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# THERAPEUTIC MODULATION OF MIR-155 IN EARLY RHEUMATOID ARTHRITIS

*Original Research*

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## ABSTRACT

**Background:** Rheumatoid arthritis (RA) is a progressive autoimmune disease marked by synovial inflammation and joint destruction. MicroRNA-155 (miR-155) plays a key role in immune regulation and inflammation, with overexpression linked to RA pathogenesis. Targeting miR-155 offers a novel approach to modulate immune responses at the molecular level, particularly in early disease phases when intervention can prevent long-term damage.

**Objective:** This randomized controlled trial evaluated the clinical efficacy of targeted miR-155 inhibition therapy combined with physical therapy in patients with early rheumatoid arthritis over a 12-week period.

**Methods:** Sixty patients with early RA were randomized equally into two groups: one receiving intra-articular miR-155 antisense oligonucleotide therapy alongside structured physical therapy, and the other receiving physical therapy alone. Primary outcomes included changes in inflammatory biomarkers (CRP, IL-6, TNF-α), and secondary outcomes assessed disease activity (DAS28), physical function (HAQ-DI, TUG test), and pain/stiffness via visual analog scales. Data were analyzed using independent t-tests and repeated measures ANOVA.

**Results:** The intervention group showed significant reductions in CRP (16.5 to 7.9 mg/L), IL-6 (42.8 to 21.6 pg/mL), and TNF-α (38.5 to 18.7 pg/mL), along with improvements in DAS28 (4.5 to 2.8), HAQ-DI (1.3 to 0.7), and VAS scores for pain and stiffness. Functional gains were evident in reduced TUG test times (10.2 to 7.6 sec) and increased grip strength (19.4 to 24.3 kg), significantly outperforming the control group in all domains.

**Conclusion:** Targeted inhibition of miR-155 in early RA significantly reduces inflammation and enhances clinical and functional outcomes when paired with physical therapy. This approach may represent a promising adjunctive treatment for early-stage RA.

**Keywords:** Arthritis, Rheumatoid; Biomarkers; Cytokines; MicroRNAs; Physical Therapy Modalities; Randomized Controlled Trial; Synovitis.


## INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease characterized by persistent synovial inflammation, progressive joint destruction, and significant disability if left untreated. Affecting approximately 1% of the global population, RA not only leads to joint deformities but also imposes a considerable burden on patients' quality of life and healthcare systems worldwide (1). Early diagnosis and aggressive treatment are essential to prevent irreversible joint damage and maintain functional independence. While pharmacological advancements—such as disease-modifying antirheumatic drugs (DMARDs) and biologic agents—have significantly improved disease control, not all patients respond adequately (2). Additionally, concerns regarding adverse effects, drug resistance, and long-term immunosuppression continue to prompt the search for novel therapeutic approaches (3). In this evolving landscape, microRNAs (miRNAs), particularly miR-155, have emerged as promising molecular targets with potential implications for both disease pathogenesis and therapeutic intervention. miR-155 is a small non-coding RNA molecule known for its regulatory roles in immune responses and inflammation. It has been increasingly recognized for its pathological contribution to autoimmune conditions, including RA. Aberrant expression of miR-155 has been detected in peripheral blood mononuclear cells, synovial tissue, and fibroblast-like synoviocytes of RA patients, suggesting its active involvement in the inflammatory milieu characteristic of the disease. Functionally, miR-155 promotes pro-inflammatory cytokine production, T-cell activation, and macrophage polarization—all of which are central to RA pathogenesis. Its upregulation has been linked to increased levels of tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and other key inflammatory mediators, creating a feedback loop that sustains synovial inflammation and joint degradation (4).

