E-ISSN: 2980-1559

https://qrheumatol.com/

Volume 3 | Issue 2

RHEUMATOLOGY QUARTERLY

RQ
Rheumatology Quarterly

galenos yayınevi

June
2025

Please refer to the journal's webpage (**https://qrheumatol.com/**) for "Aims and Scope", "Ethical Policy", "Instructions to Authors" and "Instructions to Reviewers".

The editorial and publication processes of the journal are shaped in accordance with the guidelines of the ICMJE, WAME, CSE, COPE, EASE, and NISO. Rheumatology Quarterly is indexed in **EBSCO Host Research Databases** and **Gale/Cengage Learning**.

The journal is published online.

Owner: Galenos Publishing House

Responsible Manager: Sekib Sokolovic

Publisher Contact
Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1
34093 İstanbul, Türkiye
Phone: +90 (530) 177 30 97
E-mail: info@galenos.com.tr/yayin@galenos.com.tr
Web: www.galenos.com.tr | **Publisher Certificate Number:** 14521

Publication Date: June 2025
E-ISSN: 2980-1559
International scientific journal published bimonthly.

CONTENTS

INVITED REVIEW

Rheumatology Quarterly

DOI: 10.4274/qrheumatol.galenos.2025.96158
Rheumatol Q 2025;3(2):40-8

CLASSIFICATION CRITERIA SETS FOR RHEUMATOID ARTHRITIS: HISTORICAL PERSPECTIVE AND CLINICAL IMPLICATIONS

İbrahim Gündüz[1], Ahmet Karataş[2]

[1]Diyarbakır Selahaddin Eyyubi State Hospital, Clinic of Rheumatology, Diyarbakır, Türkiye
[2]Fırat University Faculty of Medicine, Department of Rheumatology, Elazığ, Türkiye

Abstract

The classification criteria for rheumatoid arthritis (RA) have undergone significant evolution since their inception, a process driven by the need to address evolving clinical requirements and shifting research priorities. To comprehensively review the historical development, comparative strengths, and limitations of major RA classification criteria sets, with emphasis on their clinical and research applications. A narrative review of the literature was conducted, examining the 1956 diagnostic criteria, 1987 American College of Rheumatology (ACR) classification criteria, 2010 ACR/European Alliance of Associations for Rheumatology (EULAR) classification criteria, and early RA classification frameworks. The 1956 criteria established the first standardized approach but presented implementation challenges. The 1987 ACR criteria demonstrated excellent specificity (87-94%) for established disease but limited sensitivity (47-58%) for early disease. The 2010 ACR/EULAR criteria resulted in a marked improvement in the early detection of disease, with higher sensitivity (62-91%) but a reduction in specificity (21-78%). Recent early RA classification frameworks have attempted to balance sensitivity (85-86%) and specificity (87-88%) specifically in early disease presentations. It is evident that each set of criteria exhibits distinct advantages, contingent on factors such as disease duration, patient population characteristics, and research objectives. Understanding the evolution and appropriate implementation of RA classification criteria is essential for both clinical research and practice. While the 2010 criteria represent significant advancement in early identification, challenges remain for seronegative patients. Incorporating imaging and novel biomarkers may further enhance classification accuracy in ambiguous presentations.

Keywords: Rheumatoid arthritis, classification criteria, American College of Rheumatology criteria, European Alliance of Associations for Rheumatology criteria, early diagnosis, seronegative arthritis

INTRODUCTION

Rheumatoid arthritis (RA) represents a chronic, inflammatory, autoimmune disease that leads to symmetrical synovitis, joint damage, and disability. RA is a heterogeneous disease with unique challenges and management for each patient. Various studies have reported its incidence between 0.1 to 0.5 per thousand and the prevalence between 10 to 18 per thousand (1). It is impossible to completely treat this disease, which can lead to disabilities and impair quality of life, under today's conditions. However, it has been demonstrated that early therapeutic interventions and new treatment agents introduced recently improve clinical outcomes and reduce joint damage and disability (2).

Address for Correspondence: İbrahim Gündüz, Diyarbakır Selahaddin Eyyubi State Hospital, Clinic of Rheumatology, Diyarbakır, Türkiye
E-mail: abrahim724gunduz@hotmail.com **ORCID ID:** orcid.org/0000-0001-8431-7184
Received: 18.03.2025 **Accepted:** 13.05.2025 **Epub:** 03.06.2025 **Publication Date:** 25.06.2025

Cite this article as: Gündüz İ, Karataş A. Classification criteria sets for rheumatoid arthritis: historical perspective and clinical implications. Rheumatol Q. 2025;3(2):40-8

Although diagnostic and classification criteria may comprise the same type of clinical, laboratory, or other markers, they have different purposes. Classification criteria aim to provide homogeneity among patients in epidemiological and clinical studies (Figure 1). These treatments must be applied to diagnosed patients and ideally have high specificity. In this way, individuals without disease will not be misclassified. Classification criteria must provide a binary answer (yes/no). On the contrary, diagnostic criteria make it easier for clinicians to establish a diagnosis in an individual patient. Ideally, diagnostic criteria must have a high positive predictive value and estimate the probability of a disease.

Since RA has a complex clinical picture, it requires a common definition that can classify patients for epidemiological and clinical studies. There are no RA diagnostic criteria that can be used. Moreover, classifying a patient who actually has a self-limiting disease as having RA can potentially lead to unnecessary long-term exposure to a toxic drug. Hence, it is recommended that classification criteria be employed more in epidemiological and clinical studies and not in diagnosis.

The objective of this review is to examine the historical evolution of RA classification criteria, to assess their strengths and limitations across various clinical scenarios, and to explore their implications for research methodology and clinical practice. A particular emphasis is placed on the challenges associated with the early identification and classification of seronegative patients, where existing frameworks exhibit significant limitations.

Revised 1956 Diagnostic Criteria for Rheumatoid Arthritis

The American Rheumatism Association [under the new name of the American College of Rheumatology (ACR)] first developed the RA diagnostic criteria set in 1956 (3). The 1956 criteria classified patients as definite, probable, and possible. The classic RA class was added to this classification criteria set revised in 1958 (4).

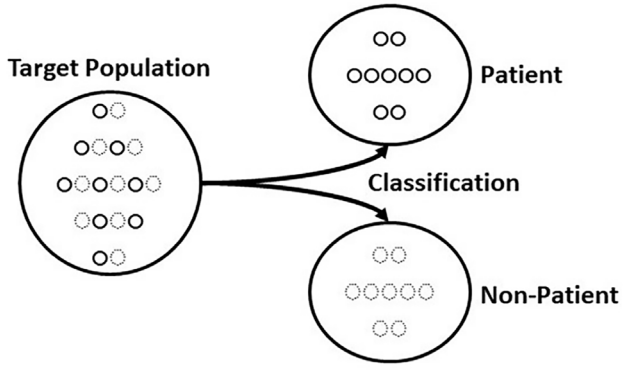

Figure 1. The primary objective of establishing classification criteria is to classify the target population into patients and non-patients

The presence of 7 of the 11 criteria, at least one of which was among the joint findings in the first five items, and the symptoms continuing uninterruptedly for at least 6 weeks were required for a classic RA diagnosis (Table 1). The presence of at least 5 criteria (at least one of which was one of the joint findings in the first five items) and the symptoms continuing uninterruptedly for a minimum of 6 weeks were required for a definite RA diagnosis. The presence of at least 3 criteria and the symptom duration of at least 6 weeks were required for a probable RA diagnosis. Separate criteria were established for a probable RA diagnosis. In the classification criteria, 20 different conditions were determined as exclusion criteria (other rheumatologic diseases, shoulder-hand syndrome, infectious arthritis, hypertrophic pulmonary osteoarthropathy, neuropathic arthropathy, paraneoplastic arthritis, and agammaglobulinemia).

The revised 1956 set of diagnostic criteria for RA was used for about 30 years. Clinical knowledge and experience in rheumatic diseases have improved considerably during this period. Many patients previously classified as having RA started to be classified as having a different disease (e.g., spondyloarthritis, polymyalgia rheumatica, and pseudorheumatoid form of pseudogout). All of these, the fact that three of the 1956 criteria were invasive procedures rarely applied, that the criteria were sensitive but not specific enough for epidemiological studies, and finally, that the exclusion criteria were impractical, necessitated the development of the 1987 classification criteria.

1987 ACR Rheumatoid Arthritis Classification Criteria Set

The ACR developed the "RA classification criteria set" in 1987 (5). Five items from the "revised 1956 diagnostic criteria set for RA" were retained in these criteria; developed from data on 263 RA and 262 control patients (patients with other rheumatic diseases). Five main changes were made to the new criteria. The definition of "probable" RA was removed in these criteria. The terms definite and classic RA concepts were replaced with the term "RA". Criteria involving invasive techniques such as synovial biopsy, joint aspiration, or a rheumatoid nodule biopsy were removed. It was reported that a patient evaluated for classification purposes could be classified as having RA if they meet at least 4 of the specified 7 criteria. It was stipulated that the first 4 criteria must be present for a minimum of 6 weeks (Table 2).

Table 1. Revised 1956 diagnostic criteria for rheumatoid arthritis* (4)
1. Morning stiffness.
2. Pain on motion or tenderness in at least one joint (determined by a physician).
3. Swelling in at least one joint (determined by a physician).
4. New joint swelling within 3 months at most (determined by a physician).
5. Symmetric joint swelling (determined by a physician) (absolute symmetry is not sought in the PIP, MCP, and MTP joints).
6. Subcutaneous nodules on bony prominences, extensor surfaces, or juxta-articular regions (determined by a physician).
7. Rheumatoid arthritis-specific X-ray changes (not just degenerative changes).
8. Positive rheumatoid factor agglutination test in two measurements.
9. Poor mucin precipitation from the synovial fluid (with fragmented and turbid solution).
10. Characteristic histological changes in the synovial membrane.
11. Characteristic histological changes in nodules.
*Seven criteria are necessary for the classic rheumatoid arthritis diagnosis, whereas 5 criteria are necessary for the definitive rheumatoid arthritis diagnosis. PIP: Proximal interphalangeal, MCP: Metacarpophalangeal, MTP: Metatarsophalangeal

Table 2. 1987 ACR rheumatoid arthritis classification criteria*	
1. Morning stiffness	Morning stiffness in and around joints that lasts for a minimum of 1 hour.
2. Arthritis of 3 or more joint areas	Observed simultaneously by a physician in at least 3 joint areas (not bony enlargement alone). Right or left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints are among the 14 possible areas.
3. Arthritis of hand joints	Swelling in at least 1 area of the wrist, MCP, or PIP joints.
4. Symmetric arthritis	Simultaneous involvement of the same joint areas on both body sides (absolute symmetry is not sought in the bilateral involvement of PIP, MCP, or MTP joints).
5. Rheumatoid nodules	Subcutaneous nodules over bony prominences or extensor surfaces or in joint areas observed by a physician.
6. Serum rheumatoid factor	Demonstration of abnormal amounts of serum rheumatoid factor by any method.
7. Radiographic changes	RA-specific typical radiographic changes on posteroanterior hand and wrist radiographs (osteoarthritic changes alone are inadequate).
*The patient is classified as having RA when meeting at least 4 of the 7 criteria. ACR: American College of Rheumatology, PIP: Proximal interphalangeal, MCP: Metacarpophalangeal, MTP: Metatarsophalangeal	

2010 Classification Criteria for Rheumatoid Arthritis

The 1987 criteria performed very well in distinguishing individuals with long-standing and active RA from individuals with other arthritis (with 95% sensitivity and 87% specificity). Nevertheless, they were inadequate in diagnosing the disease in its early stages. Numerous research have revealed that early aggressive treatment can stop or slow the progression of bone erosions, reduce disability due to the disease, and increase the remission rate (2,6,7). Hence, the ACR and European League Against Rheumatism (EULAR) joint working group was created to develop a new approach for earlier detection of RA in the clinic. A 3-phase study established the "2010 RA classification criteria" (8). In phase 1, possible criteria were identified, and the diagnostic significance of variables was computed (Table 3). In phase 2, clinician-based data on the relative contribution of clinical and laboratory factors to the development of RA were obtained. In phase 3, the scoring system was developed using the data obtained from phases 1 and 2.

The 2010 ACR/EULAR RA classification criteria set was established by considering joint (number and type), serology, level of acute phase reactants, and symptom duration (Table 4). A score between 0-10 is obtained as a result of applying the aforesaid criteria, and a score of 6 and above indicates the definite presence of RA. A patient who scores below 6 cannot be classified as having definite RA, but may be re-evaluated since they might meet the criteria in the future. The differential diagnosis varies from patient to patient. Psoriatic arthritis, systemic lupus erythematosus, crystal arthritis, and infectious arthritis should be considered and tested in order to rule out these diseases if necessary.

The 2010 ACR/EULAR RA classification criteria set is for individuals with newly diagnosed disease. This classification criterion set does not consider radiographic findings, which are the most important diagnostic value of the disease and provides important clues about the disease course. However, it should be remembered that even though RA is typical erosive arthritis, but does not completely meet the 2010 criteria, it can still be considered RA (Figure 2). Patients who have had the disease for a long period but whose disease is inactive (whether or not they receive treatment), and who have typical erosions detected in the current records, whether or not they meet the 2010 criteria, can also be considered to have RA.

This criterion set can ensure that RA is diagnosed earlier. Its sensitivity is higher than that of the previous criterion, but its specificity is lower. It is challenging for seronegative patients to meet the criteria (9,10). In a patient with a four-month history who has swelling in eight small joints, and morning stiffness in arthritic joints, C-reactive protein (CRP) is high, but rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA) are negative. This patient scores 5 according to the 2010 set (not considered as having RA) but meets four criteria from the 1987 set (considered as having RA). In a patient with swelling in a proximal interphalangeal joint (PIP) joint for 6 days, CRP is high, and ACPA is positive at high titer; this patient scores 6 according to the 2010 set (considered as having RA) and meets 3 criteria from the 1987 set (not considered as having RA).

A study evaluated 313 patients who presented for the first time, 76 of whom were diagnosed with RA. In the study in question,

Table 3. Significance levels of the parameters determined in phase-1

Variables	Comparisons	Weights
Swollen MCP joint	Yes vs. no	1.5
Swollen PIP joint	Yes vs. no	1.5
Swollen wrist	Yes vs. no	1.6
Hand sensitivity	Yes vs. no	1.8
AFR level	Slightly high vs. normal	1.2
AFR level	High vs. normal	1.7
Serology	Low titer vs. negative	2.2
Serology	High titer vs. negative	3.9

PIP: Proximal interphalangeal, MCP: Metacarpophalangeal, AFR: Albumin-to-fibrinogen ratio

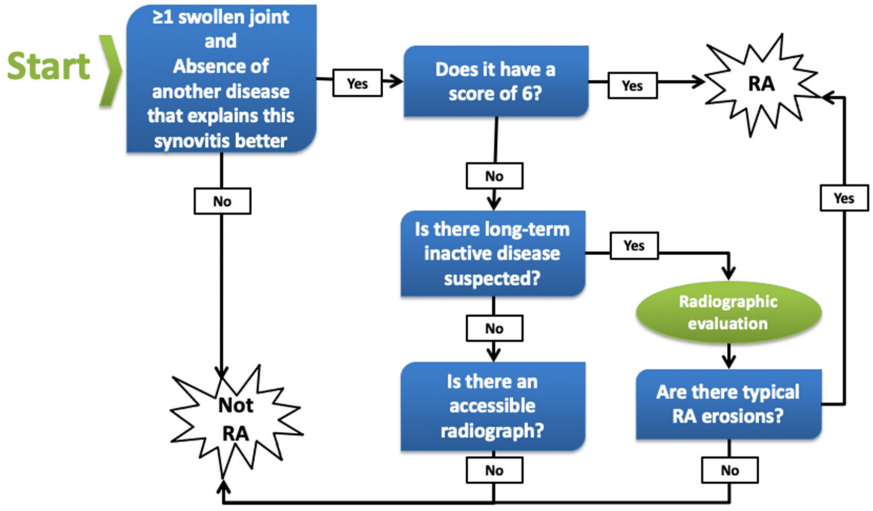

Figure 2. Patients who do not meet the 2010 ACR/EULAR rheumatoid arthritis classification criteria but have typical radiographic findings
ACR/EULAR: American College of Rheumatology/European Alliance of Associations for Rheumatology, RA: Rheumatoid arthritis

Table 4. 2010 rheumatoid arthritis classification criteria

Patients meeting the 2 criteria below constitute the target population: 1. Presence of definite clinical synovitis (swelling) in at least one joint (a) 2. Absence of another disease that explains this synovitis better (b)	A score of ≥6/10 is required to classify the patient as having definite RA (c)
A. Joint involvement (d)	**Score**
1 large joint (e)	0
2-10 large joints	1
1-3 small joints (with or without concomitant large joint involvement) (f)	2
4-10 small joints (with or without concomitant large joint involvement)	3
>10 joints (a minimum of one small joint) (g)	5
B. Serologic results (at least 1 test result required for classification) (h)	**Score**
Negative RF and negative ACPA	0
Low-positive RF or low-positive ACPA	2
High-positive RF or high-positive ACPA	3
C. Acute phase reactants (at least 1 test result required for classification) (i)	**Score**
Normal CRP or normal ESR	0
Abnormal CRP or abnormal ESR	1
D. Symptom duration (j)	**Score**
<6 weeks	0
≥6 weeks	1

a) These criteria aim to classify newly emerging patients. Additionally, if RA is typical erosive arthritis and patients have previously met the 2010 criteria, they are still considered to have RA. Patients who have had the disease for a long period but whose disease is inactive (whether or not they receive treatment) but who are determined to have met the 2010 criteria in the current records should also be considered to have RA.
b) Differential diagnosis varies according to patients' different clinical presentations. Furthermore, SLE, PsA, and gout should also be considered. If the diseases to be considered in the differential diagnosis are unclear, it is necessary to consult an expert rheumatologist.
c) Although patients scoring <6/10 cannot be classified as having RA, their conditions should be re-evaluated. Patients may meet the criteria in the future.
d) The condition expressed by joint involvement is the presence of swelling or tenderness in any joint during examination. This condition can also be provided by evidence of synovitis with imaging techniques. DIP, 1st carpometacarpal, and 1st MTP joints are excluded from the evaluation. Joint distribution is categorized in accordance with the location and number of the affected joints. The joint involvement pattern should be addressed in the highest possible category.
e) Large joints: Shoulder, elbow, hip, knee, and ankle.
f) Small joints: MCP, PIP, 2nd, 3rd, 4th, and 5th metatarsophalangeal, thumb interphalangeal, and wrist.
g) At least one of the affected joints in this category should be a small joint. There may be any association of large or small joints with other joints, including joints not specifically listed anywhere such as temporomandibular, acromioclavicular, and sternoclavicular.
h) A negative result refers to a value below the upper limit of the specified range. A low positive result indicates a value above the upper limit of normal but three times and less than the upper limit. A high positive result is a value greater than three times the upper limit of normal. If the laboratory cannot quantify RF and only reports it as (+) or (-), it must be evaluated as a low positive result.
i) Normal or abnormal values are determined based on the reference values of the laboratory.
j) Symptom duration: It is the duration of synovitis symptoms such as pain, swelling, and tenderness in the joints determined to be impacted during the examination, as reported by the patient.

