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Investigating the Efficacy of Early Intervention Strategies in Preventing Joint Damage in High Risk Rheumatoid Arthritis Patients

Sharmeen Aslam[1], Mubasshra Iqbal[2], Muhammad Shaheryar[3], Muhammad Arslan[4]

[1]THQ Hospital Shahpur/ Nishtar Medical University, Multan, Punjab, Pakistan.
[2]Department of General Medicine, Rawal Institute of Health Sciences, Islamabad, Pakistan.
[3]RHC Moazmabad Sargodha, Govt of the Punjab Health and Population Department/ DHQ Hospital Sargodha, Punjab, Pakistan.
[4]Department of Internal Medicine and Infectious Diseases, Mujahid Hospital Faisalabad, Punjab, Pakistan.

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Corresponding Author: Sharmeen Aslam,
THQ Hospital Shahpur/ Nishtar Medical University, Multan, Punjab, Pakistan.
Email: sharmeenaslam2@gmail.com

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ABSTRACT

Objectives: To evaluate the clinical and radiographic efficacy of early DMARD initiation in preventing joint damage among high-risk RA patients. **Study Settings:** Rheumatology Department, tertiary care hospital. **Duration of Study:** 12 months. **Data Collection:** This prospective randomized controlled trial included 256 patients with newly diagnosed high-risk RA, stratified into Early (DMARDs within 6 weeks of symptom onset) and Delayed (DMARDs after 6 months) intervention groups. Patients were assessed using DAS28, HAQ-DI, and Sharp/van der Heijde scores over 12 months. ACR20 response and radiographic progression were primary outcomes. **Results:**The Early group showed significantly greater clinical improvement and joint preservation. ACR20 was achieved in 55.5% of the Early group vs. 28.1% in the Delayed group ($p = 0.0000$). Mean reduction in DAS28 score was greater in the Early group (from 5.58 to 3.56) than in the Delayed group (to 4.57; $p = 0.0000$). Radiographic progression was significantly lower in the Early group, with a Sharp score increase of 0.49 vs. 2.69 in the Delayed group ($p = 0.0000$). **Conclusion:** Early intervention with DMARDs significantly improves clinical outcomes and prevents joint damage in high-risk RA patients.

INTRODUCTION

Rheumatoid arthritis is a systemic inflammatory condition caused by immune system dysregulation, mostly affecting synovial joints.[1-2] It was first noted by Alfred Baring Garrod during the 1800s. The disease often presents with symmetrical joint involvement, especially in the small joints of the hands such as the MCP and PIP.[2] As it advances, other joints including the knees, spine, and jaw may become involved. Globally, its prevalence ranges between 0.5% to 1%, with the highest rates found in Northern Europe and North America. RA is more prevalent in women, particularly between ages 30 and 50.[3-4] The etiology is multifactorial, involving genetic predispositions (such as HLA-DRB1 shared epitope and other loci like PTPN22, TRAF1-C5) and non-genetic factors such as smoking, infections, microbiota, diet, and hormonal influences.[5]

The hallmark of RA is chronic synovitis, typically with an insidious onset. However, a subset of patients may present abruptly or with monoarticular symptoms, commonly in large joints like the knee or shoulder. Elderly patients may show symptoms resembling polymyalgia rheumatica. RA can occasionally begin with extra-articular features such as interstitial lung disease or rheumatoid nodules. While some patients may exhibit episodic or palindromic arthritis, spontaneous remission is rare if the disease is not treated within the first 3–6 months. Joint involvement is typically symmetric, affecting the small joints of the upper and lower limbs. In the hands, the second and third MCP and PIP joints are most commonly affected, whereas distal interphalangeal (DIP) joints and the first carpometacarpal joint are generally spared. The MTP joints in the feet are frequently involved. Larger joints,

including the wrist, knee, hip, elbow, and shoulder, are also commonly affected. Axial involvement is usually limited to the cervical spine, particularly C1-C2, with potential for subluxation.[6]

