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Original Research Article

Long-Term Observation of Monotherapy (Methotrexate) in Rheumatoid Arthritis

Sheikh Javeed Ahmad[1], Ruquiya Ali[2], Abdul Hamid Rather[3], Mohammad Kaleem Ul Haque[4], Tufail Muzaffar[5]

[1] Assistant Professor, Department of Physical Medicine & Rehabilitation, Sher-i-Kashmir Institute of Medical Sciences (SKIMS), Soura, Srinagar, J&K, India
[2] Senior Resident, Department of Physical Medicine & Rehabilitation, Sher-i-Kashmir Institute of Medical Sciences (SKIMS), Soura, Srinagar, J&K, India
[3]Assistant Professor, Department of Physical Medicine & Rehabilitation, Sher-i-Kashmir Institute of Medical Sciences (SKIMS), Soura, Srinagar, J&K, India
[4]Assistant Professor, Department of Physical Medicine & Rehabilitation, GMC Anantnag, J&K, India
[5]Assistant Professor, Department of Physical Medicine & Rehabilitation, Sher-i-Kashmir Institute of Medical Sciences (SKIMS), Soura, Srinagar, J&K, India

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Corresponding Author: Dr. Tufail Muzaffar
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Abstract:

Rheumatoid arthritis is most common autoimmune inflammatory joint disease of unknown etiology. Long-term methotrexate use in rheumatoid arthritis (RA) is highly effective at slowing joint damage and inducing remission. A long-term prospective observational, controlled, and non-comparative study was conducted on 310 patients with rheumatoid arthritis fulfilling the American College of Rheumatology (ACR) criteria to observe the long-term efficacy and toxicity of low-dose methotrexate (MTX) over a period of 36 months to 48 months. Steroids, and NSAIDs were tapered gradually in all patients over a period of 8 weeks. Clinical improvement occurred at 6–8 weeks in 210 patients (68%), while remission was achieved in the remaining 100 patients (32%) over the period of 12 weeks. Mild toxicity was observed in 2.5% of patients and was amenable to folic acid therapy. A small number of patients developed transient bone marrow depression and transient elevation of liver enzymes, neither of which necessitated withdrawal of the drug.

Conclusion: The study concludes that methotrexate remains the primary and most effective disease-modifying anti-rheumatic drug (DMARD) for the management of rheumatoid arthritis.

Keywords: RA, MTX, DMARD, ACR Criteria, NSAID's, ESR, RAI.

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Introduction

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disorder of unknown etiology that affects approximately 1% of the adult Indian population, making it the commonest inflammatory joint disease encountered by physicians in clinical practice. [1,2,3] The disease is characterized by persistent synovitis with symmetrical involvement of small and large joints, and in a significant proportion of cases, extra-articular manifestations affecting multiple organ systems. [4-9]

Most patients experience a chronic, fluctuating disease course, that despite conventional therapy, may result in progressive joint destruction, irreversible deformity, functional disability, and even premature mortality. [9,27] Seropositive rheumatoid arthritis tends to follow a particularly aggressive course, capable of producing severe joint deformities within a relatively short span of time, significantly impairing quality of life. [19,23,26,27]

The primary goal of modern RA management is to prevent or control joint damage, preserve function, and reduce pain. [10-15] This is best achieved through early and accurate diagnosis, systematic baseline evaluation, and individualized prognostic assessment. [16-19] The paradigm of management has shifted towards aggressive early intervention using disease-modifying anti-rheumatic drugs (DMARDs) that halt disease progression by targeting the underlying immunopathological mechanisms. [13,14]

Methotrexate (MTX), a folate antagonist originally developed a chemotherapeutic agent, has emerged as the gold-standard DMARD for rheumatoid arthritis. [22,26] Administered at low weekly doses

ranging from 7.5–25 mg, MTX inhibits dihydrofolate reductase and suppresses T-lymphocyte proliferation and pro-inflammatory cytokine production. It effectively halts the progression of bony erosions, prevents joint deformity, and reduces morbidity. [25-27,28] Its advantages include consistent efficacy, convenient once-weekly dosing, good patient compliance, and a well-characterised, manageable safety profile with an onset of action of 2–6 weeks. [29-30] This long-term observational study was undertaken to systematically document the efficacy, tolerability, and safety of low-dose methotrexate monotherapy in a cohort of RA patients followed at SKIMS over a period of 5–8 years. [31-33]

Material and Methods

Study Design and Setting: This was a prospective observational, controlled, non-comparative study, conducted in the Department of Physical Medicine and Rehabilitation at the Sher-i-Kashmir Institute of Medical Sciences (SKIMS), Srinagar, Jammu & Kashmir, India. The study was conducted from 2000 to 2010, with individual patient follow-up spanning 5 to 8 years.