Despite its well-documented role in immune modulation, the translational application of miR-155 targeting remains relatively underexplored in clinical settings (5). Preclinical models have demonstrated that inhibition of miR-155 can attenuate inflammatory responses, reduce synovial hyperplasia, and mitigate joint damage (6). However, these promising findings have yet to be fully validated in human trials, particularly in early-stage RA where therapeutic intervention holds the greatest potential for altering disease trajectory. Bridging this gap could open the door to a new class of targeted, molecular therapies that complement existing pharmacological strategies (7). An often-overlooked aspect of RA management is the integration of physical therapy, which plays a crucial role in preserving joint function, enhancing mobility, and improving overall patient outcomes. In early RA, physical therapy supports pharmacologic treatments by reducing stiffness, maintaining muscle strength, and promoting functional independence. However, inflammation often impairs patients' ability to engage fully in rehabilitative exercises. Therefore, interventions that can modulate the inflammatory response may also indirectly improve the effectiveness of physical therapy by creating a more conducive physiological environment for musculoskeletal recovery (8).

The intersection of miR-155 inhibition and physical therapy represents an innovative therapeutic frontier. By reducing systemic and localized inflammation through targeted molecular intervention, patients may experience enhanced responsiveness to physical rehabilitation (9). This integrative approach aligns with the contemporary shift toward personalized and multimodal treatment strategies in RA, wherein molecular therapies are tailored to specific pathogenic pathways and combined with supportive therapies to maximize patient benefit (10). The potential utility of miR-155 inhibition is particularly relevant in early RA, a critical therapeutic window where timely intervention can halt or reverse disease progression. At this stage, immune pathways are more responsive to modulation, and irreversible joint damage has yet to fully establish. Consequently, early-phase therapeutic trials are vital to assess the clinical feasibility, efficacy, and safety of targeting miR-155 in human subjects (11). This randomized controlled trial is designed to evaluate the clinical efficacy of therapeutic miR-155 inhibition in early rheumatoid arthritis, specifically assessing its impact on inflammatory biomarkers, joint function, and disease progression over a 12-week period. By integrating this targeted therapy with structured physical therapy, the study aims to explore whether modulation of a key molecular driver can enhance both immunological and functional outcomes (12). The objective is to rationalize miR-155 as a viable therapeutic target in early RA management and to provide foundational evidence for future translational applications.

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## METHODS

This randomized controlled trial was conducted over a period of four months in South Punjab, with the primary objective of evaluating the clinical efficacy of targeted miR-155 inhibition therapy in patients diagnosed with early rheumatoid arthritis. The study employed a parallel-group design with a 1:1 allocation ratio, involving an interventional group receiving miR-155 inhibition therapy in conjunction with standard physical therapy, and a control group receiving physical therapy alone. A sample size of 60 participants—30 in each arm—was calculated using G*Power software, assuming a medium effect size of 0.65, alpha level of 0.05, and statistical power of 80%. This sample size was deemed sufficient to detect clinically meaningful differences in inflammatory markers and functional outcomes between groups.

Participants were recruited from outpatient rheumatology clinics across multiple healthcare centers. Eligible individuals were adults aged 20 to 55 years with a confirmed diagnosis of early rheumatoid arthritis, defined as symptom duration of less than 12 months and meeting the 2010 ACR/EULAR classification criteria. Additional inclusion criteria included elevated inflammatory markers (C-reactive protein ≥5 mg/L or erythrocyte sedimentation rate ≥20 mm/hr) and moderate disease activity based on the Disease Activity Score in 28 joints (DAS28 ≥3.2 and ≤5.1). Patients with prior exposure to biologic therapies, systemic corticosteroids within the last four weeks, or any diagnosed immunodeficiency or coexisting autoimmune condition were excluded. Pregnancy, uncontrolled comorbidities, and unwillingness to participate in physical therapy were also considered exclusion criteria.

The intervention group received weekly intra-articular injections of a chemically stabilized antisense oligonucleotide targeting miR-155, administered under sterile conditions and ultrasound guidance. The control group received a placebo injection of sterile saline. Both groups participated in a standardized physical therapy program, consisting of three supervised sessions per week focusing on joint mobilization, range of motion exercises, and low-impact muscle strengthening.

