IV twice a year
Sarilumab (Kevzara)	Anti-interleukin-6 receptor blocker	Opportunistic infection	150-200mg SC twice a month
Tocilizumab (Actemra)	Anti-interleukin-6 receptor blocker	Opportunistic infection, hyperlipidemia	IV 4-8 mg/kg/month or 162 mg/week or twice a month, SC
Tofacitinib (Xeljanz)	Janus kinase inhibitor	TB, opportunistic infection	5 mg OD or BD

SAFETY PROFILE OF MTX AND DMARDs

Although DMARDs have demonstrated greater efficacy in terms of improved disease symptoms and decreasing disease progression, it is associated with some side effects. Side effects of conventional synthetic DMARDS is less as compared to targeted and biological DMARDs. Adverse effects of MTX include myelosupression, liver function abnormalities and pulmonary changes, poor tolerability (nausea, fatigue, oral ulcers, diarrhea).[30,31] The common side effects are listed in Table 4. Additionally, in order to reduce the side effects, before initiating DMARD therapy, hepatitis B and C status, tuberculosis should also be tested. Use of MTX and DMARDs in pregnancy is not contraindicated, however should be used in caution.[1] Similarly, by starting the MTX therapy earlier in the disease period aids in identification of responder from an non-responder, thereby assessing the need for aggressive therapies.[32] The American College of Rheumatology guidelines recommend laboratory monitoring every 8–12 weeks and advise liver biopsy in patients with raised liver enzymes.[33] Therefore, regular monitoring of the patients' blood count, renal function and liver function tests are mandatory in patients undergoing Methotrexate therapy. Also, risk of cirrhosis must be

explained to the patient and advised on restriction of alcohol consumption. Various studies have evaluated the safety profile of methotrexate and DMARD's therapy.

Table 4: Side effects of Methotrexate

System/ organ	Side effects
Gastrointestinal	Nausea Vomiting Diarrhoea Gastrointestinal bleeding Complication of ulcers
Mucocutaneous	Oral ulcers Alopecia Rash Anaphylactic reactions Photosensitivity Vasculitis Nodulosis
Hematological	Mild leucopenia Thrombocytopenia Cytopenia Pancytopenia
Liver	Elevation of liver enzymes Fibrosis (mild to severe) Cirrhosis
Immunological/infections	Opportunistic infections
Nervous	Headache Dizziness Vertigo Fatigue Mood alteration Memory impairment
Respiratory	Dry cough Interstitial pneumonitis Pneumocystis carinii pneumonia

In a retrospective study, **Furuya et al.**[34] **(1996)** evaluated the possible adverse effects of MTX therapy in 276 RA patients. Around 117 (39%) patients reported adverse side effects including liver dysfunction (n=57), gastrointestinal events (n=24), cutaneous symptoms (n=6), respiratory and malignancy in 6 patents each. Dry cough without infiltration was seen in 3 patients which rapidly resolved after treatment discontinuation and recurred during re-administration in 1 patient. The study suggests a close

relationship between MTX and dry cough. It also suggested the higher oncogenic potential of MTX in RA patients than in general population.

Hirshberg et al.[7] (2000) evaluated the weekly safe dose of MTX in 35 RA patients attending the Rheumatology unit. Patients were treated with 7.5mg/week MTX dose and followed up for two years. In comparison to baseline, significant increase in mean Hemoglobin levels (12.4g/dl vs 13.0g/dl; $p<0.005$), reduction in mean white blood cells (7.9×10^9/l vs 6.8×10^9/l; $p<0.05$) and mean Erythrocyte sedimentation rates (56.8mm/h vs 35.2 mm/h; $p<0.01$) were noted at the end of 2 years. Decrease in platelet count was non-significant and no episodes of neutropenia or agranulocytosis were reported. The authors concluded that low MTX dose of 7.5mg/week is safe in elderly RA patients. However, routine determination of serum enzymes and renal function test is mandatory to reduce individual risk.

Hoekstra et al.[35] **(2003**) conducted a study to evaluate the factors related to toxicity and efficacy of MTX in 411 RA patients. Most common adverse effects reported were nausea (37%), headache (24%), dizziness (24%), rash (22%), fatigue/malaise (20%), abdominal pain (19%), cough (17%), stomatitis (17%), alopecia (13%) and diarrhea (10%). Using a logistic regression analysis, relationship between baseline variables and outcome variables (hepatotoxicity, MTX withdrawal, final MTX dose of at least 15mg/week and efficacy) were compared between Folate supplementation group and placebo group. Increased BMI was associated with hepatotoxicity, while the addition of folates reduced hepatotoxicity. Younger age and baseline GI events were related to diarrhea. As per the results, low disease activity at baseline, male gender, concomitant use of NSAIDs, lower creatinine clearance were determinants of efficacy.

Singal et al.[36] **(2005)** conducted a study to evaluate the toxicity and efficacy profile of MTX-chloroquine combination in 24 active RA patients. During the study period, clinical disease variables were measured at every visit including the number of joints with swelling, tenderness and pain, duration of morning stiffness and disease activity. 50% improvement was seen in 10 patients at the end of study. Treatment withdrawal was associated with adverse effects including excessive nausea and vomiting. Hyperpigmentation, photosensitivity, skin rashes, stomatitis and raised liver enzymes were also reported.

Buhroo and Baba[37] **(2006)** conducted a study to evaluate the adverse effects of low-dose methotrexate in 245 adult RA patients of Kashmir valley. Incidence of adverse events including gastrointestinal, hepatic, hematological and mucocutaneous were seen in 32% patients, however were mild in nature. All the adverse events were treatable and reversible. The authors advocated the use of MTX in RA patients so as to achieve maximum benefit to the patient. They further recommended routine folic acid supplementation to reduce the side effects and routine monitoring during the treatment period.

In a Pooled analysis of 21 prospective studies, **Salliot C and van der Heijde D**[38] **(2008)** studied the adverse events of MTX among 3463 RA patients who received an average low dose of MTX (8.8 mg/week) for a mean duration of 36.5 months. Adverse reactions were reported in 72.9% of patients. Gastrointestinal and elevation of liver enzymes were the most common adverse events. Prevalence of increased liver enzymes was approximately 13%. Long term MTX therapy was not associated with serious infections. The systematic study concluded that MTX monotherapy with relatively low-dose for at least 2 years shows favorable long-term safety.

In a retrospective study, **Attar S**[39] **(2010)** evaluated the frequency of side effects and factors associated with side effects in 71 RA patients treated with MTX over 3 years. Gastrointestinal side effects (31%) were commonly noted, followed by central nervous system symptoms (18%), hepatotoxicity (14%), stomatitis (10%), alopecia (10%), macrocytosis (7%), fever, malar rash and pancytopenia (4%) and MTX-induced lung injury (1%). With logistic regression analysis, renal impairment, male-gender, smoking, steroids use, hypoalbuminemia and the presence of extra-articular manifestations were determined as the major factors increasing the risk of side effects.

Pedrazas et al[40] **(2010)** evaluated the oral side effects in RA patients undergoing MTX therapy (5-20 mg weekly) for at least six months. Among patients undergoing MTX therapy, oral lesions were reported in 78.6% of patients, while only 23.8% patients undergoing other therapies reported side effects ($p < 0.001$). Most common oral events reported were ulcerative/erosive lesions (60.7%) and candidiasis (10.7%) in MTX group. The RR for developing oral lesions was 11.73 (CI 2.57 – 58.98), with low-dose MTX therapy. However, oral lesions were not significantly differentiated with respect to age, gender or dosage.

Gilani et al.[41] **(2012)** conducted a cross-sectional observational study to evaluate the frequency of adverse effects and serum minimum toxic MTX concentration in 140 RA patients undergoing low dose MTX therapy (10 mg/week) for at least 3 months. Toxicity was noted in 27% of patients. Most common toxicity associated with MTX therapy were hepatotoxicity (8.6%), nephrotoxicity (2.1%), anemia (5.7%), leucopenia (1.4%), thrombocytopenia (2.1%), pancytopenia (1.4%), gastrointestinal adverse effects (3.6%) and mucocutaneous problems (2.1%). A minimum toxic concentration of MTX at cutoff value of 0.71 μmol/l with a 71% sensitivity and 76% specificity was determined.

Mittal et al.[42] **(2012)** conducted a retrospective study to evaluate the prescription patterns, incidence, time and reasons for treatment failure of DMARDs in RA patients. Among the 474 enrolled patients, >60% received combination DMARDs. Higher prescription of Hydroxychloroquine (79.7%) and MTX (55.6%) was seen. Most common reason for treatment failure was adverse events in patients taking sulfasalazine (88.9%) and MTX (75%) and lack of efficacy leading to treatment switching with Hydroxychloroquine (>70%). Common adverse events reported were bone marrow suppression and hepatotoxicity. The authors concluded that adverse events are the major predictor of treatment compliance and failure.

Calasan et al.[43] **(2013)** evaluated the prevalence of gastrointestinal and behavioral symptoms in patients taking MTX therapy for 291 RA and psoriatic arthritis. MTX intolerance was scored using the Methotrexate Intolerance Severity Score (MISS). Gastrointestinal side effects including abdominal pain, nausea or vomiting were reported by 42% patients, MTX intolerance was seen in 11%. Prevalence of MTX intolerance was higher in patients taking parenteral MTX than oral form (20.6% vs. 6.2%; p=<0.001). The authors concluded that patients on MTX therapy should be closely monitored with MISS for early detection of MTX intolerance for timely intervention and to avoid treatment discontinuation.

Islam et al.[44] **(2013)** conducted a prospective study of 6 months duration to assess the efficacy, safety and compliance of subcutaneous MTX in 92 active RA patients. Patients were divided into injectable MTX and oral MTX groups having 46 patients each. Mean age of patients in injectable and oral groups was 45.5±12.4 and 44.6±14 years, respectively. Female predominance was seen in both groups. Mean disease duration was similar in both groups (49 months) and 35 patients in each group were positive for RA factor. While, the ACR response rates were higher in injectable group,

adverse events were relatively less than oral group. Most common adverse effects in injectable and oral MTX were nausea (37% vs. 63%), vomiting (11% vs. 30%), dyspepsia (29% vs. 48%), dizziness (4l% vs. 52%) and alopecia (72% vs. 85%). The authors conferred that injectable MTX is more effective than oral MTX at similar dosages.

In a cross sectional observational study, **Dubey et al.**[45] **(2016)** evaluated the prevalence of hepatic and hematological adverse effects with long term low dose MTX therapy of ≤15mg/week for at least 2 years in RA patients. Concomitant DMARD therapy including hydroxychloroquine (53.9%), sulfasalazine (20.1%), leflunomide (15.7%), systemic corticosteroids (54.4%) and NSAIDS 47.5%). Based on ALT cut off level of 35 IU/L, 13.73% had increased ALT levels. Adverse events including nausea, vomiting and heatburn was reported in 14 patients. Anemia was seen in 40% patients, leukopenia in 4.4% of patients was observed. None of the patients reported thrombocytopenia. Except age (p=0.025), no significant association between gender, disease duration, duration of MTX intake, concomitant drug usage and increased ALT was reported (p>0.05). The authors concluded that disease duration, cumulative MTX dose and concomitant DMARD intake are not associated with hepatic or hematological adverse events.

Alsubaie et al.[46] **(2018)** conducted a cross sectional study to evaluate the frequency and factors influencing the discontinuation rates of MTX therapy among 200 RA patients. Female predominance (84.5%) was noted in the study cohort. Mean age of patients was 45 years. Among patients with MTX therapy, 27% failed treatment compliance and adherence. Stomach ache was the most commonly reported side effect. Factors including sex, education level and disease duration did not affect the treatment

discontinuation. The authors concluded that MTX is safe drug with relatively less discontinuation rates secondary to adverse events.

Solomon et al.[47] (2020) compared the risk and rate of adverse events between low dose-MTX (maximum of 20mg/week) and placebo among RA patients with known cardiovascular disease and diabetes. Rate of adverse events was slightly higher in low dose-MTX than placebo (87% vs. 82%) with Hazard ratio of 1.17(95% CI: 1.10 – 1.25). The relative hazards of gastrointestinal (HR 1.91, 95% CI 1.75 – 2.10), pulmonary (HR 1.52, 95% CI 1.16 – 1.98), infectious (HR 1.15, 95% CI 1.01 – 1.30), and hematologic (HR 1.15, 95% CI 1.07 – 1.23) AEs were elevated, comparing LD-MTX to placebo. The authors concluded that use of low dose MTX is associated with mild or moderate risk of adverse events.

In a cross-sectional questionnaire study among 400 RA patients and 100 rheumatologists, **Sun et al.[48] (2021)** studied the safety and compliance of csDMARDs in RA treatment. MTX was the most commonly prescribed csDMARD (50.5%). The estimated incidence of side effects by rheumatologists was less as compared to the actual side effects experienced by the patients. Similarly, the understanding of common side effects differed from patients and rheumatologists. Interestingly, only 86% patients claimed to have reported the side effects to the consultant, while 40% patients did not adhere to prescribed treatment. Reasons of non-compliance to treatment were less severe symptoms and busy life-style. The results of the study highlight the gaps in rheumatologists' understanding of the occurrence and types of AEs reported by their patients.

AIM AND OBJECTIVE

- To evaluate the safety profile of Methotrexate in Rheumatoid Arthritis patients.

STUDY DESIGN AND METHODS

STUDY SITE

This study was conducted in the Department of General Medicine, KLES, Dr. Prabhakar Kore Hospital & MRC, Belagavi.

STUDY POPULATION

Study population consisted of all Rheumatoid Arthritis patients attending the Rheumatology OPD for follow up or admitted at KLES, Dr. Prabhakar Kore Hospital & MRC, Belagavi.

STUDY DESIGN

Cross sectional study

SAMPLE SIZE

117

SAMPLING METHOD

Universal sampling method was used for recruitment of patients.

STUDY DURATION

One year from 1st January 2020 to 31st December 2020

INCLUSION CRITERIA

- All diagnosed cases of rheumatoid arthritis as per ACR/EULAR Criteria 2010 already on methotrexate treatment at least for 6 months as monotherapy or in combination with other DMARDs.[21]
- Patients willing to participate in the study

EXCLUSION CRITERIA

- Patients with known Hepatic and Renal diseases prior to initiation of treatment.
- Patients with known Bone marrow disorders prior to initiation of treatment

ETHICAL CONSIDERATIONS

The present study was approved by the Institutional Committee of Human Ethics. Informed written consent was obtained from all the subjects included in the study. All the subjects participating in the study were informed about the risks and benefits of the study. We maintained the study participant's confidentiality.