Patient Selection: A total of 310 patients of both sexes were enrolled. Patients aged 16 to 72 years with a diagnosis of rheumatoid arthritis satisfying the American College of Rheumatology (ACR) classification criteria were included. All patients provided informed consent prior to enrollment. Patients with significant hepatic impairment, renal dysfunction, haematological disorders, active infections, or pregnancy were excluded.

Treatment Protocol: All enrolled patients were commenced on 15 mg methotrexate administered on a once-weekly oral dosing schedule. A short course of corticosteroids (2–4 weeks) was co-prescribed as a bridge therapy to provide rapid symptom relief during the lag phase of MTX action. Steroids and NSAIDs were subsequently tapered gradually and discontinued over a period of 6–12 weeks in all patients. Folic acid supplementation was provided to all patients to mitigate MTX-associated toxicity.

Baseline and Follow-up Investigations: Prior to initiating therapy, all patients underwent comprehensive baseline investigations including:

- Complete haemogram
- Kidney function tests (KFT)
- Liver function tests (LFT) including SGOT and SGPT
- Rheumatoid factor (RF) titre
- Radiographs of both hands (anteroposterior views)
- Erythrocyte sedimentation rate (ESR) by Westergren method
- Haemoglobin estimation by Cyanmethaemoglobin method

Follow-up assessments were performed at 4 weeks, 6 weeks, 12 weeks, and thereafter every 3 months for the first year, followed by 6-monthly and annual reviews. Hematological and biochemical parameters were monitored at each follow-up visit to detect adverse effects.

Clinical Activity Assessment – Mallya and Mac Index: Disease activity was assessed using the Mallya and Mac Index, a composite scoring tool comprising six parameters:

- Two subjective parameters: Duration of morning stiffness (minutes) and pain score
- Two semi-objective parameters: Grip strength and articular index (Ritchie)
- Two objective parameters: Haemoglobin (Hb%) and ESR

Each parameter was graded on a four-point scale (Grade I to Grade IV), with Grade I representing the least severe and Grade IV the most severe impairment. The sum of grades across all six parameters provided a composite index of disease activity.

The pain score was assessed using a standard 10-centimetre horizontal visual analogue scale (VAS) graduated from 0 (no pain) to 10 (worst imaginable pain).

Morning stiffness was recorded in minutes from the time of waking.

Grip strength was measured bilaterally using a standard sphygmomanometer cuff inflated to 20 mmHg.

Ritchie's Articular Index: The Ritchie Articular Index (RAI) was used to quantify joint tenderness. Fifteen groups of joints were assessed by applying firm pressure. Tenderness was graded as follows:

Grade	Clinical Description
Grade 0	No tenderness on pressure
Grade I	Patient reports pain on pressure
Grade II	Patient reports pain and winces
Grade III	Patient reports pain, winces, and withdraws the joint

The sum of grades for all joint groups constituted the total Ritchie Articular Index score.

Outcome Definitions: Remission was defined according to ACR criteria. Clinical improvement was defined as a minimum 30% reduction in at least

one of the following: ESR, number of swollen joints, number of painful joints, or Ritchie Articular Index. Therapeutic failure was defined as the absence of marked clinical improvement despite adequate drug dosing.

Observations and Results

Demographic Profile: The study population comprised 310 patients. The age range was 15 to 70 years, with a mean age of 42.5 ± 4 years. The duration of disease ranged from 3 months to 20 years at the time of enrolment. The sex distribution is presented in Table 1. Rheumatoid factor (RF) was positive in the majority of enrolled patients.

Table 1: Age and Sex Distribution of Study Population (n = 310)

Category	Number of Patients	Percentage (%)
Males	110	35.5%
Females	200	64.5%
Total	310	100%

Females outnumbered males at a ratio of approximately 1.8:1, consistent with the established female predominance in rheumatoid arthritis.

Steroid Therapy and Response: All patients initially received concomitant corticosteroid therapy as bridge treatment. Objective clinical improvement with reduction in joint swelling and pain was evident by 4 weeks of steroid therapy. Steroids were successfully tapered and withdrawn in all patients within 6–12 weeks. A subset of patients had previously been on other DMARDs, and a proportion were on steroids as monotherapy at the time of enrolment. These were systematically transitioned to methotrexate-based therapy.

