# Clinical and Immunological Characteristics of Patients with Rheumatoid Arthritis on Synthetic DMARDS Therapy

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**ABSTRACT**

This observational cohort study evaluated the efficacy and safety of different combinations of adalimumab and methotrexate in patients with rheumatoid arthritis (RA) who had an inadequate response to methotrexate monotherapy. The study population was divided into three groups based on their treatment regimen: Group IA (adalimumab 40 mg bi-weekly + methotrexate 7.5 mg weekly), Group IB (adalimumab 40 mg biweekly + methotrexate 15 mg weekly), and a comparison group (methotrexate 15 mg weekly). The primary outcome was the change in the Disease Activity Score based on 28 joints (DAS28) from baseline to 6 months. Secondary outcomes included the American College of Rheumatology (ACR) 20, 50, and 70 responses, changes in the Health Assessment Questionnaire-Disability Index (HAQ-DI) scores, and radiographic progression assessed using the modified Sharp/van der Heijde score (mTSS). Results demonstrated comparable baseline characteristics across groups, with no significant differences in age, gender distribution, disease duration, tender and swollen joint counts, and inflammatory markers. The analysis of immunological indexes, specifically interleukin-6 (IL-6) and interleukin-17 (IL-17), showed a correlation between their levels and disease severity as measured by the DAS28. Elevated levels of IL-6 and IL-17 were observed in patients with higher DAS28 scores, highlighting their role as biomarkers for assessing and monitoring RA disease activity. The study provides valuable insights into the comparative effectiveness of different treatment regimens and underscores the importance of personalized treatment strategies for RA patients.

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## Introduction

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease characterized by inflammation of the synovial joints, leading to progressive joint destruction, pain, and disability. The etiology of RA is complex and multifactorial, involving genetic, environmental, and immunological factors that contribute to the pathogenesis of the disease. The clinical manifestations of RA are diverse, ranging from mild joint stiffness to severe joint damage and systemic complications, impacting the quality of life of affected individuals [1–4].

The management of RA has evolved significantly over the past few decades, with the advent of disease-modifying antirheumatic drugs (DMARDs) and biologic agents that target specific components of the immune system. Methotrexate is a conventional DMARD that has been a cornerstone in the treatment of RA due to its efficacy in controlling disease activity and slowing disease progression. However, not all patients respond adequately to methotrexate monotherapy, necessitating the use of combination therapy or alternative agents [1,4].

Biologic agents, such as tumor necrosis factor (TNF) inhibitors, have revolutionized the treatment landscape of RA. Adalimumab, a fully human monoclonal antibody that inhibits TNF-α, has demonstrated significant efficacy in reducing the signs and symptoms of RA, inhibiting the progression of joint damage, and improving physical function when used alone or in combination with methotrexate [5,6].

Despite the availability of effective therapies, the optimal treatment strategy for individual patients remains a challenge. The heterogeneity of the disease and the variability in patient response to treatment underscore the need for personalized approaches and the exploration of different treatment regimens. In this context, the present study aims to compare the efficacy and safety of different combinations of adalimumab and methotrexate in patients with RA who have an inadequate response to methotrexate monotherapy [7,8].

This study is designed to provide insights into the comparative effectiveness of these treatment regimens, which may inform clinical decision-making and contribute to the optimization of therapeutic strategies for patients

with RA. The results section of this article presents the findings of this investigation, including the demographic and baseline clinical characteristics of the patients, the impact of the treatment regimens on disease activity, and the safety profile of the combinations.

## Materials and methods

This observational cohort study was conducted to compare the efficacy and safety of different combinations of adalimumab and methotrexate in patients with rheumatoid arthritis (RA) who had an inadequate response to methotrexate monotherapy. Adult patients (aged ≥18 years) diagnosed with RA according to the 2010 American College of Rheumatology/European League Against Rheumatism criteria, with a disease duration of at least 6 months, were included in the study. Eligible participants had active disease, defined as having at least 6 swollen joints and 6 tender joints, along with either an erythrocyte sedimentation rate (ESR) >28 mm/hour or a C-reactive protein (CRP) level >1.0 mg/dL.

