

A Prospective Comparative Study of Two Drug Regimens for Early Rheumatoid Arthritis

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Abstract

Background

Rheumatoid arthritis (RA) is a chronic autoimmune disease that leads to progressive joint damage, disability, and reduced quality of life. Early initiation of disease-modifying ant-rheumatic drugs (DMARDs) is crucial to control disease activity and improve patient outcomes. This study was designed to compare the effectiveness of Methotrexate (MTX) + Sulfasalazine (SSZ) versus Methotrexate (MTX) + hydroxy chloroquine (HCQ) in patients with early RA.

Aims and objectives

To evaluate and compare the clinical efficacy of MTX + SSZ and MTX + HCQ in early RA. To assess pain severity using the Visual Analogue Scale (VAS). To monitor disease progression using EULAR criteria. To measure medication adherence using the Morisky Medication Adherence (MMA) scale. To evaluate patient quality of life using the Thrinay questionnaire. To highlight the role of clinical pharmacists in improving adherence and patient outcomes.

Methods

A prospective observational study was conducted over six months (November 2024–April 2025) at Sri Balaji Medical College Hospital & Research Institute, Tirupati. A total of 46 subjects (>30 years) diagnosed with early RA were enrolled and divided into two groups: Group A (MTX + SSZ, n=23) and Group B (MTX + HCQ, n=23). Disease activity, pain severity, adherence, and quality of life were assessed using standardized tools. Data were analyzed using Student's t-test, with $p < 0.05$ considered statistically significant.

Results

Both regimens significantly reduced disease activity and improved patient outcomes. Group B (MTX + HCQ) showed slightly greater improvement, with VAS scores decreasing from 7.00 ± 1.19 to 1.50 ± 0.60 compared to 7.00 ± 1.19 to 2.00 ± 0.78 in Group A. EULAR scores also showed a greater reduction in Group B. MMA scores improved in both groups, reflecting enhanced adherence, while Thrinay questionnaire results indicated better quality of life outcomes in Group B. The involvement of clinical pharmacists contributed to improved adherence, patient education, and overall well-being.

Conclusion

Both MTX + SSZ and MTX + HCQ combinations are effective in managing early RA. However, MTX + HCQ demonstrated superior tolerability and slightly better efficacy, making it a favorable option for long-term management. Clinical pharmacists played a vital role in enhancing adherence, patient counseling, and quality of life, underscoring their importance in multidisciplinary RA care.

Keywords: Rheumatoid Arthritis; Methotrexate; Sulfasalazine, Hydroxychloroquine, EULAR Criteria, VAS (Visual Analog Scale), MMA Scale, Thrinay Questionnaire, Disease Progression, Quality of life, Combination Therapy.