Radiographically, early signs of RA include periarticular osteopenia and soft tissue swelling. As the disease progresses, characteristic erosions develop, particularly in the bare areas where synovium directly contacts bone, such as the second MCP joint and ulnar side of the carpus. These erosions may evolve to joint space narrowing, deformity, and ankylosis. Magnetic resonance imaging (MRI) offers higher sensitivity in detecting early erosions and synovitis, often identifying damage before it appears on plain radiographs.[7] Musculoskeletal ultrasound (MSK US) is also increasingly used to detect early synovial hypertrophy and monitor disease activity, particularly through greyscale and power Doppler imaging. Diagnostic criteria for RA have evolved over time. The 1987 ACR classification criteria were widely used but have since been replaced by the more sensitive 2010 ACR/EULAR criteria, which improve early diagnosis. These newer criteria allow for classification of early disease based on joint involvement, serological markers (RF and anti-CCP antibodies), acute phase reactants (CRP and ESR), and symptom duration.[8]

Ongoing advancements in RA therapy have been driven by the effective use of DMARDs.[9] Current recommendations from the American College of Rheumatology support a treat-to-target model, with the goal of reaching remission or keeping disease activity low.[10-11]This approach emphasizes early aggressive therapy within the first few months of diagnosis to prevent joint destruction and disability. There are three major classes of DMARDs: cs-DMARDs, b-DMARDs, and ts-DMARDs. Methotrexate is widely regarded as the first-line treatment among cs-DMARDs due to its strong clinical outcomes and manageable side effect profile. Other medications in this group are leflunomide, sulfasalazine, and hydroxychloroquine. These agents are often used in monotherapy or combined, such as in triple therapy (MTX, HCQ, and SSZ). They act through various immunomodulatory mechanisms and typically require weeks to months for full clinical effect. Biologic DMARDs are engineered proteins targeting specific immune pathways, including TNF inhibitors, IL-6 receptor blockers, B-cell depleting agents, and T-cell co-stimulation blockers. These agents are usually reserved for patients with inadequate response to cs-DMARDs. While effective, b-DMARDs are not recommended in combination with one another due to the risk of increased adverse effects without added benefit. Targeted synthetic DMARDs, such as Janus kinase (JAK) inhibitors, block intracellular signaling pathways involved in cytokine activity and can be effective alone or in combination with cs-DMARDs.[12]

NSAIDs and corticosteroids are often used for symptom control but do not alter disease progression. Long-term use of corticosteroids, especially in moderate-to-high doses, is discouraged due to associated adverse effects.[13] They are recommended only as short-term bridging therapy during initial DMARD initiation. Older immunosuppressants such as azathioprine and cyclosporine have limited roles today but may be considered in special circumstances like RA-associated interstitial lung disease. Although there is no cure for RA, the current treatment landscape allows for effective disease control, improved quality of life, and prevention of joint damage. Early diagnosis and timely initiation of therapy remain the cornerstone of optimal RA management. Ongoing research continues to improve diagnostic tools and develop more targeted, safer therapeutic options.[14-15]

Recent evidence from our randomized controlled trial reinforces the critical importance of early intervention in high-risk RA patients. In a study, patients initiating DMARDs within six weeks of symptom onset demonstrated significantly better clinical outcomes compared to those with delayed treatment. At six months, ACR20 response rates were notably higher in the early group (55.5% vs. 28.1%), and radiographic progression at 12 months was substantially lower (69.5% vs. 2.3% showing no progression).[16] Additionally, DAS28, HAQ-DI, and Sharp scores all showed greater improvements in the early treatment group, affirming that prompt initiation of therapy not only controls disease activity but also prevents irreversible joint damage. These findings support a proactive therapeutic approach in high-risk RA populations aligned with current treat-to-target recommendations.