- Participants were categorized into three exposure groups based on their treatment regimen:
- Group IA: Adalimumab 40 mg subcutaneously every other week + methotrexate 7.5 mg orally once weekly
- Group IB: Adalimumab 40 mg subcutaneously every other week + methotrexate 15 mg orally once weekly
- Comparison Group: Methotrexate 15 mg orally once weekly

The primary outcome was the change in the Disease Activity Score based on 28 joints (DAS28) from baseline to 6 months. Secondary outcomes included the American College of Rheumatology 20% improvement criteria (ACR20), ACR50, and ACR70 responses, changes in the Health Assessment Questionnaire-Disability Index (HAQ-DI) scores, and radiographic progression assessed using the modified Sharp/van der Heijde score (mTSS).

Data on demographic characteristics, clinical parameters, treatment regimens, and outcomes were collected from medical records and patient interviews. Descriptive statistics were used to summarize baseline characteristics. Comparative analyses between the exposure groups were performed using chi-square tests for categorical variables and analysis of variance (ANOVA) or Kruskal-Wallis tests for continuous variables, as appropriate. Multivariable regression analyses were conducted to adjust for potential confounders and to estimate the adjusted effect of the treatment regimens on the outcomes.The study protocol was approved by the institutional review board or ethics committee at each participating center, and the study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. Written informed consent was obtained from all participants before enrollment in the study.

## Results

Demographic and baseline clinical characteristics of the patients reflected a population with RA and were comparable among the 3 treatment groups. We divided patients into three groups. Group - IA consisted of patients who received a combinations of adalimumab 40mg + methotrexate 7.5mg, IB- those who received a combinations of adalimumab 40mg + methotrexate 15mg and the comparison group received only methotrexate 15mg once weekly. The mean age of patients were 43.4±15.7 years in group IA, 41.8±14.7 years in group IB and 42.9±6.2 years of the patients following methotrexate (MTX) monotherapy in comparison group.

**Table 1. Characteristics of patients according to treatment group**

| | Group IA (n = 31) | Group IB (n = 27) | Comparison group (n = 100) |
|---|---|---|---|
| Age, years (m±sd) | 43.4±15.7 | 41.8±14.7 | 42.9±6.2 |
| Male n(%) | 10(32.3%) | 9 (33.3%) | 31 (31.0%) |
| Female n(%) | 21 (67.7%) | 18 (66.7%) | 69 (69.0%) |
| Disease duration (years) | 6.7±1.9 | 7.2±1.2 | 6.9±2.1 |
| Disease duration<1 years | 9 (29.0%) | 7 (25.9%) | 30 (30.0%) |
| Disease duration 1-3 years | 12 (38.7%) | 11 (40.7%) | 44 (44.0%) |
| Disease duration >3 years | 10 (32.3%) | 9 (33.3%) | 28 (28.0%) |
| Taking corticosteroids n (%) | 12 (38.7) | 10 (37.0%) | 37 (37.0%) |
| Tender joint count (0-68) | 35.8±14.8 | 36.2±15.6 | 37.3±1.1 |
| Swollen joint count (0-66) | 27.2±13.6 | 29.2±13.1 | 30.5±11.4 |
| C-reactive protein (mg/dl) | 3.9±4.2 | 4.1±3.9 | 4.0±4.0 |
| ESR (mm/h) | 29.5± 8.2 | 28.5± 8.9 | 27.2± 5.4 |
| Anti-CCP positive n (%) | 30 (96.7%) | 27 (100%) | 100 (100.0%) |
| RF positive n (%) | 28 (90.3%) | 24 (88.9%) | 81 (81.0%) |