Introduction

Rheumatoid arthritis is chronic autoimmune disease that primarily involves the joints and characterized by synovitis in which the joint lining and other tissues become inflamed as a result of over activity of body immune system. It is accompanied by extra-articular organ involvement, such as interstitial pneumonia, in addition to clinical symptoms including pain, swelling and stiffness of multiple joints, fever, and malaise [1]. Approximately 1% of the population in worldwide is affected by RA, with females being two to three times more commonly affected. The prevalence of RA increases with age in both sexes nearly 5% of women and 3% of men over the age of 65y are affected by the disease. The peak age of incidence is about 30 to 50y in women and slightly older in men. RA also affects young children and its classification and treatment differ slightly from adults [2]. Rheumatoid arthritis (RA) is a growing public health concern in India, with varying prevalence across regions and Demographics. A survey near Delhi reported a prevalence of 0.75%, similar to developed countries. In Lucknow, urban prevalence was 4.74 per 1,000 individuals, compared to 2.9 per 1,000 in rural areas. A nationwide study found prevalence rates ranging from 0.28% to 0.7%, showing differences between urban and rural regions. From 1990 to 2021, RA incidence and prevalence rates have been rising, with a significant gender disparity—females have higher rates than males. The highest incidence occurs in those aged 65-69 years, while prevalence peaks in the 75-79 age group. Geographically, Uttarakhand has the highest male prevalence, and Tamil Nadu has the highest female prevalence. These trends emphasize the need for targeted healthcare strategies to address the growing RA burden in India [3]. Rheumatoid arthritis (RA) results from a combination of genetic factors, environmental triggers, and immune system dysfunction, causing joint inflammation, pannus formation, and damage to cartilage and bones. This has led to the development of targeted treatments, such as biologics (TNF and IL-6 inhibitors) Genetic and environmental factors: Genetic factors contribute 53-65%of the risk developing disease. The HLADR4allele is associate with both the development and severity of RA. HLA-DRB1andHLA-DRB4Genes, PTPN22Genes, Other geneticvariants [4] Smoking. Infections. Diet. Gut Dysbiosis. Stress: Physiological Stress, Social stress and Work stress [5, 6]. Immune System Dysregulation: RA is primarily an autoimmune disorder where the body's immunesystem mistakenly attacks its own tissues, particularly the synovium (the membrane lining the joints).Activation of Tcells, Bcell Activation, Citrullination of Proteins [7]. Pannus Formation, Angiogenesis, Cartilage degradation, Bone erosion. Cytokines in RA Progression.

- Pro-inflammatory cytokines (disease-promoting): These cytokines drive inflammation and immune activation, worsening RA symptoms and joint damage.
- Anti-inflammatory cytokines (disease-controlling): These cytokines regulate the immune response and limit inflammation, but their function is often impaired in RA [8].

Stages of Rheumatoid Arthritis

1. Stage 1 (Early-Stage): Inflammation, joint pain, stiffness, and swelling.
2. Stage 2 (Moderate-Stage): Cartilage damage, bone erosion, pain, and limited mobility.
3. Stage 3 (Severe): Extensive damage, bone rubbing, pain, swelling, and mobility loss.
4. Stage 4 (End-Stage): No inflammation, joints don't function, pain, stiffness, and potential bone fusion [9].

The cause of RA remained unclear with it is caused by interaction between genes and environmental factors. It is usually symmetric and involves proximal joints. Joint destruction leads to loss of cartilage and bone erosion and leads to increase in morbidity and mortality. Genetic factors [4]. Hormonal factors: Estrogen and Testosterone Environmental factors [5,6]. Epigenetic factors: DNA Methylation, Micro RNAs [10,11]. Autoimmune Factors: Antibodies, t-cell activation [12]. The general symp-

toms of rheumatoid arthritis includes, Decreased mobility Rigidity and sensitivity, Exhaustion and discomfort, Decrease in body weight, Formation of rheumatoid nodules. Joint pain and swelling, Mild fever, Stiffness in the morning in and around the joints, persisting for at least 1 hour, Joint deformities [13]. Extra articular features includes, lymphadenopathy, vasculitis, Episcleritis, Pericarditis, amyloidosis, Pleural Effusion, Pulmonary Fibrosis [14]. Classification criteria were released in 2010 by the American College Of Rheumatology (Acr) And European League against Rheumatism (Euler) aimed at promoting the timely initiation of therapy. These criteria utilize a weighted score across four categories: joint distribution, serology, presence of acute phase response, and duration of symptoms. A score of 6 or higher out of a potential 10 qualifies as a classification of "definite RA." Total score >6 = classification of "definite RA." The score can be determined prospectively if historical data has been documented. ACPA = anti-cyclic citrullinated protein antibody; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; RF = rheumatoid factor Antistreptolysin -o Titre (ASO Test) Antinuclear Antibody (ANA Test)(1), X-ray, MRI, Ultrasonography .