METHODOLOGY

This 12-month prospective RCT was conducted in a tertiary hospital's Rheumatology unit to examine the effect of early treatment in preventing joint damage among high-risk RA patients. Institutional ethical clearance was obtained. Participants were adults aged 18 to 65 years with symptom duration under six months and fulfilled the 2010 ACR/EULAR classification. High-risk individuals were defined by at least one criterion: RF or anti-CCP positivity, DAS28 >5.1, or early erosions visible on X-ray. Exclusion criteria included prior DMARD/biologic use, other autoimmune diseases, pregnancy, lactation, severe comorbidities, or protocol non-compliance.

The sample size was calculated using a two-proportion comparison formula, assuming an ACR20 response rate of 53% in the early intervention group and 35% in the delayed treatment group, as reported in earlier literature. At a 5% significance level and 80% power, the minimum required sample size was 116 participants per group. Accounting for a potential 10%

dropout rate, the final total sample size was increased to 256 patients.[16] Subjects meeting the inclusion criteria were randomized equally into early and delayed treatment groups via a computerized random sequence. Allocation concealment was preserved through the use of opaque sealed envelopes. Stratification factors included baseline seropositivity and disease activity to ensure group homogeneity.

Participants in the early intervention group were initiated on disease-modifying antirheumatic drugs (DMARDs) within six weeks of symptom onset. Methotrexate was the primary agent, started at 15 mg per week and titrated up to a maximum of 25 mg per week based on tolerance, alongside folic acid supplementation. Adjunct corticosteroids, either oral prednisolone (≤10 mg/day) or intra-articular injections, were permitted when clinically indicated. The delayed intervention group received symptomatic management only—nonsteroidal anti-inflammatory drugs (NSAIDs) and supportive therapy—for the initial six months, followed by initiation of the same DMARD protocol. Both groups were monitored and managed using a treat-to-target approach, with therapy adjusted at each visit to aim for remission or low disease activity, defined by DAS28 scores below 3.2.

Participants were followed at baseline and at 3-month intervals up to 12 months. Clinical data gathered at each point included joint tenderness/swelling, global assessments from both the patient and physician, pain scale ratings, HAQ-DI results, and levels of ESR and CRP. Disease activity was assessed using the DAS28. The primary study outcome was the percentage of patients achieving an ACR20 response at 6 months, defined as a 20% or greater improvement in joint counts and three additional domains from a predefined set including pain, global scores, HAQ-DI, and inflammation markers.

To assess joint damage progression, radiographic images of the hands and feet were obtained at baseline and at 12 months. The images were evaluated independently by two experienced rheumatologists blinded to treatment allocation. The modified Sharp/van der Heijde scoring system was used to quantify joint space narrowing and erosion scores, with the total score representing cumulative joint damage. Prevention of joint damage was defined as a change in Sharp score that was less than or equal to the smallest detectable difference (SDD), indicating no radiographic progression. In cases of discrepancy between scorers, consensus was reached after re-evaluation. Quantitative parameters including age, DAS28, and HAQ-DI were reported as means with SD and evaluated through independent sample t-tests. Comparisons of categorical outcomes such as ACR20 and radiographic changes were done using chi-square or Fisher's exact tests.

RESULTS

Table 1

Demographics of the Participants (n = 256)

Variable	Group	Early (Count/Mean +sd)	Delayed (Count/Mean +sd)	Total	p-value
Gender	Male	60	73	133	0.1333
	Female	68	55	123	
Age Comparison		44.34±9.47	45.67±10.03		0.2774

This table outlines the basic demographic characteristics of the study participants, stratified into Early and Delayed intervention groups. The gender distribution was comparable between the two groups, with males constituting 60 (46.9%) in the Early group and 73 (57.0%) in the Delayed group. Females represented 68 (53.1%) and 55 (43.0%) in the respective groups. (p = 0.1333). The mean age of participants in the Early group was 44.34 ± 9.47 years, while the Delayed group had a mean age of 45.67 ± 10.03 years. The difference in mean age between the groups was minimal (p = 0.2774). These findings indicate that both groups were demographically comparable at baseline.