DATA COLLECTION TOOLS

All the collected data was documented in a study proforma designed specific for the study.

METHODOLOGY

A total of 117 RA patients on methotrexate therapy for more than 6 months under regular follow up at Rheumatology OPD and patients admitted at KLES, Dr. Prabhakar Kore Hospital & MRC, Belagavi fulfilling the inclusion and exclusion criteria were included.

The following data was collected

- Patient demographics including, age and sex
- Clinical characteristics including disease duration, disease activity (remission, low, moderate and high activity), RA factor and ACPA positivity.
- Treatment details including, DMARDs duration, type of treatment (Monotherapy and combination therapy) MTX dose (≥12.5mg = optimal dose; <12.5mg = suboptimal dose), MTX form (oral and subcutaneous).
- Laboratory investigations including Complete Hemogram, Liver function tests and Serum Creatinine (as and when required) were assessed to evaluate the presence of anemia, leukopenia, thrombocytopenia, hypoalbuminemia, elevated transaminases and creatinine

After collecting the demographic details, a detailed history was taken to document patient reported side effects[6,31,32] including,

- GI intolerance (Dyspepsia, Nausea, vomiting, Diarrhea, anorexia)
- Stomatitis, oral ulcers
- Hair fall
- Bone marrow toxicity like pancytopenia, anemia, leucopenia, thrombocytopenia
- Infections like Herpes
- Cough, shortness of breath and fever suggestive of Interstitial Pneumonitis, pleuritic, pleural effusion, interstitial fibrosis, non-cardiogenic pulmonary edema
- Methotrexate Flu (Nausea, Myalgia, low grade fever, chills)

STATISTICAL ANALYSIS

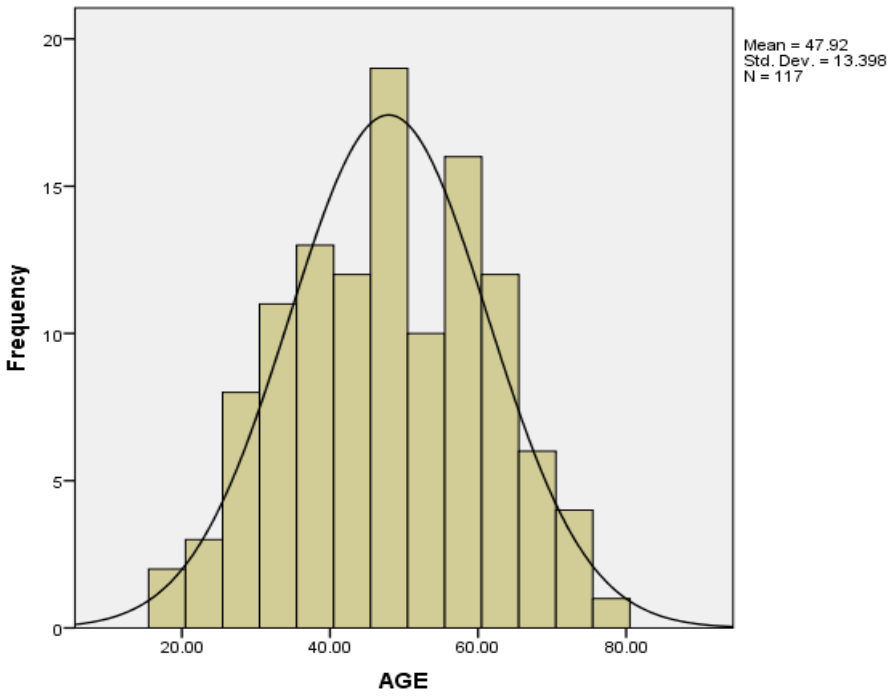
The obtained data was coded and entered into Microsoft Excel spreadsheet and then imported to SPSS for statistical analysis. Continuous variables were presented as mean and standard deviation, while the categorical variables were presented as frequency and percentages. Association between categorical variables was done using Fisher exact test or chi square test. 'p' value of <0.05 was considered statistically significant.

RESULTS

This study was conducted to evaluate the safety profile of methotrexate as monotherapy or in combination therapy with other DMARDs in patients of RA. Patients belonged to the age group of 18 to 76 years with a mean age of 47.92±13.398 (Table 5, Graph 1).

Table 5: Descriptive statistics of age in the study population

	Number	Range	Minimum	Maximum	Mean		Standard deviation
					Statistic	Standard error	
AGE (years)	117	18-76	18	76	47.92	1.23	13.398

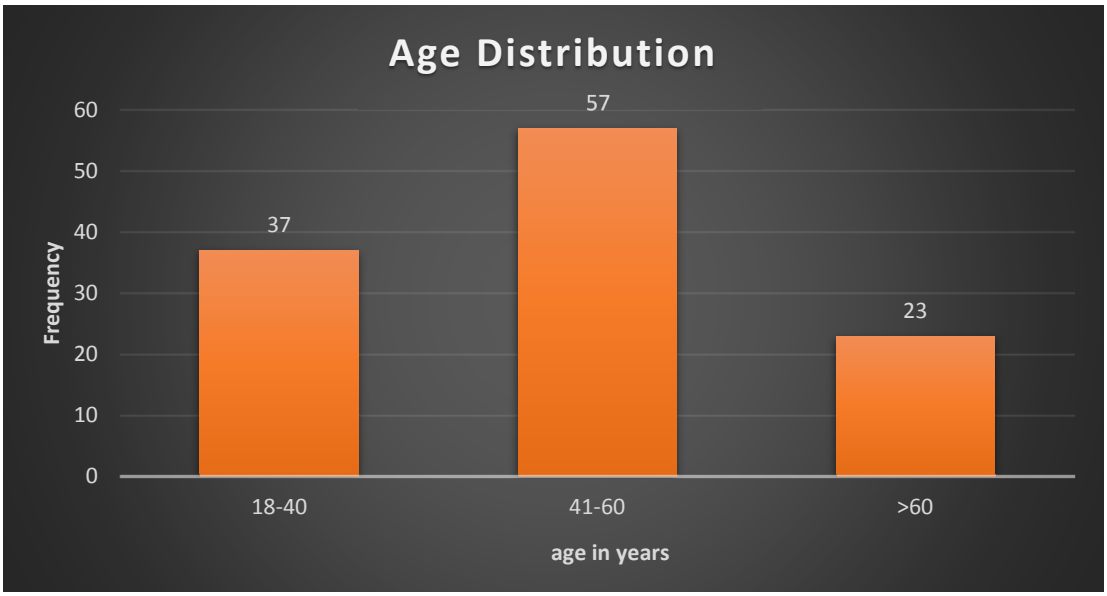


Graph 1: Histogram depicting age distribution with normal curve in the study population

Distribution of patients according to different age intervals is summarized in Table 6 and Graph 2. Among 117 patients, more than half the patients (n=57, 48.7%) belonged to the age group of 41-60 years. Around 37 (31.6%) patients belonged to the age group of 18-40 years, and 23 (19.7%) patients belonged to age group >60 years.

Table 6: Distribution of patients according to different age intervals

Age group (years)	Frequency	Percent (%)
18-40	37	31.6
41-60	57	48.7
>60	23	19.7
Total	**117**	**100.0**



Graph 2: Bar diagram showing distribution of patients according to different age intervals

The study population comprised of 101 (86.3%) females and 16 (13.7%) males. There was a female predominance with a ratio of 6:1 (Table 7)

Table 7: Gender distribution of study population

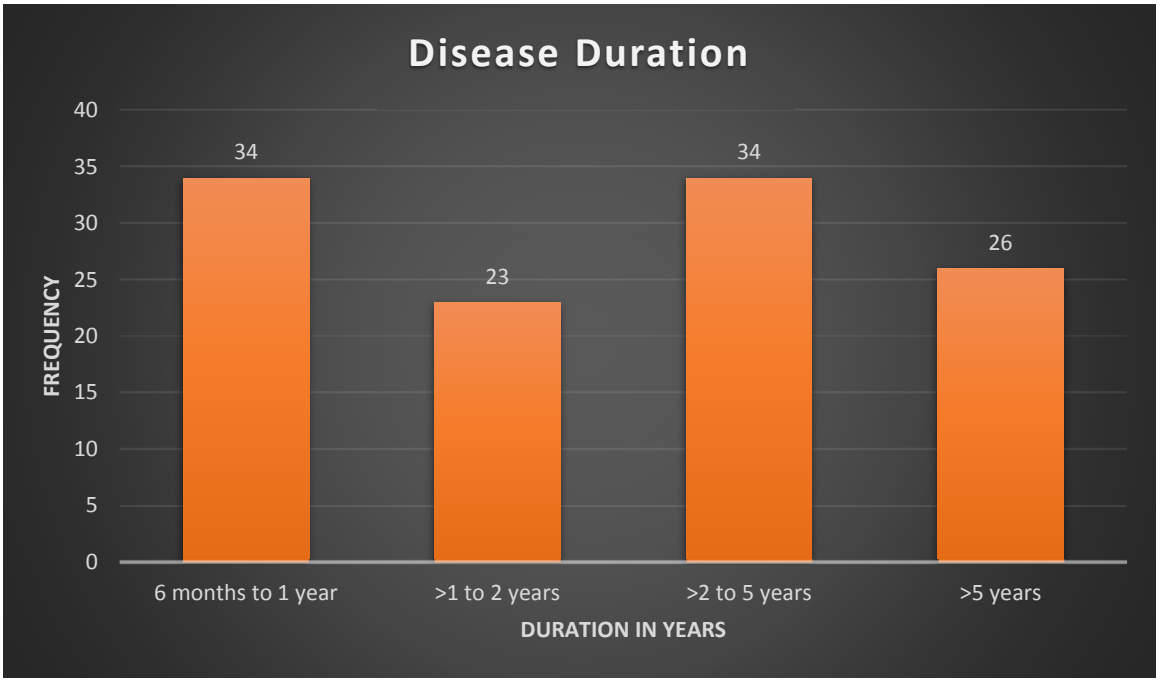
		Number	Percent (%)
Gender	**Male**	16	13.7
	Female	101	86.3
	Total	**117**	**100.0**

In our study, minimum duration of RA from the time of diagnosis was 6 months and maximum duration from the time of diagnosis was 20 years. Mean disease duration was 4.19±4.28 years. The minimum duration of DMARDs treatment was 6 months and maximum duration of DMARDs treatment was 20 years. Mean duration of treatment was 2.63±2.78 years. Minimum dose of methotrexate received by patients in our study cohort was 7.5mg and maximum dose received was 25mg. The mean methotrexate dose received by patients was 15.598±4.93mg/week (Table 8).

Table 8: Descriptive statistics of disease duration, DMARDs duration and methotrexate dose in the study population

Variable	Number	Minimum	Maximum	Mean	SD
Disease duration (years)	117	0.5	20	4.18	4.29
DMARDs duration (years)	117	0.5	15	2.61	2.79
Methotrexate dose (mg/week)	117	7.5	25	15.598	4.93

Frequency distribution of patients based on disease duration is depicted in Graph 3. Out of 117 patients, 34 (29.1%) patients each were diagnosed with RA for a year or less and >2 to 5 years, 26 (22.2%) patients had RA for more than 5 years and 23 (19.7%) patients had RA for >1 to 2 years.

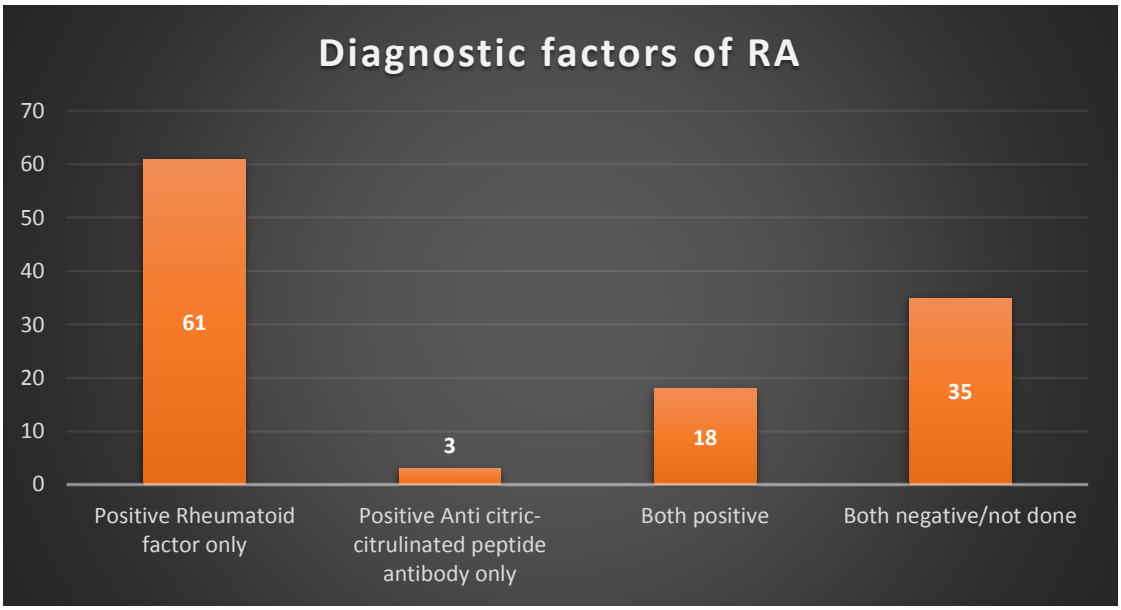


Graph 3: Bar diagram showing distribution of patients based on disease duration

In our study, among the 117 patients, only Rheumatoid factor was positive in 61 (52.1%) patients and only anti-citric-citrulinated peptide antibody was positive in 3 (2.6%) patients. Both Rheumatoid factor and anti-citric-citrulinated peptide antibody was present in 18 (15.4%) patients (Table 9, Graph 4).

