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INVITED REVIEW

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THE HISTORY AND EVOLUTION OF PSORIATIC ARTHRITIS

Burak Öz[1], İbrahim Gündüz[2]

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

Abstract

Psoriatic arthritis (PsA) is a chronic inflammatory disorder characterised by a heterogeneous clinical presentation involving both the skin and joints. Although the coexistence of psoriasis and arthritis has been recognised since antiquity, PsA remained largely unacknowledged as a distinct disease entity until the mid-20th century. Early descriptions in historical literary sources and archaeological findings provided indirect evidence of PsA, but the conceptualisation of the disease evolved significantly in the 19th and 20th centuries. The introduction of classification criteria by Moll and Wright in 1973 and subsequent developments such as the CASPAR criteria in 2006 established a framework for diagnosis and research. Advances in the understanding of PsA pathogenesis, particularly the discovery of the tumor necrosis factor-α and interleukin (IL)-23/IL-17 pathways, paved the way for biologic therapies and treat-to-target strategies, which have dramatically improved clinical outcomes. This narrative review summarises the key historical milestones and therapeutic breakthroughs that have shaped modern PsA management.

Keywords: Psoriatic arthritis, historical review, evolution of classification criteria, history of therapeutic approaches

INTRODUCTION

Psoriatic arthritis (PsA) is an inflammatory disease characterised by heterogeneous clinical features involving both the skin and joints. Historically, despite early descriptions of psoriatic lesions—including Galen's introduction of the term "psoriasis (PsO)" in the second century *anno Domini*—PsO was frequently misclassified as leprosy until the 19th century, and its association with arthritis remained insufficiently understood. Although the coexistence of PsO and arthritis has been recognised since antiquity, PsA was not formally acknowledged as a distinct clinical entity until the mid-20th century. With advances in the understanding of disease pathogenesis, numerous biological agents have been introduced for the treatment of PsO and PsA since the early 2000s. These therapeutic innovations, together with improved clinical outcomes, have substantially enhanced the awareness and recognition of both conditions (1,2).

The Historical Journey of Psoriasis

In ancient Egypt, as early as 2000 before common era (BCE), therapeutic preparations for skin conditions resembling PsO reportedly included mixtures of goose fat, cat and dog excrement, sea salt, and urine. Goose fat, much like olive oil, was thought to moisturise the skin and alleviate symptoms such as pruritus. Hippocrates (460-377 BCE) described dry, scaly skin lesions under the term "lopoi". Due to similarities in clinical appearance, PsO was frequently misdiagnosed as leprosy in antiquity. The term "psora" or "PsO" was first introduced in the 1st century BCE in

Address for Correspondence: Burak Öz, Asst. Prof., Fırat University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Elazığ, Türkiye
E-mail: burak23oz@hotmail.com **ORCID ID:** orcid.org/0000-0001-9762-2401
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the works of Pedanius Dioscorides, derived from the Greek verb "ψάω" (to scratch), referring to pruritic skin lesions. Later, Galen of Pergamon (129-216 common era) employed the term "psora" to denote scaly dermatoses. During the Middle Ages, PsO patients were often misclassified as lepers and subjected to harsh measures, including social isolation, execution, and even burning (1-3).

By the 1800s, Robert Willan had classified cutaneous lesions into eight categories, with those in the second category corresponding to PsO. The Austrian dermatologist Ferdinand Hebra, in the 1840s, developed an atlas of skin diseases that remained influential for many years. Hebra was the first to clearly distinguish leprosy from the PsO and is widely regarded as the father of dermatology (1,2).

For many years, PsO was treated primarily with coal tar preparations. In the 1950s, topical corticosteroids and methotrexate were introduced as therapeutic options, followed by the advent of phototherapy in the 1960s. The 1970s witnessed the introduction of cyclosporine for PsO treatment, which represented another important milestone in therapeutic approaches (1,2).