RA: Rheumatoid arthritis, RF: Rheumatoid factor, ACPA: Anti-citrullinated protein antibody, CRP; C-reactive protein, ESR: Erythrocyte sedimentation rate. PIP: Proximal interphalangeal, MCP: Metacarpophalangeal, MTP: Metatarsophalangeal, SLE: Systemic lupus erythematosus, PsA: Psoriatic arthritis, DIP: Distal interphalangeal

when the 2010 criteria were applied, the sensitivity and specificity were found to be 73.5% and 71.4%; when the 1987 criteria were applied, the sensitivity and specificity were determined to be 47.1% and 92.9%, respectively (11). Many studies have reported different specificity and sensitivity rates (sensitivity between 62-91% and specificity between 21-78%) (12). Another study found that when the criteria were applied simultaneously, about 10% of RA patients meeting the 1987 criteria could not be classified as having RA in line with the 2010 criteria (Table 5) (13).

In a study evaluating patients with very early arthritis (14), 303 patients with symptom duration ≤16 weeks who had not previously received disease-modifying anti-rheumatic drug (DMARD) treatment were followed up for 52 weeks. It was reported that 75% of patients diagnosed with RA scored ≥6 following the 2010 criteria in the initial evaluation, and 75% of patients diagnosed with undifferentiated arthritis scored <6 at the beginning after follow-up. These data support the effectiveness of the 2010 set in distinguishing RA from undifferentiated (poly or oligo) arthritis. When the clinical stages and pre-stages of RA are considered, the classification criteria should be prepared appropriately for the group they will be applied to (Figure 3).

Classification Criteria Set for Early Rheumatoid Arthritis

The 1987 ACR criteria set is suitable for established RA patients but is difficult to apply in the diagnosis of early RA patients. The sensitivity of the 2010 ACR/EULAR set, developed to this end, is higher than that of the 1987 ACR set, but its specificity is considerably lower. Low specificity means misdiagnosis, and incorrect and unnecessary treatments. Despite these two sets being available, it is obvious that new sets are still needed, particularly for early RA (15).

A prospective multicenter study was performed in a large cohort of patients with early inflammatory arthritis with the objective of developing criteria that could be readily utilized in clinical practice for early RA diagnosis (16). The research included 803 patients with a symptom duration of less than 1 year. Patients were followed up for one year at 3-month intervals. Five hundred fourteen patients were diagnosed with RA, other rheumatic diseases, and undifferentiated arthritis. Variables with high sensitivity for the diagnosis of RA in comparison with the initial variables included symmetric arthritis, and arthritis of the hand joints (wrist, metacarpophalangeal joint, or PIP swelling), followed by arthritis of 3 or more joint areas, positive RF, and positive anti-cyclic citrullinated peptide. Four different sets of criteria were acquired from the obtained data, and the most sensitive criteria set in identifying patients diagnosed with RA was selected at the end of one year (Table 6). The presence of 3 out of 5 criteria is adequate for early RA classification.

The sensitivity of the early RA classification criteria set defined here was computed as 85% (58% for the 1987 set and 83% for the 2010 set), and specificity was computed as 87% (94% for the 1987 set and 55% for the 2010 set).

The importance levels of the criteria used in early RA classification and the corresponding score were identified (Table 7). In the score-based classification set prepared according to these data, if patients who reached ≥5 points were accepted as having RA, the sensitivity was computed to be 86% and the specificity was 88%.

Table 5. Differences between 1987 and 2010 criteria

	1987 criteria	2010 criteria
Target population	Established RA	Early RA
CCP	No	Yes
Morning stiffness	Yes	No
Radiographic findings	Yes	No
Subcutaneous nodule	Yes	No
Sensitivity	47.1	73.5
Specificity	92.9	71.4

CCP: Cyclic citrullinated peptide, RA: Rheumatoid arthritis

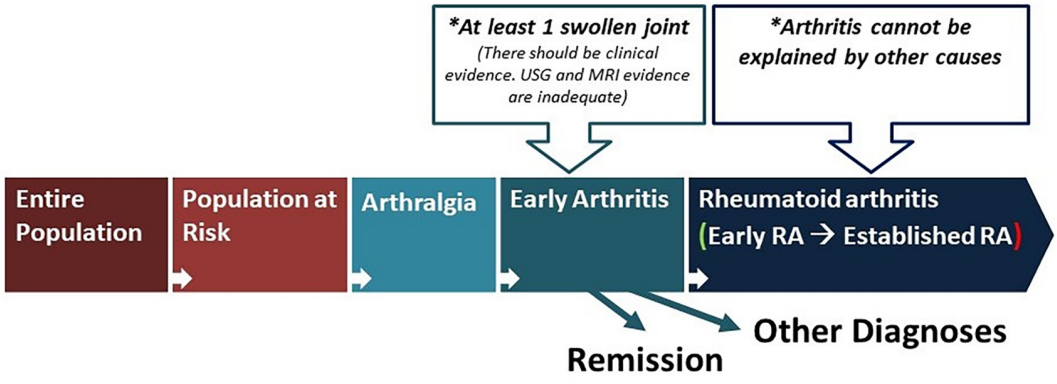

Figure 3. When considering rheumatoid arthritis disease and its pre-stages, classification criteria should be established according to the target population to be screened
USG: Ultrasonography, MRI: Magnetic resonance imaging, RA: Rheumatoid arthritis

Table 6. Early rheumatoid arthritis classification criteria set*

Criteria	Definitions
1. Morning stiffness	Morning stiffness in and around joints that lasts longer than 30 minutes.
2. Polyarthritis	Swelling in at least 3 of 14 joint areas consisting of right and left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints.
3. Arthritis in hand joints	Swelling in at least one of the wrists, MCP, or PIP joint areas.
4. RF positivity	Above normal range is considered positive.
5. ACPA positivity	Above normal range is considered positive.

*Patients who meet ≥3 of the 5 criteria specified above are classified as having rheumatoid arthritis. RF: Rheumatoid factor, ACPA: Anti-citrullinated protein antibody, PIP: Proximal interphalangeal, MCP: Metacarpophalangeal, MTP: Metatarsophalangeal

Table 7. The importance levels of the criteria determined to be used in early RA classification and the score-based classification

Variables	Correlation coefficient	Score‡
ACPA positivity	4.2	4
*Swelling in ≥3 out of 14 joint areas	1.6	2
Morning stiffness lasting ≥30 minutes	1.4	1
Symmetric arthritis	1.3	1
Arthritis in hand joints: swelling in at least one of the wrists, MCP, or PIP joint areas	0.9	1
RF positivity	0.7	1

*14 joint areas consist of right and left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints. ‡Patients who reach ≥5 points in the score-based classification set are accepted to have RA. RF: Rheumatoid factor, RA: Rheumatoid arthritis, ACPA: Anti-citrullinated protein antibody, PIP: Proximal interphalangeal, MCP: Metacarpophalangeal, MTP: Metatarsophalangeal

DISCUSSION

Diagnostic criteria are typically expansive, designed to encompass the diverse manifestations of a disease to accurately detect as many affected individuals as possible. In contrast, classification criteria are standardized frameworks aimed at forming consistent, relatively uniform groups for clinical research purposes. These criteria focus on including most patients who exhibit core common traits of the condition, rather than all potential cases. As such, classification criteria are not applied for diagnosing patients in clinical settings but are utilized to ensure uniform patient inclusion in research studies (17).

Classification criteria may have different sensitivity and specificity depending on age, gender, race, and geographic region (17). Therefore, the validity of classification criteria may vary from population to population. Therefore, there has always been a need for more sensitive and precise classification criteria that can be applied to all societies. From time to time, there has been a need to change the classification criteria.

Each set of RA classification criteria exhibits distinct advantages, contingent on the clinical context and research objectives. The 1987 criteria demonstrate proficiency in the classification of established disease with high specificity but exhibit inadequate sensitivity in the identification of early presentations. Conversely, the 2010 criteria have been shown to enhance early detection by increasing their sensitivity, though this has come at the expense of specificity, particularly in the classification of seronegative patients (9,18). This trade-off has been demonstrated in several comparative studies. In a study of 313 patients presenting with newly diagnosed arthritis, the 2010 criteria exhibited 73.5% sensitivity and 71.4% specificity, while the 1987 criteria demonstrated 47.1% sensitivity and 92.9% specificity (19). When applied concurrently, approximately 10% of patients meeting the 1987 criteria fail to be classified under the 2010 framework (20). For very early arthritis (symptom duration ≤16 weeks), the 2010 criteria have demonstrated encouraging utility. A study of 303 DMARD-naïve patients followed for 52 weeks found that 75% of those ultimately diagnosed with RA scored ≥6 on the 2010 criteria at initial assessment (21). However, the reduced specificity raises concerns about potential misdiagnosis and inappropriate treatment initiation, particularly in seronegative presentations.

The incorporation of advanced imaging techniques such as ultrasonography and magnetic resonance imaging has the potential to further enhance early detection capabilities, especially in cases where traditional classification criteria yield ambiguous results (22,23). Several studies have demonstrated

that the integration of imaging parameters can improve diagnostic accuracy in early disease, particularly when clinical manifestations remain equivocal (24).

CONCLUSION

The evolution of RA classification criteria is indicative of significant advancements in our understanding of disease pathogenesis, clinical presentation, and the critical importance of early intervention. To ensure optimal clinical application, rheumatologists must understand the comparative performance of these criteria sets while recognizing that classification criteria are primarily intended for research standardization rather than individual diagnosis.

Clinical judgment remains paramount, particularly in seronegative presentations or atypical manifestations where existing criteria may have limitations. As our understanding of RA pathophysiology continues to evolve, future classification frameworks will likely incorporate biomarkers of pre-clinical disease states, genetic risk factors, and novel imaging parameters to enable intervention at increasingly earlier stages of disease development.

Footnotes

Authorship Contributions

Surgical and Medical Practices: İ.G., A.K., Concept: İ.G., Design: A.K., Data Collection or Processing: İ.G., Analysis or Interpretation: A.K., Literature Search: İ.G., A.K., Writing: İ.G., A.K.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Alamanos Y, Voulgari PV, Drosos AA. Incidence and prevalence of rheumatoid arthritis, based on the 1987 American College of Rheumatology criteria: a systematic review. Semin Arthritis Rheum. 2006;36:182-8.
2. van der Heide A, Jacobs JW, Bijlsma JW, et al. The effectiveness of early treatment with "second-line" antirheumatic drugs. A randomized, controlled trial. Ann Intern Med. 1996;124:699-707.
3. Bennett GA, Cobb S, Jacox R, Jessar RA, Ropes MW. Proposed diagnostic criteria for rheumatoid arthritis. Bull Rheum Dis. 1956;7:121-4.
4. A Committee of the American Rheumatism Association. Diagnostic criteria for rheumatoid arthritis: 1958 revision by a committee of the American Rheumatism Association. Ann Rheum Dis. 1959;18:49-51.
5. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988;31:315-24.
6. Mäkinen H, Kautiainen H, Hannonen P, et al. Sustained remission and reduced radiographic progression with combination disease modifying antirheumatic drugs in early rheumatoid arthritis. J Rheumatol. 2007;34:316-21.
7. Puolakka K, Kautiainen H, Möttönen T, et al. Impact of initial aggressive drug treatment with a combination of disease-modifying antirheumatic drugs on the development of work disability in early rheumatoid arthritis: a five-year randomized followup trial. Arthritis Rheum. 2004;50:55-62.
8. Aletaha D, Neogi T, Silman AJ, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010;62:2569-81.
9. Boeters DM, Gaujoux-Viala C, Constantin A, van der Helm-van Mil AHM. The 2010 ACR/EULAR criteria are not sufficiently accurate in the early identification of autoantibody-negative rheumatoid arthritis: results from the Leiden-EAC and ESPOIR cohorts. Semin Arthritis Rheum. 2017;47:170-4.
10. Jung SJ, Lee S-W, Ha YJ, et al. Patients with early arthritis who fulfil the 1987 ACR classification criteria for rheumatoid arthritis but not the 2010 ACR/EULAR criteria. Ann Rheum Dis. 2012;71:1097-8.
11. Kaneko Y, Kuwana M, Kameda H, Takeuchi T. Sensitivity and specificity of 2010 rheumatoid arthritis classification criteria. Rheumatology. 2011;50:1268-74.
12. Ortiz EC, Shinada S. Evolution of classification criteria for rheumatoid arthritis: how do the 2010 criteria perform? Rheum Dis Clin North Am. 2012;38:345-53.
13. Mjaavatten MD, Bykerk VP. Early rheumatoid arthritis: the performance of the 2010 ACR/EULAR criteria for diagnosing RA. Best Pract Res Clin Rheumatol. 2013;27:451-66.
14. Biliavska I, Stamm TA, Martinez-Avila J, et al. Application of the 2010 ACR/EULAR classification criteria in patients with very early inflammatory arthritis: analysis of sensitivity, specificity and predictive values in the SAVE study cohort. Ann Rheum Dis. 2013;72:1335-41.
15. Zeidler H. The need to better classify and diagnose early and very early rheumatoid arthritis. J Rheumatol. 2012;39:212-7.
16. Zhao J, Su Y, Li R, et al. Classification criteria of early rheumatoid arthritis and validation of its performance in a multi-centre cohort. Clin Exp Rheumatol. 2014;32:667-73.
17. Aggarwal R, Ringold S, Khanna D, et al. Distinctions between diagnostic and classification criteria? Arthritis Care Res (Hoboken). 2015;67:891-7.
18. Nordberg LB, Lillegraven S, Lie E, et al. Patients with seronegative RA have more inflammatory activity compared with patients with seropositive RA in an inception cohort of DMARD-naïve patients classified according to the 2010 ACR/EULAR criteria. Ann Rheum Dis. 2017;76:341-5.
19. Sakellariou G, Scirè CA, Zambon A, Caporali R, Montecucco C. Performance of the 2010 classification criteria for rheumatoid arthritis: a systematic literature review and a meta-analysis. PLoS One. 2013;8:e56528.
20. Humphreys JH, Verstappen SM, Hyrich KL, et al. The incidence of rheumatoid arthritis in the UK: comparisons using the 2010 ACR/EULAR

classification criteria and the 1987 ACR classification criteria. Results from the Norfolk Arthritis Register. Ann Rheum Dis. 2013;72:1315-20.

21. Nakagomi D, Ikeda K, Okubo A, et al. Ultrasound can improve the accuracy of the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis to predict the requirement for methotrexate treatment. Arthritis Rheum. 2013;65:890-8.
22. Caporali R, Smolen JS. Back to the future: forget ultrasound and focus on clinical assessment in rheumatoid arthritis management. Ann Rheum Dis. 2018;77:18-20.
23. D'Agostino MA, Terslev L, Wakefield R, et al. Novel algorithms for the pragmatic use of ultrasound in the management of patients with rheumatoid arthritis: from diagnosis to remission. Ann Rheum Dis. 2016;75:1902-8.
24. Colebatch AN, Edwards CJ, Østergaard M, et al. EULAR recommendations for the use of imaging of the joints in the clinical management of rheumatoid arthritis. Ann Rheum Dis. 2013;72:804-14.