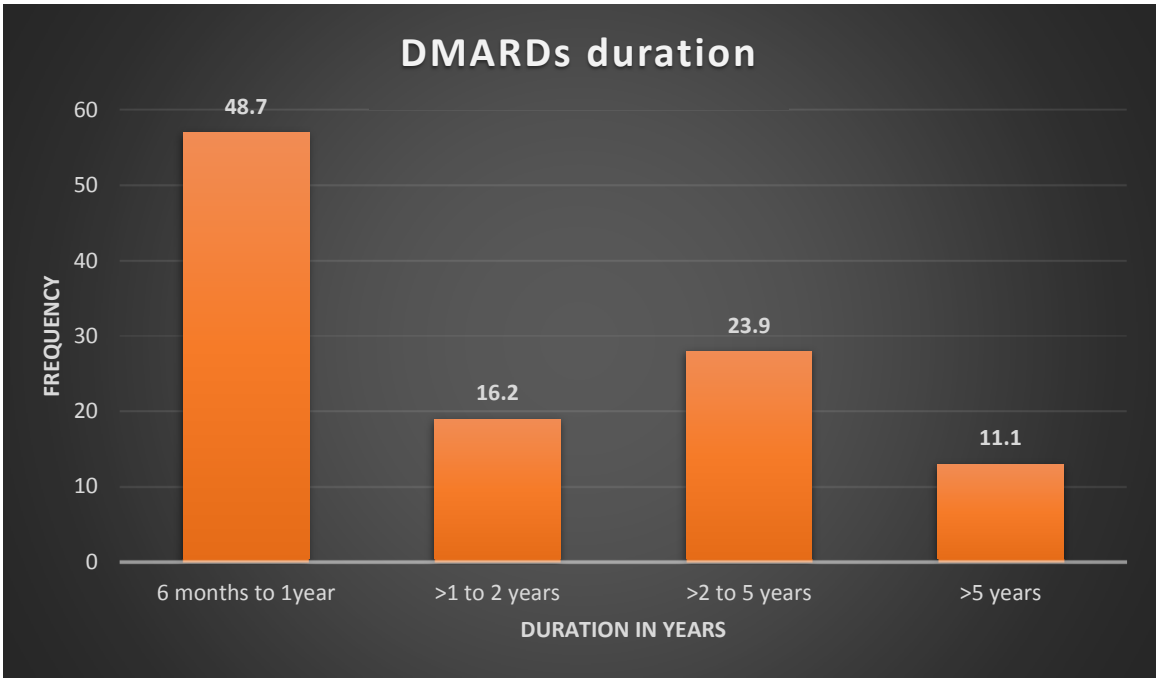
Table 9: Frequency distribution of Rheumatoid factor and anti-citric-citrulinated peptide antibody among study population

Variable	Frequency	Percent (%)
Positive Rheumatoid factor only	61	52.1
Positive anti citric-citrulinated peptide antibody (ACPA) only	3	2.6
Both Rheumatoid factor and ACPA positive	18	15.4
Both Rheumatoid factor and ACPA negative/Not done	35	29.9
Total	117	100



Graph 4: Distribution of patients based on presence/absence of RA factor and anti CCP.

Frequency distribution of patients based on DMARDs treatment duration is depicted in Graph 5. Out of 117 patients, 57 (48.7%) patients were undergoing treatment with DMARDs for a year or less, 28 (23.9) patients were undergoing treatment with DMARDs for >2 to 5 years. Duration of DMARDs was >1 to 2 years and >5 years in 19 (16.2%) patients and 13 (11.1%) patients, respectively.



Graph 5: Bar diagram showing distribution of patients based on DMARDs duration

The optimal dose of methotrexate for the treatment of RA is 12.5 mg. Categorization of patients based on the methotrexate dose received is summarized in Table 10. Out of 117 patients in our study cohort, 82 (70.1%) of patients received the optimal dose (≥12.5mg) of methotrexate, while 35 (29.9%) of patients received methotrexate in suboptimal doses (<12.5mg).

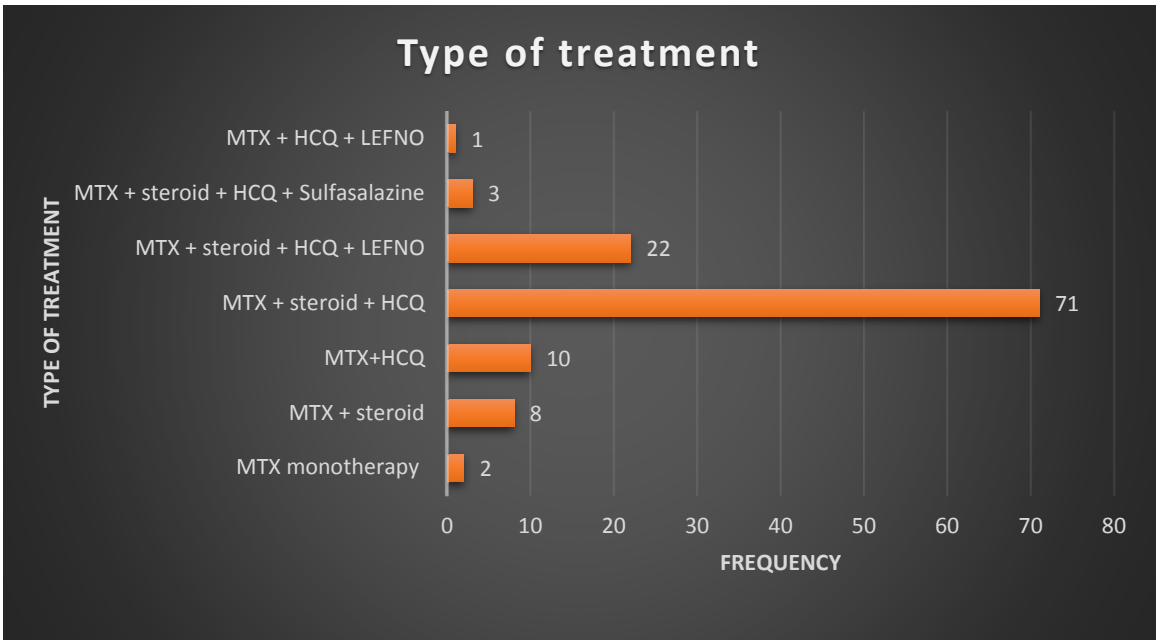
Table 10: Frequency distribution of patients based on the methotrexate dose

Methotrexate dose	**Frequency**	**Percent (%)**
Optimal dose (≥12.5mg)	82	70.1
Sub-optimal dose (<12.5mg)	35	29.9
Total	**117**	**100.0**

In our study, out of 117 patients, 2 (1.7%) patients received MTX monotherapy and 115 (98.3%) patients received combination therapy. Most of the patients (60.7%) received a combination of MTX, steroid and hydroxychloroquine. Table 11 and Graph 6 summarizes the distribution of treatment received.

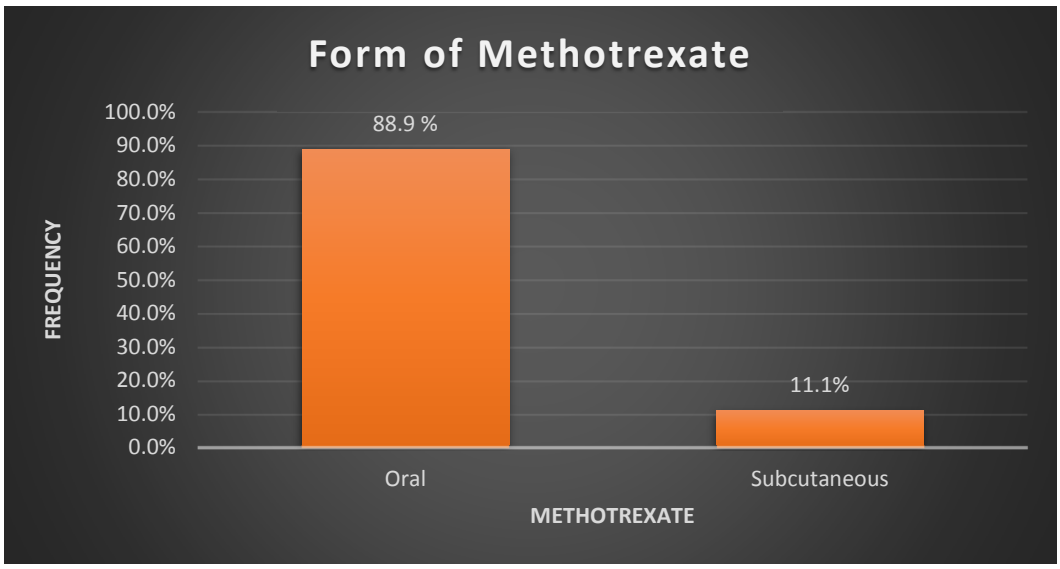
Table 11: Frequency distribution of type of treatment received by the patients

RA treatment	Frequency	Percent (%)
MTX monotherapy	2	1.7
Combination of MTX and DMARDS **MTX + low dose steroid**	8	6.8
MTX+HCQ	10	8.5
MTX + low dose steroid + HCQ	71	60.7
MTX + low dose steroid + HCQ + Leflunomide	22	18.8
MTX + low dose steroid + HCQ + Sulfasalazine	3	2.6
MTX + HCQ + Leflunomide	1	0.9
Total	**117**	**100.0**



Graph 6: Bar diagram showing distribution of patients based on type of treatment

Among the 117 patients in our study cohort, 104 (88.9%) of patients received MTX in oral form; while, 13 (11.1%) of patients received subcutaneous MTX (Graph 7).



Graph 7: Bar diagram showing distribution of patients based on methotrexate form received

Disease activity was categorized based on the CDAI/DAS28CRP scores. Nearly half the patients (n=58, 49.6%) had moderate disease activity followed by high activity in 40 (34.2%) patients, remission in 10 (8.5%) patients and low disease activity in 9 (7.7%) patients (Table 12).

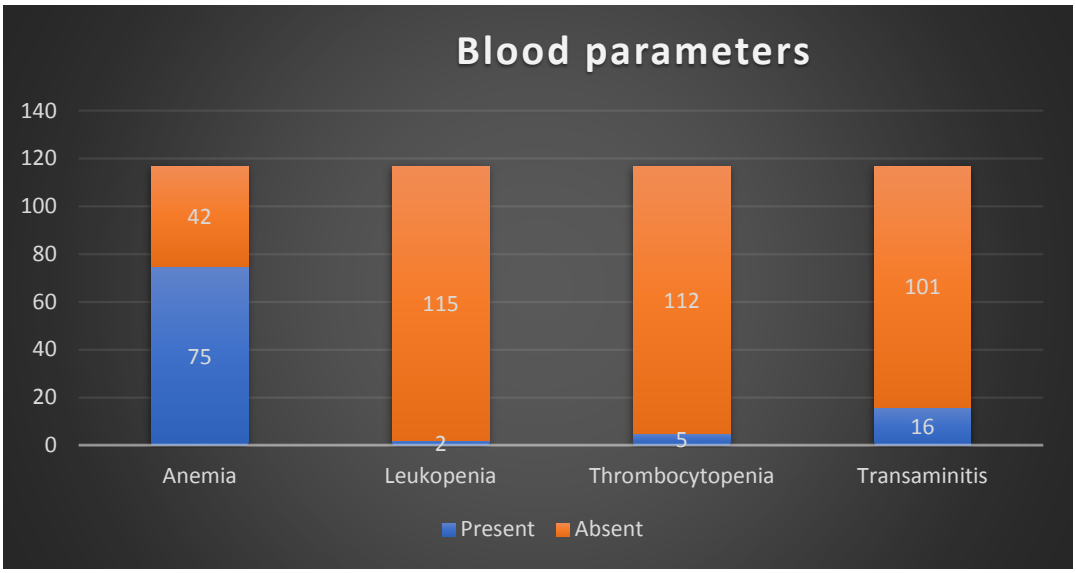
Table 12: Frequency distribution of disease activity in the study population

Disease activity	**Frequency**	**Percent (%)**
Remission	10	8.5
Low activity	9	7.7
Moderate activity	58	49.6
High activity	40	34.2
Total	**117**	**100.0**

Following MTX therapy, the blood parameters including anemia, leukopenia, thrombocytopenia and transaminitis were evaluated in our study. Among the 117 patients, 75 (64.1%) patients had anemia, 2 (1.7%) had leukopenia, 5 (4.3%) patients had thrombocytopenia and 16 (13.7%) of patients had transaminitis. Frequency distribution of blood parameters is summarized in Table 13 and Graph 8.

Table 13: Frequency distribution of blood parameters in RA patients on MTX therapy

Blood parameter	**Present n (%)**	**Absent n (%)**	**Total N (%)**
Anemia	75 (64.1%)	42 (35.9%)	**117 (100%)**
Leukopenia	2 (1.7%)	115 (98.3%)	**117 (100%)**
Thrombocytopenia	5 (4.3%)	112 (95.7%)	**117 (100%)**
Transaminitis	16 (13.7%)	101 (86.3%)	**117 (100%)**

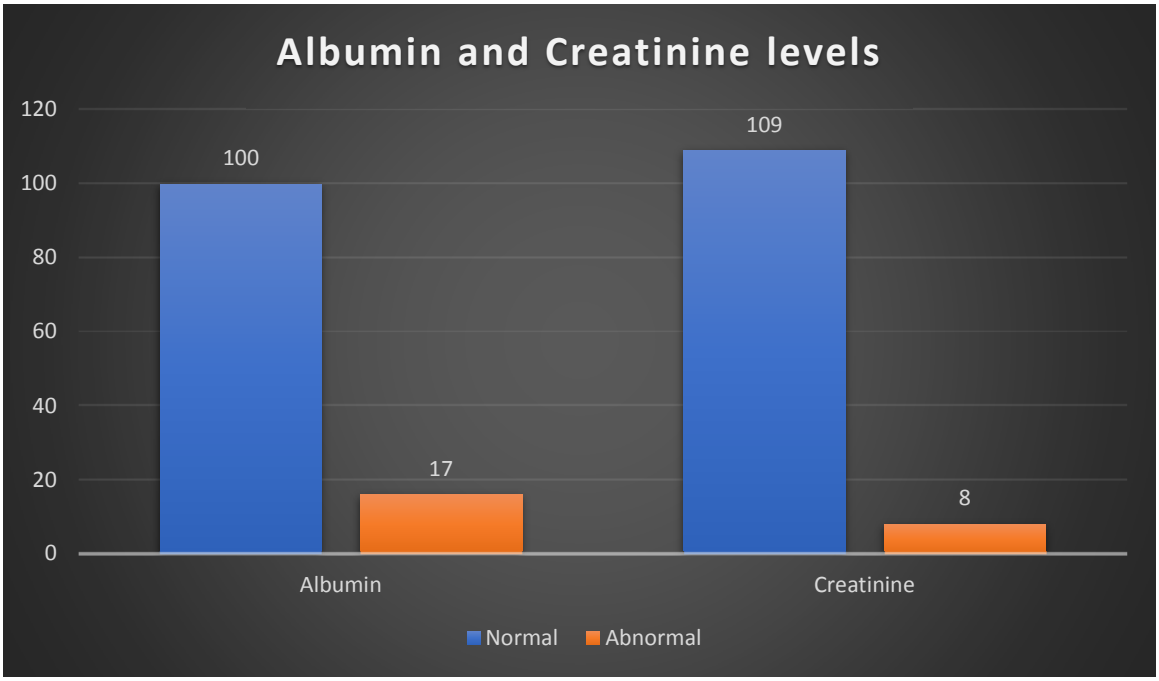


Graph 8: Distribution of blood parameters in RA patients following MTX therapy

Furthermore, the level of albumin was also evaluated. Frequency distribution of albumin level is summarized in Table 14 and Graph 9. Out of 117 patients, hypoalbuminemia was observed in 17 (14.5%) of patients; while, in 8 (6.8%) patients the creatinine levels were abnormal.

