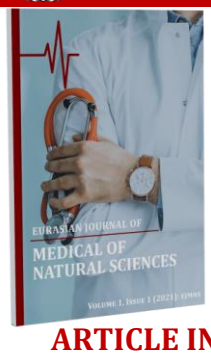
EURASIAN JOURNAL OF MEDICAL AND NATURAL SCIENCES
Innovative Academy Research Support Center
IF = 7.921 www.in-academy.uz



COMPLEX THERAPHY EFFECT IN AUTOIMMUNE DISEASES

Toshnazarova Nodira
Samarkand State Medical University, Uzbekistan
https://doi.org/10.5281/zenodo.15010079

ARTICLE INFO

Received: 04th March 2025
Accepted: 11th March 2025
Online: 12th March 2025

KEYWORDS

Rheumatoid arthritis, adalimumab, methotrexate, observational study.

ABSTRACT

This comprehensive observational cohort study meticulously evaluated the effectiveness and safety associated with the combination therapy of adalimumab and methotrexate in individuals diagnosed with the debilitating condition known as rheumatoid arthritis (RA). The participants in this investigation were systematically categorized into three distinct groups, each receiving different treatment regimens. The findings revealed that the synergistic combination of adalimumab and methotrexate demonstrated a statistically significant superiority over methotrexate used as a standalone treatment in achieving clinically meaningful responses, specifically measured by ACR20, ACR50, and ACR70, during a rigorous nine-month treatment period. In this context, Group IB, which was administered a higher dosage of methotrexate, displayed marginally improved rates of clinical improvement compared to Group IA; however, it is worth noting that the difference between these two groups did not reach statistical significance. As the study progressed to the nine-month mark, an impressive 88.9% of the patients belonging to Group IB successfully achieved an ACR20 response, in stark contrast to the 74.2% of participants in Group IA and the significantly lower 46% observed in the comparison group. Furthermore, analogous trends were noted in the responses corresponding to ACR50 and ACR70, reinforcing the efficacy of the combination therapy. The overall implications of this study strongly suggest that the combination therapy of adalimumab and methotrexate holds a clinically superior position when compared to methotrexate monotherapy in the treatment of rheumatoid arthritis, with the possibility that a higher dose of methotrexate could lead to even more favorable outcomes for patients in need of effective treatment options.

Introduction. Rheumatoid arthritis, commonly abbreviated as RA, represents a chronic and systemic autoimmune condition that is distinctly marked by inflammation of the synovial

joints, which ultimately leads to a gradual yet relentless destruction of the joints, accompanied by considerable pain and significant disability for those affected. The underlying causes of RA are intricate and multifaceted, drawing on a complex interplay of genetic predispositions, environmental influences, and immunological responses that collectively contribute to the onset and progression of this debilitating disease. The clinical manifestations of RA present a wide spectrum, ranging from mild episodes of joint stiffness that may be barely noticeable to severe instances of joint damage that can lead to systemic complications, all of which critically impact the quality of life for individuals grappling with this condition [1–4,10]. Over the past few decades, the management strategies for RA have undergone remarkable transformations, particularly with the introduction of disease-modifying antirheumatic drugs, often referred to as DMARDs, along with biologic agents that specifically target various components of the immune system to mitigate the effects of this disorder. Methotrexate, a conventional DMARD, has established itself as a foundational element in the pharmacological treatment of RA, largely due to its proven effectiveness in managing disease activity and curbing the progression of the illness. Nevertheless, it is important to note that not every patient will achieve satisfactory results from methotrexate monotherapy, which creates a pressing need for the exploration of combination therapies or alternative therapeutic agents [1,4,6,9-12]. The advent of biologic agents, particularly tumor necrosis factor (TNF) inhibitors, has dramatically reshaped the landscape of RA treatment options available to healthcare providers. Among these, adalimumab, a fully human monoclonal antibody designed to inhibit TNF-α, has shown profound efficacy in alleviating the signs and symptoms associated with RA, effectively hindering the progression of joint damage while simultaneously enhancing physical functionality, whether administered alone or in conjunction with methotrexate [5,6]. Despite the existence of these effective therapeutic options, determining the most appropriate treatment strategy tailored to the unique needs of individual patients remains an ongoing challenge. The inherent heterogeneity of RA, coupled with the variability in how different patients respond to treatment, highlights the pressing necessity for personalized medicine approaches and the ongoing investigation into various treatment regimens. In light of this context, the current study seeks to rigorously compare the efficacy and safety profiles of different combinations of adalimumab and methotrexate in patients suffering from RA who have not responded adequately to methotrexate as a standalone treatment option [7,8, 9-12].