ORIGINAL ARTICLE

Rheumatology Quarterly

DOI: 10.4274/qrheumatol.galenos.2025.28290
Rheumatol Q 2025;3(2):49-52

POST-EARTHQUAKE MUSCULOSKELETAL PAIN IN MEDICAL FACULTY STUDENTS: STRESS-RELATED PAIN PROCESS

Tuba Tülay Koca, Cem Zafer Yıldır

Kahramanmaraş Sütçü İmam University Faculty of Medicine, Department of Physical Medicine and Rehabilitation, Kahramanmaraş, Türkiye

Abstract

Aim: In the last decade, humans have been faced with natural disasters such as earthquakes, floods, and forest fires worldwide. In the long term, the effects of the trauma experienced after these disasters continue. We aimed to detect musculoskeletal pain and earthquake-related conditions in term 5 faculty of medicine, students after the high-intensity earthquake.

Material and Methods: The study was planned as a cross-sectional, descriptive study. All term 5 students (n=110) were included in the study. Data was obtained through the online survey Google Forms and participants were enabled to complete it as soon as possible.

Results: In the study, n=82 students (48 girls, 34 boys) participated in our survey voluntarily. 34.1% of the participants were 23 years old, 29.3% were 24 years old, 19.5% were 22 years old, and 14.6% were 25 years old. Forty-eight point eight percent of the participants stated that they moved away from the city after the earthquake. 24.4% indicated that they lost a relative in the earthquake. 48.8% of the participants said that there was an increase in musculoskeletal pain after the earthquake. The most common area of pain was in the low back with a rate of 37%. This rate was followed by the neck with 18.5% and the back and shoulder areas with 14.8%. 36.8% of the participants stated that post-earthquake pain negatively affected academic performance. 36.6% of the participants had sleep problems after the earthquake, 29.3% had post-earthquake dizziness, 24.4% had gait instability, 19.5% had anxiety/depression, and 12.2% started to use medications for these problems.

Conclusion: In the post-earthquake period, musculoskeletal complaints were observed in the term 5 students of the faculty of medicine, most frequently in the low back, neck, and back/shoulder regions. In addition, problems that will negatively affect their academic success, such as insomnia, depression/anxiety, dizziness, and imbalance, are also observed.

Keywords: Earthquake, musculoskeletal pain, dizziness, chronic pain, medical student

INTRODUCTION

Earthquakes are an ideal natural trigger factor for acute/chronic stress. Earthquake disasters are associated with numerous complaints, especially pain in the musculoskeletal system. These complaints arise from the physical damage that may occur during the earthquake, great stress experienced, housing and sleeping problems in the subsequent period, and the stressors caused by tens of thousands of aftershocks. Physiological effects

Address for Correspondence: Tuba Tülay Koca, Kahramanmaraş Sütçü İmam University Faculty of Medicine, Department of Physical Medicine and Rehabilitation, Kahramanmaraş, Türkiye
E-mail: tuba_baglan@yahoo.com **ORCID ID:** orcid.org/0000-0002-4596-858X
Received: 20.11.2024 **Accepted:** 06.01.2025 **Epub:** 26.03.2025 **Publication Date:** 25.06.2025

Cite this article as: Koca TT, Yıldır CZ. Post-earthquake musculoskeletal pain in medical faculty students: stress-related pain process. Rheumatol Q. 2025;3(2):49-52

of sympathetic nervous system activation can be seen in the human body in the acute and chronic periods (1). On February 6, 2023, two consecutive major earthquake disasters occurred in Kahramanmaraş, Türkiye, with magnitudes of 7.4 and 7.6 on the Richter scale. Tens of thousands of people died after this disaster, and millions of people were affected.

Central sensitization causes differences in the processing of the pain response through multiple mechanisms, such as abnormal processing of pain signals by the central nervous system, an increase in neurotransmitter levels, changes in the transmission and perception of pain signals, nerve cells becoming sensitive to pain through structural or functional changes (neuronal plasticity), and a decrease in the pain threshold (2). Acute and chronic stress response may play a role in the development of chronic pain through central sensitization.

Chronic stress can increase the sensitivity of the nervous system and thus contribute to central sensitization. Stress can change the body's perception of pain and cause it to feel more intense and widespread. Additionally, the effects of stress on the immune system (neuroinflammation) may also contribute to central sensitization. Stress status must be taken into consideration in the evaluation of pain response (3).

Individuals who experience an earthquake may suffer an increase in their existing pain or new pain complaints due to the central sensitization mechanism. In addition, depression, anxiety, and sleep problems can negatively influence pain complaints in the musculoskeletal system (4). Here, we aimed to evaluate the prevalence and severity of musculoskeletal pain, along with accompanying complaints such as sleep disturbance, dizziness, depression, anxiety, and imbalance, in term v medical faculty students who experienced the 2023 Kahramanmaraş Earthquake.

MATERIAL AND METHODS

The study was planned as a cross-sectional, descriptive study. All term 5 students (n=110) receiving a 2-week physical medicine and rehabilitation internship training were included in the study. Data were obtained through the online survey, Google Forms and participants were encouraged to complete it as soon as possible. Participants were asked yes/no questions about the following: age; gender; whether muscle pain increases after the earthquake; whether muscle pain affects academic success; the region the pain is in; its severity on the visual analog scale (VAS); whether they were left in the rubble and, if so, for how long; whether they lost a relative in the earthquake; sleep problems after the earthquake; and whether they had any accompanying problems such as dizziness, imbalance, and medication use. The study was completed when the entire target population was reached. VAS, a VAS, is a scale (0-10 cm), that shows the subjective evaluation of pain. Since face-to-face medical education was provided at our university, in the earthquake zone, in the second year following the earthquake, the research was carried out during this period.

Inclusion Criteria

- To be a term 5 medical student,
- Having experienced the 2023 February Kahramanmaraş Earthquake,
- To volunteer.

Exclusion Criteria

- Having a serious orthopedic disability before the earthquake,
- Not volunteering,
- Not having experienced an earthquake.

Statistical Analysis

Since the entire population (n=110) will be included, the sample size was not calculated by power analysis. Variables are presented as numbers (n) and percentages (%). Figures were obtained from Google Forms. The study was planned in accordance with the principles of the international Helsinki Declaration and approved by Kahramanmaraş Sütçü İmam University Faculty of Medicine Non-invasive Clinical Research Ethics Committee (approval number: 08, dated: 24.06.2024). A written online informed consent form was obtained from the participants.

RESULTS

In the study, n=82 students (48 girls, 34 boys) participated in our survey voluntarily. 34.1% of the participants were 23 years old, 29.3% were 24 years old, 19.5% were 22 years old, and 14.6% were 25 years old (Figure 1). No participant was trapped under debris. 48.8% of the participants stated that they moved away from the city after the earthquake. 24.4% indicated that they lost a relative in the earthquake. Descriptive characteristics were listed in Table 1.

Forty-eight point eight percent of the participants stated that there was an increase in musculoskeletal pain after the earthquake. The most common area of pain was in the low back region, with a rate of 37% (Figure 2). This rate was followed by the neck with 18.5%, and the back and shoulder areas with 14.8%. Post-earthquake pain intensity was evaluated via VAS (Figure 3). VAS=1 scored the highest with 33.3%.

Thirty-six point eight percent of the participants stated that post-earthquake pain negatively affected their school performance.

Thirty-six point six percent of the participants were have sleep problems after the earthquake, 29.3% have post-earthquake dizziness (dizziness, feeling of an earthquake, and imbalance attacks), 24.4% have gait instability, 19.5% have anxiety/depression, and 12.2% started to use medication for these problems. Sixty-three point four percent stated that they woke up in the morning without having had enough sleep.

Table 1. Descriptive characteristics of the participants

	n=82
Gender (F/M)	48/34
Median age, year	23
Participants trapped under the debris	0
Participants, lost at least one relative because of earthquake	20 (24.4%)
Post-earthquake increased musculoskeletal pain	40 (48.8%)

F: Female, M: Male

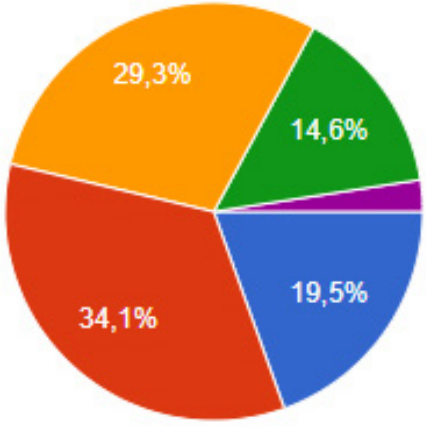

Figure 1. Age distribution of the participants

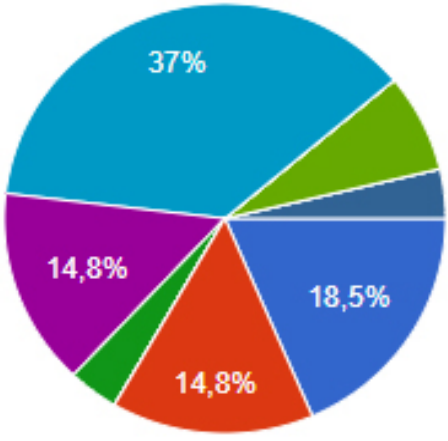

Figure 2. Distribution of the pain area

DISCUSSION

Türkiye is located in a region with widespread seismic fault lines, and has witnessed many devastating earthquakes from the past to the present. Two major earthquakes occurred in Kahramanmaraş province in February 2023. Tens of thousands of people were trapped under the rubble. Most post-earthquake injuries occur due to objects falling on people, crushing injuries caused by being directly under the debris, and disruptions during rescue and transfer from the debris.

Millions of people were woken up from their sleep by a massive earthquake and then experienced housing problems for a long time. This major earthquake trauma, along with tens of thousands of aftershocks, can cause anxiety, sleep disturbance, feeling like an earthquake is happening, dizziness, loss of balance, sleep problems, and head, neck, back pain in earthquake victims. Functional disability is frequently encountered after natural disasters. Complaints related to the musculoskeletal system are frequently encountered with or without musculoskeletal injury. Post-disaster housing problems and post-traumatic stress-related sleep disorders are also associated with musculoskeletal complaints (5,6).

It is necessary to identify earthquake-related musculoskeletal system problems. After a disaster, previously existing musculoskeletal complaints may increase and new complaints may also arise. Depression and anxiety from psychological stress after an earthquake are very common, and these two clinical conditions are closely related to pain. Scientific data support that the severity of pain increases and becomes chronic in the presence of depression. The opposite is also true. This situation may negatively affect the person's recreational, community, professional activities, and school success (7-9).

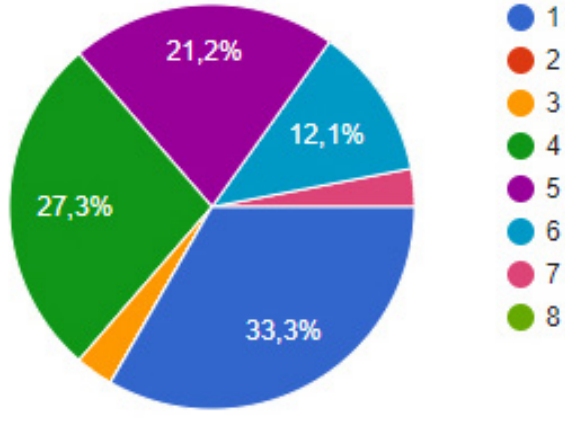

Figure 3. Evaluation of pain with VAS (1-10)
VAS: Visual analog scale

Although none of the participants was trapped under the rubble, and nearly half of them moved away from the city after the earthquake, the high rates of problems indicate that they experienced difficulties following the acute period of earthquake trauma.

We know that pain complaints differ between sexes and are more common in females (10). The fact that more than half of our group was female may have affected the study results. Medical school students constitute a group with higher education and intellectual capacity than the general population. Since this group is both educated and healthcare personnel, their awareness and influence regarding events may be higher. We also know that a group of volunteers, including medical students, worked actively in the hospital after the earthquake. Although there is a lot of data in the literature on the prevalence of musculoskeletal pain in the geriatric age group, there is little data on the frequency of pain in the young population. This article will contribute to the literature in this area.

The survey being conducted one year after the earthquake, data being taken from only one region, and a lack of full societal representation due to participants' education levels, prevent the generalizability of the results. Evaluations are based only on the person's statement; no measurements such as sensitization scales (central sensitization scale, S-LANNS) were taken into account.

CONCLUSION

In the 2nd year of the earthquake disaster, musculoskeletal pain was observed with high frequency in term v students of the faculty of medicine, most frequently in the low back, neck, and back and shoulder regions. In addition, problems such as insomnia, depression/anxiety, dizziness, and gait instability, that will negatively affect their academic success, are also observed.

Ethics

Ethics Committee Approval: The study was planned in accordance with the principles of the international Helsinki Declaration and approved by Kahramanmaraş Sütçü İmam University Faculty of Medicine Non-invasive Clinical Research Ethics Committee (approval number: 08, dated: 24.06.2024).

Informed Consent: A written online informed consent form was obtained from the participants.

Footnotes

Authorship Contributions

Concept: T.T.K., Design: T.T.K., Data Collection or Processing: T.T.K., C.Z.Y., Analysis or Interpretation: C.Z.Y., Writing: T.T.K.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. J Pain. 2009;10:895-926.
2. Modena MG, Pettorelli D, Lauria G, Giubertoni E, Mauro E, Martinotti V. Gender differences in post-traumatic stress. Biores Open Access. 2017;6:7-14.
3. Lima MG, Silva RX, Silva Sde N, et al. Time-dependent sensitization of stress responses in zebrafish: a putative model for post-traumatic stress disorder. Behav Processes. 2016;128:70-82.
4. Usui C, Hatta K, Aratani S, et al. Vulnerability to traumatic stress in fibromyalgia patients: 19 month follow-up after the great East Japan disaster. Arthritis Res Ther. 2013;15:130.
5. Yabe Y, Hagiwara Y, Sekiguchi T, et al. Musculoskeletal pain and new-onset poor physical function in elderly survivors of a natural disaster: a longitudinal study after the great East Japan earthquake. BMC Geriatr. 2019;19:274.
6. Yabe Y, Hagiwara Y, Sekiguchi T, et al. Sleep disturbance is associated with neck pain: a 3-year longitudinal study after the Great East Japan Earthquake. BMC Musculoskelet Disord. 2022;23:459.
7. Jinnouchi H, Ohira T, Kakihana H, et al. Lifestyle factors associated with prevalent and exacerbated musculoskeletal pain after the Great East Japan Earthquake: a cross-sectional study from the Fukushima Health Management Survey. BMC Public Health. 2020;20:677.
8. Hagiwara Y, Yabe Y, Sekiguchi T, et al. Association of musculoskeletal pain in other body parts with new-onset shoulder pain: a longitudinal study among survivors of the Great East Japan Earthquake. BMJ Open. 2021;11:e041804.
9. Kulakoğlu B, Uzunay Z, Pota K, Varhan N, Fırat MG. Evaluation of musculoskeletal injuries after the 2023 Kahramanmaras Earthquake: a local hospital experience. Jt Dis Relat Surg. 2023;34:509-15.
10. Koca TT, Aykan D, Berk E, Koçyiğit BF, Güçmen B. Effect of hypertension on pain threshold in patients with chronic pain. Cent Asian J Med Hypotheses Ethics. 2022:3:232-40.

ORIGINAL ARTICLE

Rheumatology Quarterly

DOI: 10.4274/qrheumatol.galenos.2025.30592
Rheumatol Q 2025;3(2):53-9

IMPACT OF VARIOUS RHEUMATOID ARTHRITIS TREATMENTS ON BONE MINERAL DENSITY IN POSTMENOPAUSAL WOMEN

Alper Uysal[1], Ali Nail Demir[2], Uğur Güngör Demir[1]

[1]University of Health Sciences Türkiye, Mersin City Training and Research Hospital, Clinic of Physical Medicine and Rehabilitation, Mersin, Türkiye
[2]University of Health Sciences Türkiye, Mersin City Training and Research Hospital, Clinic of Rheumatology, Mersin, Türkiye

Abstract

Aim: The objective of this study was to evaluate the impact of various treatment options on bone mineral density (BMD) in postmenopausal women with rheumatoid arthritis (RA).

Material and Methods: A retrospective analysis was conducted on the data of 163 postmenopausal women, including 121 RA patients meeting the 2010 American College of Rheumatology/European League Against Rheumatism criteria and 42 healthy controls. RA patients were categorized into four groups based on their treatment regimens: Group 1, receiving conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) alone; Group 2, receiving csDMARDs in combination with glucocorticosteroids (GCs); Group 3, receiving csDMARDs with GCs and biological/targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs); and Group 4, receiving b/tsDMARDs combined with methotrexate. Data collected included demographic information, BMD T-scores at lumbar spine (L1-L4), femoral neck, total hip, and serum calcium, and vitamin D levels.