Table 14: Frequency distribution of albumin levels and creatinine levels among RA patients

Blood parameter	Normal n (%)	Abnormal n (%)	Total N (%)
Albumin	100 (85.5%)	17 (14.5%)	**117 (100%)**
Creatinine	109 (93.2%)	8 (6.8%)	**117 (100%)**

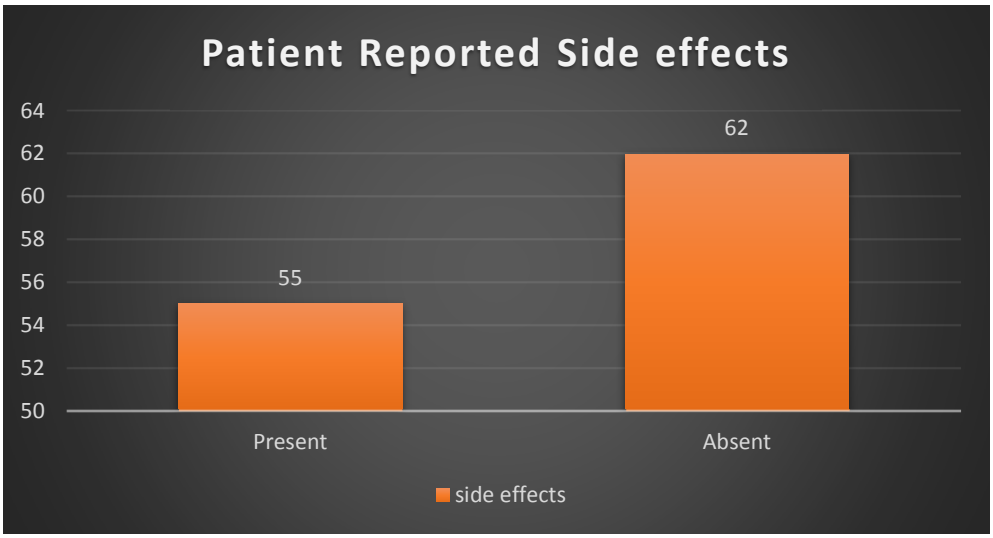


Graph 9: Distribution of patients based on albumin and creatinine levels

In our study population, 55 (47%) patients reported side effects and 62 (53%) patients had no reported side effects (Table 15, Graph 10) following MTX therapy.

Table 15: Frequency distribution of patient reported side effects

		Frequency	Percent (%)
Patient reported Side effects	**Present**	55	47
	Absent	62	53
	Total	**117**	**100.0**

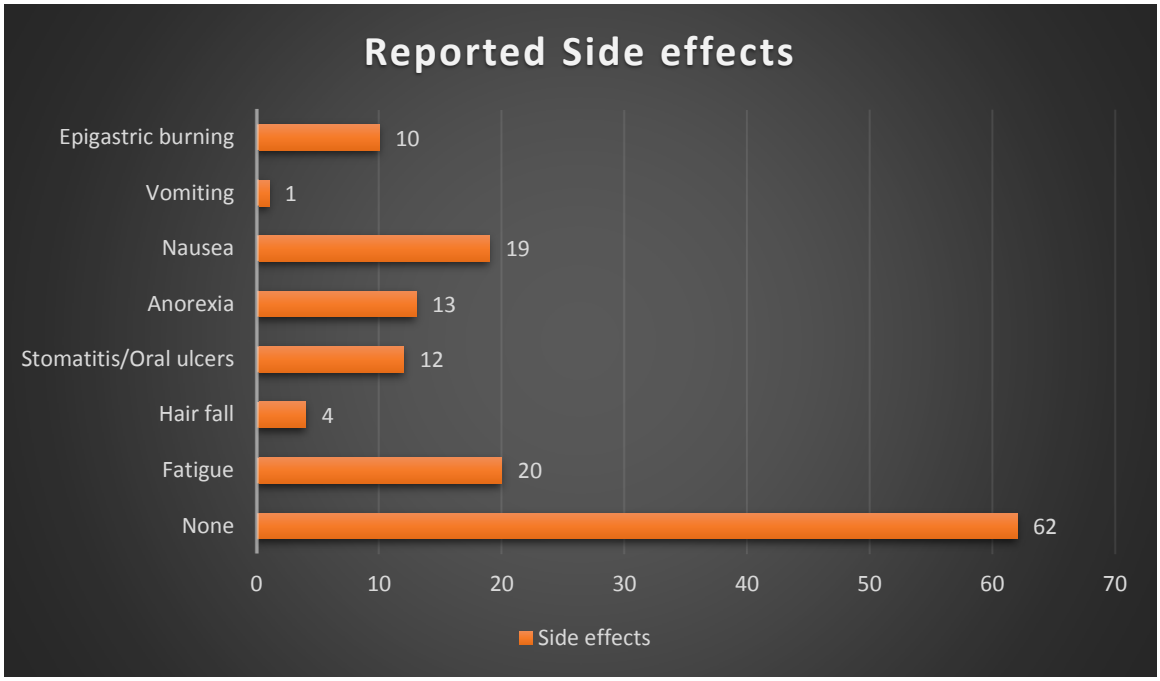


Graph 10: Graphical representation of presence/absence of side effects

Frequency distribution of patient reported side effects is summarized in Table 16 and Graph 11. Most common reported side effect was fatigue (17.1%), followed by nausea (16.2%), anorexia (11.1%), stomatitis/oral ulcers (10.3%), epigastric burning (8.5%), hair fall (3.4%), and vomiting in 0.9% of patients.

Table 16: Frequency distribution of reported side effects in the study population

Reported Side effects	Frequency (n=117)	Percent (%)
Epigastric burning	10	8.5
Vomiting	1	0.9
Nausea	19	16.2
Anorexia	13	11.1
Stomatitis/oral ulcers	12	10.3
Hair fall	4	3.4
Fatigue	20	17.1
None	62	53



Graph 11: Bar diagram depicting the distribution of reported side effects in the study population

Table 17 summarizes the association of age and patient reported side effects. 48.6% (n=18) patients in the age group of 18-40 years, 43.9% (n=25) in age group of 40-60 years and 5.22% (n=12) in age group of >60 years had reported side effects following MTX therapy. No significant association noted between incidence of side effects and age (p=0.774).

Table 17: Association of age and side effects

Variable		Side effects			Chi square value	p value
		Present	Absent	Total		
Age	**18-40**	18 (48.6%)	19 (51.4%)	37 (100.0%)	0.513	0.774 (NS)
	41-60	25 (43.9%)	32 (56.1%)	57 (100.0%)		
	>60	12 (52.2%)	11 (47.8%)	23 (100.0%)		
	Total	55 (47.0%)	62 (53.0%)	117 (100.0%)		

Association of gender on side effects is summarized in Table 18. Compared to males, side effects were higher in female patients (25% vs. 50.5%). There was no significant association between gender and patient reported side effects (p=0.058).

Table 18: Association of gender and side effects

Variable		Side effects			Chi square value	p value
		Present	Absent	Total		
Gender	**Male**	4 (25%)	12 (75%)	16 (100.0%)	3.604	0.058
	Female	51 (50.5%)	50 (49.5%)	101 (100.0%)		
	Total	55 (47%)	62 (53%)	117 (100.0%)		

No significant association noted between the duration of DMARDs therapy and side effects (p=0.079) (Table 19).

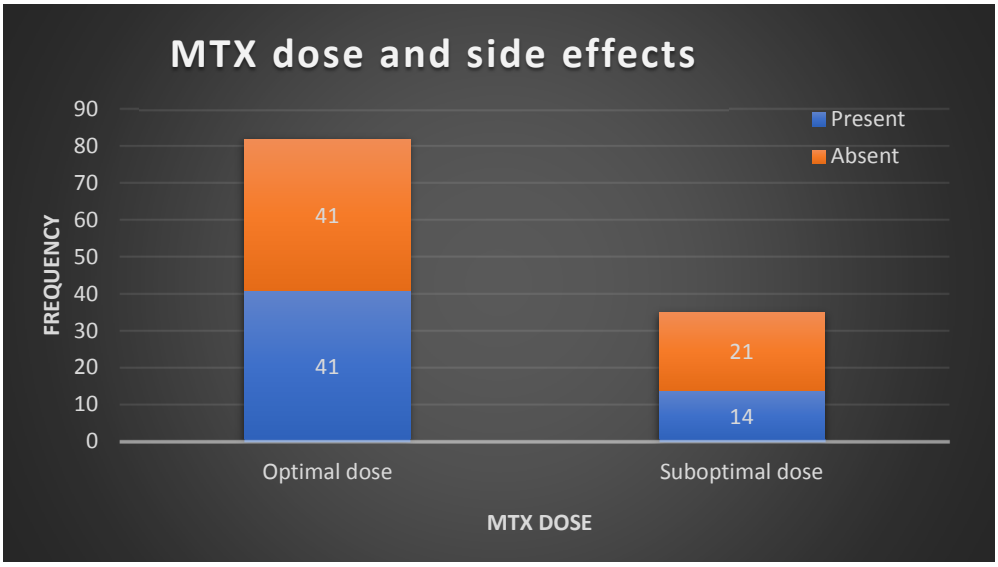
Table 19: Association between duration of DMARDS and side effects

Variable		Side effects			Chi square value	p value
		Present	Absent	Total		
Duration of DMARDs	**6 months to 1 year**	10 (29.4%)	24 (70.6%)	34 (100.0%)	6.798	0.079
	>1 to 2 years	12 (52.2%)	11 (47.8%)	23 (100.0%)		
	>2 to 5 years	17 (50%)	17 (50%)	34 (100.0%)		
	>5 years	11 (61.5%)	2 (38.5%)	26 (100.0%)		
	Total	55 (47%)	62 (53%)	117 (100.0%)		

Out of 82 patients who received optimum MTX dose of ≥12.5mg, 41 (50%) of patients reported side effects. Out of 35 patients with suboptimal dose of MTX (<12.5mg), 14 (40%) reported side effects. However, there was no significant association between MTX dose and reported side effects (p=0.321) (Table 20 and Graph 12)

Table 20: Association between MTX dose and side effects

Variable		Side effects			Chi square value	p value
		Present	Absent	Total		
Dose	**Optimal**	41 (50%)	41 (50%)	82 (100.0%)	0.985	0.321 (NS)
	Sub-optimal	14 (40%)	21 (60%)	35 (100.0%)		
	Total	55 (47%)	62 (53%)	117 (100.0%)		



Graph 12: Distribution of side effects based on MTX dose

In our study, out of 117 patients, 2 patients received MTX monotherapy and 115 patients received combination therapy. Side effects were reported in one patient who received MTX monotherapy and 54 of patients who received combination therapy. No significant association was noted between type of treatment and side effects (p=0.610) (Table 21).

Table 21: Association between type of treatment and side effects

Type of treatment	**Side effects**			**Chi square value**	**p value**
	Present	**Absent**	**Total**		
MTX monotherapy	1 (50%)	1 (50%)	2 (100.0%)	4.494	0.610 (NS)
Combination of MTX and DMARDS MTX + low dose steroid	2 (25%)	6 (75%)	8 (100.0%)		
MTX+HCQ	6 (60.0%)	4 (40.0%)	10 (100.0%)		
MTX + low dose steroid + HCQ	32 (45.1%)	39 (54.9%)	71 (100%)		

MTX + low dose steroid + HCQ + Leflunomide	11 (50%)	11 (50%)	22 (100.0%)		
MTX + low dose steroid + HCQ + Sulfasalazine	2 (66.7%)	1 (33.3%)	3 (100.0%)		
MTX + HCQ + Leflunomide	1 (100.0%)	0 (0.0%)	1 (100.0%)		

Association between MTX form and patient reported side effects is summarized in Table 22. Side effects were reported among 48 (46.2%) patients who received MTX in oral form and 7 (53.8%) patients who received MTX in injectable form. There was no significant association between the form of MTX and incidence of side effects (p=0.600).

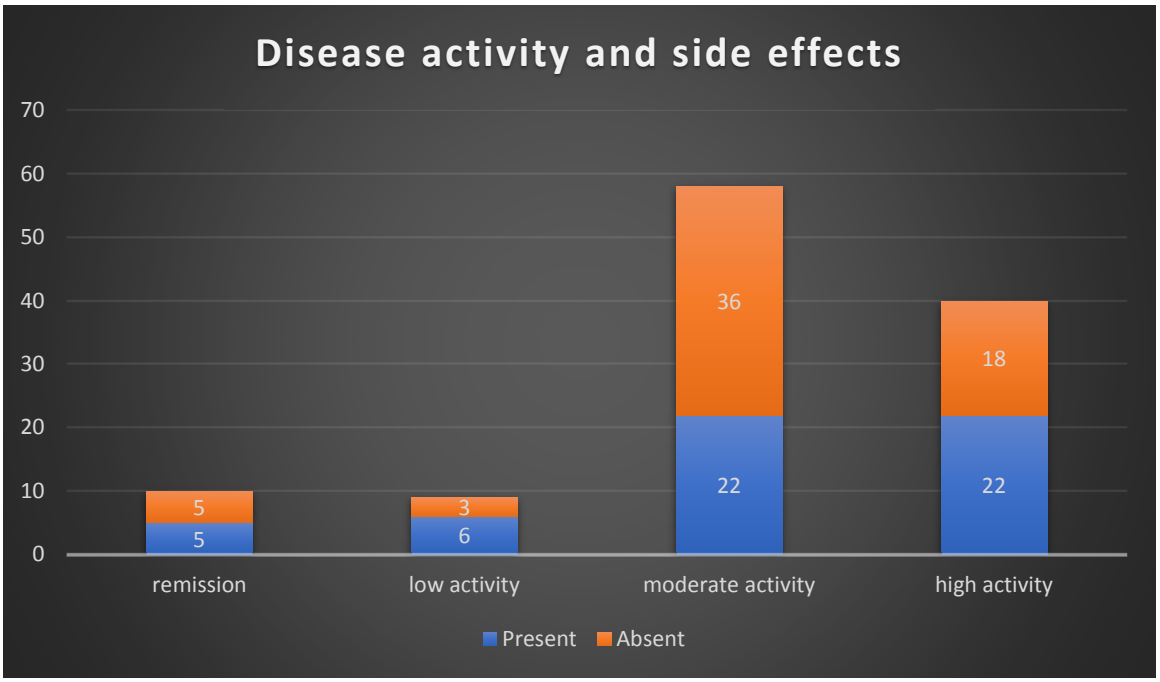
Table 22: Association between MTX form and side effects

Variable		**Side effects**			**Chi square value**	**p value**
		Present	**Absent**	**Total**		
MTX form	**Oral**	48 (46.2%)	56 (53.8%)	104 (100.0%)	0.274	0.600
	Injectable	7 (53.8%)	6 (46.2%)	13 (100.0%)		
	Total	55 (47.0%)	62 (53.0%)	117 (100.0%)		

Association between disease activity and patient reported side effects is summarized in Table 23 and graph 13. Reported side effects was higher among patients with moderate and high disease activity (n=22, each). Significant association noted between the disease activity and patient reported side effects (p=0.220).