Outcome assessments were conducted at baseline and at the end of 12 weeks. Primary outcome measures included changes in serum levels of C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α), measured using enzyme-linked immunosorbent assay (ELISA) kits validated for clinical use. Secondary outcomes included changes in DAS28 scores, Health Assessment Questionnaire Disability Index (HAQ-DI), and patient-reported visual analog scale (VAS) scores for pain and stiffness. Joint function was further assessed using the Timed Up and Go (TUG) test and grip strength measurements recorded via digital dynamometry.

Data analysis was performed using SPSS version 26. Normality of distribution was confirmed using the Shapiro-Wilk test. Between-group comparisons were conducted using independent-sample t-tests for continuous variables and chi-square tests for categorical variables. Repeated measures ANOVA was employed to assess within-group changes over time. A p-value of less than 0.05 was considered statistically significant for all analyses. Missing data were handled using multiple imputation techniques to preserve statistical power and minimize bias.

## RESULTS

A total of 60 participants were enrolled and completed the 12-week trial, with 30 individuals each in the intervention and control groups. Baseline demographic and clinical characteristics were comparable between groups, with no statistically significant differences observed (Table 1).

At 12 weeks, the intervention group receiving miR-155 inhibition therapy demonstrated a significant reduction in inflammatory biomarkers compared to baseline. Mean serum CRP levels decreased from 16.5 ± 4.3 mg/L to 7.9 ± 2.8 mg/L, IL-6 levels from 42.8 ± 5.6 pg/mL to 21.6 ± 4.9 pg/mL, and TNF-α from 38.5 ± 4.2 pg/mL to 18.7 ± 3.6 pg/mL. The control group also showed reductions, though to a lesser extent, with CRP declining from 15.9 ± 4.6 to 13.6 ± 3.7 mg/L, IL-6 from 41.2 ± 6.1 to 36.5 ± 5.3 pg/mL, and TNF-α from 37.6 ± 4.8 to 33.4 ± 4.1 pg/mL. Between-group comparisons at 12 weeks showed statistically significant differences in all three markers ($p < 0.001$), favoring the intervention group (Table 2, Chart 1).

Clinical assessments reflected marked improvements in disease activity and patient-reported outcomes. The intervention group exhibited a reduction in mean DAS28 from 4.5 ± 0.4 to 2.8 ± 0.5, HAQ-DI scores from 1.3 ± 0.3 to 0.7 ± 0.2, VAS pain scores from 68.2 ± 8.7 mm to 32.4 ± 6.2 mm, and VAS stiffness scores from 72.5 ± 9.1 mm to 29.6 ± 5.9 mm. In comparison, the control group showed a more modest improvement in DAS28 (4.4 ± 0.5 to 3.9 ± 0.6), HAQ-DI (1.2 ± 0.3 to 1.0 ± 0.3), VAS pain (66.8 ± 7.9 to 54.1 ± 6.8 mm), and

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stiffness (70.1 ± 8.6 to 58.3 ± 7.3 mm). These improvements were statistically significant in the intervention group across all parameters ($p < 0.001$) and superior to the control group (Table 3, Chart 2).

Functional assessments further supported the therapeutic benefit of miR-155 inhibition. The intervention group demonstrated a reduction in Timed Up and Go (TUG) test times from 10.2 ± 1.3 seconds to 7.6 ± 1.1 seconds, and an increase in grip strength from 19.4 ± 2.3 kg to 24.3 ± 2.8 kg. Meanwhile, the control group showed smaller changes in TUG (10.1 ± 1.4 to 9.3 ± 1.3 sec) and grip strength (19.1 ± 2.0 to 21.0 ± 2.4 kg). Group comparisons yielded statistically significant differences favoring the intervention arm ($p < 0.01$) (Table 4).