*Note: ESR- Erythrocyte Sedimentation Rate; MTX-methotrexate. RF-rheumatoid factor. CCP- cyclic citrullinated peptide. statistical significance *-p<0.05*

We found no statistically significant difference between the comparison groups in terms of mean age of participants (p>0.05). Majority of the patients were females in all three groups with no difference in the female male ratio between the groups (67.7%, 66.7% and 69.0% respectively). In each treatment group, the mean duration of RA at baseline was 6.7, 7.2 and 6.9 years respectively. Majority of patients had disease duration of between 3-7 years. Of notes, 12 (38.7%) patients in IA group, 11 (40.7%) patients in IB group and 44 (44.0%) patients taking methotrexate monotherapy had disease duration of between 3 to 7 years. Moreover, over 60% of the study patients in all groups had RA for over 5 years. We found no statistically significant difference between the comparison groups in the disease duration (p>0.05). Similar percentages of patients in each treatment group had previously received treatment with a DMARD (other than MTX). Among all patients who previously received DMARDs, 41% had received leflunomide and 39% had received sulfasalazine. Approximately one-third of patients in each treatment group were taking corticosteroids at baseline (38.7%, 37.0% and 37.0% respectively). The mean corticosteroid dosage (prednisone equivalent) was 12.7 mg/day in the IA treatment arm, 13.1 mg/day in the IB treatment arm, and 14.8 mg/day in the comparison group (table 1).

In terms of joint involvement, both tender and swollen joint counts exhibited similar values across Group IA (35.8±14.8 and 27.2±13.6, respectively), Group IB (36.2±15.6 and 29.2±13.1, respectively), and the comparison group (37.3±1.1 and 30.5±11.4, respectively). These figures imply a consistency in the severity of joint tenderness and swelling at the baseline within this patient cohorts. Similarly, the levels of inflammatory markers, CRP (Group IA: 3.9±4.2, Group IB: 4.1±3.9, Comparison group: 4.0±4.0) and ESR (Group IA: 29.5±8.2, Group IB: 28.5±8.9, Comparison group: 27.2±5.4), did not display significant variations, indicating uniform disease activity among the groups at the baseline.

Furthermore, the prevalence of anti-CCP positivity was notably high in all groups, with percentages of 96.7% in Group IA, 100% in Group IB, and 100.0% in the Comparison group. Similarly, RF positivity was prevalent, with percentages of 90.3% in Group IA, 88.9% in Group IB, and 81.0% in the Comparison group. These numbers underscore a consistent immunological profile among patients with RA at the commencement of the study. The lack of significant differences in the percentages of positive patients emphasizes the uniformity of autoimmune characteristics in the studied populations.

The presented baseline characteristics elucidate a remarkable homogeneity among patients with rheumatoid arthritis in terms of joint involvement, inflammatory markers, and autoimmune markers. These actual numerical findings provide a concrete understanding of the initial disease presentation and lay the groundwork for further exploration of treatment responses and disease progression in these distinct patient groups (table 2).

**Table 2. Characteristics of disease activity and disability indexes in patients with RA**

| | Group IA (n = 31) | Group IB (n = 27) | Comparison group (n = 100) |
|---|---|---|---|
| HAQ - disability index | 1.1±0.42 | 1.0±0.35 | 1.1±0.52 |
| VAS score – physician (100-mm) | 39.1±9.6 | 41.2±10.2 | 42.1±7.3 |
| VAS score – patient (100-mm) | 36.2±10.1 | 37.8±11.3 | 38.0±8.0 |
| Patient's assessment of pain | 32.5 ±10.3 | 34.6±11.6 | 29.6±10.3 |
| DAS28 | 6.3±0.9 | 6.4±0.9 | 6.3±0.9 |

*Note: HAQ = Health Assessment Questionnaire; VAS = visual analog scale; DAS28 = 28-joint Disease Activity Score; Statistical significance *-p<0.05*

The mean HAQ disability index was 1.1±0.42 in group IA, 1.0±0.35 in group IB and 1.1±0.52 in the comparison group among those who received only methotrexate. There were not any statistically significant baseline differences among treatment groups in the HAQ disability score (p>0.05). The mean VAS score assessed by physician's global assessment of disease activity did not show statistically significant baseline differences among the comparing groups with VAS score of 39.1±9.6, 41.2±10.2 and 42.1±7.3 respectively (p>0.05). Similarly, the analysis of mean VAS score assessed by patient's global assessment of disease activity did not show significant baseline differences among the comparing groups (p>0.05).