Table 23: Association between disease activity and patient reported side effects

		Side effects		Total	Chi square value	p value
		Present	Absent			
Disease activity	**Remission**	5 (50.0%)	5 (50.0%)	10 (100.0%)	4.414	0.220
	Low	6 (66.7%)	3 (33.3%)	9 (100.0%)		
	Moderate	22 (37.9%)	36 (62.1%)	58 (100.0%)		
	High	22 (55.0%)	18 (45.0%)	40 (100.0%)		
Total		55 (47.0%)	62 (53.0%)	117 (100.0%)		



Graph 13: Distribution of patient reported side effects and disease activity

Association between anemia with other blood and laboratory parameters, MTX dose and side effects is summarized in table 24. Among 75 patients with anemia, 43 reported side effects and 32 patients had no side effects. The difference was statistically significant (p=0.003). Association between anemia and MTX dose (p=0.854), transaminases (p=0.886), leukopenia (p=0.180), thrombocytopenia (p=0.428), hypoalbuminemia (p=0.955) and creatinine (p=0.494) were not statistically significant.

Table 24: Association of anemia with patient reported side effects, MTX dose, other laboratory and blood parameters.

Variable		Anemia			Chi square value	p value
		Present (n=75)	Absent (n=42)	Total (N=117)		
Patient reported Side effects	**Present**	43 (78.2%)	12 (21.8%)	55 (100.0%)	8.941	**0.003**
	Absent	32 (51.6%)	30 (48.4%)	62 (100.0%)		
MTX dose	**Optimal**	53 (64.6%)	29 (35.4)	82 (100%)	0.034	0.854
	Suboptimal	22 (62.9%)	13 (37.1%)	35 (100%)		
Transaminases	**Normal**	65 (64.4%)	36 (35.6%)	101 (100.0%)	0.021	0.886 (NS)
	Elevated	10 (62.5%)	6 (37.5%)	16 (100.0%)		
Leukopenia	**Present**	2 (100%)	0 (0%)	2 (100%)	1.798	0.180
	Absent	73 (63.5%)	42 (36.5%)	115 (100%)		
Thrombocytopenia	**Present**	4 (80.0%)	1 (20.0%)	5 (100.0%)	0.627	0.428
	Absent	71 (63.4%)	41 (36.6%)	112 (100.0%)		
Hypoalbuminemia	**Present**	11 (64.7%)	6 (35.3%)	17 (100.0%)	0.003	0.955
	Absent	64 (64.0%)	36 (36.0%)	100 (100.0%)		
Creatinine	**Normal**	69 (63.3%)	40 (36.7%)	109 (100%)	0.467	0.494
	Elevated	6 (75%)	2 (25%)	8 (100%)		

Association between leukopenia with other blood and laboratory parameters, MTX dose and side effects is summarized in table 25. None of the patients with leukopenia reported side effects (p=0.109). Association between leukopenia and MTX dose (p=0.231), transaminases (p=0.441), thrombocytopenia (p=0.675), hypoalbuminemia (p=0.426) and creatinine (p=0.593) were not statistically significant.

Table 25: Association of Leukopenia with patient reported side effects, MTX dose, other laboratory and blood parameters.

Variable		Leukopenia			Chi square value	p value
		Present (n=2)	Absent (n=115)	Total (n=117)		
Patient reported Side effects	**Present**	0 (0%)	55 (100.0%)	55 (100.0%)	2.571	0.109
	Absent	2 (3.2%)	60 (96.8%)	62 (100.0%)		
MTX dose	**Optimal**	2 (2.4%)	80 (97.6%)	82 (100%)	1.437	0.231
	Suboptimal	0 (0%)	35 (100%)	35 (100%)		
Transaminases	**Normal**	2 (2%)	99 (98%)	101 (100.0%)	0.594	0.441
	Elevated	0 (0%)	16 (100.0%)	16 (100.0%)		
Thrombocytopenia	**Present**	0 (0%)	5 (100.0%)	5 (100.0%)	0.176	0.675
	Absent	2 (1.8%)	110 (98.2%)	112 (100.0%)		
Hypoalbuminemia	**Present**	0 (0%)	17 (100.0%)	17 (100.0%)	0.634	0.426
	Absent	2 (2%)	98 (98%)	100 (100.0%)		
Creatinine	**Normal**	2 (1.8%)	107 (98.2%)	109 (100%)	0.286	0.593
	Elevated	0 (0%)	8 (100%)	8 (100%)		

***Association between anemia and leukopenia is included in table 24**

Association between thrombocytopenia with other blood and laboratory parameters, MTX dose and side effects is summarized in table 26. Only one patient with thrombocytopenia reported side effects (p=0.199). Association between thrombocytopenia and MTX dose (p=0.624), transaminases (p=0.134), hypoalbuminemia (p=0.734) and creatinine (p=0.395) were not statistically significant.

Table 26: Association of thrombocytopenia with patient reported side effects, MTX dose, other laboratory and blood parameters.

Variable		Thrombocytopenia			Chi square value	p value
		Present (n=5)	Absent (n=112)	Total (n=117)		
Patient reported Side effects	**Present**	1 (1.8%)	54 (98.2%)	55 (100.0%)	1.651	0.199
	Absent	4 (6.5%)	58 (93.5%)	62 (100.0%)		
MTX dose	**Optimal**	3 (3.7%)	79 (96.3%)	82 (100%)	0.241	0.624
	Suboptimal	2 (5.7%)	33 (94.3%)	35 (100%)		
Transaminases	**Normal**	3 (3%)	98 (97%)	101 (100.0%)	2.245	0.134
	Elevated	2 (12.5%)	14 (87.5%)	16 (100.0%)		
Hypoalbuminemia	**Present**	1 (5.9%)	16 (94.1%)	17 (100.0%)	0.115	0.734
	Absent	4 (4%)	96 (96%)	100 (100.0%)		
Creatinine	**Normal**	5 (4.6%)	104 (95.4%)	109 (100%)	0.724	0.395
	Elevated	0 (0%)	8 (100%)	8 (100%)		

***Association of thrombocytopenia with anemia and leukopenia are not included as they are described in the tables 24 and 25.**

Association between transaminases with other laboratory parameters, MTX dose and side effects is summarized in table 27. Among 16 patients with elevated transaminases levels, 7 patients reported side effects and 9 patients had no side effects. No statistically significant difference noted (p=0.778). Association between thrombocytopenia and MTX dose (p=0.275), hypoalbuminemia (p=0.62) and creatinine (p=0.374) were not statistically significant.

Table 27: Association of transaminases with patient reported side effects, MTX dose, other laboratory and blood parameters.

Variable		Transaminases			Chi square value	p value
		Normal (n=101)	Elevated (n=16)	Total (n=117)		
Side effects	**Present**	48 (87.3%)	7 (12.7%)	55 (100.0%)	0.079	0.778
	Absent	53 (85.5%)	9 (14.5%)	62 (100.0%)		
MTX dose	**Optimal**	69 (84.1%)	13 (15.9%)	82 (100%)	1.189	0.275
	Suboptimal	32 (91.4%)	3 (8.6%)	35 (100%)		
Hypoalbuminemia	**Present**	12 (70.6%)	5 (29.4%)	17 (100.0%)	3.471	0.62
	Absent	89 (89%)	11 (11%)	100 (100.0%)		
Creatinine	**Normal**	95 (87.2%)	14 (12.8%)	109 (100%)	0.791	0.374
	Elevated	6 (75%)	2 (25%)	8 (100%)		

***Association of transaminases with thrombocytopenia, anemia and leukopenia are not included as they are described in the tables 24-26**

Association between hypoalbuminemia with other laboratory parameters, MTX dose and side effects is summarized in table 28. Among 17 patients with hypoalbuminemia, 8 patients reported side effects and 9 patients had no side effects. No statistically significant difference noted (p=0.996). Association between hypoalbuminemia and MTX dose (p=0.961) and creatinine (p=0.418) were not statistically significant.

Table 28: Association of hypoalbuminemia with patient reported side effects, MTX dose, other laboratory and blood parameters.

Variable		Hypoalbuminemia			Chi square value	p value
		Present (n=17)	Absent (n=100)	Total (n=117)		
Side effects	**Present**	8 (14.5%)	47 (85.5%)	55 (100.0%)	0.000	0.996
	Absent	9 (14.5%)	53 (85.5%)	62 (100.0%)		
MTX dose	**Optimal**	12 (14.6%)	70 (85.4%)	82 (100%)	0.002	0.961
	Suboptimal	5 (14.3%)	30 (85.7%)	35 (100%)		
Creatinine	**Normal**	15 (13.8%)	94 (86.2%)	109 (100%)	0.655	0.418
	Elevated	2 (25%)	6 (75%)	8 (100%)		

***Association of hypoalbuminemia with transaminases, thrombocytopenia, anemia and leukopenia is described in the tables 24-27.**

Association of creatinine with hypoalbuminemia, transaminases, thrombocytopenia, anemia and leukopenia are described in the tables 24-27. Association between elevated creatinine with MTX dose and side effects is summarized in table 29 and table 30. Among 8 patients with elevated creatinine levels, 4 patients reported side effects (p=0.861). Association between elevated creatinine levels and MTX dose (p=0.217) was not statistically significant.

Table 29: Association of creatinine levels with patient reported side effects

Variable		Side effects			Chi square value	p value
		Present (n=55)	Absent (n=62)	Total		
Creatinine	Normal	51 (46.8%)	58 (53.2%)	109 (100.0%)	0.031	0.861
	Elevated	4 (50%)	4 (50%)	8 (100.0%)		

Table 30: Association of creatinine levels with MTX dose

Variable		MTX dose			Chi square value	p value
		Optimal (n=82)	Suboptimal (n=35)	Total		
Creatinine	Normal	78 (71.6%)	31 (28.4%)	109 (100.0%)	1.522	0.217
	Elevated	4 (50%)	4 (50%)	8 (100.0%)		

Association between treatment type and outcome is summarized in table 31. Out of 117 patients, 10 patients had reported side effects only, 42 patients had deranged laboratory-blood parameters only, 45 patients had both side effects and deranged laboratory-blood parameters. No statistically significant association between the type of treatment and adverse treatment outcome was noted (p=0.686). Similarly, difference between the dose of MTX and adverse treatment outcomes were not significant (p= 0.725).

Table 31: Association between treatment type, MTX dose and outcome

		Side effect only (n=10)	Lab-blood parameter positive only (n=42)	both side effect and lab-blood parameter positive (n=45)	None (n=20)	Chi square and p value
Type of treatment	**MTX monotherapy**	0	1	1	0	14.653 (p=0.686)
	Combination of MTX and DMARDS MTX + low dose steroid	1	3	1	3	
	MTX+HCQ	0	4	6	0	
	MTX + low dose steroid + HCQ	6	28	26	11	
	MTX + low dose steroid + HCQ + Leflunomide	2	6	9	5	
	MTX + low dose steroid + HCQ + Sulfasalazine	1	0	1	1	
	MTX + HCQ + Leflunomide	0	0	1	0	
MTX dose	**Optimal dose**	7	27	34	14	1.316 (p=0.725)
	Suboptimal dose	3	15	11	6	

DISCUSSION

The global prevalence of RA ranges from 0.4 to 1.3.[1,49] The associated signs and symptoms include fever, tiredness, malaise and weight loss, paralleled with joint tenderness, swelling, morning stiffness.[52] In rheumatoid arthritis, the potential for joint damage is present during the early phases of disease. Therefore, early treatment that is effective in inhibiting the inflammatory and destructive mechanisms has been recommended in recent times. Methotrexate, as monotherapy or in combination with other DMARDs, glucocorticoids or biologics, is the preferred treatment for most of the patients of RA.[1] However, the common side effects related to MTX therapy are inevitable which often results in treatment discontinuation. In view of this, this study was conducted to evaluate the safety profile of Methotrexate in RA patients.

Mean age of patients in our study cohort was 47.92 years which is lower than the mean age 55.6 years noted by Myasoedova E et al.[51] and higher than 41.72 reported by Mittal et al.[42] Previous studies have suggested that RA diagnosis is higher in the sixth decade of life.[1] In our study, although 19.7% patients belonged to age group >60 years, majority patients (48.7%) belonged to the age group of 41-60 years. According to Myasoedova et al.,[51] women are affected 3-4 times as that of men. In their study, incidence of RA increased by 2.5%/year from 1995 to 2007 compared to men in whom there was a decrease in 0.5% incidence of RA per year. Similar female predominance (85.5%) was noted in our study with a female to male ratio of 6:1.

In our study, the mean disease duration was 4.19 years which is slightly lower than 6.8 years reported by Buhroo and Baba.[37] Diagnosis of RA is mainly by positivity of Rheumatic factor and ACPA. In our study, both Rheumatoid factor and ACPA were present in 18 (15.4%) patients. Rheumatoid factor was positive in (67.5%) patients,

which is in accordance with reports by Myasoedova et al.[51] (69%) and Attar SM[39] (68%). ACPA positivity was much lower than that reported by Verschueren et al.[25] (78.3%).

Choice of treatment is related to either patient preference or physician recommendation.[48] According to Quach et al.,[52] only 30% RA patients reach a low disease activity with MTX monotherapy with a dose of 20 mg/week, while the rest of them need additional medications for improvements. In a study by Dubey et al.[45] systemic corticosteroids (54.4%) were the commonly used additional DMARDs followed by hydroxychloroquine (53.9%), NSAIDS (47.5%), sulfasalazine (20.1%) and leflunomide (15.7%). The mean duration of DMARDs treatment was 2.63 years; among 117 patients, only 1.7% of patients received MTX monotherapy, while 98.3% patients received combination therapy (different combinations of MTX, steroid, hydroxychloroquine and leflunomide).