Results: RA patients had significantly lower BMD T-scores at L1-L4, femoral neck, and total hip compared to controls ($p=0.041$, $p=0.026$, and $p=0.003$, respectively). Among treatment groups, patients receiving csDMARDs with GCs exhibited greater bone loss, particularly in femoral neck scores, compared to other regimens (all $p\leq0.005$). Conversely, b/tsDMARDs showed a protective effect on BMD, mitigating bone loss despite the use of low-dose GCs.

Conclusion: This study demonstrates that RA treatments significantly influence BMD in postmenopausal women. b/tsDMARDs appear to mitigate the adverse effects of GCs on bone health, while prolonged GC use is associated with greater bone loss, especially in the csDMARDs group.

Keywords: Rheumatoid arthritis, postmenopausal women, biologic therapies, corticosteroids, DMARDs, bone mineral density

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disorder primarily characterised by joint inflammation and systemic involvement, including significant skeletal complications (1). Beyond joint pathology, RA is related with lower bone mass, decreased bone mineral density (BMD), and a heightened risk of osteoporosis and fractures. These fractures, considered among the most severe complications of RA, significantly impair quality of life and may shorten life expectancy (2).

Address for Correspondence: Alper Uysal, University of Health Sciences Türkiye, Mersin City Training and Research Hospital, Clinic of Physical Medicine and Rehabilitation, Mersin, Türkiye
E-mail: alperuysal82@gmail.com **ORCID ID:** orcid.org/0000-0002-4114-1649
Received: 26.12.2024 **Accepted:** 03.02.2025 **Publication Date:** 25.06.2025

Cite this article as: Uysal A, Demir AN, Demir UG. Impact of various rheumatoid arthritis treatments on bone mineral density in postmenopausal women. Rheumatol Q. 2025;3(2):53-9

The pathways leading to bone loss in RA involve a complex interplay of inflammatory mechanisms. Pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β, IL-6, and IL-17 stimulate osteoclastogenesis through the receptor activator of nuclear factor-κB ligand (RANKL)-RANK-osteoprotegerin (OPG) pathway, thereby increasing bone breakdown while concurrently suppressing osteoblast function. Autoimmune responses associated with RA further exacerbate bone loss by altering Wnt signalling and other pathways essential for maintaining bone homeostasis. Additionally, systemic factors such as glucocorticosteroids (GCs) therapy, reduced physical activity due to joint pain, and chronic systemic inflammation intensify bone deterioration (3,4).

The treatment of RA involves conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) such as methotrexate (MTX), hydroxychloroquine (HCQ), and sulfasalazine, alongside biological/targeted synthetic DMARDS (b/tsDMARDs) TNF-α, IL-6, and Janus kinases (JAK) inhibitors (upadacitinib, baricitinib). Combination approaches using synthetic and bDMARDs are also effective in managing the disease (5).

This study aims to evaluate the impact of diverse RA treatment regimens on bone health in postmenopausal women, and to provide observations on how biologic therapies may affect the adverse effects of long-term GC use.

MATERIAL AND METHODS

This retrospective study was approved by the Clinical Research Ethics Committee of Mersin University (approval number: 2024/987, dated: 16.10.2024). Patient data collected between January 1, 2021, and September 30, 2024, was analyzed. In the retrospectively analyzed data, only cases in which disease activity scores 28 (DAS28), BMD measurements, calcium, and vitamin D levels were recorded during the same clinical visit were included in the study. Only RA patients who remained on the same treatment regimen for at least 24 months were included in the study. The study involved a total of 163 postmenopausal women aged over 50 years. Of these, 121 were identified as having RA and were included in the RA group, while 42 healthy, RA-negative individuals with similar demographic characteristics formed the control group.

Patients in the RA group were required to meet the following criteria: a confirmed RA diagnosis based on the 2010 American College of Rheumatology and European League Against Rheumatism (EULAR) classification criteria (6), postmenopausal status, availability of bone densitometry (dual-energy X-ray absorptiometry) results, and serum measurements of calcium and vitamin D in the hospital automation system. For the control group, inclusion required postmenopausal status, an absence of RA, and the availability of bone DXA together with serum vitamin D and calcium levels. Exclusion criteria applied to both groups included the existence of chronic infections, systemic inflammatory diseases other than RA, malignancies, prior treatment with osteoporosis medications (e.g., bisphosphonates, denosumab, teriparatide, romosozumab), other conditions leading to osteoporosis, such as hyperthyroidism, hyperparathyroidism, liver failure, or kidney failure, and the presence of medical implants or devices that could interfere with DXA results.

RA patients were categorized into five groups according to their treatment protocols: (1) those treated with csDMARDs (MTX and HCQ); (2) those treated with csDMARDs (MTX + HCQ) in combination with GC (e.g., prednisolone), characterized by low-dose steroid use (≤7.5 mg/day) administered over a long duration (≥3 months); (3) those treated with csDMARDs, GC, and b/tsDMARDs (including anti-TNF drugs such as etanercept, adalimumab, golimumab, infliximab, and certolizumab; JAK inhibitors such as upadacitinib, baricitinib, and tofacitinib; or the anti-IL-6 agent tocilizumab), with steroid use matching the low-dose, long-duration criteria; (4) those treated exclusively with b/tsDMARDs (e.g., anti-TNF drugs, JAK inhibitors, or the anti-IL-6 agent) combined with MTX a (csDMARD); and (5) a control group of RA-negative postmenopausal individuals matched for demographic characteristics. Each group consisted of participants as follows: Group 1 (28); Group 2 (43); Group 3 and 4 (25 each); and Group 5 (42), yielding a total of 163 participants across the five groups. Data were retrieved from the hospital's electronic database. Recorded information included demographic details such as age, weight, and height. Bone health measurements included T-scores of the L1-L4 region, the hip (total) and the neck of the femur, obtained from DXA scans. Laboratory parameters such as serum levels of vitamin D and calcium at the point of DXA measurement were also recorded.

Statistical Analysis

The statistical analysis was conducted to summarize the data, presenting continuous variables as mean ± standard deviation or median (minimum-maximum), depending on the distribution. The Shapiro-Wilk test was utilized to examine the normality of the data. Parametric tests were applied to data sets with normal distributions, whereas non-parametric tests were used for those that did not meet normality assumptions. For comparisons between two groups, the independent samples t-test or Mann-Whitney U test was employed. For multiple-group comparisons, one-way analysis of variance (ANOVA) or the

Kruskal-Wallis test was applied. Significant outcomes from one-way ANOVA were further assessed using the Tukey's post-hoc test, while significant results from the Kruskal-Wallis test underwent additional analysis with Bonferroni-adjusted pairwise Mann-Whitney U tests. The analysis of the distribution of bone health statuses among five patient groups was conducted using Fisher's exact test. Subsequently, post-hoc analysis was performed using Z-scores obtained from crosstabulation to further evaluate pairwise comparisons between groups. A Z-score threshold of ±1.96 was used, corresponding to a 95% confidence interval, to determine whether the observed counts significantly deviated from the expected counts in each category. Statistical analyses were performed using SPSS version 22.

RESULTS

Age, weight, height, body mass index (BMI), calcium, and vitamin D levels showed statistical similarity across the groups (p>0.05). However, significant differences were identified among the groups for T-score of L1-L4 (p=0.041), femoral neck (p=0.026), and hip (p=0.003) parameters (Table 1).

The five subgroups were statistically similar in terms of age, weight, height, and BMI (p>0.05). The disease duration among RA subgroups was also similar (p=0.568). Calcium and vitamin D levels did not differ significantly across the groups (p=0.420 and p=0.115, respectively). However, the DAS28 scores of each RA subgroup were statistically different (p<0.001). Significant differences were observed among the groups for T-score of L1-L4 (p=0.015), femoral neck (p<0.001), and total hip (p<0.001). T-scores of the femoral neck, and the total hip differed significantly between Groups 1 and 2 (p<0.001), and between Groups 2 and 3 (p=0.005 and p=0.004, respectively). Additionally, Groups 2 and 5 showed differences in T-scores of femoral neck, total hip (both p <0.001), and L1-L4 (p=0.005). Between Groups 4 and 2, only femoral neck T score was significantly different (p=0.004) (Table 2). Other BMD parameters were similar between the groups. Specifically, the direct comparative data of Group 2 and Group 3 at L1-L4 did not show a significant difference, (p=0.615).

Table 1. Demographic and laboratory parameters of the patient and healthy groups

	Patient group	Control group	p-value
Age (years), mean ± SD	61.96±9.29	61.73±8.01	0.879
Weight (kg), mean ± SD	73.47±14.71	76.28±11.74	0.216
Height (meter), mean ± SD	1.58±0.06	1.58±0.04	0.432
BMI (kg/m^2), mean ± SD	29.24±5.15	30.23±4.71	0.253
Disease duration (years), mean ± SD	9.88±5.86	N/A	-
Calcium, mean ± SD	9.18±0.55	9.30±0.39	0.115
Vitamin D (ng/dL), mean ± SD	19.22±9.26	19.25±8.40	0.983
L1-L4 T score, mean ± SD	-1.56±0.98	-1.06±1.40	**0.041**
Femoral neck T score, mean ± SD	-1.40±0.98	-1.02±0.90	**0.026**
Total hip T score, mean ± SD	-1.05±1.09	-0.48±1.04	**0.003**

SD: Standard deviation, kg: Kilogram, m: Meter, BMI: Body mass index, N/A: Not applicable

A significant statistical difference was observed in the bone health status of patients across different groups (p=0.008). The adjusted residuals indicated that Group 5 had a statistically higher number of healthy patients in terms of bone health than expected (Z-score =+3.3). Similarly, Group 3's observed osteopenic count was significantly higher than expected (z-score =+2.0), whereas Group 5 had fewer osteopenic patients than anticipated (z-score =-2.7). For osteoporotic patients, the adjusted residuals indicated that Group 2 had significantly more cases than expected (z-score =+2.5) (Table 3).

No correlation was observed between T-scores and DAS28 scores (all p>0.05).

DISCUSSION

The present study investigates the significant impact of RA and its treatment regimens on BMD in postmenopausal women. The RA patient group exhibited reduced T-scores in all bone density parameters relative to the healthy control group. Moreover, this study demonstrated that treatment regimens for RA significantly affect BMD in postmenopausal women. It showed that GC + csDMARDs treatment was associated with worse T-scores in the femoral neck and hip regions compared to csDMARDs treatment alone, or csDMARD + GC + b/tsDMARDs treatment. Additionally, the study showed that the femoral neck scores of the b/tsDMARDs + MTX treatment group were higher than those of the csDMARDs + GC treatment group.

Osteoporosis is a chronic skeletal condition characterized by reduced bone density and structural degradation, which result in increased bone fragility and a heightened risk of fractures (7).

Bone remodeling is an essential physiological process regulated by pathways like RANK-RANKL, OPG and the wingless-related integration site (Wnt) signaling, which are influenced by immune cells and cytokines. In RA, elevated proinflammatory cytokines

Table 2. Demographic and laboratory parameters of the groups

	Group 1 csDMARDs n=28	Group 2 csDMARDs + GCs n=43	Group 3 csDMARDs + GCs + b/tsDMARDs n=25	Group 4 b/tsDMARDs + MTX n=25	Group 5 Healthy n=42	p-value
Age (years), mean ± SD	61.79±10.14	63.91±9.71	60.08±7.61	60.72±9.0	61.73±8.01	0.461
Weight (kg), mean ± SD	76.39±15.82	70.30±14.74	73.92±14.21	73.80±14.27	76.28±11.74	0.549
Height (meter), mean ± SD	1.58±0.07	1.58±0.06	1.59±0.05	1.59±0.06	1.58±0.04	0.731
BMI (kg/m^2), mean ± SD	30.61±5.28	28.95±5.32	28.49±5.13	28.97±4.76	30.23±4.71	0.406
Disease duration (years), mean ± SD	9.11±7.05	9.93±5.29	9.32±4.64	11.24±6.62	NA	0.568*
DAS28 score, mean ± SD	1.39±0.73	2.67±0.61	3.53±0.71	4.20±0.78	NA	**p<0.001***
Calcium (mg/dL), med. (min.-max.)	9.40 (7.60, 10.90)	9.20 (7.70, 9.70)	9.20 (7.80, 10.10)	9.15 (8.00-10.60)	9.30 (8.50-10.20)	0.420
Vitamin D (ng/dL), mean ± SD	22.50±11.62	19.12±9.47	19.18±8.31	15.76±5.04	19.25±8.40	0.115
L1-L4 T score, med. (min.-max.)	-1.3 (-2.7, 0.3)	-1.9 (-4.0, 0.8)	-1.6 (-4.4, -0.5)	-1.1 (-3.5, 1.7)	-1.1 (-4.9, 2.2)	0.015
Femoral neck T score, med. (min.-max.)	-0.85 (-3.5, 0.6)	-1.8 (-4.2, 1.2)	-1.3 (-3.8, -0.4)	-1.3 (-2.7, 1.6)	-0.95 (-2.7, 1.1)	**p<0.001**
Total hip T score, med. (min.-max.)	-0.3 (-3.5, 1.6)	-1.6 (-4.9, 1.6)	-1.0 (-3.0, 1.3)	-0.7 (-2.7, 0.6)	-0.35 (-2.8, 2.4)	**p<0.001**

*p-value for comparisons among patient subgroups. SD: Standard deviation, kg: Kilogram, m: Meter, BMI: Body mass index, N/A: Not applicable, med.: Median, min.-max.: Minimum-maximum, DAS28 score: Disease activity score 28, csDMARDs: Conventional synthetic disease-modifying anti-rheumatic drugs, GCs: Glucocorticoids, b/tsDMARDs: Biologic or targeted synthetic disease-modifying anti-rheumatic drugs, MTX: Methotrexate

such as TNF-α, IL-1β, IL-6, and IL-17 enhance osteoclastogenesis and bone resorption, contributing to bone loss (3,8).

Besides chronic systemic inflammation, the frequently lower serum vitamin D concentrations in RA patients compared to healthy individuals may exacerbate bone health deterioration (9,10). According to the literature, patients with RA generally show lower vitamin D levels compared to the control group, and these reduced levels are often associated with higher DA (11,12). However, we observed in our study similar vitamin D levels between the RA group and controls. This discrepancy may be explained by our study's retrospective nature, as some patients might have been using vitamin D supplements or related compounds either regularly and prior to their assessment.

RA treatment aims to control inflammation and prevent disease progression through various pharmacological strategies. These include non-steroidal anti-inflammatory drugs and GCs, which provide symptomatic relief. csDMARDs, such as MTX, leflunomide, HCQ, and sulfasalazine, remain the cornerstone of RA management. tsDMARDs, including JAK inhibitors like tofacitinib and baricitinib, offer a more focused approach by modulating specific intracellular signaling pathways. Furthermore, bDMARDs, including anti-TNF medications (etanercept, golimumab, adalimumab, infliximab, and certolizumab) and IL-6 inhibitors such as tocilizumab, target key cytokines in the inflammatory cascade, representing significant advancements in RA therapy (13).

Most csDMARDs used in the treatment of RA are believed to exert a beneficial impact on bone density and metabolism, primarily through their ability to suppress systemic inflammation. Despite their potential to modulate inflammation, evidence supporting the efficacy of csDMARDs in reducing bone loss remains limited (3).

In a study evaluating the effects of MTX on bone mass in patients with RA, it was found that BMD in the neck of the femur and lumbar bones remained unchanged following long-term MTX use (14). Another study found that MTX does not seem to detrimentally change BMD among premenopausal early RA patients, comparable to sulfasalazine, after 12 months of treatment (15). A study reported that HCQ use does not significantly affect the risk of osteoporosis in patients with RA (16).