Table 3.3 delineates the baseline radiographic findings in patients with rheumatoid arthritis (RA) across three distinct groups. In terms of the TSS score, the numeric values indicate that group IA has a mean score of 2.2±0.8, group IB has 2.3±0.8, and the comparison group has 2.4±0.7. The associated p-values (p1>0.05, p2>0.05) suggest that there were low to moderate level of joint damages across groups and are no statistically significant differences in the overall joint damage, as measured by the TSS scale between the groups.

Further examination of the erosion score reveals similar trends. Group IA demonstrates an erosion score of 1.1±0.7, group IB has 1.0±0.5, and the comparison group has

1.2±0.7. The p-values indicate no significant distinctions in bone damage among the groups.

Similarly, the joint space narrowing score demonstrates comparable values across the groups. Group IA has a score of 1.2±0.8, group IB has 1.3±0.8, and the comparison group has 1.2±0.6, with p-values denoting no statistically significant differences in cartilage loss levels.

**Table 3. Baseline radiographic findings in patients with rheumatoid arthritis**

| | Group IA (n = 31) | Group IB (n = 27) | Comparison group (n = 100) |
|---|---|---|---|
| mTSS score | 2.2±0.8 | 2.3±0.8 | 2.4±0.7 |
| Erosion score | 1.1±0.7 | 1.0±0.5 | 1.2±0.7 |
| Joint space narrowing score | 1.2±0.8 | 1.3±0.8 | 1.2±0.6 |

*Note: TSS = total Sharp score; Statistical significance *-p<0.05*

The baseline radiographic findings, elucidated by actual numerical values and supported by p-values, portray a consistency in joint damage, bone erosion, and cartilage loss among patients with RA in the studied groups (table 3).

The table 4 presents the baseline characteristics of three groups in a study focusing on rheumatoid arthritis treatment. The study encompassed various metabolic and liver function markers to discern potential differences among the treatment regimens. The mean fasting blood glucose levels were 5.7 ± 1.4 in Group IA, 5.5 ± 1.9 in Group IB, and 5.9 ± 1.0 in the comparison group. Both p-values (p1 and p2) exceeded 0.05, indicating no significant differences in fasting blood glucose levels among the three groups.

**Table 4. Baseline general biochemical analysis results in patients with rheumatoid arthritis**

| | Group IA (n = 31) | Group IB (n = 27) | Comparison group (n = 100) |
|---|---|---|---|
| Fasting Blood Glucose (mmol/l) | 5.7 ±1.4 | 5.5±1.9 | 5.9 ±1.0 |
| Total Bilirubin (mmol/L) | 14.2±3.6 | 13.8±3.9 | 15.1±5.3 |
| ALT (Alanine Aminotransferase) U/L | 27.4±7.3 | 26.5±6.4 | 28.9±8.4 |
| AST (Aspartate Aminotransferase) U/L | 26.9±8.1 | 28.9 ±7.2 | 30.1±11.2 |
| ALP (Alkaline Phosphatase) U/L | 65.2±11.8 | 68.5±12.5 | 67.3±10.5 |
| GGT (Gamma-Glutamyl Transferase) U/L | 33.8±12.1 | 36.2±11.1 | 34.1±9.1 |

*Note: In all comparisons Mann Whitney Wilcoxon test was performed; statistical significance *-p<0.05*

Total bilirubin levels exhibited consistency across the groups. Group IA had a mean of 14.2 ± 3.6, Group IB had 13.8 ± 3.9, and the comparison group showed 15.1± 5.3. Similar to blood glucose, p-values (p1 and p2) were both greater than 0.05, suggesting no significant variations. Alanine aminotransferase (ALT) levels remained comparable among the groups, with mean values of 27.4 ± 7.3, 26.5 ± 6.4, and 28.9 ± 8.4 for Group IA, Group IB, and the comparison group, respectively.