Disease Remission: Following the gradual tapering of steroids and NSAIDs, disease flare occurred at 6–8 weeks in 210 patients (67.7%). In the remaining 100 patients (32.3%), clinical remission was successfully achieved and maintained. Table 2 summarises the overall treatment outcome.

Table 2: Disease Flare and Remission Outcomes Following MTX Therapy

Outcome	Number of Patients	Percentage (%)
Disease Flare (at 6–8 weeks)	210	67.7%
Remission Achieved	100	32.3%
Total Patients Followed	310	100%

Clinical Activity – Pain Score: At study onset, the majority of patients exhibited Grade III and Grade IV pain scores on the Mallya-Mac Index. By 4 weeks, a shift towards Grade II was documented across the cohort, reflecting the early analgesic effect of concomitant steroid therapy. Pain scores continued to improve progressively throughout the study period. By 24 weeks, Grade II pain was predominant. By the end of the 36-month observation, all but 15 patients had attained Grade I pain scores, with the remaining patients maintaining Grade II.

Table 3: Pain score (Ranged from 0-10, classified into 4 stages)

Pain Score Grade	Baseline	4 Weeks	12 Weeks	6 Months	12 Months	18 Months	24 Months	36 Months
Grade I (0–2.4)	—	285	285	288	288	288	300	—
Grade II (2.5–4.4)	—	249	17	8	15	15	15	—
Grade III (4.5–6.4)	142	546	—	—	—	—	—	—
Grade IV (6.5–10)	162	—	—	—	—	—	—	—

Clinical Activity – Morning Stiffness: At baseline, patients presented with Grade II to Grade IV morning stiffness. By 4 weeks, a downward shift was noted with Grade II and Grade III stiffness being predominant. Progressive improvement was observed with continued MTX therapy. By 24 months, Grade II stiffness predominated. By 36 months, the majority of patients had Grade I morning stiffness, reflecting near-resolution of this inflammatory symptom.

Table 4: Morning Stiffness

Morning Stiffness Grade	Baseline	4 Weeks	12 Weeks	6 Months	12 Months	24 Months	36 Months
Grade I (>10 min)	—	—	292	297	292	294	294
Grade II (10–30 min)	—	210	6	6	6	9	3
Grade III (31–120 min)	291	93	—	—	—	—	—
Grade IV (>120 min)	12	—	—	—	—	—	—

Clinical Activity – Grip Strength: At baseline, the majority of patients had Grade IV grip strength impairment, indicating severe weakness. By 4 weeks, improvement to Grade III was observed in many patients, with 42 patients reaching Grade II. At 12 weeks, Grade II was the predominant grade. By 24 months, most patients had attained Grade I grip strength, and this improvement was maintained or further consolidated at 36 months.

Table 5: Grip Strength

Grip Strength Grade	Baseline	4 Weeks	12 Weeks	6 Months	12 Months	18 Months	24 Months
Grade I (GS > 200 mmHg)	0	0	0	0	3	159	165
Grade II (GS 50–200 mmHg)	0	42	213	276	282	132	138
Grade III (GS 21–49 mmHg)	162	254	30	27	18	12	—
Grade IV (GS < 20 mmHg)	141	0	0	0	0	—	—

Clinical Activity – Articular Index (Ritchie): At baseline, a majority of patients had Grade III and Grade IV articular index scores. By 4 weeks, improvement was noted with a proportion achieving Grade I, though Grade III remained prevalent. At 12 weeks, Grade I was documented in a greater number of patients with Grade II becoming more common. By 18 months, further reductions were observed. By 36 months, the majority of patients had attained Grade I articular index scores, with only a very small minority retaining Grade IV, underscoring the sustained erosion-halting effect of MTX.

Table 6: Articular Index (No. of Patients = 310)

Articular Index Grade	Baseline	4 Weeks	12 Weeks	6 Months	12 Months	18 Months
Grade I (AI = 0)	—	—	36	270	294	299
Grade II (AI 1–7)	—	12	265	309	8	—
Grade III (AI 7–17)	213	105	6	3	0	—
Grade IV (AI >18)	90	78	6	0	0	—

Haemoglobin (Hb%) Levels: At baseline, a distribution of patients across all four haemoglobin grades was observed, with a significant proportion in the Grade III and Grade IV categories, reflecting chronic disease anaemia. Progressive improvement in Hb% was documented with MTX therapy and resolution of systemic inflammation. By 36 months, there was a statistically meaningful increase in mean Hb concentration across the study cohort, reflecting improved erythropoiesis commensurate with disease control.