Short-term GCs therapy remains part of the 2023 EULAR recommendations for RA management, with a strong emphasis on tapering and discontinuation as quickly as clinically feasible. Despite this, approximately 10% of patients continue GC use at

Table 3. Comparison of bone health status of patients in different groups

Status of bone health		Group 1 csDMARDs n=28	Group 2 csDMARDs + GCs n=43	Group 3 csDMARDs + GCs + b/tsDMARDs n=25	Group 4 b/tsDMARDs + MTX n=25	Group 5 healthy n=42
Healthy	Count	6	5	2	4	16
	Expected count	5.7	8.7	5.1	5.1	8.5
	% within grup	21.4%	11.6%	8.0%	16.0%	38.1%
	Adjusted residual	0.2	-1.6	-1.7	-0.6	3.3
Osteopenic	Count	18	23	19	18	17
	Expected count	16.3	25.1	14.6	14.6	24.5
	% within grup	64.3%	53.5%	76.0%	72.0%	40.5%
	Adjusted residual	0.7	-0.7	2.0	1.5	-2.7
Osteoporotic	Count	4	15	4	3	9
	Expected count	6.0	9.2	5.4	5.4	9.0
	% within grup	14.3%	34.9%	16.0%	12.0%	21.4%
	Adjusted residual	-1.0	2.5	-0.7	-1.3	0.0

*Fisher's exact test p-value for this analysis: 0.008. csDMARDs: Conventional synthetic disease-modifying anti-rheumatic drugs, GCs: Glucocorticoids, b/tsDMARDs: Biologic or targeted synthetic disease-modifying anti-rheumatic drugs, MTX: Methotrexate

6, 12, or even 24 months, highlighting challenges in achieving optimal disease control and discontinuing GCs in clinical practice (17). GCs disrupt bone remodeling by suppressing osteoblast function through downregulation of Wnt signaling and insulin-like growth factor-1 (IGF-1), enhancing osteoclast activity via RANKL/OPG imbalance, inducing osteocyte apoptosis, and reducing vascular endothelial growth factor (VEGF)-mediated vascular support (18). Despite this well-established and widely accepted knowledge, the influence of low-dose GCs on bone health in RA remains a topic of ongoing debate. While their use is linked to a higher risk of bone loss and fractures, they simultaneously play a critical role in mitigating systemic inflammation (19). Some randomized controlled trials have found evidence that these beneficial effects of GCs may offset their potential harm to bone health. The randomized controlled trial conducted by Haugeberg et al. (20) demonstrated a significant reduction in bone loss in the hands of RA patients treated with 7.5 mg of prednisolone daily compared to those receiving a placebo. Engvall et al. (21) observed that over a two-year follow-up, treatment with DMARDs combined with low-dose GC was more effective in preserving femoral BMD in patients with early RA compared to DMARD therapy alone. However, they also noted that this regimen failed to prevent a decline in lumbar spine BMD, particularly in postmenopausal women. In contrast, our findings indicate that GC + csDMARD therapy was linked to lower BMD scores compared to csDMARD therapy alone, especially in femur neck and total hip scores.

Abtahi et al. (22) found that low daily doses of GCs in RA patients increased vertebral fractures but not non-vertebral ones. Kroot et al. (23) highlighted that prednisone use is consistently associated with bone loss in patients with RA and underscored the importance of carefully monitoring and managing GC use to mitigate the risk of osteoporosis and other bone-related complications over time. The conflicting evidence regarding the effects of low-dose daily oral GC use on bone health in RA, coupled with the uncertainty over whether these effects are predominantly beneficial or harmful, highlights the need for a more detailed investigation of this relationship. Our study makes a significant contribution to the literature by addressing this gap and providing new insights into the dual role of GCs.

bDMARDs, particularly TNF-α inhibitors, positively impact bone health in RA by inhibiting osteoclast-mediated bone resorption and promoting osteoblast activity. TNF-α inhibitors achieve this by reducing RANKL expression, increasing OPG, and lowering the RANKL/OPG ratio, which suppresses osteoclastogenesis. Additionally, they enhance osteoblastogenesis by decreasing Dickkopf-1, a key inhibitor of bone formation (3). In their study on RA patients, Marotte et al. (24) found that over a one-year follow-up, femoral neck and spine BMD decreased in the MTX + GC treatment group, whereas the addition of infliximab to MTX + GC therapy successfully prevented bone loss. The majority of patients in both groups (over 60%) were also receiving a daily GC dose of approximately 5 mg. In line with the findings of Marotte et al. (24), our study also highlights that while

csDMARD combined with low-dose GC therapy may result in decreased BMD, the addition of BA to csDMARD and low-dose GC therapy effectively prevents bone loss. Similarly, the study by Chen et al. (25) observed that RA patients treated with csDMARDs experienced greater bone loss compared to those receiving b/tsDMARDs. Interestingly, GC use was observed in approximately 85% of patients in both groups in this study. Based on the 24-year analysis conducted by Oelzner et al. (26), RA patients with a disease duration exceeding two years displayed higher BMD when receiving biologic therapies, despite the elevated cumulative GC exposure. This study clearly indicates that biological treatments can play a protective role against the negative effects of GCs on bone. In our study, despite the use of GCs in Group 3, BMD values did not differ significantly between Group 3 and Group 4. This finding may be attributed to the potential protective effects of b/tsDMARDs on bone health.

GC drugs induce hypophosphatemia by reducing phosphate reabsorption in the kidneys (27). In contrast, vitamin D enhances phosphate absorption in both the kidneys and intestines (28). Steroid use and vitamin D deficiency are both associated with hypophosphatemia, which may contribute to increased bone resorption (27-29). However, due to the retrospective design of our study, phosphate levels were not available in the records of some patients, and these values could not be included in our analysis.

In our study, DAS28 scores, which reflect DA and the level of acute phase reactants (30), were statistically different between the groups. This variation may be attributed to differences in DA and treatment regimens among the groups. While it is expected that osteoporosis would be more prevalent in RA patients with high DAS28 scores, bone health is influenced by multiple factors, including DA, GCs' use, cDMARDs, and biologic agents, which can complicate the interpretation. The absence of a direct relationship between T-scores and DAS28 scores in our study may be a result of this multifactorial interplay of both protective and detrimental factors.

Preserved BMD levels observed in Groups 3 and 4 were thought to be associated with the use of biologic therapies. Conversely, the maintained BMD levels in Group 1 may be attributed to low DA (indicating reduced inflammation) and a relatively lower utilisation of GCs compared to other groups. Patients in Group 2, who showed significant bone loss compared to other groups, may benefit from reassessing their treatment. If there are no contraindications and the patient agrees to switch, initiating biologic therapy could help reduce the adverse effects of prolonged steroid use.

Study Limitations

Although this study provides important findings, it has some limitations. The retrospective design, small sample size, heterogeneity in treatment agents, and inadequate details about dose and duration regarding GC use and other RA treatment agents are the main study limitations. Despite patients remaining on the same treatment for at least 24 months, the study duration of approximately 10 years and the treatment switches made during this period in some patients make it difficult to present consistent data. Insufficient data on adherence to treatment and inadequate control of other osteoporosis risks, like dietary habits, physical activity levels, and the assessment of vitamin D and calcium supplementation, are additional limitations of the study. Finally, the absence of data on phosphate levels is another limitation.

CONCLUSION

BMD seems to be higher in patients receiving b/tsDMARDs, with or without GCs, compared to those receiving cDMARDs with GCs. In the context of csDMARDs treatment, the prolonged use of low-dose GCs is associated with marked adverse effects on bone health. Optimizing treatment regimens by minimizing GC exposure and incorporating b/tsDMARDs may help preserve bone health in RA patients.

Ethics

Ethics Committee Approval: This study was approved by the Clinical Research Ethics Committee of Mersin University (approval number: 2024/987, dated: 16.10.2024).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.U., A.N.D., U.G.D., Concept: A.U., A.N.D., U.G.D., Design: A.U., A.N.D., U.G.D., Data Collection or Processing: A.U., A.N.D., U.G.D., Analysis or Interpretation: A.U., A.N.D., Literature Search: A.U., A.N.D., U.G.D., Writing: A.U., A.N.D.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. Alam J, Jantan I, Bukhari SNA. Rheumatoid arthritis: recent advances on its etiology, role of cytokines and pharmacotherapy. Biomed Pharmacother. 2017;92:615-33.
2. Fardellone P, Salawati E, Le Monnier L, et al. Bone loss, osteoporosis, and fractures in patients with rheumatoid arthritis: a review. J Clin Med. 2020;9:3361.

3. Kim Y, Kim G-T. Positive effects of biologics on osteoporosis in rheumatoid arthritis. J Rheum Dis. 2023;30:3-17.
4. Shim JH, Stavre Z, Gravallese EM. Bone loss in rheumatoid arthritis: basic mechanisms and clinical implications. Calcif Tissue Int. 2018;102:533-46.
5. Prasad P, Verma S, Surbhi, et al. Rheumatoid arthritis: advances in treatment strategies. Mol Cell Biochem. 2023;478:69-88.
6. Aletaha D, Neogi T, Silman AJ, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010;62:2569-81.
7. Mauck KF, Clarke BL, editors. Diagnosis, screening, prevention, and treatment of osteoporosis. Mayo Clin Proc. 2006;81:662-72.
8. Oo WM, Naganathan V, Bo MT, Hunter DJ. Clinical utilities of quantitative ultrasound in osteoporosis associated with inflammatory rheumatic diseases. Quant Imaging Med Surg. 2018;8:100.
9. Van Schoor N, Visser M, Pluijm S, Kuchuk N, Smit J, Lips P. Vitamin D deficiency as a risk factor for osteoporotic fractures. Bone. 2008;42:260-6.
10. Pietschmann P, Butylina M, Kerschan-Schindl K, Sipos W. Mechanisms of systemic osteoporosis in rheumatoid arthritis. Int J Mol Sci. 2022;23:8740.
11. Brance ML, Brun LR, Lioi S, Sánchez A, Abdala M, Oliveri B. Vitamin D levels and bone mass in rheumatoid arthritis. Rheumatol Int. 2015;35:499-505.
12. Sharma R, Saigal R, Goyal L, et al. Estimation of vitamin D levels in rheumatoid arthritis patients and its correlation with the disease activity. J Assoc Physicians India. 2014;62:678-81.
13. Aletaha D, Smolen JS. Diagnosis and management of rheumatoid arthritis: a review. JAMA. 2018;320:1360-72.
14. di Munno O, Mazzantini M, Sinigaglia L, et al. Effect of low dose methotrexate on bone density in women with rheumatoid arthritis: results from a multicenter cross-sectional study. J Rheumatol. 2004;31:1305-9.
15. Rexhepi S, Rexhepi M, Sahatçiu-Meka V, Mahmutaj V, Boshnjaku S. The impact of low-dose disease-modifying anti-rheumatics drugs (DMARDs) on bone mineral density of premenopausal women in early rheumatoid arthritis. Med Arch. 2016;70:101.
16. Dong C, Chen BS, Wu CH, Chiu YM, Liao PL, Perng WT. Hydroxychloroquine and risk of osteoporosis in patients with rheumatoid arthritis: a population-based retrospective study of 6408 patients. Int J Rheum Dis. 2024;27:e15286.
17. Smolen JS, Landewé RB, Bergstra SA, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. Ann Rheum Dis. 2023;82:3-18.
18. Hsu CH, Hsu CL, Langley A, Wojcik C, Iraganje E, Grygiel-Górniak B. Glucocorticoid-induced osteoporosis-from molecular mechanism to clinical practice. Drugs Ther Perspect. 2024;40:315-29.
19. Dimitroulas T, Nikas SN, Trontzas P, Kitas GD. Biologic therapies and systemic bone loss in rheumatoid arthritis. Autoimmun Rev. 2013;12:958-66.
20. Haugeberg G, Strand A, Kvien TK, Kirwan JR. Reduced loss of hand bone density with prednisolone in early rheumatoid arthritis: results from a randomized placebo-controlled trial. Arch Intern Med. 2005;165:1293-7.
21. Engvall I-L, Svensson B, Tengstrand B, Brismar K, Hafström I, Group BS. Impact of low-dose prednisolone on bone synthesis and resorption in early rheumatoid arthritis: experiences from a two-year randomized study. Arthritis Res Ther. 2008;10:1-12.
22. Abtahi S, Driessen JH, Burden AM, et al. Low-dose oral glucocorticoid therapy and risk of osteoporotic fractures in patients with rheumatoid arthritis: a cohort study using the Clinical Practice Research Datalink. Rheumatology. 2022;61:1448-58.
23. Kroot EJJ, Nieuwenhuizen MG, De Waal Malefijt MC, Van Riel PL, Pasker-De Jong PC, Laan RF. Change in bone mineral density in patients with rheumatoid arthritis during the first decade of the disease. Arthritis Rheum. 2001;44:1254-60.
24. Marotte H, Pallot-Prades B, Grange L, Gaudin P, Alexandre C, Miossec P. A 1-year case-control study in patients with rheumatoid arthritis indicates prevention of loss of bone mineral density in both responders and non-responders to infliximab. Arthritis Res Ther. 2007;9:1-7.
25. Chen J-F, Hsu C-Y, Yu S-F, et al. The impact of long-term biologics/target therapy on bone mineral density in rheumatoid arthritis: a propensity score-matched analysis. Rheumatology. 2020;59:2471-80.
26. Oelzner P, Mueller P-H, Hoffmann T, et al. Significant decrease of osteoporosis and osteoporotic fractures in rheumatoid arthritis within a period of 24 years: experiences of a single centre. RMD Open. 2024;10:e004564.
27. Kinoshita Y, Masuoka K, Miyakoshi S, Taniguchi S, Takeuchi Y. Vitamin D insufficiency underlies unexpected hypocalcemia following high dose glucocorticoid therapy. Bone. 2008;42:226-8.
28. Akimbekov NS, Digel I, Sherelkhan DK, Razzaque MS. Vitamin D and phosphate interactions in health and disease. Phosphate metabolism: from Physiology to Toxicity: Springer; 2022. p. 37-46.
29. Martín AG, Varsavsky M, Berdonces MC, et al. Phosphate disorders and the clinical management of hypophosphatemia and hyperphosphatemia. Endocrinol Diabetes Nutr (Engl Ed). 2020;67:205-15.
30. Van Riel P, Renskers L. The disease activity score (DAS) and the disease activity score using 28 joint counts (DAS28) in the management of rheumatoid arthritis. Clin Exp Rheumatol. 2016;34:S40-S4.

ORIGINAL ARTICLE

Rheumatology Quarterly

DOI: 10.4274/qrheumatol.galenos.2025.20592
Rheumatol Q 2025;3(2):60-7

LONG-TERM RETENTION RATE OF CERTOLIZUMAB PEGOL IN PATIENTS WITH AXIAL SPONDYLOARTHRITIS: DATA FROM THE TURKBIO REGISTRY

Ahmet Karataş[1], Yavuz Pehlivan[2], Servet Akar[3], Soner Şenel[4], Aslıhan Avanoğlu Güler[5], Özgül Soysal Gündüz[6], Ayten Yazıcı[7], Sema Yılmaz[8], Rabia Pişkin Sağır[1], Nevsun İnanç[9], Gözde Yıldırım Çetin[10], Mehmet Pamir Atagündüz[9], Fatoş Önen[11]

[1]Fırat University Faculty of Medicine, Department of Rheumatology, Elazığ, Türkiye
[2]Uludağ University Faculty of Medicine, Department of Rheumatology, Bursa, Türkiye
[3]Katip Çelebi University Faculty of Medicine, Department of Rheumatology, İzmir, Türkiye
[4]Erciyes University Faculty of Medicine, Department of Rheumatology, Kayseri, Türkiye
[5]Gazi University Faculty of Medicine, Department of Rheumatology, Ankara, Türkiye
[6]Celal Bayar University Faculty of Medicine, Department of Rheumatology, Manisa, Türkiye
[7]Kocaeli University Faculty of Medicine, Department of Rheumatology, Kocaeli, Türkiye
[8]Selçuk University Faculty of Medicine, Department of Rheumatology, Konya, Türkiye
[9]Marmara University Faculty of Medicine, Department of Rheumatology, İstanbul, Türkiye
[10]Sütçü İmam University Faculty of Medicine, Department of Rheumatology, Kahramanmaraş, Türkiye
[11]Dokuz Eylül University Faculty of Medicine, Department of Rheumatology, İzmir, Türkiye

Abstract

Aim: Selecting the most effective treatment plan for a patient represents one of the most challenging issues in contemporary rheumatology. Clinicians must consider the long-term retention rate and the reasons for discontinuing candidate drugs.This study aimed to assess the drug survival of certolizumab pegol (CZP) in patients with axial spondyloarthritis (ax-SpA) and identify predictors for discontinuation.

Material and Methods: Data on patient characteristics, demographics, diagnosis, disease duration, treatment, and outcomes have been collected from the Turkish Biological (TURKBIO) Registry since 2011. By December 2020, 410 ax-SpA patients, treated with CZP, were included. Assessment of disease activity parameters was conducted at baseline and at regular follow-up intervals throughout the study period. Additionally, drug retention rates were evaluated through Kaplan-Meier survival analysis over the observation period.

Results: The analysis revealed that CZP demonstrates a high long-term retention rate in ax-SpA. At 36 months, the retention rate of CZP among patients with ax-SpA was 71.5%. During follow-up, 92 (22.4%) patients discontinued CZP treatment, with inefficacy being the main reason for discontinuation (58.7% of patients who discontinued therapy, n=54). Patients who discontinued CZP had significantly higher health assessment questionnaire, bath ankylosing spondylitis (AS) functional index, and bath AS disease activity index values compared to those who continued with CZP. They were relatively older, had longer symptom duration, and had a higher prevalence of

Address for Correspondence: Ahmet Karataş, Fırat University Faculty of Medicine, Department of Rheumatology, Elazığ, Türkiye
E-mail: drakaratas@yahoo.com **ORCID ID:** orcid.org/0000-0002-6725-4182
Received: 22.03.2025 **Accepted:** 03.06.2025 **Publication Date:** 25.06.2025

Cite this article as: Karataş A, Pehlivan Y, Akar S, et al. Long-term retention rate of certolizumab pegol in patients with axial spondyloarthritis: data from the TURKBIO registry. Rheumatol Q. 2025;3(2):60-7

uveitis. Compared to patients who continued with CZP, those who discontinued CZP were more frequently co-treated with non-steroidal anti-inflammatory drugs (NSAIDs) (68.5% vs. 53.1%), methotrexate (24.1% vs. 6.9%), sulfasalazine (38.9% vs. 12.6%), and leflunomide (5.6% vs. 0.6%). However, co-treatment with NSAIDs or conventional synthetic disease-modifying anti-rheumatic drugs did not increase the retention rate of CZP.