The p-values (p1 and p2) exceeded 0.05, indicating no significant differences in ALT levels. Aspartate aminotransferase (AST) levels showed similarity across the three groups. Group IA had a mean of 26.9 ± 8.1, Group IB had 28.9 ± 7.2, and the comparison group had 30.1 ± 11.2. Both p-values (p1 and p2) were greater than 0.05, suggesting no significant disparities.

**Table 5. Baseline characteristics of immunological indexes in patients with rheumatoid arthritis**

| | Group IA (n = 31) | Group IB (n = 27) | Comparison group (n = 100) |
|---|---|---|---|
| IL-6 (pg/ml) | 84.3±16.4 | 91.5±15.8 | 87.9±12.3 |
| IL-17 (pg/ml) | 231.5±66.2 | 218.6±58.4 | 237.9±44.2 |

*Note: *-p<0.05.*

Alkaline phosphatase (ALP) levels demonstrated uniformity among the groups, with mean values of 65.2 ± 11.8, 68.5 ± 12.5, and 67.3 ± 10.5 for Group IA, Group IB, and the comparison group, respectively. The p-values (p1 and p2) exceeded 0.05, indicating no significant differences in ALP levels. Gammaglutamyl transferase (GGT) levels presented with no significant differences. Group IA, Group IB, and the comparison group had mean GGT values of 33.8 ± 12.1, 36.2 ± 11.1, and 34.1 ± 9.1, respectively. Both p-

values (p1 and p2) were greater than 0.05, signifying uniformity in GGT levels.

In summary, the analysis of metabolic and liver function markers revealed no significant differences among the three groups, indicating a balanced distribution of these parameters at the baseline of the study. This uniformity provides a robust foundation for subsequent investigations into the impact of different treatment regimens for rheumatoid arthritis.

The table 5 presents baseline immunological indexes for three different groups of patients before starting their respective treatments. For IL-6, the average levels in all groups were significantly higher than the normal range, indicating active inflammation typically associated with RA. Group IA had an average IL-6 level of 84.3±16.4 pg/ml, Group IB had an average of 91.5±15.8 pg/ml, and the comparison group had an average of 87.9±12.3 pg/ml. The p-values suggest that there were no statistically significant differences in IL-6 levels between the groups at the baseline. This implies that the baseline inflammatory status, as indicated by IL-6 levels, was similar across all three groups.

The baseline immunological indexes for IL-17 showed significantly elevated levels, a pattern aligning with the inflammatory state often observed in RA. Specifically, Group IA had an average IL-17 level of 231.5±66.2 pg/ml, Group IB recorded an average of 218.6±58.4 pg/ml, and the comparison group exhibited an average level of 237.9±44.2 pg/ml. Notably, the p-values indicated no statistically significant differences in IL-17 levels between the groups at baseline. This suggests that, in terms of IL-17, the initial immunological status was similar across all groups, providing a uniform baseline for assessing the impact of the different treatment strategies.

In summary, the table shows that prior to the initiation of treatment, patients in all three groups exhibited similarly elevated levels of IL-6 and IL-17. This uniformity in elevated cytokine levels suggests a comparable degree of disease activity or systemic inflammation across the groups at the outset. The lack of significant differences in IL-6 and IL-17 levels across the groups reinforces that the baseline immunological status was similar, providing a consistent starting point for comparing the efficacy and impact of the different treatment regimens that these groups were about to commence.