For inflammatory disorders, the therapeutic dose of oral or subcutaneous MTX is generally low ranging from 5-25 mg/week; dose administration in the right setting is considered safe.[39,53] According to EULAR recommendations, MTX dosage can be rapidly escalated to 20–25 mg/week within 4–6 weeks. However, considering the lower body weight and variable phenotypic characteristics in terms of pharmacokinetics, lower dosages of MTX are preferred in Asian population.[54] The mean methotrexate dose received by patients was 15.6mg which is in accordance with the recommended dosages. Out of 117 patients in our study cohort, 70.1% of patients received the optimal dose (≥12.5mg) of methotrexate, while 29.9% of patients received methotrexate in suboptimal doses (<12.5mg). Route of administration does not affect the absorption of MTX.[37] In a prospective study, Islam et al[44] suggested that injectable MTX is more

effective than oral MTX at similar dosages. In our study, 88.9% of patients received MTX in oral form and 11.1% of patients received subcutaneous MTX.

In our study, the disease activity after MTX therapy was categorized into remission, low, moderate and high activity based on the CDAI/DAS28CRP scores. CRP levels positively correlate with clinical, histological and radiographic findings and are further related to disease activity. Therefore, CRP is considered as a useful marker of RA in terms of diagnosis and treatment outcome monitoring.[55] The CDAI or DAS28CRP provide continuous numerical scales representing the disease activity by taking into account the swollen joint counts and tender joint counts, ESR and CRP levels.[9] Higher values depict worse disease activity. Nearly half the patients (49.6%) had moderate disease activity followed by high activity (34.2%), remission (8.5%) and low disease activity (7.7%).

Prevalence of side effects related to MTX toxicity ranges from 10-40%.[37,38,41,56] Patients reported side effects following MTX therapy in our study was comparatively higher (47%). Frequency of patient reported side effects differs in different regions due to patient related and physician related factors.[48] Literature enumerates the following toxicities associated with MTX irrespective of clinical doses including hematologic, malignant, gastrointestinal, pulmonary, infectious, mucocutaneous, renal, neuropsychiatric and musculoskeletal side effects.[31,41,47,57-60] Most common symptoms in a study by Attar SM[39] (2010) were gastrointestinal upset (31%), central nervous system symptoms (18.3%), abnormal liver function tests (14.1%), stomatitis (9.9%), alopecia (9.9%), macrocytic red blood cells picture (7%), fever with no infection (4.2%), macular rash (4.2%) and pancytopenia (4.2%).

A 30% incidence of gastrointestinal side effects is reported by Shea et al (2014). Accumulation of MTX for a prolonged period in the intestinal mucosal cells leads to sensitivity of the epithelium resulting in gastrointestinal symptoms.[62] Similar to literature,[37] in our study, majority of symptoms were gastrointestinal related including nausea (16.2%), anorexia (11.1%), epigastric burning (8.5%) and vomiting (0.9%). The gastrointestinal symptoms can be managed with drugs including H2 blockers, antacids, folate supplementation. Incidence of fatigue (17.1%) was the next common side effect after gastrointestinal side effects.

Pedrazas et al.[40] (2010) in their study showed that RA patients undergoing low dose MTX therapy (78.6%) had higher relative risk (11.73; CI: 2.57-58.98) of developing oral events than patients using other combination of drugs (23.8%). Mucocutaneous changes are due to impairment of oral mucosa and immunosuppression. Frequency of stomatitis/oral ulcers was relatively lower (10.3%) in our study cohort. Although mild pulmonary side effects such as cough and dyspnea are common with MTX, hypersensitivity pneumonitis is also reported by Conway et al. (2015).[63] Patients on MTX therapy are prone to infection due to immunosuppressive nature of MTX.[47] In our study cohort, pulmonary side effects were not experienced by any patients. Incidence of alopecia was comparatively lower (3.4%) than previous reports with MTX therapy (10%), occurrence is which is troublesome especially in young females which may hinder them from treatment continuation.[39]

Frequency of hematological side effects ranges from 1-25% and comprise of mild leukopenia and pancytopenia are common in elderly patients with baseline folate deficiency.[37,38,64] Myelotoxicity is mainly due to increased serum MTX levels caused by delayed elimination, renal dysfunction, or hypoalbuminemia secondary to

inflammation or liver disease.[65] Pancytopenia has also been seen after accidental methotrexate overdose in patients with hypoalbuminemia. We observed anemia in 64.1% patients, leukopenia in 1.7% patients, thrombocytopenia in 4.3% patients and hypoalbuminemia in 14.5% patients. Higher frequency of anemia and hypoalbuminemia seen in our study could be related to predefined anemia and hypoproteinemia present at baseline in many patients, making them more vulnerable to MTX toxicity. Elevated transaminases were seen in 13.7% of patients which is in accordance with results of Gilani et al.[41] (2012), who reported 13% incidence of raised transaminases (twice the normal ULR) in MTX therapy. But the incidence was lower than 30% to those reported by Buhroo and Baba (2006).[37] Notably, incidence of elevated serum creatinine was slightly higher with MTX therapy as compared to a study by Buhroo and Baba[37] (6.8% vs. 2.1%).

Previous studies have suggested high BMI, female gender, concomitant NSAIDs use, gastrointestinal events prior to MTX therapy and creatinine clearance as the possible risk factors for developing MTX toxicity.[39] Islam et al.[44] observed a decreased rate of side effects in injectable form than oral MTX. While Edelman et al.[66] and Dubey et al.[45] reported age as a potential risk factor for MTX toxicity, however the mechanism remains unknown. MTX toxicity related adverse effects is one of the major reasons for treatment discontinuation in approximately 12% patients after mid-long term therapy.[43] Gastrointestinal symptoms are higher with oral form leading to treatment switch from oral to parenteral forms.[57] However, despite treatment switch persistence of GI symptoms are reported Ćalasan et al (2013).[43] Compared to oral therapies with repeated dosages, Pulse dosage schedules of MTX therapy induces lower and short duration blood levels, thus reducing toxicity.[41]

In accordance with reports by Hoekstra et al.,[35] Dubey et al.,[45]Drosos et al.,[67] and Berkun et al.,[68] who reported no correlation between age, MTX dose and oral lesions, demographic and clinical factors including age (p=0.774), gender (p=0.058), disease activity (p=0.220), duration of treatment (p=0.079), MTX dose (p=0.321), type of treatment i.e. MTX monotherapy or in combination therapy with other DMARDs (p=0.610), MTX form i.e. oral or subcutaneous (p=0.600) were not associated with side effects in our study. Similarly, none of the blood and laboratory parameters were correlated with each other and with MTX dose and side effects (p>0.05) except for anemia (p=0.003) suggesting that the abnormalities are not dose related and independent of the MTX dose, type of treatment and side effects. We further categorized the adverse outcome as side effects only, deranged laboratory-blood parameters only and those with both side effects and deranged lab-blood parameters. Nearly half of patients had both side effects and deranged laboratory-blood parameters. However, type of treatment (p=0.686), dose of MTX (p= 0.725) and adverse treatment outcome were not related to each other.

Due to cytocidal effects of MTX, MTX associated folic acid deficiency worsens the side effects and tissues with rapid turnover rate, including that of bone marrow and mucosa of oral cavity and gastrointestinal tract. Therefore, clinical manifestations in the form of oral ulcers, diarrhea, abdominal pain and abnormal blood counts are seen during initial therapy. Hence, folate supplementation, preferably folic acid as prophylaxis is advised in patients undergoing MTX therapy, to prevent or decrease the incidence of side effects.[5,69] Previous studies have reported lower incidence of side effects with folate supplementation.[37] A meta-analysis in 2013 by Shea et al.[70] demonstrated that daily or weekly folic acid supplementation was effective in reducing

gastrointestinal adverse effects and transaminases, thereby reducing the incidence of treatment discontinuation.

Additionally, care must be taken to identify toxicities in patients with MTX therapy as combinations of toxicities may result in complications with poor outcome. Risk of septicemia is quadrupled in patients reporting combination of stomatitis and neutropenia. Treatment for neutropenia includes leucovorin rescue therapy, granulocyte colony stimulating factors (G-CSF) and broad-spectrum antibiotics. Recent oral overdose can be reversed with activated charcoal. Binding of activated charcoal to MTX aids urinary excretion.[71] Incorrect dose administration and improper drug interactions may also result in MTX toxicity. However, in cases of presumed toxicity secondary to drug interactions, the use of MTX should be temporarily withheld.[72]

Although abnormal liver tests during initial MTX therapy is hallmark of toxicity, this could be a result of innocuous fluctuations and normalize with little or no manipulation of low MTX dose. However, frequent monitoring is vital.[73,74] Clinician must be aware of regular monitoring of MTX toxicity and educate the patients on the same, especially in patients with anemia and hypoalbuminemia before MTX therapy as they are at greater risk of toxicity. A thorough instruction to the patient or the caregiver regarding dosage, route and day of administration, complications to watch out for must be given prior to therapy. This enables the patient to be cautious and report any toxicity related symptoms without hesitation and prevent unnecessary treatment discontinuation.

Periodic blood and laboratory monitoring is essential to detect toxicities as early as possible. Guidelines have been recommended by international Rheumatology societies to monitor patients during MTX therapy, including baseline blood counts, serum creatinine analysis, liver function tests including transaminases, followed by regular

monitoring of the above mentioned parameters at bimonthly to monthly intervals for the first 3 months followed by 2-3 months for the next 3 months and then at 3 months interval thereafter.[24,74,75] According to a study by Darmon et al.,[76] high dose MTX used in oncology patients was associated with renal toxicity. Since MTX is renally cleared, kidney function also needs to be monitored during treatment.

Interestingly, a survey by Erkan et al.[77] has suggested that Methotrexate is the most commonly opted medication for moderate to severe disease activity. Alternative to MTX has been studied in literature. Sulfasalazine or hydroxychloroquine are useful alternatives in low-risk patients with low disease activity. NSAIDs and corticosteroids are also prescribed for pain control and reduction in inflammation. Another alternative Leflunomide is although useful, however is also associated with gastrointestinal adverse effects.[35,78] Similarly, combination therapies are also associated with higher frequency of adverse events.[79] Improvement in side effects are reported was seen despite treatment continuation and in few cases MTX therapy was temporarily withdrawn and reintroduced again.[36] Study by Sun et al.[48] (2021) has reported gaps between the consultant's understanding of the adverse event incidence and those actually reported by patients suggesting that improvement in doctor-patient communications, and practical approach to evaluation and management of side effects may improve treatment adherence in RA patients.

STRENGTHS AND LIMITATIONS

In this study, different patient reported symptoms based on routes of administration, dose of MTX (suboptimal vs optimal) and different drug combinations was assessed to give a detailed understanding of the causal relationship. Cross sectional nature of the study is one of the major limitations of the study. Convenience sampling technique with its associated selection bias be considered another limitation. Although with the available sample size, the side effects and its relationships were assessed, however, more robust results would be possible with larger sample and prospective study design. Therefore, further prospective controlled trials with in depth laboratory investigations and regular monitoring of the patient reported symptoms are warranted to validate the cross-sectional study. Along with demographic features and pretreatment characteristics, genetic polymorphism has been implicated as a predictive factor for MTX toxicity,[68] Further research is warranted in this regard.

CONCLUSION

MTX is relatively safe drug. Despite the fact that almost all patients received MTX as a part of combination therapy, the incidence of patient reported side effects was 47%. Apart from common reported minor side effects such as fatigue (17.1%), nausea (16.2%), anorexia (11.1%), stomatitis/oral ulcers (10.3%), epigastric burning (8.5%), hair fall (3.4%), and vomiting in 0.9% of patients, no serious or life-threatening side effects were reported. In this study, 64.1% patients were anemic, 1.7% patients had leukopenia, 4.3% patients had thrombocytopenia and 13.7% patients had elevated transaminases levels.

Demographic and clinical factors including age (p=0.774), gender (p=0.058), disease activity (p=0.220), duration of treatment (p=0.079), MTX dose (p=0.321), type of treatment i.e. MTX monotherapy or in combination therapy with other DMARDs (p=0.610), MTX form i.e. oral or subcutaneous (p=0.600) were not associated with side effects. Similarly, no significant association between side effects and type of treatment (p=0.686), a dose of MTX (p= 0.725) was observed. Hence, this study proposes that our group of study population tolerated methotrexate well without any life-threatening side-effects. Hence, use of methotrexate in combination with other DMARDs is safe and should be encouraged as first line treatment of RA on routine basis.

SUMMARY

Methotrexate as monotherapy or in combination with other DMARDs, is recommended as first-line therapy in patients with active RA. MTX is considered as a safe drug. This study was conducted to evaluate the safety profile of Methotrexate in RA patients. Between 1st January 2020 to 31st December 2020, 117 patients diagnosed with RA and under methotrexate treatment at least for six months as monotherapy or in combination with other DMARDs with regular follow up at Rheumatology OPD and patients admitted at KLES, Dr. Prabhakar Kore Hospital & MRC, Belagavi fulfilling the inclusion and exclusion criteria were included in this cross sectional study.

Patient demographics including, age and sex; clinical characteristics including disease duration, disease activity (remission, low, moderate and high activity), RA factor and ACPA positivity; treatment details including, DMARDs duration, type of treatment (Monotherapy and combination therapy) MTX dose (≥12.5mg = optimal dose; <12.5mg = suboptimal dose), MTX form (oral and subcutaneous); laboratory and blood investigations including Complete Hemogram, Liver function tests and Serum Creatinine (as and when required) were assessed to evaluate the presence of anemia, leukopenia, thrombocytopenia, elevated transaminases; and patient reported side effects were also recorded in the study proforma.

The study population consisted of predominantly females (85.5%), and the mean age of patients was 47.92±13.398 years. Mean disease duration and treatment duration were 4.19±4.28 years and 2.63±2.78 years, respectively. Around 98.3% of patients received MTX as a combination therapy, 70.1% received the optimal dose (≥12.5mg) of MTX, and 88.9% received an oral form of MTX. Patient-reported side effects were reported in 47% of patients. Apart from common reported minor side effects such as fatigue (17.1%), nausea (16.2%), anorexia (11.1%), stomatitis/oral ulcers (10.3%), epigastric

burning (8.5%), hair fall (3.4%), and vomiting in 0.9% of patients, no serious or life-threatening side effects were reported. In this study, 64.1% patients were anemic, 1.7% patients had leukopenia, 4.3% patients had thrombocytopenia and 13.7% patients had elevated transaminases levels.