In the 1990s, advances in the understanding of the molecular and cellular pathogenesis of autoimmune inflammatory diseases laid the groundwork for the era of biologic therapies. The first biologic agents, alefacept and efalizumab, targeted co-stimulatory signals involved in T-lymphocyte activation. However, their efficacy was limited, and their use was discontinued due to an increased risk of serious infections. Subsequently, the introduction of tumor necrosis factor inhibitors (TNFi), particularly etanercept and infliximab, revolutionised the treatment of PsA. TNFi agents became the gold standard owing to their ability to prevent joint damage. Later, the development of interleukin (IL)-12/23 inhibitors (ustekinumab), IL-17 inhibitors (secukinumab, ixekizumab), and IL-23 inhibitors (guselkumab), marked a significant turning point in PsA management (4).

Archaeological Evidence of Psoriatic Arthritis

In 1981, Rogers et al. (5) reported radiological findings consistent with PsA in Saxon skeletons dated to the 13th century, excavated in England. The presence of a "pencil-in-cup" appearance and spinal syndesmophytes led the authors to conclude that these individuals likely had PsA These cases may represent the earliest known patients with PsA. Retrospectively identifying observations of PsA prior to the 19th century is highly challenging and, in most cases, impossible. However, there are a few notable exceptions. In 1992, Ronald A. Bloom and Patricia Smith described a skeleton dated approximately 2,000 years ago from the Ein Gedi necropolis in Israel and suggested PsA (or arthritis secondary to inflammatory bowel disease) as a possible diagnosis. Moreover, in 1996, skeletal remains dated to the 5th-6th centuries, discovered near the Martyrius Monastery in Jerusalem, were consistent with arthritis mutilans, the most destructive form of PsA (3). In recent years, advanced methodologies such as paleogenetics and computed tomography (CT)/micro-CT re-evaluation of skeletal remains have been increasingly utilized to differentiate PsA from other forms of arthritis in antiquity, thereby strengthening the validity of paleopathological interpretations (6,7).

Psoriatic Arthritis in Historical Literary Sources

In 1674, Fray Felipe Colombo documented the life of Fray Pedro de Urraca, a Mercedarian monk who had served in Peru (8). The report noted a diagnosis of gouty arthritis at the age of 29, accompanied by cutaneous lesions resembling leprosy and progressive deformities affecting the small joints of the hands, as well as, the knees and shoulders. This description is regarded as one of the earliest literary accounts suggestive of PsA.

The Recognition of the Psoriasis-Arthritis Association

In their 1813 book A Practical Synopsis of Cutaneous Diseases, Robert Willan and Thomas Bateman noted the presence of arthritis in patients with PsO. Subsequently, in 1818, Jean Louis Marc Alibert described a case of PsA in his writings, representing one of the earliest documented accounts of the condition (9).

The Origin of the Term Psoriatic Arthritis

In 1860, Pierre Bazin introduced the term "PsO arthritique" (10). Thus, Bazin is considered the originator of the concept and nomenclature of PsA. Later, in 1888, Charles Bourdillon used the term "PsO et arthropathies" in his writings.

In the past, arthritis associated with PsO was known by various terms, such as rheumatisme psoriasique; PsO arthropathique; PsO arthritique; polyarthrite psoriasique; arthropatia psoriatica; arthropathia psoriatica; PsO arthropathica; PsO arthritica; arthritis psoriatica; polyarthritis psoriatica; artrite psoriasica; psoriatischen arthropathie; PsO-arthritis; and artropatia łuszczycowa (11). Pierre Bazin classified all dermatological diseases pragmatically into two groups—"arthritic" and "herpetic"—rather than adopting a conceptual approach. In this context, his definition of PsO arthritica does not fully correspond to the current concept of PsA but instead refers to a specific subset of PsO (3). Today, the most widely used terms are PsA and psoriatic arthropathy.

In their 1937 publication, Jeghers and Robinson (12) used the term PsA for the first time. Later, in 1951, Vilanova and Piñol

(13) emphasised that PsA represented a distinct entity from other inflammatory arthropathies. The discovery of rheumatoid factor in 1940 (14) undeniably contributed to this conclusion.