Management

Treatment focuses on slowing the disease's progression, reducing inflammation and pain, preserving joint functions to limit joint damage and complications, as well as improving physical function and overall quality of life. The optimal care for patients with RA involves a comprehensive approach that incorporates both non-pharmacologic and pharmacologic treatment methods. Engaging in physical activity serves as a significant intervention for enhancing systemic manifestations in rheumatic and musculoskeletal diseases [13]. Non-Pharmacological Methods for managing pain throughout the lifespan. Non-Pharmacological Methods such as psychological interventions, physical activity, patient education, and alternative strategies for managing pain in individuals with rheumatic disorders and frequent musculoskeletal pain conditions [14,15]. Dietary Modifications: Anti-inflammatory diets: Omega-3 fatty acids (found in fish oils) and antioxidants (found in fruits and vegetables) may reduce inflammation, Weight management [16]. Physical Therapy: Physical therapy (PT) is one of the most important non-pharmacological interventions. The goal is to enhance mobility, strength, and flexibility, as well as reduce joint damage, includes Range-of-motion exercises, Strengthening exercises, Aerobic exercises [17,18]. Occupational Therapy: Occupational therapy (OT) helps people with RA perform daily tasks with minimal pain and strain OT interventions include: Joint protection techniques, Energy conservation techniques [18]. Stress Management: Stress can exacerbate RA symptoms. Techniques like meditation, yoga, and deep breathing can help manage stress and promote relaxation [19]. Patient Education and Self-Management Programs: Education about the disease, joint protection, and self-management strategies is crucial for empowering patients to manage their condition. Structured self-management improve functional status and quality of life [20,21]. Cognitive Behavioral Therapy (CBT): CBT can be used to help patients cope with chronic pain and the psychological stress associated with living with RA. CBT focuses on modifying negative thoughts and behaviors, improving emotional well-being, and enhancing coping strategies [20,22]. Sleep Management: Stress can exacerbate RA symptoms. Techniques like meditation, yoga, and deep breathing can help manage stress and promote relaxation [23]. Complementary Therapies: Acupuncture, Massage therapy.

Pharmacological Management

There were a new therapeutic options have managed to reduce the symptoms, slow progression and prevent complications. The primary goal in treating patients with rheumatoid arthritis (RA) is to improve long-term health-related quality of life by reducing symptoms, preventing structural damage, restoring functionality, and promoting participation in social and work activities. It is important to refer patients to a Rheumatologist for timely initiation of treatment [24,25]. The treatment options include DMARD'S, NSAID'S, Glucocorticoids.

Surgery

Joint surgery is only performed in advanced cases of RA. The incidence of surgery for rheumatoid arthritis is low. Surgical methods alleviate pain and restore joint function. There are several treatments accessible now because of recent developments in surgery, including total joint replacement, metatarsal head excision arthroplasties, joint fusion, osteotomy, arthroscopy, radio synovectomy, and tens-synovectomy [20].

Clinical Pharmacist

A clinical pharmacist provides direct patient care, medication therapy management and patient counseling. clinical pharmacists work directly with other healthcare professions to optimize patient care.

Role of Clinical Pharmacist in Early Rheumatoid Arthritis

- 1) Medication Therapy Management
- 2) Disease Monitoring
- 3) Patient Education.
- 4) Adherence Support
- 5) Toxicity monitoring
- 6) Interdisciplinary collaboration

Pharmacists play an important part in multidisciplinary teams that treat patients with rheumatic illnesses. They are physicians, educators, and researchers. Pharmacists play an important role in providing evidence-based clinical care, drug information, and patient advocacy to ensure safe and cost-effective drug therapy. Clinical pharmacy services in rheumatology have expanded during the last four decades and continue to adapt to new therapeutic goals, technologies, and pharmacologic techniques [26].