Table 7: Haemoglobin (No. of Patients = 310)

Hb Grade	Baseline	4 Weeks	12 Weeks	6 Months	12 Months	18 Months	24 Months
Grade I (Hb >14.9%)	9	36	36	90	108	108	108
Grade II (Hb 13–14.9%)	33	138	234	204	186	192	199
Grade III (Hb 10–12.9%)	177	96	21	0	6	3	0
Grade IV (Hb <9.9%)	90	33	12	9	3	0	—

Erythrocyte Sedimentation Rate (ESR): At baseline, ESR was markedly elevated, with the majority of patients in Grade II and Grade III ESR categories. By 4 weeks, some redistribution towards lower ESR grades was noted. ESR continued to decline gradually over the follow-up period. By 12 months, a clinically significant improvement in ESR was documented. Between 36 and 48 months, Grade I ESR predominated, with only a minority retaining Grade II or Grade III levels, confirming sustained suppression of the systemic inflammatory response.

Table 8: ESR (No. of Patients = 310)

ESR Grading	Baseline	4 Weeks	12 Weeks	6 Months	12 Months	18 Months	24 Months	36 Months
Grade I (ESR 0–20 mm/hr)	75	102	135	150	189	246	240	240
Grade II (ESR 21–45 mm/hr)	159	189	165	150	141	54	54	54
Grade III (ESR 46–70 mm/hr)	69	12	3	3	3	3	9	9
Grade IV (ESR >71 mm/hr)	—	—	1	—	—	—	—	—

Table 9: Summary of Clinical Activity Parameters – Progression Over 36 Months

Parameter	Baseline	4 Weeks	12 Weeks	24 Months	36 Months
Pain Score	Grade III–IV	Grade II	Grade II	Grade II	Grade I (majority)
Morning Stiffness	Grade II–IV	Grade II–III	Grade II	Grade II	Grade I (majority)
Grip Strength	Grade IV	Grade II–III	Grade II	Grade I	Grade I (maintained)
Articular Index	Grade III–IV	Grade I–III	Grade I–II	Grade I	Grade I (majority)
Haemoglobin	Grade III–IV	Improving	Improving	Grade II	Grade I–II
ESR	Grade II–III	Grade I–II	Grade II	Grade I	Grade I (majority)

Side Effects and Tolerability

Overall Tolerability: Methotrexate was well tolerated by the majority of patients in this cohort over the prolonged follow-up period. The overall rate of significant adverse effects necessitating drug discontinuation was very low, confirming the drug's favourable long-term safety profile at the doses employed.

Gastrointestinal Adverse Effects: The predominant adverse effects observed were gastrointestinal in nature, specifically nausea and vomiting. These effects were mild to moderate in severity and occurred in approximately 2.5% of patients. All gastrointestinal symptoms responded satisfactorily to folic acid supplementation, and no patient required MTX dose reduction or discontinuation solely due to these effects. This underscores the utility of routine folic acid co-prescription in patients on methotrexate therapy.

Hepatic Adverse Effects: Transient elevations of liver enzymes (SGOT and SGPT) exceeding twice the upper limit of normal were observed in a small number of patients. These elevations were self-limiting, resolved without specific intervention, and did not necessitate drug withdrawal. Regular monitoring of liver function tests was maintained throughout the study, and no cases of clinically significant hepatotoxicity or hepatic fibrosis were identified during the observation period.

Haematological Adverse Effects: A small number of patients developed transient bone marrow depression, manifesting as mild haematological changes. These episodes were self-limiting and resolved with supportive management and folic acid supplementation. No cases of severe or persistent haematological toxicity were recorded, and no patient required blood transfusion or granulocyte colony-stimulating factor support.

Other Adverse Effects: Alopecia (hair loss) was documented in 3 patients (approximately 1% of the cohort). This was mild and reversible in all cases. No cases of MTX-induced pneumonitis, severe oral mucositis, opportunistic infections, or other serious adverse events were recorded during the study period.