In 1952, the American orthopaedic surgeon Mary Stults Sherman published one of the earliest comprehensive studies on PsA in the English-language literature. Sherman highlighted distinctive features such as distal interphalangeal (DIP) joint involvement, arthritis mutilans, and axial disease, emphasizing that PsA is a unique clinical entity. She also evaluated the effects of ACTH and cortisone on both cutaneous and articular manifestations but noted that these therapies provided only transient benefits (15).

With the publication of Wright's (16) 1956 paper, PsA became more widely recognised and was accepted as a distinct disease entity. Wright subsequently published two additional articles in 1959 in which he compared clinical data from patients with rheumatoid arthritis, PsO, and PsA (17,18). Following these developments, the American Rheumatism Association [now the American College of Rheumatology (ACR)] officially recognized PsA as a separate entity in 1964 (19).

During the 1960s, the overlapping clinical features among various seronegative arthritides, including PsA, and their strong association with spondylitis were recognised. Moll and colleagues subsequently proposed the term 'seronegative spondyloarthritides' to describe this group of disorders (11). The identification of the association between *HLA-B27* and ankylosing spondylitis in 1973, followed by its extension to other spondylitis-associated diseases, such as ulcerative colitis and PsO, provided further evidence supporting the concept of these conditions as a related family of disorders (11).

By the late 20th century, the misconception of PsA as a "benign disease" had been refuted, and the existence of severe forms capable of causing deformity and disability was recognised. Longitudinal studies conducted at the Toronto PsA Clinic underscored the importance of early and aggressive treatment, laying the foundation for modern therapeutic paradigms (20).

Early studies delineated the subtypes of PsA, including asymmetric oligoarthritis, polyarticular arthritis, and spondyloarthritis. DIP joint involvement and periostitis were also highlighted as distinguishing features of PsA. In the 1980s, *HLA-B27* was identified as being associated with axial disease, while *HLA-B38* and *HLA-B39* were linked to peripheral polyarthritis, contributing significantly to the understanding of the phenotypic heterogeneity of the disease (20).

The Development of PsA Classification Criteria

In their landmark 1973 publication, Wright—regarded as the father of spondyloarthritis—and Moll described the clinical subtypes of PsA and proposed the first set of classification criteria (21). According to the Moll and Wright (21) criteria (Table 1), patients meeting three specified criteria can be classified as having PsA. Later, in 1984, Vasey and Espinoza (22), who authored the PsA section in a textbook on spondyloarthritis, introduced an alternative classification system. Although similar to the Moll and Wright (21) criteria, this system provided a more refined definition of peripheral and axial patterns (Table 2).

In 1991, the European Spondyloarthropathy Study Group proposed a set of criteria (23) that included the presence of synovitis or inflammatory back pain in combination with PsO or a history of PsO. The most recent classification system, developed by the Classification Criteria for Psoriatic Arthritis (CASPAR) study group, was published in 2006 (24). Notably, the CASPAR criteria allow for the classification of patients as having PsA even in the absence of PsO (Table 3). Recent revisions have further improved the sensitivity of PsA classification criteria.

Group for Research and Assessment of Psoriasis and Psoriatic Arthritis

The first large-scale collaborative group established to address PsA was the CASPAR group. The contributions of CASPAR members, who are predominantly comprised of European rheumatologists, to the development of the classification criteria published in 2006 cannot be overstated. During the group's 2001 meeting, it was decided to include PsA experts from outside Europe, as well as specialists from non-rheumatology disciplines, in recognition of the multisystemic nature of the disease. Consequently, at a meeting held in 2003, the expanded group adopted the name Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA). Today, GRAPPA is a highly influential organisation that collaborates with institutions such as the ACR, Assessment of SpondyloArthritis International Society, European Alliance of Associations for Rheumatology (EULAR), and Outcome Measures in Rheumatology to guide decisions on the diagnosis, monitoring, and treatment of PsA (25).