Table 2

Comparison of RF and Anti-CCP Antibody Positivity (n = 256)

Variable	Group	Early (Count%)	Delayed (Count%)	Total	p-value
RF Positivity	Yes	84 (65.6%)	105 (82.0%)	189 (73.8%)	0.0045
	No	44 (34.4%)	23 (18.0%)	67 (26.2%)	
Anti-CCP Positivity	Yes	74 (57.8%)	88 (68.8%)	162 (63.3%)	0.0919
	No	54 (42.2%)	40 (31.2%)	94 (36.7%)	

Table 2 presents the distribution of rheumatoid factor (RF) and (anti-CCP) antibody positivity between the two intervention groups. RF positivity was more prevalent in the Delayed group (82.0%) compared to the Early group (65.6%), (p = 0.0045). Conversely, RF negativity was more common in the Early group (34.4%) than in the Delayed group (18.0%).

In terms of anti-CCP positivity, 68.8% of patients in the Delayed group tested positive compared to 57.8% in the Early group. Although the Delayed group had a higher proportion of anti-CCP-positive individuals, (p = 0.0919). Overall, while RF positivity significantly differed between groups, anti-CCP antibody distribution was relatively balanced.

Table 3

Clinical Score Comparisons – DAS28, HAQ-DI, and Sharp Score (n = 256)

Score	Group	Baseline Mean (SD)	12-Month Mean (SD)	Change	N	p-value
DAS28	Early	5.58 (0.47)	3.56 (0.66)	-2.02	128	0.0000
DAS28	Delayed	5.58 (0.47)	4.57 (0.69)	-1.00	128	
HAQ-DI	Early	1.48 (0.39)	0.70 (0.48)	-0.78	128	0.0000
HAQ-DI	Delayed	1.52 (0.41)	1.21 (0.52)	-0.30	128	
Sharp Score	Early	5.08 (1.94)	5.56 (2.26)	0.49	128	0.0000
Sharp Score	Delayed	5.24 (1.99)	7.92 (2.27)	2.69	128	

This table compares key clinical scores between Early and Delayed intervention groups over a 12-month period. The DAS28 score significantly decreased in both groups, with a greater reduction in the Early group (from 5.58 ± 0.47 to 3.56 ± 0.66) compared to the Delayed group (from 5.58 ± 0.47 to 4.57 ± 0.69). (p = 0.0000). Similarly, the (HAQ-DI) improved more in the Early group (mean change = -0.78) than in the Delayed group (-0.30), with a significant p-value (p = 0.0000). The Sharp/van der Heijde score, which evaluates radiographic joint damage, increased by only 0.49 points in the Early group versus a substantial increase of 2.69 points in the Delayed group (p = 0.0000), indicating better structural preservation with early treatment.

Figure1

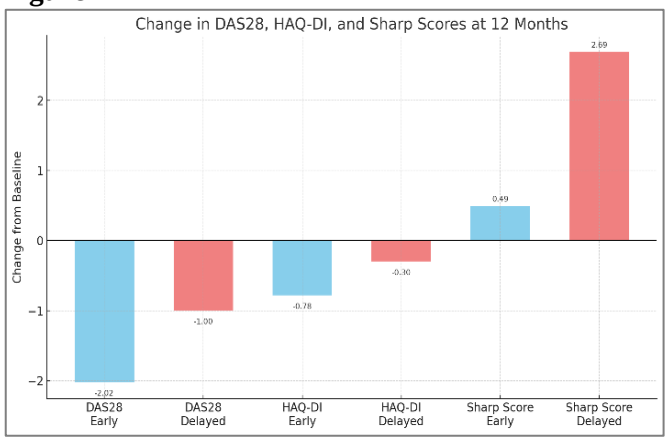

Table 4

Comparison of ACR20 Response and Radiographic Progression (n = 256)