Materials and Methods

It is a prospective observational study, the study was conducted in Department of Orthopedics at Sri Balaji Medical College Hospital & Research Institute, Renigunta, and Tirupati. The study was carried out in 6 months, from November (2024) – April 2025. A total of 46 subjects from orthopedics department were enrolled in the study after evaluating for inclusion & exclusion criteria. A written informed consent has been taken from the patients after explaining the nature of the study. The patients were not forced for participation if they were not willing. Pregnancy and Lactation women Patients on DMARDS & Biologics, with liver disease, hypersensitivity to medications were excluded from the study. Patient informed consent form, Patient data collection Proforma, The information recorded included demographic details of the patient, past medical history, diagnosis, medications being used. The scales used in the study were Euler criteria, Morisky Medication Adherence Visual analogue scale (VAS) ADR reporting Form Naranjo scale Patient information leaf let (PIL) Thrinay questionnaires'. The data so obtained were analyzed using simple descriptive statistics.

Results

A total of 46 subjects were enrolled and equally divided into two groups: Group A (methotrexate + sulfasalazine, n=23) and Group B (methotrexate + hydroxy chloroquine, n=23). Females predominated (67%) over males (33%). The majority of patients were aged 30–49 years (56%), followed by 60–69 years (22%), 50–59 years (20%), and >70 years (2%). Most participants were homemakers (30%) and daily labours (22%). Thyroid disorders were the most common comorbidity (37%), followed by polyarthritis (24%), while 13% had no comorbidities. Based on EULAR criteria, Group A showed a reduction in mean score from 7.13 ± 1.38 to 1.74 ± 0.81 , while Group B improved from 8.13 ± 1.72 to 2.39 ± 1.05 , indicating greater disease activity reduction in Group B. Pain scores (VAS) decreased from 7.0 ± 1.19 to 2.0 ± 0.78 in Group A and from 7.0 ± 1.19 to 1.5 ± 0.60 in Group B, suggesting slightly better pain relief in Group B. Quality of life assessment showed good outcomes in 14 subjects in both groups, with no poor outcomes in Group B. Medication adherence improved overall, with high adherence increasing from 46% to 57%. Clinical pharmacist intervention was rated positively by 98% of patients, highlighting its role in improving adherence and outcomes.

Table 1: Demographics & characteristics of patients

Variable	Category	n (%)
Gender	Male	15 (33)
	Female	31 (67)
Age (yrs)	30–39	13 (28)
	40–49	13 (28)
	50–59	9 (20)
	60–69	10 (22)
	>70	1 (2)
Occupation	Homemaker	30%
	Daily labourer	22%
	Software	15%
	Others	33%

Table 2: Comorbidities

Condition	Number (%)
Thyroid disorders	17 (37%)
Polyarthritis	11 (24%)
DM + Polyarthritis	2 (4%)
HTN + DM + Thyroid + PA	2 (4%)
HTN + Thyroid	1 (2%)
DM + Thyroid	1 (2%)
No comorbidities	6 (13%)

Table 3: EULAR Score & VAS Score

Group	Baseline	Final	Group	Initial Mean \pm SD	Final Mean \pm SD
A	7.0 \pm 1.19	2.0 \pm 0.78	A	7.13 \pm 1.38	1.74 \pm 0.81
B	7.0 \pm 1.19	1.5 \pm 0.60	B	8.13 \pm 1.72	2.39 \pm 1.05

Table 4: Quality of life

Outcome	A	B
Good	14	14
Moderate	8	9
Poor	1	0

Table 5: Medication adherence

Level	Initial (%)	Final (%)
High	46	57
Medium	26	30
Low	2	13

Table 6: Clinical pharmacist impact

Score	(%)
10	1 (2)
6-9	45 (98)