Conclusion: Real-world data from the TURKBIO registry reveal that CZP exhibits a high long-term retention rate in patients diagnosed with ax-SpA.

Keywords: Axial spondyloarthritis, certolizumab pegol, drug survival, tumor necrosis inhibitors, biological therapy

INTRODUCTION

Axial spondyloarthritis (ax-SpA) is a chronic inflammatory condition affecting the sacroiliac joints and vertebral column that can lead to irreversible disabilities (1,2). Tumor necrosis factor (TNF)-α has been demonstrated to play a significant role in ax-SpA pathogenesis (1,2). Consequently, TNF-α inhibitors (TNFi) are widely used in ax-SpA treatment (1-3). Certolizumab pegol (CZP), adalimumab, golimumab, infliximab, and etanercept represent the available TNFi options. The efficacy of these drugs has been demonstrated in randomized controlled trials (RCTs) meeting strict inclusion and exclusion criteria (1-3). However, in routine clinical practice, the presence of various comorbidities, concomitant medications, and atypical disease manifestations leads to the emergence of different patient phenotypes (4,5). Consequently, diverse sources of information are needed to confirm RCT findings.

These findings can offer valuable insights for healthcare professionals, particularly in developing effective treatment strategies for patients with ax-SpA. This topic is of particular concern for physicians due to various factors affecting the efficacy, safety, and adherence of selected therapeutic agents. Consequently, further investigation into the characteristics of patients exposed to TNFi, treatment adherence, and response rates to TNFi, is needed.

CZP has been documented to be both effective and safe in the treatment of ankylosing spondylitis (AS) and non-radiographic ax-SpA (nr-ax-SpA). Additionally, available long-term extension data of CZP in ax-SpA have been reported (6-8). The aim of this study was to evaluate drug survival of CZP in patients with ax-SpA and to determine the reasons and predictors for treatment discontinuation.

MATERIAL AND METHODS

Study Population

The Turkish Biological (TURKBIO) registry system is the Turkish version of the Danish rheumatological database (DANBIO), established in 2011. In this database, data on rheumatology patients, who will be initiated on biological treatment by many tertiary rheumatology centers across the country, are collected.

Patient characteristics, demographic features, diagnosis, disease duration, treatment, and outcome data have been collected in the TURKBIO registry system since 2011. Data extraction was performed in December 2020. Patients with ax-SpA diagnosis, ≥18 years of age, who were prescribed CZP between January 2011 and December 2020 in 11 tertiary centers of TURKBIO, were included. Approval was obtained from the Dokuz Eylül University Clinical Research Ethics Committee (approval number: 2024/02-79, date: 08.02.2024), and the study was performed in compliance with the principles outlined in the Declaration of Helsinki. All patients signed informed consent to be included in the TURKBIO registry system. The diagnosis of ax-SpA was established according to the Assessment of SpondyloArthritis international Society (ASAS) classification criteria. This study included both radiographic ax-SpA (r-ax-SpA) and nr-ax-SpA patients, with AS specifically classified according to the modified New York criteria (9,10).

Outcome Measures

The main outcome was the retention rates of CZP for ax-SpA at one, two, and three years. Reasons for discontinuing CZP were categorized as inefficacy (primary and secondary lack of response), adverse events, remission, desire for pregnancy, and patient preference. Assessment of disease activity parameters was conducted at baseline and at regular follow-up intervals throughout the study period. Disease activity and functional status were evaluated using validated assessment instruments. The bath AS disease activity index (BASDAI) was utilized to assess disease activity on a scale of 0-10, where higher scores indicate greater disease activity. This self-reported instrument encompasses six questions addressing fatigue, spinal pain, peripheral joint pain, enthesitis, and morning stiffness (both severity and duration). The bath AS functional index (BASFI) was employed to evaluate functional limitations across 10

activities related to daily living, with scores ranging from 0-10; where higher scores reflect greater functional impairment. The health assessment questionnaire (HAQ) was used as a measure of disability, consisting of 20 questions across eight domains of physical function (with scores ranging from 0-3), where higher scores indicate increased disability. All questionnaires were administered in their validated Turkish versions.

Statistical Analysis

Summary descriptive statistics were presented as means with standard deviations, medians with interquartile ranges, and percentages, as appropriate. The likelihood of survival of CZP treatment was assessed using the Kaplan-Meier survival analysis. Statistical analysis was performed using international business machines (IBM) Statistical Package for the Social Sciences Statistics for Windows, version 22 (IBM Corp., Armonk, NY, USA). The statistical significance threshold was defined as $p<0.05$, and all p-values were two-sided.

RESULTS

A total of 410 ax-SpA patients were enrolled in the study, with a median follow-up duration of 54 months. At 36 months, the retention rate of CZP among patients with ax-SpA was 71.5% (Figure 1). The long-term efficacy of CZP treatment was demonstrated by continuous improvements in ASDAS responses, BASDAI, and BASFI scores (Figure 2).

During follow-up, 92 (22.4%) patients discontinued CZP treatment. The main reason for treatment discontinuation (58.7% of patients who discontinued therapy) was inefficacy (n=54). Reasons included adverse events (n=6), surgery (n=4), pregnancy (n=3), transfer to other centers (n=3), neglect (n=3), and other reasons (n=17). Baseline characteristics of patients who continued with CZP and those who discontinued due to inefficacy are shown in Table 1.

Patients who discontinued CZP had significantly higher HAQ, BASFI, and BASDAI values compared to those who continued with CZP (Table 1). They were relatively older, had longer symptom duration, and had a higher prevalence of uveitis, compared to patients who continued with CZP.

CZP was the first biological disease-modifying anti-rheumatic drug (bDMARD) for 253 patients (61.7%), while 157 (38.3%) patients had previously used other bDMARDs. CZP was switched from adalimumab in 54 patients, etanercept in 53 patients, infliximab in 39 patients, and golimumab in 11 patients (Table 2). CZP retention rates were calculated as 77.8% for patients switching from adalimumab, 75.5% for those switching from etanercept, 63.6% for those switching from golimumab, and 89.7% for those switching from infliximab.

Compared to patients who continued with CZP, those who discontinued CZP were more frequently co-treated with non-steroidal anti-inflammatory drugs (NSAIDs) (68.5% vs. 53.1%), methotrexate (24.1% vs. 6.9%), sulfasalazine (38.9% vs. 12.6%), and leflunomide (5.6% vs. 0.6%), in addition to CZP (Table 2). However, co-treatment with NSAIDs or conventional synthetic DMARDs (csDMARDs) did not increase the retention rate of CZP. The risk of discontinuing the drug was higher when CZP was co-administered with NSAIDs or csDMARDs compared to CZP alone. This finding may be due to physicians attempting to add NSAIDs and/or csDMARDs to improve treatment adherence in anticipation of potential bDMARD treatment failure.

DISCUSSION

ax-SpA is a type of spondyloarthritis that can affect the sacroiliac joints and vertebral column, potentially leading to long-term impairments (1,2). Reducing patient complaints and preventing disabilities are the two main objectives of ax-SpA medical care. It involves the use of anti-cytokine drugs that target TNF-α and interleukin-17, as well as NSAIDs (3). The current study, which documents practical experience, indicates that CZP, a TNFi, is effective in treating ax-SpA over a considerable period.

RCTs and open-label extension studies have shown that CZP is effective in treating ax-SpA (7,8). Additionally, one-year follow-up data from a Turkish tertiary center on CZP treatment for ax-SpA was published by Bilgin et al. (6). In the first year, the CZP retention rate was 72.5%. The CZP retention rates for the study's first, second, and third years were 83.3%, 76.1%, and 71.5%, respectively. Our real-world experience demonstrates that CZP has a high retention rate in patients with ax-SpA, and that this rate holds steady over time.

The main reasons for stopping treatment were both the primary and secondary inefficacy of the medication. Because CZP was ineffective, patients who stopped taking it had significantly lower HAQ, BASDAI, and BASFI scores than those who continued to take it. These findings imply that patients with higher degrees of disability are more likely to stop their treatment. Tracking ax-SpA, including identifying patients who are appropriate for bDMARDs, is commonly done using patient-reported outcome (PRO)-based indices like HAQ, BASDAI, and BASFI (11). Furthermore, Krabbe et al. (12) demonstrated that ax-SpA patients with poor PROs had lower TNFi retention rates. It is important to keep in mind that PROs, because they can alter ax-SpA due to competing conditions like depression, fibromyalgia, and degenerative disc disease, are not pathognomonic (12,13).

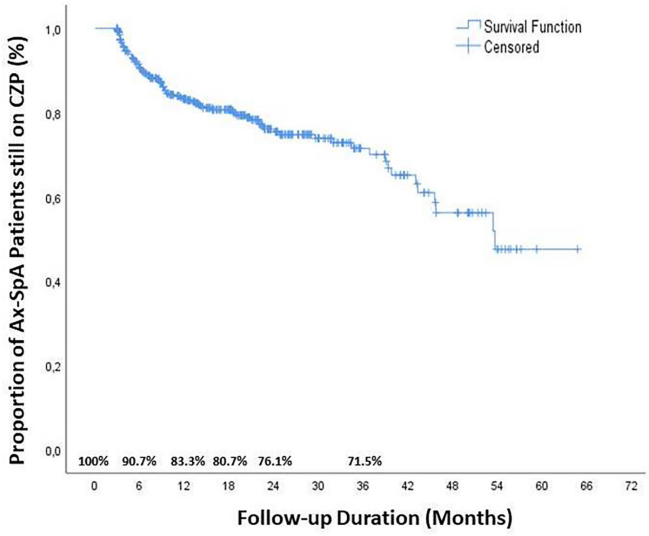

Figure 1. Drug survival of CZP in patients with ax-SpA. Kaplan-Meier survival curve showing drug retention of certolizumab pegol in 410 ax-SpA patients. The retention rate at 36 months was 71.5%. Vertical lines indicate censored data
CZP: Certolizumab pegol, ax-SpA: Axial spondyloarthritis

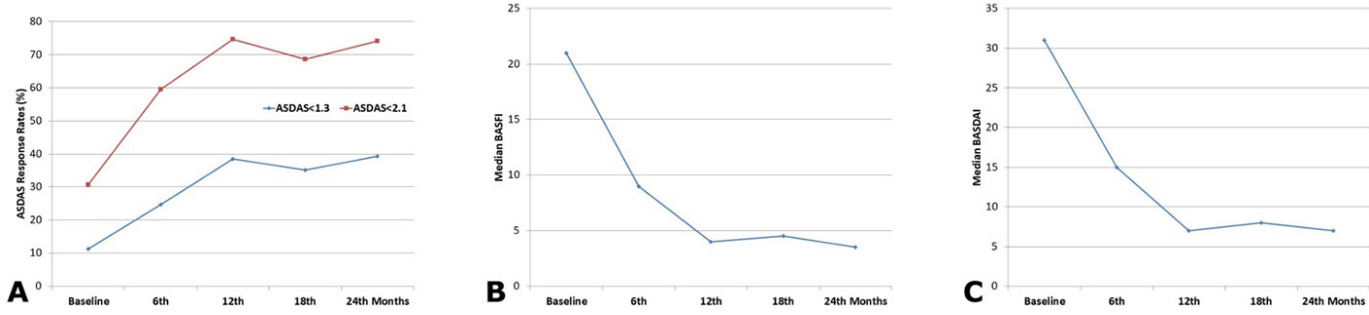

Figure 2. Clinical responses in patients with ax-SpA treated with CZP. Sustained improvements in BASDAI, BASFI and ASDAS scores in ax-SpA patients treated with CZP. Baseline BASDAI score decreased from 5.8±1.3 to 2.1±1.6 at month 36, BASFI score from 5.3±1.5 to 2.0±1.4, and ASDAS score from 3.7±0.9 to 1.8±0.8 ($p<0.001$ for all comparisons)
CZP: Certolizumab pegol, ax-SpA: Axial spondyloarthritis, BASDAI: The bath ankylosing spondylitis disease activity index, BASFI: The bath ankylosing spondylitis functional index, ASDAS: Ankylosing spondylitis disease activity score

Along with the efficacy shown in controlled clinical trials, our examination of CZP retention rates provides valuable information about the treatment's actual efficacy in ax-SpA. Landewé et al. (14) RAPID-axSpA study, was crucial in demonstrating the efficacy of CZP, as it showed significant improvements at 24 weeks in patients with both r-ax-SpA and nr-ax-SpA. Notably, only 38.3% and 19.8% of patients treated with a placebo received ASAS20 and ASAS40 responses, compared to 57.7% and 43.1% of patients treated with CZP, respectively.

Additional supporting information is provided by Deodhar et al. (8), who conducted a 52-week randomised placebo-controlled study with an emphasis on nr-ax-SpA. Their study found that by week 52, 47.2% of patients treated with CZP had significantly improved their ASDAS scores (ASDAS-MI), compared to only 7.0% of the placebo group. As a result, even in the early stages of ax-SpA, CZP is now thought to be helpful.

In our study, patients who had more functional limitations were more likely to stop taking CZP. The findings of López-Medina et al. (15), who observed that certain comorbidities, specifically fibromyalgia and depression, were linked to lower TNFi survival in ax-SpA patients across European registries, seem to be consistent with these observations. The authors of the study proposed a "comorbidity burden index" as a possible instrument to assist physicians in determining the probability of TNFi persistence in patients with ax-SpA.

Table 1. Baseline characteristics of ax-SpA patients who continue and discontinue to CZP

	All patients (n=410)	Continue to CZP (n=318)	Discontinue to CZP‡ (n=54)	p-value
Females, n (%)	185 (49.7)	157 (49.4)	28 (51.9)	0.736
Age*, years	42 (34-49)	41 (34-49)	45 (34-54)	0.064
Disease duration*, years	8 (5-12)	8 (5-12)	8 (6-14)	0.128
Symptom duration*, years	11 (7-17)	11 (6-16)	12 (8.5-20)	0.054
HLA-B27, n (%)	150 (63.8)	129 (64.5)	21 (60)	0.609
Enthesitis, n (%)	228 (61.3)	201 (63.2)	27 (50)	0.065
Dactylitis, n (%)	40 (10.8)	34 (10.7)	6 (11.1)	0.927
Uveitis, n (%)	38 (10.2)	29 (9.1)	9 (16.7)	0.090
IBD, n (%)	20 (6)	15 (5.2)	5 (10.6)	0.177
ESR*, mm/h	21.5 (10-37)	21 (10-37)	23 (10-34)	0.999
CRP*, mg/dL	7 (3-20)	7 (3-20)	7 (3-22)	0.727
HAQ*	**0.63 (0.25-0.94)**	**0.5 (0.25-0.88)**	**0.75 (0.38-1.25)**	**0.009**
VAS-physicians*	20 (10-40)	19 (10-40)	25 (10-36)	0.468
VAS-patient global*	50 (21-70)	50 (20-70)	54 (36-70)	0.156
VAS-patient pain*	50 (20-70)	50 (20-70)	51 (40-73)	0.080
VAS-patient fatigue*	50 (20-70)	48 (17.5-70)	50 (27-70)	0.223
BASFI*	21 (7-45)	20.5 (6-41)	31 (13-58)	0.011
BASDAI*	30.5 (13-52)	30 (12-50)	43 (23-61.5)	0.002
ASDAS*	2.7 (1.8-3.7)	2.7 (1.8-3.6)	2.9 (2.3-4)	0.062

‡Discontinue due to inefficacy. *Data are expressed as median (IQR1-IQR3). ASDAS: Ankylosing spondylitis disease activity score, ax-SpA: Axial spondyloarthritis, BASDAI: The bath ankylosing spondylitis disease activity index, BASFI: The bath ankylosing spondylitis functional index, CRP: C-reactive protein, CZP: Certolizumab pegol, ESR: Erythrocyte sedimentation rate, HAQ: Health assessment questionnaire, HLA: Human leukocyte antigen, IBD: Inflammatory bowel disease, IQR: Interquartile range; VAS: Visual analog scale

Table 2. Previous bDMARDs and co-administered treatments in ax-SpA patients who continue and discontinue CZP

	All patients (n=410)	Continue to CZP (n=318)	Discontinue to CZP* (n=54)	p-value
Previous bDMARDs, n (%)				
Adalimumab	54 (14.5)	42 (13.2)	12 (22.2)	0.082
Etanercept	53 (14.2)	40 (12.6)	13 (24.1)	0.025
Golimumab	11 (3)	7 (2.2)	4 (7.4)	0.060
Infliximab	39 (10.5)	35 (11)	4 (7.4)	0.425
Co-treated drugs, n (%)				
NSAID	206 (55.4)	169 (53.1)	37 (68.5)	0.036
Analgesics	136 (36.6)	113 (35.5)	23 (42.6)	0.319
Methotrexate	35 (9.4)	22 (6.9)	13 (24.1)	<0.001
Sulphasalazine	61 (16.4)	40 (12.6)	21 (38.9)	<0.001
Leflunomide	5 (1.3)	2 (0.6)	3 (5.6)	0.023
Glucocorticosteroids	12 (3.2)	8 (2.5)	4 (7.4)	0.080

ax-SpA: Axial spondyloarthritis, bDMARDs: Biological disease-modifying antirheumatic drugs, CZP: Certolizumab pegol, NSAID: Non-steroidal anti-inflammatory drug

In comparison with patients who continued to receive CZP, those who ceased treatment were more likely to be co-treated with NSAIDs, methotrexate, sulfasalazine, and leflunomide. However, concomitant treatment with NSAIDs or csDMARDs did not result in an increased retention rate of CZP. For ax-SpA, the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network advises against the routine prescription of csDMARDs (3). However, physicians may elect to administer NSAIDs and/or csDMARDs in cases where they predict that bDMARD treatment will prove ineffective.