Demographic and clinical factors including age (p=0.774), gender (p=0.058), disease activity (p=0.220), duration of treatment (p=0.079), MTX dose (p=0.321), type of treatment i.e. MTX monotherapy or in combination therapy with other DMARDs (p=0.610), MTX form i.e. oral or subcutaneous (p=0.600) were not associated with side effects in our study. Similarly, no significant association between side effects and type of treatment (p=0.686), a dose of MTX (p= 0.725) was observed. Our group of study population tolerated methotrexate well without any life-threatening side-effects.

By evaluating different patient reported symptoms based on routes of administration, dose of MTX (suboptimal vs optimal) and different drug combinations, results of our study add on value to the existing understanding of the causal relationship. However, cross sectional nature and convenience sampling technique with its associated selection bias be considered another limitation. Although with the available sample size, the side effects and its relationships were assessed, however, more robust results would be possible with larger sample and prospective study design. Therefore, further prospective controlled trials with in depth laboratory investigations and regular monitoring of the patient reported symptoms are warranted to validate the cross-sectional study. Nonetheless, we believe that MTX is a reasonably safe drug; however**,** periodic blood and laboratory monitoring along with patient follow-ups are essential to detect toxicities as early as possible.

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ANNEXURE – I

ETHICAL CLEARANCE CERTIFICATE

K.L.E. ACADEMY OF HIGHER EDUCATION AND RESEARCH
(Deemed - to- be- University)
Accredited 'A' Grade by NAAC (2nd Cycle) Placed in Category 'A' by MHRD (GoI)
JAWAHARLAL NEHRU MEDICAL COLLEGE,
NEHRU NAGAR, BELAGAVI-590010 (KARNATAKA-INDIA)
Website: http//www.jnmc.edu
E-Mail : dome@jnmc.edu
Phone: (+ 91-(0)831 Office : 2472550
Principal: 2471701
Fax No. +91 (0)831 – 2470759

Ref: MDC/DOME/ 208 **Date: 24/12/2019**

To,
BG0119006
PG student in Medicine,
J.N.Medical College,
BELAGAVI.

Sub: Institutional Ethical Clearance for the study.

With reference to the above, we wish to inform you that your proposed research project titled **"SAFETY PROFILE OF METHOTREXATE IN PATIENTS WITH RHEUMATOID ARTHRITIS",** is ethical and justifiable. The proposed research project has been cleared by the JNMC Institutional Ethics Committee on Human Subjects Research.

(Dr. Anita Dalal)
Member Secretary
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

(Dr. Roopa M Bellad)
Chairman,
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

ANNEXURE - II

CONSENT FORM - ENGLISH

Title Of Research Study: SAFETY PROFILE OF METHOTREXATE IN PATIENTS WITH RHEUMATOID ARTHRITIS.

I voluntarily agree to take part in this study by signing below. I may withdraw at any time. I am not giving up any of my legal rights by signing this form. My signature below indicates that I have read this consent form, or it has been read to me and has been explained to me in my vernacular language and all my questions have been answered. I will be given a copy of this consent form.

Signature/Left Thumb print of the Participant or legally authorized representative

Participant's name :……...

Signature/Left thumb impression :……...
of the participant

Name of the legally authorized :……...
representative/guardian

Signature/Left thumb impression :……...

Witness' name :……...

Signature/Left thumb impression :……...

Investigator's name and signature :……...

Date:

Place:

ANNEXURE - III

PROFORMA

OPD NO: IP NO.

NAME: DATE:

AGE: SEX:

ADDRESS:

PHONE NO:

DOA: DOD:

COMPLAINTS AT PRESENTATION:

DURATION OF DISEASE: Diagnosed in

DURATION OF DMARDs Use: Started Treatment in

Methotrexate	Leflunomide	Hydroxychloroquine	Steroid	NSAIDs	Sulphasalazine

DRUG HISTORY in Last 1 year

Duration/Drug	Methotrexate	Leflunomide	HCQ	Steroid	NSAIDs	Sulphasalazine
3 months						
6 months						
9 months						
12 months						

CUMULATIVE DOSE OF METHOTREXATE:

PATIENT REPORTED SIDE EFFECTS:

Side Effect	YES	NO
Epigastric burning		
Vomiting		
Diarrhea		
Anorexia		
Stomatitis/oral ulcers		
Hair fall		
Cough		
Fatigue		
Methotrexate Flu		
Nausea		
Others		

GENERAL PHYSICAL EXAMINATION:

Icterus:

Pallor:

LOCAL EXAMINATION:

Disease Activity -

Tender Joint Count –

Swollen Joint Count -

Investigations:

Parameter	Actual Value	Reference Range
Hemoglobin		
Total Leucocyte Count		
Platelets		
SGOT		
SGPT		
Albumin		
Total Bilirubin		
Sr. Creatinine		
Rheumatoid Factor		
Anti-CCP Antibody		
HS-CRP		

ANNEXURE – IV → MASTER CHART

SR.NO	NAME	OP.No/IP.No	AGE GROUP	SEX	DURATION OF DMARDs	DISEASE DURATION	MTX Dose	MTX Form	TREATMENT	TJC	SJC	GLOBAL VAS	Disease Activity	RA FACTOR	ACPA	REPORTED SIDE EFFECTS	BLOOD PARAMETERS					
																	Anemia	Leucopenia	Thrombocytopenia	Transaminases	Hypoalbuminemia	Creatinine
1	NIRMALA RAJSHEKAR HIREMATH	5210706	1	2	2	2	15	1	5	18	8	8	4	POSITIVE	NOT DONE	2,3	A	B	B	1	B	1
2	ROOPA RAMCHANDRA ARKASALI	4336603	2	2	3	3	10	1	4	20	8	6	4	NEGATIVE	NEGATIVE	5	A	B	B	1	B	1
3	SUNANDA BASAPPA MADAPUR	5314518	2	2	3	3	20	2	5	18	6	7	4	POSITIVE	NEGATIVE	10	A	B	B	1	A	1
4	MANGAL MANGESH YALLARI	5307159	1	2	2	3	15	1	7	8	2	7	3	POSITIVE	POSITIVE	7	A	B	B	1	B	1
5	GIRIJAWWA YALLAPPA MURGOD	648149	2	2	4	4	20	1	3	2	0	1	2	POSITIVE	NOT DONE	6,9	A	B	A	1	B	1
6	SIDDARAY TAMMANNA BIRADAR	4762597	2	1	2	3	15	1	4	2	1	2.5	3	POSITIVE	NOT DONE	10	A	B	B	2	A	1
7	GANGUBAI BHIMRAYGOUDA GOUDAPPAGOL	5729706	1	2	2	2	10	1	4	3	2	2	2	NEGATIVE	NOT DONE	10	A	B	B	1	B	1
8	LEENA BASAVARAJ KEMPANNAVAR	4259689	2	2	2	3	15	1	4	0	0	2.5	1	NEGATIVE	NOT DONE	5	A	B	B	1	B	1
9	FARZANA KHWAJA MUJAWAR	1012186	1	2	1	2	15	1	4	8	6	5	4	POSITIVE	NOT DONE	10	A	B	A	1	A	1
10	MAHADEV UMAN CHORLEKAR	4792358	3	1	2	3	20	1	4	11	6	6	3	NEGATIVE	NEGATIVE	3	A	B	B	1	B	1
11	CHANGUNA NARAYAN PATIL	5190593	2	2	2	3	25	2	5	2	1	3	3	POSITIVE	NOT DONE	10	A	B	B	1	B	1
12	MANGAL NARSO LATHE	4323189	2	2	3	4	15	1	4	3	2	2.5	3	POSITIVE	NOT DONE	10	A	B	B	1	B	1
13	ANASIN MICHAEL ALMEDA	5434477	2	2	3	4	15	1	4	6	6	5	4	POSITIVE	NOT DONE	10	A	B	A	2	B	1
14	YALLAVA BASAPPA MELAMATHI	526777	2	2	2	3	15	1	5	3	1	2	3	POSITIVE	NOT DONE	10	A	B	B	1	B	1
15	MADIWALAPPA G. AGASIBAGIL	6126025	2	1	5	5	15	1	4	14	14	5	4	POSITIVE	POSITIVE	1	B	B	B	1	B	1
16	SONALI ABHAY DEVIDAS	5484343	1	2	1	1	15	1	3	5	2	3	3	POSITIVE	NOT DONE	1,3	A	B	B	1	B	1
17	GEETA GAJANAN GURAV	4297457	1	2	3	3	20	1	4	0	0	6	1	POSITIVE	POSITIVE	10	B	B	B	1	B	1
18	ALOK ADIVEPPA TAVAGAD	5429071	1	1	2	2	7.5	1	2	1	1	5	3	NEGATIVE	NEGATIVE	10	B	B	B	1	A	1
19	SUNDRA KOLKAR	5489218	1	2	2	3	10	1	4	1	1	2.5	2	POSITIVE	NOT DONE	10	A	B	B	1	B	1
20	SUSHILAVVA GIRIMALLA HUNNUR	5430778	2	2	2	4	15	1	5	3	3	2	3	POSITIVE	NOT DONE	10	A	B	B	1	B	1
21	NAGRATNA FAKIRAPPA INGALAGI	5250012	1	2	2	3	15	1	4	0	0	0	1	POSITIVE	NOT DONE	3,4	A	B	B	1	B	1
22	ARADHANA SANJAY JAYKAR	3404007	1	2	2	3	25	2	6	2	2	2	2	NEGATIVE	NEGATIVE	6	B	B	B	1	B	1
23	VIJAYALAXMI NARAYAN NAIK	4726842	2	2	3	3	20	2	5	0	0	1	1	POSITIVE	POSITIVE	1,3,7	B	B	B	1	B	1
24	LATA SURESH KURANE	5185143	2	2	2	2	15	1	4	8	1	1	3	POSITIVE	NOT DONE	10	A	A	B	1	B	1
25	SUSHILA RUDRAGOUDA TIGADI	4306591	2	2	3	4	25	1	4	2	0	1	1	NEGATIVE	NEGATIVE	5	B	B	B	1	B	1
26	VAISHNAVI PRAKASH BOKADE	5285938	2	2	2	2	15	1	4	0	0	1	1	POSITIVE	POSITIVE	10	B	B	B	1	B	1
27	MAHANANDA BASAVARAJ PAPADI	4710678	2	2	4	4	25	1	5	3	3	5	3	POSITIVE	NOT DONE	5	B	B	B	1	B	1
28	MADEVI GURULINGAPPA JAGADAL	4685616	2	2	3	4	25	2	5	3	1	5	3	NEGATIVE	NOT DONE	10	B	B	B	1	B	1
29	APSARA MUBEENA MULLA	5501838	1	2	2	2	10	1	4	10	10	4	4	POSITIVE	NOT DONE	10	B	B	B	1	B	1
30	ANITA ANANT JADHAV	588163	2	2	3	3	17.5	2	3	3	3	3	3	NEGATIVE	POSITIVE	9	A	B	B	1	B	1
31	PARWATI SHIVAPPA CHINCHALI	5331437	3	2	2	3	10	1	5	11	1	5	3	POSITIVE	NOT DONE	4	A	B	B	1	B	1
32	SAROJ SHIVAKUMAR	5516435	2	2	4	4	20	2	5	3	5	3	3	POSITIVE	NOT DONE	10	B	B	B	2	B	1
33	SUMANGALA SHITAL RANGOLI	5163090	3	2	3	3	20	1	4	12	2	5	3	NEGATIVE	NOT DONE	10	B	B	B	1	B	1
34	NAGAVVA BASAPPA NARAGUND	3852328	1	2	3	3	25	1	4	7	7	8	3	NEGATIVE	NOT DONE	9	A	B	B	1	B	1
35	SAVITRI MALLAPPA HIPPARAGI	5226241	2	2	2	2	15	2	5	3	2	5	3	POSITIVE	NOT DONE	10	B	B	B	1	B	1
36	VEENA SOMANING HUDIMANI	5527790	1	2	2	2	10	1	4	1	1	5	3	POSITIVE	NOT DONE	10	A	B	B	1	B	1
37	LALITA APPASAHEB SOLKAN-PATIL	3919057	3	2	4	4	17.5	2	3	3	0	7	3	NEGATIVE	NOT DONE	3,4	A	B	B	1	B	1
38	RAJASHREE NINGAPPA SHIRAGANVI	5185840	1	2	4	4	20	1	4	3	1	2.5	3	POSITIVE	NOT DONE	3,6	B	B	B	1	B	1
39	RANJANA BALKRISHNA PATIL	4077376	2	2	3	3	15	1	5	8	2	7	3	POSITIVE	POSITIVE	10	B	B	B	1	B	1
40	SUSHMABEN RAVINDRABHAI PATEL	5393463	3	2	2	4	15	1	4	3	3	7	3	NEGATIVE	NOT DONE	10	A	B	B	1	B	1
41	JUBEDA ADAM PENDARI	3893808	2	2	3	3	20	1	5	18	6	8	4	NEGATIVE	NOT DONE	10	B	B	B	1	B	1
42	ANUSAYA LAXMAN HUNDALEWADKAR	5055332	3	2	2	3	15	1	3	24	12	5	4	POSITIVE	NEGATIVE	10	A	B	B	1	B	1
43	MAHADEVI VEERBHADRA KAJAGAR	3959824	2	2	3	3	25	1	4	1	0	1	1	POSITIVE	POSITIVE	10	A	B	B	1	B	1
44	SUSHILA KUMAR AKKOLE	4496393	2	2	3	4	25	1	4	1	0	1	1	NEGATIVE	NOT DONE	10	A	B	B	2	B	1
45	SURESH SHANKAREPPA BHADRANNAVAR	2146675	1	1	3	4	20	1	6	3	2	5	3	NEGATIVE	NOT DONE	10	B	B	B	1	B	1
46	LAXMI GANPAT TORASKAR	4555134	2	2	3	4	20	1	5	1	1	5	3	POSITIVE	NOT DONE	9	A	B	B	2	B	1
47	AJAM GANACHARI	4212348	1	2	3	3	25	2	6	2	2	2	2	POSITIVE	NOT DONE	9	A	B	B	1	B	1
48	GOURAVVA MADIWALI PENTED	5033020	2	2	3	3	15	1	4	10	10	4	4	POSITIVE	NOT DONE	4	A	B	B	2	A	1
49	NUTAN SIDDGOUDA PATIL	4773686	1	2	2	2	15	1	4	0	0	1	1	POSITIVE	NOT DONE	9	A	B	B	1	B	1
50	SHASHIKANT CHANDU KATAKDHOND	1014870	1	1	1	1	10	1	3	3	2	2.5	3	POSITIVE	NEGATIVE	10	A	B	B	1	A	1
51	ASHOK BABURAO BIRAJ	1031240	3	1	1	2	10	1	1	5	4	3	3	POSITIVE	POSITIVE	4	B	B	B	2	A	2
52	SHOBHA SADASHIV MUDNOOR	1033351	3	2	2	3	15	1	4	8	6	5	4	NEGATIVE	NOT DONE	10	B	B	B	1	A	1
53	SHOBHA NARAYAN SAGANVAKAR	4294714	1	2	3	3	25	2	5	7	2	2	3	POSITIVE	NOT DONE	1,3	A	B	B	1	B	1
54	SHANTAVVA MAHAVEER DUMANNAVAR	4276331	3	2	3	4	20	1	4	0	0	2.5	2	NEGATIVE	NOT DONE	1	A	B	B	2	B	1
55	KASHAVVA BHUPAL KAMATE	5007141	3	2	3	3	10	1	4	6	5	5	3	POSITIVE	NOT DONE	10	A	B	B	1	B	1
56	KUNDA SRISHAIL KARADI	5958486	3	2	1	1	7.5	1	4	5	0	7.5	3	POSITIVE	POSITIVE	10	A	B	B	1	B	2
57	ANJANA LAV ATAWADKAR	4328488	2	2	1	2	10	1	4	10	5	3	3	POSITIVE	NOT DONE	10	A	B	A	1	B	1
58	HEENA IMRAN MOMIN	1814534	1	2	1	2	12.5	1	4	3	2	2.5	3	POSITIVE	POSITIVE	10	A	B	B	2	B	1
59	G SUJATHA VENKATESH	1032115	1	2	1	2	10	1	2	8	6	5	3	NEGATIVE	NEGATIVE	7	A	B	B	1	B	1
60	LAXMI PARSHARAM GAVADE	5483104	1	2	2	3	10	1	4	5	4	2.5	3	POSITIVE	NOT DONE	10	A	B	B	1	B	1
61	TARAMMA MULLA	5113345	2	2	3	3	15	1	2	0	0	0	1	POSITIVE	POSITIVE	10	B	B	B	1	B	1
62	AMINA ABDUL HAMID MULLA	1039659	2	2	1	1	10	1	1	5	4	2.5	3	POSITIVE	NOT DONE	10	A	B	B	1	B	1
63	LALITA SHANKARGOUDA HOSAKOTI	4787719	2	2	3	3	20	1	4	3	2	5	3	POSITIVE	NOT DONE	3,4	A	B	B	1	A	1
64	NIKITA SAVANTA KHOT	5958426	1	2	1	1	10	1	4	5	3	4	3	NEGATIVE	NEGATIVE	5	B	B	B	1	B	1
65	SANGAVVA KALLAPA NAGARAL	4031182	1	2	3	4	20	1	4	2	1	5	3	NEGATIVE	NOT DONE	10	B	B	B	1	B	1
66	LEELAVATI SHAMBULING WANTAMUTTE	1223728	3	2	1	1	12.5	1	4	24	24	8	4	POSITIVE	NOT DONE	10	A	B	B	1	B	2
67	GAITRI PUNDALEEK KUMATHE	1057114	2	2	3	3	15	1	4	4	3	3	3	POSITIVE	NOT DONE	10	A	B	B	1	B	1
68	SHAKUNTALA DEVI Y. MADIWALAR	1044933	3	2	2	3	10	1	3	2	1	2	3	POSITIVE	POSITIVE	10	A	B	B	1	A	1
69	RENUKA BABU KOLAJI	1047047	3	2	2	4	15	1	4	3	2	2	4	POSITIVE	NOT DONE	3	A	B	B	1	B	1
70	SHRUTI DASHRATH PAWAR	1040461	1	2	2	3	25	1	4	5	4	3	3	POSITIVE	NOT DONE	3,9	A	B	B	1	B	1
71	ERAMMA TIRUPATTEPPA GADDI	1044794	2	2	1	2	15	1	4	10	8	5	4	POSITIVE	NOT DONE	10	B	B	B	2	B	1
72	MANGALA RAJASHEKHAR TARALE	1044656	2	2	2	4	20	1	4	12	11	7.5	4	POSITIVE	NOT DONE	5	A	B	B	1	B	1