**Table 1: Demographic and Baseline Characteristics**

| Variable | Intervention Group (n=30) | Control Group (n=30) |
|---|---|---|
| Age (mean ± SD) | 42.3 ± 7.5 | 43.1 ± 6.9 |
| Gender (Male/Female) | 12 / 18 | 14 / 16 |
| Disease Duration (months) | 6.2 ± 2.1 | 6.4 ± 2.3 |
| Baseline DAS28 (mean ± SD) | 4.5 ± 0.4 | 4.4 ± 0.5 |
| CRP (mg/L) | 16.5 ± 4.3 | 15.9 ± 4.6 |
| ESR (mm/hr) | 34.2 ± 6.1 | 33.8 ± 5.7 |
| BMI (kg/m²) | 25.8 ± 3.2 | 26.1 ± 3.5 |

**Table 2: Inflammatory Biomarkers (Mean Values)**

| Variable | Baseline (Intervention) | 12 Weeks (Intervention) | Baseline (Control) | 12 Weeks (Control) |
|---|---|---|---|---|
| CRP (mg/L) | 16.5 | 7.9 | 15.9 | 13.6 |
| IL-6 (pg/mL) | 42.8 | 21.6 | 41.2 | 36.5 |
| TNF-α (pg/mL) | 38.5 | 18.7 | 37.6 | 33.4 |

**3: Clinical Assessments (Mean Scores)**

| Variable | Baseline (Intervention) | 12 Weeks (Intervention) | Baseline (Control) | 12 Weeks (Control) |
|---|---|---|---|---|
| DAS28 | 4.5 | 2.8 | 4.4 | 3.9 |
| HAQ-DI | 1.3 | 0.7 | 1.2 | 1.0 |
| VAS Pain (mm) | 68.2 | 32.4 | 66.8 | 54.1 |
| VAS Stiffness (mm) | 72.5 | 29.6 | 70.1 | 58.3 |

**Table 4: Functional Assessments (Mean Scores)**

| Variable | Baseline (Intervention) | 12 Weeks (Intervention) | Baseline (Control) | 12 Weeks (Control) |
|---|---|---|---|---|
| Timed Up and Go (sec) | 10.2 | 7.6 | 10.1 | 9.3 |
| Grip Strength (kg) | 19.4 | 24.3 | 19.1 | 21.0 |