**Table 6. Baseline characteristics of immunological indexes in patients with rheumatoid arthritis**

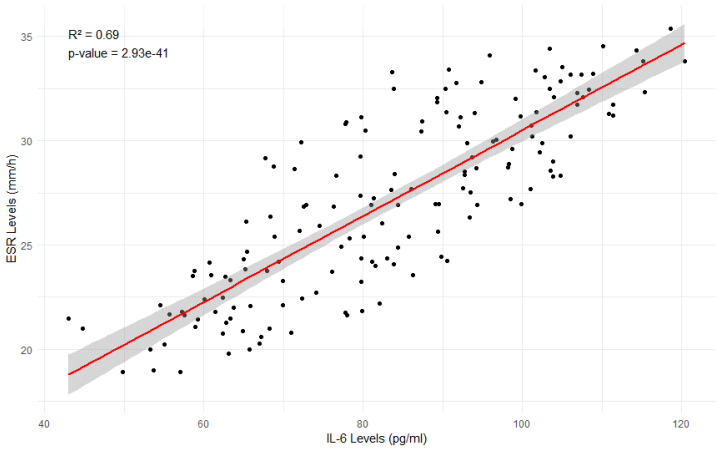
| | Moderate activity (DAS28) n=69 | High activity (DAS28) n=89 |
|---|---|---|
| IL-6 (pg/ml) | 68.2±13.1 | 98.4±15.8* |
| IL-17 (pg/ml) | 166.9±45.0 | 248.7±54.2* |

*Note: *-p<0.05.*

In table 6, we observed the relationship between IL-6 and IL-17 levels and the severity of RA by the DAS28. The data delineate a clear escalation in the levels of these cytokines correlating with increased disease activity. For patients with moderate RA activity, the average IL-6 level was recorded at 68.2±13.1 pg/ml, a notable elevation from the normal range, which is less than 7 pg/ml. This trend was even more pronounced in the high activity group, where the average IL-6 level surged to 98.4±15.8 pg/ml. The statistical significance of this difference is underscored by a p-value of less than 0.001, emphasizing the strong association between IL-6 levels and RA severity.

Similarly, IL-17 levels exhibited a significant increase in tandem with RA severity. Patients in the moderate activity category showed an average IL-17 level of 166.9±45.0 pg/ml, while those in the high activity group had an average of 248.7±54.2 pg/ml, both substantially higher than the normal range of less than 10 pg/ml. The p-value for the difference in IL-17 levels was also less than 0.001, reinforcing the correlation between elevated IL-17 levels and increased disease activity. This data effectively highlights the escalating levels of IL-6 and IL-17 as RA progresses in severity, underlining their potential as biomarkers for assessing and monitoring disease activity in RA patients.

**Graph 1. The correlation between the IL-6 levels erythrocyte sedimentation rate**



IL-6, a well-known inflammatory marker, showed a distinct increase in patients with more severe RA. The average levels of IL-6 in patients with moderate disease activity were considerably higher than the normal range, and these levels escalated further in patients with high disease activity. The statistical significance of this increase, not only validates the elevation of IL-6 levels in more active RA but also suggests its role as a reliable biomarker for assessing disease severity. Elevated IL-6 in RA is known to contribute to various pathophysiological processes, including joint destruction and systemic symptoms, making its monitoring crucial in disease management [9–11].

Similarly, IL-17 levels, another cytokine implicated in the pathogenesis of RA, also showed a marked increase with the severity of the disease. Both the moderate and high activity groups had IL-17 levels far exceeding the normal range. The significant difference in IL-17 levels between these groups, as evidenced by a similarly low p-value, mirrors the pattern observed with IL-6. IL-17 is particularly noteworthy in RA as it is involved in the inflammation and destruction of joint tissues. Its elevated levels in more severe cases of RA reinforce the notion that IL-17 is not just a bystander but an active participant in the disease's progression [12–14].