73	KAMALA TUKARAM KILLEKAR	4491739	2	2	1	1	20	1	2	2	1	3	3	POSITIVE	NOT DONE	10	B	B	B	1	B	1
74	ANJANA VISHWAS KULKARNI	1047874	3	2	2	3	10	1	3	3	2	2.5	3	POSITIVE	NOT DONE	10	A	B	B	1	B	2
15	BASAVARAJ G. ULLEGADDI	4727577	1	1	1	1	20	1	5	3	1	2	2	POSITIVE	NOT DONE	10	B	B	B	1	B	1
76	ARUNA SUBHASH HEREKAR	4724501	3	2	3	3	10	1	5	2	1	1	2	POSITIVE	NOT DONE	3,6	A	B	B	1	B	1
77	MAHADEVI BASAPPA BUDIHAL	4384503	2	2	3	4	15	1	4	23	6	7.5	4	POSITIVE	NEGATIVE	10	B	B	B	1	A	1
78	JAYASHRI SANJAY JAVALAGI	1144747	2	2	4	4	20	1	4	28	16	9	4	POSITIVE	POSITIVE	3	A	B	B	1	B	1
79	PARVATI IRAPPA TEGUR	4783837	1	2	3	4	15	1	4	11	0	2.5	3	POSITIVE	NOT DONE	10	B	B	B	2	B	1
80	MAHADEVI BABU KAMMAR	5335991	2	2	3	4	10	1	2	23	11	9	4	POSITIVE	NOT DONE	10	B	B	B	1	B	1
81	RENUKA FAKIRAPPA KARADI	5319333	2	2	2	3	15	1	4	16	6	7	4	POSITIVE	NOT DONE	10	B	B	B	1	B	1
82	TANGEVVA GANGAPPA ANGADI	3193016	2	2	2	3	10	1	4	14	5	7	4	POSITIVE	NEGATIVE	4,9	A	B	B	1	B	1
83	CHAMPAKKA SHANKARGOUDA PATIL	4825769	2	2	4	4	20	1	4	11	4	5	4	NEGATIVE	NOT DONE	9	A	B	B	1	B	1
84	PARVATI APPASAB AVUBAYAGOL	5185540	2	2	3	3	15	1	4	26	10	7.5	4	NEGATIVE	NOT DONE	1,9	A	B	B	2	B	1
85	LEELA TUKARAM CHOUGALE	5243401	2	2	1	1	10	1	4	26	6	8	4	POSITIVE	NOT DONE	10	A	B	B	1	B	1
86	MAHADEVI RAYANGOUDA PATIL	5209481	2	2	4	4	15	1	5	22	6	9	4	NEGATIVE	NOT DONE	4,9	A	B	B	1	B	1
87	VENKATAMMA ELIYA GUDIPATTI	5290168	2	2	3	4	15	1	4	25	12	9	4	POSITIVE	NOT DONE	4	A	B	B	1	B	2
88	MALA SUBHASH VANAJOL	3141376	2	2	3	4	10	1	4	17	11	8	4	POSITIVE	NOT DONE	10	B	B	B	1	B	1
89	GANGAVVA SURESH PATIL	972781	2	2	1	2	10	1	4	9	0	6	3	POSITIVE	NOT DONE	10	B	B	B	1	B	2
90	HANAMAVVA HANUMATH DHARIGOLA	5232923	1	2	1	2	10	1	4	16	8	7.5	4	POSITIVE	NOT DONE	1,4	A	B	B	1	B	1
91	SUSHILA BASAVARAJ HIREMATH	4812591	3	2	2	2	10	1	2	2	1	6	3	NEGATIVE	POSITIVE	3	B	B	B	1	B	1
92	SAVATRI RAMCHANDRA KAKATKAR	5403356	3	2	4	4	15	1	4	23	11	8.5	4	POSITIVE	POSITIVE	9	A	B	B	1	A	1
93	SHEELA MARTIN HARRY WILLIAM	970837	3	2	4	4	20	2	5	14	5	6	4	NEGATIVE	NOT DONE	4,9	A	B	B	1	B	2
94	SUREKHA DANAPPA BALI	971299	3	2	4	4	15	1	4	6	3	5	3	POSITIVE	NOT DONE	1,9	A	B	B	2	A	2
95	HASANSAB LALSAB MOMIN	5473906	3	1	3	3	25	1	5	12	2	3	3	NEGATIVE	NOT DONE	3,9	A	B	B	1	A	1
96	DEEPA MANJUNATH KAMBREKAR	5308615	1	2	3	4	15	1	4	10	6	2.5	3	NEGATIVE	NOT DONE	10	A	B	B	1	B	1
97	SUPRIYA VINAYAK KUMBHAR	5196560	1	2	2	3	10	1	3	21	17	7.5	4	NEGATIVE	POSITIVE	9	A	B	B	1	B	1
98	JAYASHREE SIDDARAMAPPA VARADAI	4462107	2	2	3	3	15	1	3	19	8	7.5	4	NEGATIVE	NOT DONE	3,4	A	B	B	1	B	1
99	YUSUF KADARKHAN PATHAN	3138620	2	1	4	4	25	1	4	27	11	8	4	POSITIVE	NOT DONE	10	A	A	B	1	B	1
100	MAHADEVI LINGANAGOUDA PATIL	4695527	2	2	4	4	20	1	4	2	0	1	2	POSITIVE	NOT DONE	1,9	A	B	B	1	B	1
101	MAHANTESH SHIVABASU MUGALE	2115638	1	1	3	3	20	1	4	19	4	8	4	NEGATIVE	NOT DONE	10	B	B	B	1	B	1
102	PARVATI RAMU KALBURGI	4694336	2	2	1	2	10	1	4	22	10	7	4	POSITIVE	POSITIVE	3	A	B	B	1	B	1
103	GANGAVVA SOMAPPA YADAL	5070916	2	2	1	2	10	1	4	24	4	7.5	4	POSITIVE	POSITIVE	4,9	A	B	B	1	B	1
104	MALLAVVA BASAPPA NUGGANATTI	5073941	2	2	1	2	10	1	4	11	1	1	3	NEGATIVE	NOT DONE	10	B	B	B	1	B	1
105	KAMALAVVA LAXMAN SANNAMALLAPPAGOL	5304667	2	2	2	3	15	1	4	6	4	5	3	POSITIVE	NEGATIVE	9	A	B	B	1	B	1
106	ARUN ANANT KELVEKAR	4967529	3	1	3	4	10	1	2	8	2	5	3	POSITIVE	NEGATIVE	10	B	B	A	2	B	1
107	SAMEER UPENDRA BHUKEBAG	4686370	1	1	1	2	10	1	4	2	1	1	3	POSITIVE	POSITIVE	10	B	B	B	1	B	1
108	MANASA MAHESH KULKARNI	4678289	1	2	1	2	10	1	4	11	0	3	3	POSITIVE	NEGATIVE	10	B	B	B	1	B	1
109	RATNA YANKAPPA ATADAMANI	4815721	1	2	3	3	10	1	4	15	2	6	4	POSITIVE	POSITIVE	3	A	B	B	2	A	1
110	ANADA SHANTARAM GAWADE	4991645	3	1	3	3	15	2	5	4	2	5	3	POSITIVE	NOT DONE	10	B	B	B	1	A	1
111	SUSHILA VAIJU PATIL	5241715	2	2	1	2	10	1	4	5	4	3	3	NEGATIVE	NEGATIVE	3,9	B	B	B	1	B	1
112	SHANKAR RAMAPPA JODATTI	5259263	2	1	1	2	15	1	4	18	12	7	4	NEGATIVE	NOT DONE	10	A	B	B	1	B	1
113	SUREKHA SHIVAJI TUPPARE	4916325	2	2	3	3	15	1	4	12	10	5	4	NEGATIVE	NOT DONE	1,5	B	B	B	1	B	1
114	RAJESHWARI BASAYYA MULIMANI	4790587	1	2	1	2	15	1	5	16	10	8	4	NEGATIVE	NEGATIVE	7	B	B	B	1	A	1
115	SANTOSH SHASHIKANT KUMBAR	5192635	1	1	1	1	20	1	2	21	10	7	4	NEGATIVE	NOT DONE	10	B	B	B	2	B	1
116	VAISHALI ASHOK BALEKUNDRI	4780171	1	2	5	5	20	1	4	8	6	3	3	POSITIVE	NOT DONE	5	A	B	B	1	B	1
117	RESHMA BIDKAR	5113394	2	2	2	3	15	1	4	8	4	2	3	NEGATIVE	NEGATIVE	10	A	B	B	1	B	1

OPTIMUM DOSE OF MTX
>12.5 MG

SUB-OPTIMUM DOSE <12.5 MG

BLOOD PARAMETERS
A-PRESENT; B-ABSENT

AGE GROUPS: 1) 18-40 Y 2) 41-60 3) >60

1-MALE 2-FEMALE

TJC - TENDER JOINT COUNT; SJC - SWOLLEN JOINT COUNT

ACPA - ANTI-CYCLIC CITRULINATED PEPTIDE ANTIBODY

CREATININE/TRANSAMINASES
1-NORMAL; 2-ELEVATED

DURATION: 1) 6M-1Y 2) 1-2Y 3) 2-5Y 4) >5Y

DISEASE ACTIVITY
1-REMISSION; 2-LOW ACTIVITY
3-MODERATE ACTIVITY; 4-HIGH ACTIVITY

REPORTED SIDE EFFECTS
1-EPIGASTRIC BURNING; 2-VOMITTING; 3-NAUSEA;
4-ANOREXIA; 5-STOMATITIS; 6-ORAL ULCERS;
7-HAIR FALL; 8-METHTREXATE FLU;
9-FATIGUE; 10-NONE

MTX FORM: 1-ORAL 2-INJECTIBLE
MTX - METHOTREXATE; HCQ - HYDROXYCHLOROQUINE; LEFNO - LEFLUNOMIDE

1 - MTX MONOTHERAPY; 2 - MTX+STEROID; 3 - MTX+HCQ
4 - MTX+STEROID+HCQ; 5 - MTX+STEROID+HCQ+LEFNO
6 - MTX+STEROID+HCQ+SULFASALAZINE; 7-MTX+HCQ+LEFNO