This observation gives rise to a number of significant inquiries regarding treatment strategy. The most recent ASAS-European League Against Rheumatism recommendations (16), reaffirm the absence of sufficient evidence to support the conventional co-prescription of csDMARDs alongside TNFi in cases of axial illness. In addition to the use of combinations of pharmaceuticals, the results of the present study emphasise the importance of the patient's previous treatment history in the prediction of outcomes. The observations presented herein are in alignment with the existing research, which has indicated that prior treatment response and disease activity are associated with the long-term retention of biological agents. A study conducted by Glintborg et al. (17) utilised the DANBIO registry system to analyse 432 individuals with AS. The objective of the study was to investigate parameters influencing clinical response and medication survival after switching TNFi therapy. The findings demonstrated that the survival rate of a second TNFi was significantly reduced in patients who discontinued the first TNFi due to inefficacy, in contrast to those who terminated it due to adverse effects.

Lie et al. (18) indicated that concomitant administration of csDMARDs, such as methotrexate and sulfasalazine, correlated with improved retention of TNFi therapy in AS. A recent study indicated that concurrent methotrexate administration was linked to a reduced likelihood of medication discontinuation in psoriatic arthritis, but not in ax-SpA (19). Sepriano et al. (20) reported that the co-administration of csDMARDs or NSAIDs was not linked to the drug survival of TNFi in the treatment of ax-SpA. Methotrexate and leflunomide may be favoured due to their anticipated effects on immunogenicity, which is regarded as a factor contributing to the inefficacy of bDMARDs. Sulfasalazine has been demonstrated to have no influence on immunogenicity and has been found to be efficacious in the treatment of peripheral spondyloarthritis, but not in ax-SpA. In the present investigation, concomitant use of CZP with sulfasalazine, methotrexate, and leflunomide did not correlate with enhanced retention rates of CZP in ax-SpA.

The findings of the present study are in alignment with those of recent research conducted by Ørnbjerg et al. (5), which examined over 24,000 biologic-naïve ax-SpA patients from 12 European registries within the EuroSpA collaboration. The study revealed that prior TNFi treatment correlated with diminished drug survival rates and responses to subsequent TNFi therapies. This suggests that the quantity of previously unsuccessful TNFi treatments serves as a significant predictor of future treatment outcomes. Furthermore, Ciurea et al. (21) established that the failure mechanism of the prior TNFi, whether primary or secondary, is crucial in ascertaining the efficacy of transitioning to an alternative TNFi. Their research on ax-SpA patients from the Swiss Clinical Quality Management Cohort indicated that those with primary non-response exhibited markedly reduced response rates to a subsequent TNFi compared to those with secondary non-response.

The immunogenic nature of CZP necessitates particular consideration when analysing the findings of this study. CZP is a polyethylene glycosylated fragment antigen-binding fragment of a humanised anti-TNF monoclonal antibody, which may influence its immunogenicity profile. Nesbitt et al. (22) demonstrated that CZP exhibits lower immunogenicity relative to other monoclonal antibody TNFi treatments, which may partially elucidate the favourable retention rates noted in this group. The absence of the fragment crystallized region in CZP may be responsible for its reduced immunogenicity profile, as demonstrated in vitro comparisons with other anti-TNF alpha drugs.

The results of the present study carry significant implications for clinical practice. The three-year retention rate of CZP in ax-SpA patients is 71.5%, indicating that CZP may serve as a viable long-term treatment option. The observations made in this study indicate a potential relationship between baseline disease activity, functional limitations, and treatment outcomes. These observations suggest that early intervention with appropriate therapy may help prevent progressive functional decline. The patterns observed in the present study subtly emphasise the possible advantages of prompt therapeutic interventions in preserving patient functionality over time. A treat-to-target strategy that seeks low disease activity or remission within the initial 3-6 months, as proposed by Landewé et al. (23), may enhance long-term outcomes. The observation that co-treatment with csDMARDs did not enhance CZP retention suggests that clinicians must thoroughly assess the risk-benefit ratio associated with combination therapy. This is of particular

significance when considering the findings of Sepriano et al. (16), whose prospective cohort study on this topic demonstrated variable outcomes associated with the combination of TNFi and csDMARDs in patients with spondyloarthritis. The combination of these treatments may offer potential benefits for patients with peripheral involvement; however, the addition of csDMARDs has demonstrated only limited net clinical advantages in cases of purely axial disease. It is imperative that potential adverse effects be taken into consideration during risk-benefit evaluations.

If bDMARD treatment for ax-SpA does not yield the desired results or causes adverse effects, switching to an alternative bDMARD option is recommended (3). While the optimal bDMARD selection is yet to be determined, this presents a significant opportunity for clinicians to refine their decision-making processes. As is thoroughly documented, the efficacy and retention rates of bDMARDs can vary according to the number of previous treatments.

Limitations

This study has several limitations due to its observational design, including potential selection bias and unmeasured confounders. The registry lacks comprehensive data on certain variables, such as socioeconomic factors, that may influence treatment adherence. In addition, the sample size limited the robustness of subgroup analyses, and radiographic progression data, critical for assessing structural outcomes, were not available.

CONCLUSION

A multitude of positive factors influence drug retention, including long-term efficacy, safety, patient adherence, and ease of administration. A study of real-world data from the nationwide TURKBIO registry in Türkiye has demonstrated that CZP exhibits a noteworthy long-term retention rate in patients diagnosed with ax-SpA. The analysis indicates that baseline disease activity and functional status are pertinent factors in assessing treatment patterns involving CZP. The findings of this study indicate that the combination of NSAIDs and csDMARDs may not enhance CZP retention rates in patients exhibiting difficult prognostic indicators. These insights have the potential to refine clinical approaches and inform future discussions regarding individualised treatment planning for patients with ax-SpA.

Ethics

Ethics Committee Approval: The data for this study were sourced from the TURKBIO registry, which serves as the Turkish equivalent of the DANBIO. The TURKBIO database project has been designated as a Phase IV observational study by the Dokuz Eylül University Clinical Research Ethics Committee (approval number: 2024/02-79, date: 08.02.2024). This ensures that the project adheres to the ethical norms that are in place for clinical research.

Informed Consent: A written informed consent was obtained from the participants.

Footnotes

Authorship Contributions

Concept: A.K., Design: A.K., Data Collection or Processing: A.K., Y.P., S.A., S.Ş., A.A.G., Ö.S.G., A.Y., S.Y., N.İ., G.Y.Ç., M.P.A., F.Ö., Analysis or Interpretation: A.K., R.P.S., Literature Search: A.K., R.P.S., Writing: A.K.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. Sieper J, Braun J, Dougados M, Baeten D. Axial spondyloarthritis. Nat Rev Dis Primers. 2015;1:15013.
2. Sieper J, Poddubnyy D. Axial spondyloarthritis. Lancet. 2017;390:73-84.
3. Ward MM, Deodhar A, Gensler LS, et al. 2019 update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network recommendations for the treatment of ankylosing spondylitis and non-radiographic axial spondyloarthritis. Arthritis Care Res (Hoboken). 2019;71:1285-99.
4. Zink A, Askling J, Dixon WG, Klareskog L, Silman AJ, Symmons DP. European biologicals registers: methodology, selected results and perspectives. Ann Rheum Dis. 2009;68:1240-6.
5. Ørnbjerg LM, Brahe CH, Askling J, et al. Treatment response and drug retention rates in 24 195 biologic-naïve patients with axial spondyloarthritis initiating TNFi treatment: routine care data from 12 registries in the EuroSpA collaboration. Ann Rheum Dis. 2019;78:1536-44.
6. Bilgin E, Farisoğulları B, Armağan B, et al. Predictors of drug retention and treatment response in axial spondyloarthritis patients treated with bDMARD certolizumab: real-life results from the HURBIO registry. Clin Exp Rheumatol. 2020;38:609-14
7. van der Heijde D, Dougados M, Landewé R, et al. Sustained efficacy, safety and patient-reported outcomes of certolizumab pegol in axial spondyloarthritis: 4-year outcomes from RAPID-axSpA. Rheumatology (Oxford). 2017;56:1498-509.
8. Deodhar A, Gensler LS, Kay J, et al. A fifty-two-week, randomized, placebo-controlled trial of certolizumab pegol in nonradiographic axial spondyloarthritis. Arthritis Rheumatol. 2019;71:1101-11.

9. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum. 1984;27:361-8.

10. Rudwaleit M, van der Heijde D, Landewé R, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis. 2009;68:777-83.

11. van der Heijde D, Ramiro S, Landewé R, et al. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. Ann Rheum Dis. 2017;76:978-91.

12. Krabbe S, Glintborg B, Østergaard M, Hetland ML. Extremely poor patient-reported outcomes are associated with lack of clinical response and decreased retention rate of tumour necrosis factor inhibitor treatment in patients with axial spondyloarthritis. Scand J Rheumatol. 2019;48:128-32.

13. Bello N, Etcheto A, Béal C, Dougados M, Moltó A. Evaluation of the impact of fibromyalgia in disease activity and treatment effect in spondyloarthritis. Arthritis Res Ther. 2016;18:42.

14. Landewé R, Braun J, Deodhar A, et al. Efficacy of certolizumab pegol on signs and symptoms of axial spondyloarthritis including ankylosing spondylitis: 24-week results of a double-blind randomised placebo-controlled phase 3 study. Ann Rheum Dis. 2014;73:39-47.

15. López-Medina C, Molto A, Sieper J, et al. Prevalence and distribution of peripheral musculoskeletal manifestations in spondyloarthritis including psoriatic arthritis: results of the worldwide, cross-sectional ASAS-PerSpA study. RMD Open. 2021;7:e001450.

16. Ramiro S, Nikiphorou E, Sepriano A, et al. ASAS-EULAR recommendations for the management of axial spondyloarthritis: 2022 update. Ann Rheum Dis. 2023;82:19-34.

17. Glintborg B, Østergaard M, Krogh NS, et al. Clinical response, drug survival and predictors thereof in 432 ankylosing spondylitis patients after switching tumour necrosis factor α inhibitor therapy: results from the Danish nationwide DANBIO registry. Ann Rheum Dis. 2013;72:1149-55.

18. Lie E, Kristensen LE, Forsblad-d'Elia H, et al. The effect of comedication with conventional synthetic disease modifying antirheumatic drugs on TNF inhibitor drug survival in patients with ankylosing spondylitis and undifferentiated spondyloarthritis: results from a nationwide prospective study. Ann Rheum Dis. 2015;74:970-8.

19. Favalli EG, Selmi C, Becciolini A, et al. Eight-year retention rate of first-line tumor necrosis factor inhibitors in spondyloarthritis: a multicenter retrospective analysis. Arthritis Care Res (Hoboken). 2017;69:867-74.

20. Sepriano A, Ramiro S, van der Heijde D, et al. Effect of comedication with conventional synthetic disease-modifying antirheumatic drugs on retention of tumor necrosis factor inhibitors in patients with spondyloarthritis: a prospective cohort study. Arthritis Rheumatol. 2016;68:2671-9.

21. Ciurea A, Finckh A, Ciurea AS, et al. Does the reason for discontinuation of a first TNF inhibitor influence the effectiveness of a second TNF inhibitor in axial spondyloarthritis? Results from the Swiss Clinical Quality Management Cohort. Arthritis Res Ther. 2016;18:71.

22. Nesbitt A, Fossati G, Bergin M, et al. Mechanism of action of certolizumab pegol (CDP870): in vitro comparison with other anti-tumor necrosis factor alpha agents. Inflamm Bowel Dis. 2007;13:1323-32.

23. Landewé RBM, van der Heijde D, Dougados M, et al. Maintenance of clinical remission in early axial spondyloarthritis following certolizumab pegol dose reduction. Ann Rheum Dis. 2020;79:920-8.

CASE REPORT AND LITERATURE REVIEW

Rheumatology Quarterly

DOI: 10.4274/qrheumatol.galenos.2025.94830
Rheumatol Q 2025;3(2):68-70

SYSTEMIC SCLEROSIS PRESENTING AS A PARANEOPLASTIC SYNDROME IN RENAL CELL CARCINOMA: A RARE CASE REPORT

Ahmet Kor

Aksaray Education and Research Hospital, Clinic of Rheumatology, Aksaray, Türkiye

Abstract

Systemic Sclerosis (SSc) is a chronic autoimmune disease of unknown aetiology characterized by vasculopathy and organ fibrosis. Renal cell carcinoma (RCC) is associated with paraneoplastic syndromes. RCC has been reported in association with paraneoplastic SSc, and eight cases have been reported since 1992 to date. In this case, we present a patient with SSc who showed rapid systemic progression within a period of 6 months. A mass was detected in the left kidney on imaging two months after the diagnosis of SSc, and the patient underwent a left partial nephrectomy. The histopathology of the mass was consistent with RCC. Despite intensive treatment, the patient developed progressive SSc involvement in the skin, lungs, and gastrointestinal tract within 6 months after the diagnosis of SSc. This case report emphasizes that SSc, which progresses with rapid and widespread systemic organ involvement, can occur as a paraneoplastic syndrome and that there should be a high suspicion for underlying malignant diseases in such cases.

Keywords: Paraneoplastic syndrome, renal cell carcinoma, systemic sclerosis

Introduction

Systemic Sclerosis (SSc) is a chronic autoimmune disease of unknown aetiology, characterized by vasculopathy and organ fibrosis. Multiple factors, such as genetic, environmental, infectious, and hormonal factors, are responsible for the disease's development. Previous studies have reported the association of paraneoplastic SSc with various neoplasms, especially breast, lung, and skin malignancies (1). However, the incidence of paraneoplastic SSc together with renal cell carcinoma (RCC) is quite rare, and only eight cases have been reported to date (1-8).

Case Report

We present a 68-year-old female patient who showed rapid SSc systemic involvement within 6 months under treatment with 15 mg/week oral methotrexate, 4 mg/day prednisone, 200 mg/day hydroxychloroquine, 100 mg/day acetylsalicylic acid, and 60 mg/day nifedipine. At the time of diagnosis, the patient had sclerodactyly, skin hardness, avascular areas, and dilated capillaries on capillaroscopy. There was no dysphagia, exertional dyspnea, or orthopnea. Laboratory values showed an anti-nuclear antibody nucleolar staining pattern of 1/3200 (++++) titer and positivity for an anti-scl70 (++++) titer. The patient developed abdominal pain 2 months after the diagnosis of SSc. Abdominal computed tomography (CT) (Figure 1), and subsequent positron emission tomography revealed a 32x14 mm mass with high fluorodeoxyglucose uptake in the left kidney. The pathology of the patient who underwent left partial nephrectomy was consistent with clear cell RCC. In histopathological examination, no tumour tissue or

Address for Correspondence: Ahmet Kor, Aksaray Education and Research Hospital, Clinic of Rheumatology, Aksaray, Türkiye
E-mail: ahmetkor_61@hotmail.com **ORCID ID:** orcid.org/0000-0002-5794-6951
Received: 20.05.2025 **Accepted:** 12.06.2025 **Publication Date:** 25.06.2025

Cite this article as: Kor A. Systemic sclerosis presenting as a paraneoplastic syndrome in renal cell carcinoma: a rare case report. Rheumatol Q. 2025;3(2):68-70

lymphovascular invasion was detected in the surgical margins of the tissue.

SSc systemic involvement developed in the skin, renal, pulmonary, and gastrointestinal (GI) systems over the specified periods. Digital ulcers increased, skin hardness extended to the elbow, effort dyspnea progressed, and uncontrolled hypertension and dysphagia developed. High-resolution CT showed lung involvement in a non-specific interstitial pneumonia pattern and dilated oesophagus. Despite 2 g/day mycophenolate mofetil treatment, the patient's GI and pulmonary system involvement progressed, and the patient reached a stage where she could no longer tolerate oral feeding. Despite 2 g/day mycophenolate mofetil treatment, the patient's GI and pulmonary system involvement progressed, and they became unable to tolerate oral feeding. Percutaneous endoscopic gastrostomy was performed; nutritional needs were met; and monthly cyclophosphamide treatment was started. The patient is being followed up during the third month of a monthly 1000 mg cyclophosphamide treatment course without progression of SSc complications.