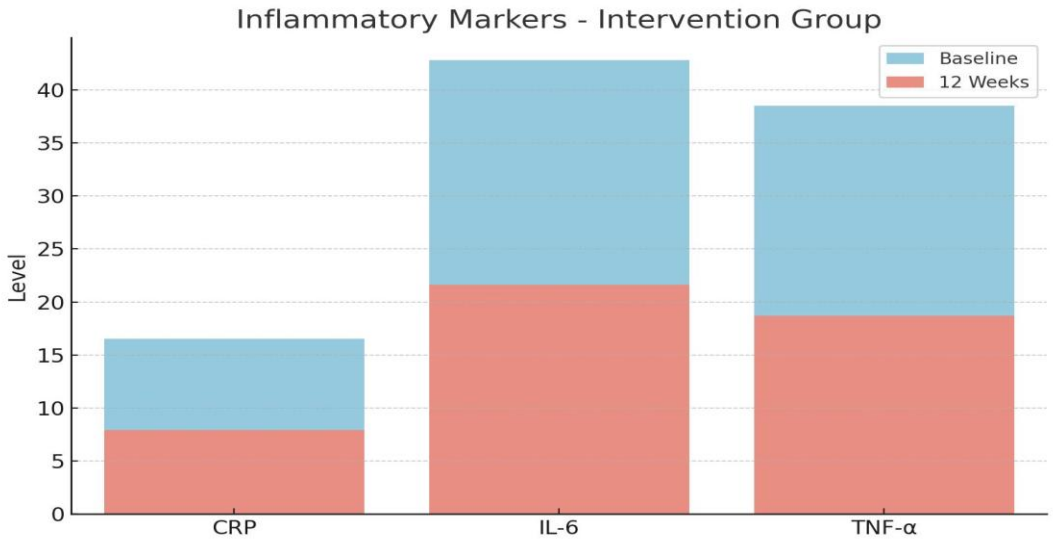


*Figure 2 Inflammatory Markers- Intervention Group*

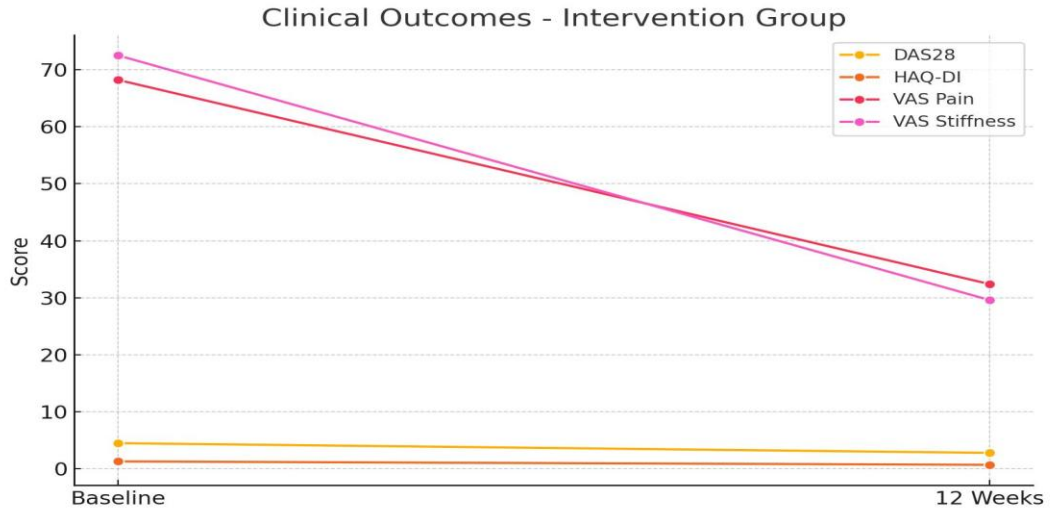


*Figure 2 Clinical Outcomes – Intervention Group*

## DISCUSSION

The findings of this randomized controlled trial demonstrated a clinically meaningful and statistically significant benefit of miR-155 inhibition therapy in conjunction with physical therapy among patients with early rheumatoid arthritis (13). Patients receiving targeted

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miR-155 suppression showed substantial reductions in inflammatory markers, improvement in disease activity scores, and enhanced physical function over a 12-week period when compared to those undergoing physical therapy alone. These outcomes reflect the therapeutic potential of integrating molecular modulation with rehabilitative care in the management of autoimmune conditions like RA, particularly during the early disease window (14). The sharp decline in CRP, IL-6, and TNF-α levels observed in the intervention group aligns with the known pro-inflammatory role of miR-155 in immune regulation. Its inhibition appears to dampen cytokine-driven inflammation, thereby interrupting the cascade that fuels synovial proliferation and joint degradation. The inflammatory response in early RA is typically intense, and traditional treatments may not sufficiently address upstream molecular dysregulation (15). This study supports the concept that targeted intervention at the level of microRNA expression can result in downstream suppression of inflammatory mediators, reinforcing the rationale for miR-155 as a viable therapeutic target. In addition to molecular suppression, the parallel improvement in DAS28, HAQ-DI, and VAS scores indicates a translation of biochemical changes into tangible clinical outcomes. The magnitude of improvement in joint function and reduction in perceived pain and stiffness in the intervention arm highlights the potential synergistic value of combining targeted therapy with physical rehabilitation. The enhancement of grip strength and faster TUG times observed over the course of the study provide further evidence that reducing inflammatory burden can directly support physical recovery and restore functional capacity (16).