The discovery of the TNF-α and IL-23/IL-17 axes has deepened the understanding of PsA pathogenesis and paved the way for the development of biologic agents. TNF inhibitors such as etanercept, infliximab, and adalimumab, along with next-generation biologics such as ustekinumab, secukinumab, and ixekizumab, have established the foundation for a targeted treatment paradigm in PsA. These advances have markedly altered the natural course of PsA and facilitated the widespread adoption of treat-to-target strategies (26). In the past decade, targeted oral therapies have further expanded the therapeutic armamentarium. Janus kinase (JAK) inhibitors such as tofacitinib

Table 1. Moll and Wright (21) criteria for PsA classification

1. Inflammatory joint disease (arthritis, spondylitis, or sacroiliitis), and
2. Psoriasis, and
3. Absence of rheumatoid factor

PsA: Psoriatic arthritis

Table 2. Vasey and Espinoza (22) criteria for PsA classification (1984)

1. Psoriasis or psoriatic nail lesions, and
2. Peripheral pattern* or axial pattern**

*More than 4 weeks of arthritis of DIPJ; or asymmetrical peripheral arthritis (included sausage digit); absent RF or rheumatoid nodule; or radiographic changes (pencil-in-cup deformity, whittling of terminal phalanges, fluffy periostitis and bony ankylosis).
**More than 4 weeks of spinal pain and stiffness with the restriction of motion, or grade 2 symmetric sacroiliitis or grade 3 or 4 unilateral sacroiliitis according to the New York criteria.
PsA: Psoriatic arthritis, DIPJ: Distal interphalangeal joint, RF: Rheumatoid factor

Table 3. CASPAR criteria for the classification of PsA (24)

A patient with arthritis, spondylitis, sacroiliitis, or enthesitis is classified as diagnosed with PsA if the patient score based on the following parameters

Parameters	Points
Current psoriasis	**2**
Personal or family history of psoriasis	**1**
Nail dystrophy on physical examination	**1**
Negative rheumatoid factor	**1**
Dactylitis, current or history of dactylitis (confirmed by a rheumatologist)	**1**
Radiographic evidence of juxta-articular new bone formation	**1**

CASPAR: Classification Criteria for Psoriatic Arthritis, PsA: Psoriatic arthritis

and upadacitinib are now approved for PsA, and incorporated into treatment recommendations, while the selective tyrosine kinase 2 inhibitor deucravacitinib, currently approved for plaque PsO, is under evaluation for PsA. The most recent EULAR 2024 recommendations and the GRAPPA 2022 update endorse a domain-based, treat-to-target approach, emphasizing early initiation of conventional synthetic disease-modifying anti-rheumatic drugs (DMARDs) (preferably methotrexate) for peripheral arthritis, avoidance of chronic oral glucocorticoids, and escalation to biologic DMARDs or targeted synthetic DMARDs—including JAK inhibitors—according to clinical domains and comorbidities (27,28).

CONCLUSION

The historical trajectory of PsA spans from early misclassifications and literary descriptions to its recognition as a distinct clinical entity with validated classification criteria. Advances in immunopathogenesis have shifted treatment from traditional approaches to biologics and targeted synthetic agents, shaping today's treat-to-target paradigm. Continued progress in molecular phenotyping and precision medicine is expected to further refine patient stratification and optimise future management strategies.

Footnotes

Authorship Contributions

Concept: B.Ö., İ.G., Design: B.Ö., İ.G., Data Collection or Processing: İ.G., Literature Search: B.Ö., İ.G., Writing: B.Ö.

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

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ORIGINAL ARTICLE

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THE EVALUATION OF HEALTH STATUS OF FAMILIAL MEDITERRANEAN FEVER PATIENTS WITH HOMOZYGOUS M694V MUTATION

Ayşegül Çakar[1], Lale Saka Baraz[2], Demet Yalçın Kehribar[3], Metin Özgen[4]

[1]Gölcük Necati Çelik State Hospital, Clinic of Internal Medicine, Kocaeli, Türkiye
[2]Manisa City Hospital, Clinic of Internal Medicine, Manisa, Türkiye
[3]Dokuz Eylül University Faculty of Medicine, Department of Internal Medicine, İzmir, Türkiye
[4]İzmir Ekonomi University, Medical Point Hospital, Department of Rheumatology, İzmir, Türkiye

Abstract

Aim: Familial Mediterranean fever (FMF) is an autosomal recessive autoinflammatory disorder characterized by recurrent episodes of fever, serositis, and systemic inflammation. The M694V mutation in the *MEFV* gene is associated with a more severe disease phenotype, including early onset, frequent attacks, and an increased risk of amyloidosis. This study aimed to evaluate the clinical features, comorbidities, and treatment outcomes of FMF patients homozygous for the M694V mutation.