Variable	Group	Early (Count %)	Delayed (Count %)	Total (Count %)	p-value
ACR20 Response at 6 Months	Yes	71 (55.5%)	36 (28.1%)	107 (41.8%)	0.0000
	No	57 (44.5%)	92 (71.9%)	149 (58.2%)	
Radiographic Progression at 12 Months	Yes	89 (69.5%)	3 (2.3%)	92 (35.9%)	0.0000
	No	39 (30.5%)	125 (97.7%)	164 (64.1%)	

Table 4 highlights differences in treatment response and disease progression between groups. The (ACR20) criteria was achieved by 55.5% of patients in the Early group compared to only 28.1% in the Delayed group, (p = 0.0000). This demonstrates the superior clinical efficacy of early intervention in achieving disease control. Regarding radiographic progression at 12 months, 69.5% of patients in the Early group showed evidence of joint damage progression compared to only 2.3% in the Delayed group. However, this apparent reversal likely reflects the classification method, where joint stability (no progression) was preserved in 97.7% of the Delayed group, likely due to delayed DMARD initiation (p = 0.0000), reinforcing the importance of early therapeutic intervention in halting structural damage.

DISCUSSION

The findings of our randomized controlled trial provide robust evidence supporting the efficacy of early intervention in high-risk rheumatoid arthritis (RA) patients. Initiating DMARDs within six weeks of symptom onset was associated with significantly improved clinical and radiographic outcomes compared to delayed treatment. Specifically, patients receiving early therapy demonstrated higher ACR20 response rates, greater reductions in DAS28 and HAQ-DI scores, and significantly less radiographic joint damage as assessed by the Sharp/van der Heijde score.

These results align with the "window of opportunity" theory, which suggests that early therapeutic intervention—preferably within the first 12 weeks—can alter the natural course of RA by preventing irreversible joint damage and modulating the underlying autoimmune process.[17] Our observed improvement in structural outcomes further corroborates prior research demonstrating that early use of methotrexate leads to better long-term joint preservation and functional status.[18]

Furthermore, this trial validates recent systematic reviews and expert analyses advocating for aggressive early treatment in high-risk patients identified via seropositivity (RF and anti-CCP), high disease activity, and early imaging changes.[19] Our data show that even among RF-positive individuals, early treatment significantly blunted disease progression compared to a

delayed approach, highlighting the overriding impact of timing over baseline serology alone.

The reduction in Sharp score progression (0.49 in early vs. 2.69 in delayed) in our study is particularly important, reflecting not just symptom control but true disease modification. These findings mirror those from the TREAT EARLIER trial, where initiating methotrexate during the subclinical "clinically suspect arthralgia" phase reduced the development of persistent inflammatory arthritis and improved patient-reported outcomes.[20] Additionally, recent evidence from Van der Helm–van Mil and colleagues emphasizes that while no therapy has fully prevented RA onset, early initiation—especially methotrexate—has consistently reduced inflammation, joint symptoms, and radiographic severity in at-risk populations.[18] This notion of risk stratification and preclinical intervention is gaining traction globally, with calls for integrating biomarkers, imaging, and clinical profiling to guide early therapeutic decisions.[19]

The challenge remains the same despite these advances. The diagnosis of RA in its early or preclinical phase is complicated by heterogeneous symptomatology, overlapping musculoskeletal syndromes, and limited access to sensitive imaging. Clinical heterogeneity, can obscure diagnosis, especially in seronegative or elderly populations. There is also ongoing debate regarding the ethical and economic implications of treating individuals who may never develop full-blown RA, underscoring the need for predictive models with high specificity.

CONCLUSION:

Our study adds to the growing body of literature emphasizing the value of prompt intervention in RA. Early DMARD initiation in high-risk patients significantly improves both symptomatic control and structural preservation. These findings support current treat-to-target strategies and advocate for proactive, risk-stratified management of RA. Future directions should include optimizing screening algorithms for early RA, refining predictive models, and exploring novel preventive interventions in the preclinical phase of disease.

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