Objectives. The primary aim of this study is meticulously structured to provide valuable insights into the comparative effectiveness of the aforementioned treatment regimens, which could significantly aid in clinical decision-making processes and contribute to the enhancement and optimization of therapeutic strategies specifically tailored for patients living with RA.

Materials and methods. This meticulous observational cohort study was meticulously designed and executed with the primary objective of comparing the efficacy and safety of various combinations of adalimumab and methotrexate in a specific population of patients diagnosed with rheumatoid arthritis (RA). The study focused on adult individuals who were aged 18 years or older and had received a diagnosis of RA, with a requirement that their disease had persisted for a minimum duration of six months prior to their inclusion in the

research. To facilitate a thorough analysis, participants were strategically categorized into three distinct exposure groups, each based on the specific treatment regimen they were prescribed: Group IA consisted of patients receiving adalimumab at a dose of 40 mg administered subcutaneously every other week, coupled with methotrexate at a dose of 7.5 mg taken orally once weekly. Group IB included those receiving the same dose of adalimumab but paired with a higher dose of methotrexate at 15 mg taken orally once weekly. Finally, the Comparison Group was represented by patients who were solely undergoing treatment with methotrexate at a consistent dose of 15 mg taken orally once weekly. The primary outcome measure for this study was the assessment of the change in the Disease Activity Score based on 28 joints (DAS28) from the baseline measurement taken at the start of the study through to the six-month follow-up period. Additionally, secondary outcomes were meticulously defined to encompass the American College of Rheumatology (ACR) 20% improvement criteria (referred to as ACR20), along with ACR50 and ACR70 responses, as well as changes in the Health Assessment Questionnaire-Disability Index (HAQ-DI) scores, and finally, an evaluation of radiographic progression which was assessed using the modified Sharp/van der Heijde score (mTSS).

Results. Upon analyzing the data collected, it became evident that the mean age of patients participating in the study was calculated to be 43.4±15.7 years for those in Group IA, whereas those in Group IB had a mean age of 41.8±14.7 years, and patients following the methotrexate (MTX) monotherapy in the Comparison Group showed a mean age of 42.9±6.2 years, with statistical analysis indicating no significant differences among these age groups ($p>0.05$). A notable observation was that the overwhelming majority of the patients across all three groups were female, and there was no significant variation in the female-to-male ratio when comparing the different groups (67.7%, 66.7%, and 69.0% respectively). Furthermore, when evaluating the duration of the RA among participants at baseline, it was found that the mean durations were 6.7 years for Group IA, 7.2 years for Group IB, and 6.9 years for the Comparison Group, indicating a relatively stable disease duration across the board. The majority of patients in all groups had a disease duration that fell within the range of three to seven years, which is critical for understanding the disease's progression. In terms of joint involvement, both tender and swollen joint counts demonstrated comparable values across the treatment arms, with Group IA displaying counts of 35.8±14.8 and 27.2±13.6, respectively, while Group IB showed counts of 36.2±15.6 and 29.2±13.1, respectively, and the Comparison Group had counts of 37.3±1.1 and 30.5±11.4, respectively. Additionally, when examining the inflammatory markers, levels of C-reactive protein (CRP) were measured with Group IA showing an average of 3.9±4.2, Group IB showing 4.1±3.9, and the Comparison Group presenting with 4.0±4.0, indicating no significant differences among them, while the erythrocyte sedimentation rate (ESR) was recorded as 29.5±8.2 for Group IA, 28.5±8.9 for Group IB, and 27.2±5.4 for the Comparison Group, further supporting the notion that there were no notable variations in inflammatory activity, thus indicating a uniformity in disease activity among the groups at the baseline measurement.