The obtained evidence suggests that the levels of IL-6 and IL-17 correspond with disease activity and severity, making them valuable in both diagnosing RA and monitoring its progression. Furthermore, this correlation underscores the importance of targeted therapies in RA, such as IL-6 and IL-17 inhibitors, which have been shown to be effective in reducing disease activity and improving clinical outcomes. In conclusion, the observed trends in IL-6 and IL-17 levels in relation to RA severity not only enhance our understanding of the disease's immunological underpinnings but also aid in the clinical management of RA, offering pathways for more personalized and effective treatment strategies [15,16].

The linear regression plot illustrates the relationship between IL-6 levels (pg/ml) and Erythrocyte Sedimentation Rate (ESR) levels (mm/h) in patients with moderate to high activity Rheumatoid Arthritis (RA). The red line represents the best fit linear regression line through the data points, indicating a positive correlation between IL-6 and ESR levels. This suggests that as IL-6 levels increase, ESR levels also tend to rise. Such a trend is expected in RA, as both IL-6 and ESR are markers of inflammation, with IL-6 being a pro-inflammatory cytokine and ESR being an indirect measure of inflammation.

The plot indicates a relatively strong linear relationship with an R-squared value of 0.69. This means that approximately 69% of the variability in ESR levels can be explained by the variability in IL-6 levels amongst these patients. An R-squared value close to 0.70 is considered substantial in biological sciences, implying that IL-6 is a significant predictor of ESR levels and vice-versa in this patient population.

The graph supports the hypothesis that in patients with moderate to high activity RA, IL-6 levels are a significant predictor of ESR levels. The strength of this relationship is quantitatively supported by the high R-squared value and the very low p-value, emphasizing the reliability of IL-6 as a biomarker for inflammation in the context of RA disease activity.

## Conclusions

In conclusion, the study groups were well-matched in terms of age, gender distribution, duration of RA, and baseline use of corticosteroids. The tender and swollen joint counts, along with CRP and ESR levels, were similar across all groups, indicating a comparable moderate to high levels of disease severity and activity at the baseline. The high and even prevalence of anti-CCP and RF positivity across all groups underscores the autoimmune nature of RA and comparable distribution in the study population. The HAQ disability index and VAS scores showed no significant baseline differences among the groups, suggesting comparable mild to moderate functional disability and disease activity at the baseline. The radiographic findings in the study, represented by the Total Sharp Score (TSS), indicated a low to moderate level of joint damage at baseline with consistent results across the study groups. The patients in all treatment groups had similar and normal metabolic and liver function profiles at the baseline. Elevated levels of IL-6 and IL-17 in all groups indicate active inflammation, typical of RA. Elevated levels of IL-6 and IL-17 in patients with higher DAS28 scores highlight the correlation between these cytokines and disease severity and underscores their role as biomarkers for assessing and monitoring RA disease activity. In summary, the baseline characteristics of the study population show a well-matched cohort in terms of demographic, clinical, and immunological parameters. This establishes a solid baseline for evaluating the comparative effectiveness of the different treatment regimens.

## References

1. Akram, M. S., Pery, N., Butler, L., Shafiq, M. I., Batool, N., Rehman, M. F. U., Grahame-Dunn, L. G., & Yetisen, A. K. (2021). Challenges for biosimilars: Focus on rheumatoid arthritis. *Critical Reviews in Biotechnology*, *41*(1), 121–153. https://doi.org/10.1080/07388551.2020.1830746
2. Aletaha, D., & Smolen, J. S. (2018). Diagnosis and management of rheumatoid arthritis: A review. *Jama*, *320*(13), 1360–1372.
3. Anderson, K. O., Bradley, L. A., Young, L. D., McDaniel, L. K., & Wise, C. M. (1985). Rheumatoid arthritis: Review of psychological factors related to etiology, effects, and treatment. *Psychological Bulletin*, *98*(2), 358.
4. Bang, L. M., & Keating, G. M. (2004). Adalimumab: A Review of its Use in Rheumatoid Arthritis. *BioDrugs*, *18*(2), 121–139. https://doi.org/10.2165/00063030-200418020-00005