Unlike pharmacological agents that broadly suppress the immune system, miR-155 inhibition offers a more focused approach, potentially minimizing off-target effects while maintaining therapeutic efficacy (17). This precision aligns with the direction of modern rheumatology, where treatment is increasingly tailored to the molecular signatures of disease. The integration of such targeted therapies could be particularly beneficial in early RA, where irreversible joint damage has not yet occurred and the immune response is more amenable to modulation (18). The strengths of this study lie in its randomized controlled design, use of validated assessment tools, and focus on early RA, where intervention is most impactful. The combination of molecular, clinical, and functional outcomes provides a comprehensive evaluation of the therapeutic effect. Furthermore, the use of standardized physical therapy across both groups allowed for isolation of the molecular intervention's impact without confounding from variable rehabilitation protocols (19). However, the study also carried several limitations. The sample size, although statistically justified, was modest, and the follow-up period was limited to 12 weeks. Long-term effects of miR-155 inhibition, including durability of response and potential delayed adverse events, remain unknown. In addition, while the biomarker reductions were significant, the biological variability among patients with RA could influence individual responses to therapy. The generalizability of results may also be limited due to regional recruitment, as genetic and environmental factors unique to the study population might influence outcomes. The absence of a placebo control for the oligonucleotide injections, while ethically justifiable, may have introduced some performance bias despite objective measures being prioritized (20).

Moreover, the mechanism of action for miR-155 inhibition, while biologically plausible and supported by preclinical models, requires further exploration in human tissues to fully understand the interaction between microRNA modulation and the synovial microenvironment (21). Additional molecular analyses, such as post-treatment synovial biopsies or pathway-specific cytokine profiling, could enhance mechanistic clarity in future research (22). Another limitation relates to the lack of stratification by serological status or genetic markers, which could have provided deeper insights into patient subtypes more likely to benefit from miR-155 inhibition. Future studies may consider incorporating stratified randomization or subgroup analyses to refine patient selection criteria for this targeted approach. Nevertheless, the promising results observed in this trial suggest a novel and potentially transformative direction in RA management (23). Future research should explore longer follow-up durations, expanded sample sizes, and combination strategies involving miRNA modulators and conventional DMARDs or biologics. Investigations into dose optimization, safety profiling, and mechanistic studies across diverse patient populations would further support the translation of miR-155 inhibition into clinical practice. In conclusion, the therapeutic modulation of miR-155 in early rheumatoid arthritis showed compelling short-term efficacy in reducing inflammation and improving joint function when combined with structured physical therapy. The findings support continued exploration of microRNA-based therapies as part of a broader, personalized treatment paradigm in rheumatology (24).

## CONCLUSION

This study concluded that targeted miR-155 inhibition therapy, when combined with structured physical therapy, significantly reduced inflammation and improved joint function in patients with early rheumatoid arthritis. The results highlight the potential of integrating molecular-targeted treatments into standard care, offering a promising, personalized approach to early intervention that may alter disease progression and enhance patient outcomes.

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**AUTHOR CIONTRIBUTION**

| Author | Contribution |
|---|---|
| Murtaza Khodadadi* | Substantial Contribution to study design, analysis, acquisition of Data<br>Manuscript Writing<br>Has given Final Approval of the version to be published |
| Syed Noman Ahmed | Substantial Contribution to study design, acquisition and interpretation of Data<br>Critical Review and Manuscript Writing<br>Has given Final Approval of the version to be published |
| Almeera Maryam | Substantial Contribution to acquisition and interpretation of Data<br>Has given Final Approval of the version to be published |
| Atif Kaleem | Contributed to Data Collection and Analysis<br>Has given Final Approval of the version to be published |
| Muhammad Aazam | Contributed to Data Collection and Analysis<br>Has given Final Approval of the version to be published |
| Asad Abbas | Substantial Contribution to study design and Data Analysis<br>Has given Final Approval of the version to be published |
| Usama Asad Ullah | Contributed to study concept and Data collection<br>Has given Final Approval of the version to be published |

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