Moreover, it is worth noting that the occurrence of anti-CCP positivity was remarkably prevalent across all the participant groups, showcasing a strikingly high percentage of 96.7% in Group IA, an astonishing 100% in Group IB, and a perfect 100.0% in the overall comparison

group. When we delve into the mean HAQ disability index scores, we observe that they are measured at 1.1±0.42 for group IA, slightly lower at 1.0±0.35 for group IB, and maintaining the same level of 1.1±0.52 in the comparison group, with a statistical significance that yields p-values greater than 0.05, indicating no significant difference among the groups. In terms of the Total Sharp score (TSS score), which serves as an indicator of joint damage, group IA recorded a score of 2.2±0.8, while group IB achieved a score of 2.3±0.8, and the comparison group, in a close range, reported a score of 2.4±0.7, with both p1 and p2 values exceeding 0.05, which suggests that there exists only a low to moderate level of joint damage throughout the various groups. The analysis of the data further revealed that the combination therapy involving adalimumab and methotrexate demonstrated a strikingly superior effectiveness compared to methotrexate alone, over a treatment duration of 9 months, particularly in terms of achieving a clinically significant response rate, which was defined by thresholds of 20%, 50%, and 70% improvements from the initial baseline measurements. By the conclusion of the 9-month treatment period, an impressive 88.9% of the patients in the IB group achieved a clinically significant 20% improvement, in contrast to only 74.2% of patients in group IA and a mere 46% of those in the comparison group, with statistical significance indicated by p1 and p2 values both being less than 0.05. A similarly favorable trend in response rates was observed when analyzing the data for clinically significant improvements of 50% and 70% from baseline levels among the patients. As per the results obtained, by the end of the 9-month period, it was documented that 66.7% of the patients in group IB had achieved a remarkable 70% improvement in clinical, functional, and laboratory findings, compared to 54.8% of patients in the IA group, and only 33.0% of those who were receiving methotrexate monotherapy, as illustrated in table 1.

Table 1.

Baseline characteristics of immunological indexes in patients with rheumatoid arthritis

	Group IA (n = 62)	Group IB (n = 54)	Comparison group (n = 200)
ACR20	22 (71.0%)*	23 (85.2%)*	45 (45.0%)
ACR50	18 (58.1%)*	20 (74.1%)*	38 (38.0%)
ACR70	16 (51.6%)*	17 (63.0%)*	32 (32.0%)
*Note: *-p<0.05*			

The results that have been meticulously obtained from this comprehensive study suggest quite strongly that the clinical effectiveness of a combination therapy involving adalimumab and methotrexate is significantly superior in the management and treatment of rheumatoid arthritis, especially when compared to the use of methotrexate alone as a monotherapy. Notably, while it appears that the combination of adalimumab with a higher dosage of 15 mg methotrexate tends to exhibit a greater level of efficacy than the combination involving a lower dosage of 7.5 mg methotrexate, it is important to point out that no statistically significant difference was actually observed between these two different combination groups within the context of the study. As we analyze the data from baseline through to the 9-month mark, we can observe a remarkable and notable increase in the percentage of patients achieving the ACR20 criteria across all the participant groups involved in the study. In particular, Group IA displays a consistent upward trend characterized by a

steady increase, commencing at a percentage of 22.0% improvement during the first month, and achieving an impressive 74.2% improvement by the time the ninth month arrives. Meanwhile, Group IB, which benefited from a higher dosage of methotrexate in conjunction with adalimumab, starts off at a comparable level of improvement in the first month at 26.0%, but interestingly shows a much faster rate of increase, ultimately achieving the highest percentage of improvement across all groups by the conclusion of the study period, culminating in a remarkable 88.9% at the ninth month. This observation suggests a potential dose-response relationship, indicating that higher doses of methotrexate may lead to more favorable outcomes when they are effectively combined with adalimumab, particularly as indicated by the statistical significance ($p<0.05$). On the other hand, the comparison group that was treated exclusively with methotrexate as monotherapy illustrates a more gradual and less pronounced improvement, ultimately reaching only 46.0% by the end of the observation period. Although there is indeed some improvement noted within this group, it pales in comparison to the significant gains observed in the combination therapy groups, highlighting the stark differences in treatment efficacy.

In conclusion, the findings of our study have definitively confirmed the superior effectiveness of the combined approach of adalimumab and methotrexate when juxtaposed against methotrexate monotherapy for patients suffering from rheumatoid arthritis (RA) who have demonstrated an inadequate response to methotrexate used alone. Over the span of nine months, this strategic combination therapy yielded substantially greater clinical improvements, which were meticulously measured using ACR20, ACR50, and ACR70 criteria to assess the outcomes. Furthermore, it was observed that administering a higher dose of methotrexate, specifically 15 mg weekly, in combination with adalimumab proved to be slightly more effective than utilizing a lower dose of 7.5 mg weekly. The study underscored the critical importance of personalizing both the type of medication and the dosage administered in the management of rheumatoid arthritis to optimize patient outcomes effectively. Additionally, the consistent reduction in both tender and swollen joint counts throughout the treatment period provides robust support for the effectiveness of this combined therapeutic approach in effectively controlling symptoms and significantly reducing inflammation associated with this challenging autoimmune condition.