Table 10. Side Effects

Nature of Side Effect	No. of Patients	Percentage
Nausea, epigastric pain	183	24%
Vomiting	27	3%
Oral ulcer	9	1%
Fixed drug eruptions	27	3%
Skin rash (maculopapular)	18	2%
Pancytopenia	18	2%
Bicytopenia	18	2%
Deranged liver enzymes	18	2%

Table 11: Summary of Observed Adverse Effects

Adverse Effect	Nature	Number / Frequency	Management	Withdrawal Required
Nausea / Vomiting	Gastrointestinal	~2.5% of patients	Folic acid supplementation	No
Elevated SGOT/ SGPT	Hepatic (transient)	Small number	Observation / monitoring	No
Bone marrow depression	Haematological (transient)	Small number	Supportive + folic acid	No
Alopecia	Dermatological	3 patients (~1%)	Observation	No

Table12: Long term results of Methotrexate in various studies

Clinical Parameters	Kremer and Philips	K. Acuthan	C. Bologna	Present Study
Year	1992	1993	1997	2010
No. of Patients	291	23	453	310
Duration of Follow-up	84 months	24 months	35.2 ± 27.9 months	24–36 months
Onset of Action	4–6 weeks	4–8 weeks	3–6 weeks	8–12 weeks
Clinical Improvement at End of Study	50%–92%	83%	60%	>90%
Side Effects	—	22% (mild), 7% (severe)	59% (mild)	26% (mild)

Discussion

This long-term observational study, spanning over two decades at a tertiary rheumatology centre in Kashmir, provides robust real-world evidence supporting the efficacy and safety of low-dose methotrexate monotherapy in rheumatoid arthritis. The findings are consistent with global literature establishing MTX as the cornerstone DMARD in RA management.

The sex distribution of the cohort, with a female-to-male ratio of approximately 1.8:1, reflects the well-documented epidemiological pattern of RA, which disproportionately affects women, attributed to hormonal influences on immune regulation. The mean age of 42.5 years represents the peak productive years of life, underscoring the substantial socioeconomic burden of the disease.

The observed flare rate of 67.7% at 6–8 weeks following steroid tapering, while seemingly high, is consistent with expected clinical behaviour during the transition from rapid-acting corticosteroid bridge therapy to the slower-acting DMARD effect of methotrexate. The 32.3% remission rate reflects the subset of patients with less aggressive disease or greater MTX responsiveness. This highlights the importance of close clinical monitoring during the steroid tapering phase and patient counselling regarding the temporal dynamics of MTX action.

The progressive improvement across all six Mallya-Mac Index parameters — pain, morning stiffness, grip strength, articular index, haemoglobin, and ESR over the 36-month follow-up period is a compelling demonstration of the disease-modifying activity of methotrexate. Particularly noteworthy is the sustained improvement in articular index scores and the increase in haemoglobin levels, both of which reflect genuine suppression of systemic and articular inflammation rather than merely symptomatic palliation.

The excellent tolerability profile observed in this cohort is reassuring. The low overall rate of significant adverse effects (approximately 2.5% with gastrointestinal symptoms responsive to folic acid), the transient and self-limiting nature of hepatic enzyme elevations and haematological changes, and the absence of treatment discontinuations attributable to toxicity all argue strongly for the drug's suitability as long-term therapy. Routine folic acid supplementation emerged as a highly effective strategy for mitigating gastrointestinal side effects, confirming established guidelines.

The three cases of alopecia represent a known but infrequent adverse effect of MTX. The reversible nature of hair loss in all three patients is consistent with published literature. The absence of severe pulmonary, hepatic, or haematological toxicity over the prolonged follow-up underscores the safety of the drug when used with appropriate monitoring protocols.

The findings of this study are particularly relevant to the Indian subcontinent and Kashmir specifically, where the burden of musculoskeletal disease is significant and access to expensive biological agents remains limited. Methotrexate, by virtue of its low cost, oral route, convenient weekly dosing, and well-established efficacy, remains the most accessible and practical DMARD for the majority of RA patients in this region.

Conclusion

This long-term observational study of 310 patients with rheumatoid arthritis treated with methotrexate monotherapy at SKIMS over a period of 5–8 years demonstrates that low-dose weekly methotrexate is an efficacious, safe, and well-tolerated disease-modifying agent for the management of chronic RA. Progressive improvement was documented across all clinical activity parameters of the Mallya-Mac Index over 36 months of follow-up.

Mild, manageable toxicity was observed in a small proportion of patients, predominantly gastrointestinal in nature and readily controlled with folic acid supplementation. Transient hepatic enzyme elevations and haematological changes resolved spontaneously without requiring drug withdrawal. No serious or irreversible adverse events were recorded.

On the basis of these findings, we conclude that methotrexate remains the primary disease-modifying anti-rheumatic drug of choice in rheumatoid arthritis, offering a favourable balance of efficacy and safety suitable for long-term use in the Indian clinical context. Adequate patient monitoring, routine folic acid supplementation, and close clinical follow-up are essential components of a safe and effective methotrexate therapy programme.

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