Discussion

Our studies suggest that females are 2 to 3 times more prone to Rheumatoid arthritis (RA) than males. In our study, 46 subjects were diagnosed with early RA, of which 67% were females, demonstrating that women are twice as likely to develop RA compared to men (33%). This aligns with findings reported by Chauhan K., Singh J., et al., which indicate that females are more prone to developing RA than males. In our study, we observed and categorized the 46 subjects based on their age groups, which were as follows: 30-39 years (28 subjects), 40-49 years (28 subjects), 50-59 years (20 subjects), 60-69 years (22 subjects), and >70 years (2 subjects). This age distribution helps identify the most affected age groups for early RA in our study. Similar results were found by Fernandez-Avila, D. G., Rincon-Riano et al. which reported a higher prevalence of RA in individuals aged 60-69 years, aligning with our observation of a higher number of subjects in this age group. We observed and categorized the 46 subjects based on their age groups, which were as follows: 30-39 years (28 subjects), 40-49 years (28 subjects), 50-59 years (20 subjects), 60-69 years (22 subjects), and >70 years (2 subjects). This age distribution helps identify the most affected age groups for early RA in our study. Similar results were found by Fernandez-Avila, D. G., Rincon-Riano et al. which reported a higher prevalence of RA in individuals aged 60-69 years, aligning with our observation of a higher number of subjects in this age group.

In Group A, the average VAS pain score decreased from 7.00 \pm 1.19 at baseline to 2.00 \pm 0.78 at the final follow-up. In Group B, the score decreased from 7.00 \pm 1.19 to 1.50 \pm 0.60. These results indicate that both groups experienced a reduction in pain, with Group B showing a more significant improvement. Similar results have been found in study by Marijke van den Dikkenberg et al., where treatments for rheumatoid arthritis, reduced pain, as shown by lower VAS scores. The average EULAR criteria score for Group A at the initial and final follow-up was 7.13 \pm 1.38 and 1.74 \pm 0.81, respectively. For Group B, the average

scores at the initial and final follow-up were 8.13 ± 1.72 and 2.39 ± 1.05 , respectively. While both groups showed improvement, Group B exhibited a slightly greater reduction in the score. Similar results were found by Bharat S, Srivastava B, et al. in their study, where both MTX+HCQ and MTX+SLS showed improvements in disease activity, with MTX+HCQ showing slightly better results. The MMA score increased from 2.07 ± 0.82 at the first follow-up to 3.52 ± 0.67 at the final follow-up, suggesting improvement over time. This shows the positive impact of the clinical pharmacist in managing medication, supporting better patient outcomes, and improving adherence. A similar study by Rowley, E., et al. also highlights the role of clinical pharmacists in chronic disease management, showing their contribution to better patient outcomes. A total of 46 subjects were categorized based on their THRINAY Questionnaire scores, reflecting improvements in quality of life for patients with early RA. In Group B, 14 subjects scored 'Good', 9 scored 'Moderate', and none scored 'Poor'. In Group A, 14 subjects scored 'Good', 8 scored 'Moderate', and 1 scored 'Poor'. This finding is similar to the study by Verma et al. (2020), which also found that pharmacist counseling improved both physical and mental health in RA patients. These results highlight the important role of pharmacists in helping patients manage their condition and improve their quality of life.

Conclusion

This study provides valuable insights into the effectiveness of Methotrexate (MTX) combined with Sulfasalazine (SSZ) & Methotrexate combined with Hydroxychloroquine (HCQ) in the management of early Rheumatoid Arthritis (RA). Both combinations were found to significantly reduce the disease activity and improve clinical outcomes in patients. While both regimens demonstrated substantial efficacy, the MTX+HCQ combination stood out for its superior tolerability with fewer side effects reported compared to the MTX+SSZ group. This highlights the importance of selecting treatment strategies that balance both efficacy & patient comfort. However, the choice of treatment should remain individualized, as patient factors, including tolerance to medication and disease progression, play a crucial role in treatment decision making. In addition, the clinical pharmacist played a vital role in enhancing patient's quality of life & slowing down the progression of the disease in this study. Through effective medication counselling, continuous monitoring, & providing patient support, pharmacist significantly improved treatment adherence & overall well-being. The leaflets helped patient's gain a clearer understanding of their treatment, possible side effects, and strategies for managing their condition. By increasing patients' knowledge about their care, PIL'S promoted better adherence to medication & supported improved health outcomes.

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