References:

1. Ibragimov, K. I. (2022a). The risk of cardiovascular disease in rheumatoid arthritis patients treated with disease-modifying antirheumatic drugs: A clinic based case control study. Journal of Global Health Reports, 4(2). http://joghr.com/index.php/JGHR/article/view/32
2. Ibragimov, K. I. (2022b). The risk of cardiovascular disease in rheumatoid arthritis patients treated with disease-modifying antirheumatic drugs: A clinic based case control study. Journal of Global Health Reports, 4(2). http://joghr.com/index.php/JGHR/article/view/32
3. Ibragimov, K., Keane, G., Glaría, C. C., Cheng, J., & Llosa, A. (2019). Haloperidol versus olanzapine for people with schizophrenia. The Cochrane Database of Systematic Reviews, 2019(10), CD013425.

4. Ibragimov, K., Keane, G. P., Glaría, C. C., Cheng, J., & Llosa, A. E. (2024). Haloperidol (oral) versus olanzapine (oral) for people with schizophrenia and schizophrenia-spectrum disorders. Cochrane Database of Systematic Reviews, 7. https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013425.pub2/abstract
5. Ibragimov, K., Palma, M., Keane, G., Ousley, J., Crowe, M., Carreno, C., Casas, G., Mills, C., & Llosa, A. (2021). Digital mental health care in humanitarian & crisis settings: A mixed-methods exploration during the COVID-19 pandemic. https://europepmc.org/article/ppr/ppr382732
6. Ibragimov, K., Palma, M., Keane, G., Ousley, J., Crowe, M., Carreño, C., Casas, G., Mills, C., Llosa, A., M. S. F. Mental Health Working Group, Marques, A., Tijerino, A.-M., Droste, A., Echeverri, C., Fredj, N., Sleit, R., & Sultan, S. F. (2022). Shifting to Tele-Mental Health in humanitarian and crisis settings: An evaluation of Médecins Sans Frontières experience during the COVID-19 pandemic. Conflict and Health, 16(1), 6. https://doi.org/10.1186/s13031-022-00437-1
7. Ibragimov, K., Perles-Ribes, J. F., & Ramón-Rodríguez, A. B. (2022). The impact of climate change on tourism demand: Evidence from Kazakhstan. Anatolia, 33(2), 293–297. https://doi.org/10.1080/13032917.2022.2029510
8. Ibragimov, K., Sultonov, I., & Ravshanova, M. (2024). The Effectiveness of the Combination Therapy with biologic DMARDS in Rheumatoid Arthritis. Frontiers of Global Science, 2(1), 17–24.
9. Khasan, I., Ibrat, A., Islomovich, S. I., Sukhrobovna, R. M., Islamova, K., & Shuxrat, Z. (n.d.). The Association Between Cardiovascular Disease and Conventional DMARDs in Patients with Rheumatoid Arthritis. International Journal of Health Sciences, 6(S8), 5053–5059.
10. Ravshanova, M., Ibragimov, K., Uralov, R., Xasanov, F., Islamova, K., Abdushukurova, K., Sultonov, I., & Axmedov, I. (2024). Clinical and Immunological Characteristics of Patients with Rheumatoid Arthritis on Synthetic DMARDS Therapy. Frontiers of Global Science, 2(1), 41–47.
11. Ravshanova, M. S., & Ibragimov, K. I. (2022). EFFECTIVENESS OF TRANSVAGINAL ULTRASOUND IN DIAGNOSIS OF ECTOPIC PREGNANCY. INTERNATIONAL SCIENTIFIC CONFERENCE" INNOVATIVE TRENDS IN SCIENCE, PRACTICE AND EDUCATION, 1(2), 114–115.
https://scholar.google.com/scholar?cluster=6826578166019760384&hl=en&oi=scholarr
12. Tashinova, L., Khamraeva, N., Mambetova, L., Khasanov, F., & Ibragimov, K. (2023). Risk factors for the development of systemic lupus erythematosus (sle) in asians: A research case-control. BIO Web of Conferences, 65, 05017. https://www.bio-conferences.org/articles/bioconf/abs/2023/10/bioconf_ebwff2023_05017/bioconf_ebwff2023_05017.html