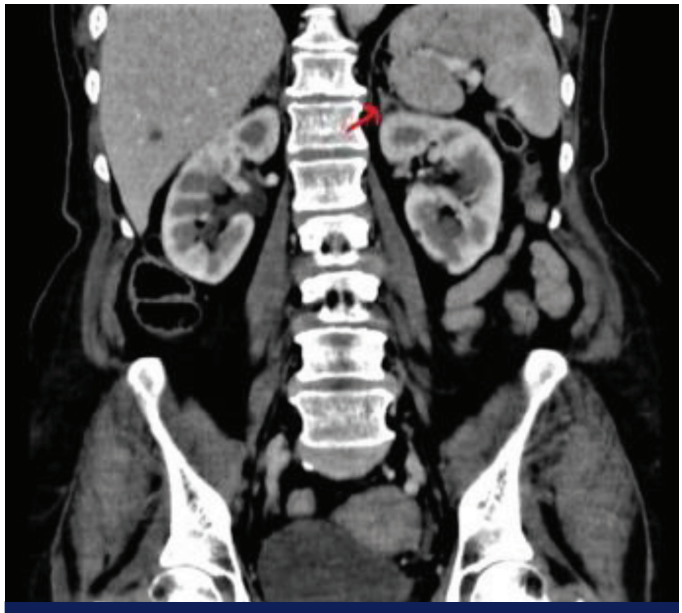

Figure 1. Contrast-enhanced abdominal computed tomography shows a 32x14 mm heterogeneously enhancing nodular lesion with exophytic extension in the upper pole of the left kidney (RCC)

RCC: Renal cell carcinoma

Discussion

This case report was prepared to emphasize that it may present as a paraneoplastic syndrome in RCC. In our case, shortly after the diagnosis of SSc, a complaint of abdominal pain developed, and RCC was subsequently detected on radiological imaging. In this case, SSc was considered a paraneoplastic syndrome of RCC. The patient underwent successful tumour resection. However, despite aggressive treatment, rapid progression occurred in the systemic organ involvement of SSc. Similar to our results, rapid progression occurred in the systemic involvement of SSc after nephrectomy, as reported in the literature, in some cases (1,2,6). At the same time, improvement in the clinical symptoms of SSc was observed after nephrectomy in some cases (3-5). Some reports indicated that RCC developed after a more extended period (approximately 2 years) after the diagnosis of SSc compared to our case (9). Table 1 shows literature studies reporting paraneoplastic SSc in RCC.

In this report, we emphasized the presence of underlying malignancies, especially in treatment-resistant cases, where the time between SSc diagnosis and systemic involvement is short. However, more research is needed on the importance of the close temporal relationship between RCC and the clinical

Table 1. Literature studies reporting paraneoplastic SSc seen in RCC

Age	Gender	RCC subtype	Timing of RCC to SSc onset	SSc outcome after nephrectomy	Reference*
68	Female	Clear cell	After 2 months	Progress	Our case
75	Male	Papillary	After 1 months	Progress	Patel et al. (1)
49	Female	Clear cell	After 7 months	Progress	Rutherford et al. (2)
55	Male	Unknown	After 14 months	Improvement	Nunez et al. (5)
75	Female	Unclassified type	3 months after progression of existing SSc	Improvement	Abrich et al. (4)
69	Male	Unknown	Unknown	Improvement	Angulo et al. (3)
31	Female	Unknown	After progression of existing SSc	Progress	Puett and Fuchs (6)
33	Female	Conventional type	After progression of existing SSc	Unknown	Eisenberg et al. (8)
37	Female	Conventional type	After progression of existing SSc	Unknown	Eisenberg et al. (8)

*Exponents indicate the reference number. RCC: Renal cell carcinoma, SSc: Systemic sclerosis

onset of SSc. Further studies in this area may provide insights into the pathogenesis of paraneoplastic SSc, which is especially prevalent in RCC. Furthermore, additional studies should clarify whether SSc is a paraneoplastic syndrome in RCC or a disease predisposing to RCC.

Conclusion

This case report emphasizes the need to investigate underlying malignant diseases in the presence of SSc, that are resistant to treatment and progress with organ involvement. Good recognition of paraneoplastic SSc that develops based on malignancy may provide early and practical approaches for diagnosing and treating severe systemic involvements such as pulmonary hypertension, malignant hypertension, interstitial lung disease, and GI involvement that may occur during the disease.

Ethics

Informed Consent: The Declaration of Helsinki was adhered to during the patient's treatment. The patient gave consent for all treatments and other procedures. The patient permitted publication as a case report.

Footnotes

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Patel HS, Aggarwal V, Thapa R. Scleroderma associated with renal cell carcinoma: a case report and literature review. J Scleroderma Relat Disord. 2021;6:316-9.
2. Rutherford P, Davison A, Ringrose T, Morley A, Tapson J. Rapidly progressive systemic sclerosis and acute renal failure associated with a renal cell carcinoma. Nephrol Dial Transplant. 1994;9:1797-9.
3. Angulo J, Lopez J, Flores N. Urologic malignancies and progressive systemic sclerosis. Minerva Urol Nefrol. 1993;45:19-22.
4. Abrich V, Duvuru S, Swanson HJ. Limited scleroderma with pauci-immune glomerulonephritis in the presence of renal cell carcinoma. Clin Med Res. 2013;11:117-9.
5. Nunez S, Konstantinov K, Servilla K, et al. Association between scleroderma, renal cell carcinoma and membranous nephropathy. Clin Nephrol. 2009;71:63-8.
6. Puett D, Fuchs H. Rapid exacerbation of scleroderma in a patient treated with interleukin 2 and lymphokine activated killer cells for renal cell carcinoma. J Rheumatol. 1994;21:752-3.
7. Ruffilli F, Padovan M, Ciancio G, Venturelli V, Maranini B, Govoni M. Scleroderma as paraneoplastic disease: a new case of a rare association with renal cell carcinoma. J Scleroderma Relat Disord. 2021;6:330.
8. Eisenberg ME, Sunkureddi PR, Baethge BA, Gonzalez EB, McNearney TA. Unusual occurrence of renal cell carcinoma (RCC) diagnosed in 2 young hispanic patients with diffuse systemic sclerosis (dSSc). J Clin Rheumatol. 2007;13:363-4.
9. Shah AA, Hummers LK, Casciola-Rosen L, Visvanathan K, Rosen A, Wigley FM. Examination of autoantibody status and clinical features associated with cancer risk and cancer-associated scleroderma. Arthritis Rheumatol. 2015;67:1053-61.

CASE REPORT AND LITERATURE REVIEW

Rheumatology Quarterly

DOI: 10.4274/qrheumatol.galenos.2025.98598
Rheumatol Q 2025;3(2):71-3

EXTREMELY HIGH-DOSE COLCHICINE INTOXICATION WITH NEUROLOGICAL COMPLICATIONS: A SURVIVAL CASE REPORT

Ömer Yıldırım[1], Fatih Albayrak[2], Orhan Zengin[2]

[1]Gaziantep University Faculty of Medicine, Department of Internal Medicine, Gaziantep, Türkiye
[2]Gaziantep University Faculty of Medicine, Department of Rheumatology, Gaziantep, Türkiye

Abstract

Familial Mediterranean fever (FMF) is an autoinflammatory disease with autosomal recessive inheritance, associated with *mediterranean fever* gene mutation, characterized by recurrent episodes of fever, serositis, and arthritis. Colchicine is the gold standard treatment but has a narrow therapeutic index. A 19-year-old male with FMF presented with abdominal pain, weakness, nausea, and vomiting after accidental ingestion of approximately 100 colchicine tablets in a suicide attempt. He developed multi-organ dysfunction, including acute kidney injury (creatinine: 2.33 mg/dL), hepatotoxicity (aspartate aminotransferase: 678 U/L), rhabdomyolysis (creatine kinase: 9996 U/L), and severe pancytopenia (white blood cell count: 710/µL, platelet count: 15,000/µL). Neurological complications included decreased consciousness, apathetic speech, and ataxia. The patient was managed in the intensive care unit with aggressive supportive therapy including intravenous hydration, broad-spectrum antibiotics, and granulocyte colony-stimulating factor (filgrastim) for bone marrow suppression. After 4 days, pancytopenia resolved, and organ functions gradually improved. The patient made a complete recovery. This case demonstrates that survival is possible even after extremely high-dose colchicine ingestion with appropriate supportive care. Close monitoring and patient education are crucial in FMF management to prevent toxicity.

Keywords: Familial Mediterranean fever, colchicine intoxication, creatine kinase

Introduction

Familial Mediterranean fever (FMF) is an autoinflammatory disease with autosomal recessive inheritance that is prevalent among populations originating from the Mediterranean basin. It is associated with mutations in the *mediterranean fever (MEFV)* gene located on chromosome 16. The disease is characterized by recurrent episodes of fever, peritonitis, pleuritis, arthritis, and rarely pericarditis lasting 1-3 days (1). In the pathogenesis of FMF, dysfunction of the pyrin protein encoded by the *MEFV* gene results in abnormal activation of inflammasomes and increased production of interleukin-1 beta (2).

Colchicine is the gold standard in the treatment of FMF, effective in reducing the frequency and severity of attacks and preventing complications such as amyloidosis. However, colchicine has a narrow therapeutic index, and overdose can lead to gastrointestinal symptoms, hepatorenal dysfunction, bone marrow suppression, and neurological disorders (3,4).

Address for Correspondence: Fatih Albayrak, MD, Gaziantep University Faculty of Medicine, Department of Rheumatology, Gaziantep, Türkiye
E-mail: drfalbayrak@yahoo.com **ORCID ID:** orcid.org/0000-0002-6052-3896
Received: 21.04.2025 **Accepted:** 12.06.2025 **Publication Date:** 25.06.2025

Cite this article as: Yıldırım Ö, Albayrak F, Zengin O. Extremely high-dose colchicine intoxication with neurological complications: a survival case report. Rheumatol Q. 2025;3(2):71-3

Case Report

A 19-year-old male patient with a known diagnosis of FMF presented to the emergency department with complaints of abdominal pain, generalized weakness, nausea, and vomiting persisting for three days. His medical history revealed that due to insufficient response to the standard colchicine dosage, he had been prescribed an imported colchicine preparation at a dosage of 2×1 tablets daily. However, the patient had been taking it at a dosage of 4×1 daily.

Physical examination revealed tenderness in all quadrants of the abdomen with guarding and rebound. Diagnostic imaging, including upright abdominal radiography and posterior-anterior chest radiography, showed no pathology. Abdominal computed tomography (CT) demonstrated jejunal loop dilatation up to 3.7 cm with air-fluid levels, but no signs of perforation were detected. Laboratory tests revealed C-reactive protein: 175 mg/L; creatinine: 2.33 mg/dL; aspartate aminotransferase: 678 U/L; alanine aminotransferase: 189 U/L; alkaline phosphatase: 401 U/L; gamma-glutamyl transferase: 30 U/L; amylase: 338 U/L; lipase: 183 U/L; creatine kinase: 9996 U/L; white blood cell count: 710/μL (0.71×10^3/μL); neutrophil count: 410/μL (0.41×10^3/μL); and platelet count: 15,000/μL (15×10^3/μL). The patient was admitted to the rheumatology service due to acute kidney injury, FMF attack, and elevated acute phase reactants.

During his hospital course, the patient's general condition deteriorated with the development of agitation, and he subsequently was admitted to having ingested approximately 100 tablets of imported colchicine in a suicidal attempt. He developed a decrease in the Glasgow Coma Scale score, apathetic speech, and ataxia. Cranial CT and diffusion-weighted magnetic resonance imaging showed no pathology. Central nervous system infection was excluded via lumbar puncture.

Due to clinical deterioration, the patient was transferred to the intensive care unit. Muscle strength was evaluated as 2/5 bilaterally in the upper and lower extremities. He developed pancytopenia secondary to bone marrow suppression, and filgrastim therapy was initiated. The pancytopenic state resolved after 4 days. With intravenous hydration, a broad-spectrum antibiotic therapy, and supportive care, renal and hepatic function improved, hematological parameters recovered, and the patient was transferred back to the rheumatology service.

Discussion

The clinical course of colchicine intoxication can be examined in three phases as described in the literature: gastrointestinal symptoms in the first 24 hours, multi-organ failure between 24 to 72 hours, and rebound leukocytosis, or bone marrow aplasia after 72 hours (5). This classic triphasic course was observed in our case.

Bismuth et al. (6) described a case of a 23-year-old FMF patient who developed hepatorenal failure and myelosuppression following ingestion of 60 colchicine tablets. Similar to the symptoms observed in our patient, gastrointestinal symptoms were predominant in the early phase, followed by the development of multi-organ dysfunction.

In a series reported by Finkelstein et al. (7), among 12 FMF patients with colchicine intoxication, pancytopenia developed in 83%, hepatic dysfunction in 75%, and acute kidney injury in 58%. Rhabdomyolysis is reported to be common in cases of colchicine toxicity. This study supports the view that the clinical presentation observed in our case is consistent with the typical course of colchicine intoxication.

Myelosuppression is one of the most serious complications of colchicine toxicity and has been closely associated with mortality in the literature. Critchley et al. (8) demonstrated that granulocyte colony-stimulating factor (G-CSF) therapy in patients with colchicine intoxication shortened the neutrophil recovery time by an average of 4 days and reduced infectious complications. The successful management of bone marrow suppression with filgrastim (G-CSF) therapy in our case is consistent with these findings.

In a case presented by Altiparmak et al. (9), neurological complications (mental status changes, ataxia) were described in a patient who ingested colchicine exceeding 0.5 mg/kg. Similarly, in our case, neurological findings such as decreased Glasgow Coma Scale, apathetic speech, and ataxia, were observed, although no central nervous system pathology was detected on radiological imaging.

In a study by Zhong et al. (10), colchicine toxicity was reported to have a more severe course in patients with pre-existing renal dysfunction, with a mortality rate reaching 16.7%. In our case, although acute kidney injury developed, renal function improved with early and aggressive hydration therapy.

Key Messages

- The consumption of more than 100 colchicine tablets results in serious neurological and hematological complications.
- G-CSF shows promise as a treatment for bone marrow suppression caused by colchicine.
- The patient needs proper education and biochemical monitoring before increasing the dose in FMF.

Conclusion

The case highlights the need for continuous patient monitoring and proper education about colchicine use for FMF treatment. Patient education about proper dosage and regular clinical check-ups helps decrease the chance of toxicity. The management of colchicine overdose requires a multidisciplinary approach together with early diagnosis and aggressive supportive therapy to minimize both mortality and morbidity.

Ethics

Informed Consent: Written informed consent was obtained from the patient.

Footnotes

Authorship Contributions

Surgical and Medical Practices: O.Y., F.A., O.Z., Concept: O.Y., F.A., O.Z., Design: O.Y., F.A., O.Z., Data Collection or Processing: O.Y., F.A., O.Z., Analysis or Interpretation: O.Y., F.A., O.Z., Literature Search: O.Y., F.A., O.Z., Writing: O.Y., F.A., O.Z.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Livneh A, Langevitz P, Zemer D, et al. Criteria for the diagnosis of familial mediterranean fever. Arthritis Rheum. 1997;40:1879-85.
2. Masters SL, Simon A, Aksentijevich I, et al. Horror autoinflammaticus: the molecular pathophysiology of autoinflammatory disease. Annu Rev Immunol. 2009;27:621-68.
3. Ben-Chetrit E, Levy M. Colchicine: 1998 update. Semin Arthritis Rheum. 1998;28:48-59.
4. Goldfrank LR, Hoffman RS. Goldfrank's toxicologic emergencies. McGraw-Hill. 2006:645-7.
5. Finkelstein Y, Aks SE, Hutson JR, et al. Colchicine poisoning: the dark side of an ancient drug. Clin Toxicol (Phila). 2010;48:407-14.
6. Bismuth C, Baud F, Dally S. Standardized prognosis evaluation in acute toxicology: its benefit in colchicine, paraquat, and digitalis poisonings. J Toxicol Clin Toxicol. 2021;24:471-92.
7. Finkelstein Y, Aks SE, Hutson JR, et al. Colchicine poisoning: the dark side of an ancient drug. Clin Toxicol (Phila). 2010;48:407-14.
8. Critchley JA, Critchley LA, Yeung EA, et al. Granulocyte-colony stimulating factor in the treatment of colchicine poisoning. Hum Exp Toxicol. 1997;16:229-32.
9. Altiparmak MR, Pamuk ON, Pamuk GE, Hamuryudan V, Ataman R, Serdengecti K. Colchicine neuromyopathy: a report of six cases. Clin Exp Rheumatol. 2002;20(4 Suppl 26):S13-6.
10. Zhong H, Zhong Z, Li H, Zhou T, Xie W. A rare case report of heavy dose colchicine induced acute kidney injury. BMC Pharmacol Toxicol. 2018;19:69.