5. Bartelds, G. M., Wijbrandts, C. A., Nurmohamed, M. T., Stapel, S., Lems, W. F., Aarden, L., Dijkmans, B. A., Tak, P. P., & Wolbink, G. J. (2007). Clinical response to adalimumab: Relationship to anti-adalimumab antibodies and serum adalimumab concentrations in rheumatoid arthritis. *Annals of the Rheumatic Diseases*, *66*(7), 921–926.
6. Buchs, N. d, Di Giovine, F. S., Silvestri, T., Vannier, E., Duff, G. W., & Miossec, P. (2001). IL-1B and IL-1Ra gene polymorphisms and disease severity in rheumatoid arthritis: Interaction with their plasma levels. *Genes & Immunity*, *2*(4), 222–228.
7. Firestein, G. S. (2003). Evolving concepts of rheumatoid arthritis. *Nature*, *423*(6937), 356–361.
8. Kim, G. W., Lee, N. R., Pi, R. H., Lim, Y. S., Lee, Y. M., Lee, J. M., Jeong, H. S., & Chung, S. H. (2015). IL-6 inhibitors for treatment of rheumatoid arthritis: Past, present, and future. *Archives of Pharmacal Research*, *38*, 575–584.
9. Narazaki, M., Tanaka, T., & Kishimoto, T. (2017). The role and therapeutic targeting of IL-6 in rheumatoid arthritis. *Expert Review of Clinical Immunology*, *13*(6), 535–551. https://doi.org/10.1080/1744666X.2017.1295850
10. Ogata, A., Kato, Y., Higa, S., & Yoshizaki, K. (2019). IL-6 inhibitor for the treatment of rheumatoid arthritis: A comprehensive review. *Modern Rheumatology*, *29*(2), 258–267.
11. Pickens, S. R., Volin, M. V., Mandelin, A. M., Kolls, J. K., Pope, R. M., & Shahrara, S. (2010). IL-17 contributes to angiogenesis in rheumatoid arthritis. *The Journal of Immunology*, *184*(6), 3233–3241.
12. Radu, A.-F., & Bungau, S. G. (2021). Management of rheumatoid arthritis: An overview. *Cells*, *10*(11), 2857.
13. Rajaei, E., Mowla, K., Hayati, Q., Ghorbani, A., Dargahi-Malamir, M., Hesam, S., & Zayeri, Z. D. (2020). Evaluating the relationship between serum level of interleukin-6 and rheumatoid arthritis severity and disease activity. *Current Rheumatology Reviews*, *16*(3), 249–255.
14. Smolen, J. S., & Aletaha, D. (2015). Rheumatoid arthritis therapy reappraisal: Strategies, opportunities and challenges. *Nature Reviews Rheumatology*, *11*(5), 276–289.
15. Van Den Berg, W. B., & Miossec, P. (2009). IL-17 as a future therapeutic target for rheumatoid arthritis. *Nature Reviews Rheumatology*, *5*(10), 549–553.
16. Ravshanova, M. S., & Ibragimov, K. I. (2022, September). EFFECTIVENESS OF TRANSVAGINAL ULTRASOUND IN DIAGNOSIS OF ECTOPIC PREGNANCY. In INTERNATIONAL SCIENTIFIC CONFERENCE" INNOVATIVE TRENDS IN SCIENCE, PRACTICE AND EDUCATION" (Vol. 1, No. 2, pp. 114-115).
17. Ziolkowska, M., Koc, A., Luszczykiewicz, G., Ksiezopolska-Pietrzak, K., Klimczak, E., Chwalinska-Sadowska, H., & Maslinski, W. (2000). High levels of IL-17 in rheumatoid arthritis patients: IL-15 triggers in vitro IL-17 production via cyclosporin A-sensitive mechanism. *The Journal of Immunology*, *164*(5), 2832–2838.