Material and Methods: A retrospective analysis was conducted on 183 FMF patients homozygous for the M694V mutation, diagnosed and followed at our hospital between 2014 and 2022. Data on demographics, clinical characteristics, laboratory findings, and treatment modalities were collected.

Results: The most common symptoms were abdominal pain (88%), joint pain (78%), and arthritis (46%). Proteinuria and amyloidosis were detected in 22.4% and 7.1% of patients, respectively. The average age of symptom onset was 14.1 years, with a mean annual attack frequency of 2.75. Comorbidities were present in 24% of patients, including spondyloarthritis and inflammatory bowel disease. Colchicine was the mainstay treatment (94.5%), while 21.8% required IL-1 inhibitors. Eight patients (4.4%) died during follow-up, five due to amyloidosis-related complications.

Conclusion: M694V homozygous FMF patients exhibit a severe disease presentation associated with this variant with frequent attacks, high amyloidosis risk, and significant comorbidities. While colchicine remains essential, biologics are increasingly used for colchicine-resistant cases. Early diagnosis, individualized treatment, and regular monitoring are crucial to improving patient outcomes.

Keywords: Familial Mediterranean fever, M694V, homozygous, phenotype, genotype

Address for Correspondence: Lale Saka Baraz, MD, Manisa City Hospital, Clinic of Internal Medicine, Manisa, Türkiye
E-mail: lalesaka-6@hotmail.com **ORCID ID:** orcid.org/0000-0003-4387-6929
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INTRODUCTION

Familial Mediterranean fever (FMF) is an autosomal recessive autoinflammatory disorder characterized by recurrent episodes of fever, serositis, and systemic inflammation. It is predominantly observed in populations of the Mediterranean basin, including Turks, Armenians, Arabs, and Jews, where its prevalence can reach as high as 1 in 200 to 1 in 1,000 individuals (1). The disease is caused by mutations in the *MEFV* gene, which encodes pyrin, a protein involved in regulating the inflammatory response (2).

Among the more than 300 identified variants in the *MEFV* gene, M694V is the most extensively studied and clinically significant variant. Homozygosity for the M694V mutation has been consistently associated with a more severe disease phenotype, including early onset, higher frequency of attacks, and increased risk of amyloidosis, a life-threatening complication of FMF (3,4). Despite recognizing its clinical importance, the full spectrum of manifestations in M694V homozygous individuals remains underexplored, particularly in diverse populations.

Recent advances in understanding the molecular mechanisms of FMF have underscored the role of pyrin in inflammasome activation and interleukin (IL)-1β secretion, linking specific *MEFV* mutations to distinct inflammatory profiles (5). This genotype-phenotype correlation is pivotal for tailoring therapeutic strategies, particularly the use of colchicine and emerging biologics such as IL-1 inhibitors (6). However, the variability in clinical presentations even among individuals with the same genotype suggests the involvement of additional genetic, epigenetic, and environmental factors (7-11).

The present study aims to comprehensively evaluate the clinical characteristics of M694V homozygous FMF patients, providing insights into the phenotypic diversity and potential modifiers of disease expression. By systematically analyzing a cohort of these individuals, we seek to identify patterns that may enhance diagnostic accuracy and guide personalized treatment approaches.

MATERIAL AND METHODS

Design and Patient Enrollment

This study was conducted retrospectively. Patients diagnosed with FMF and carrying the M694V homozygous mutation who were admitted for diagnosis and/or follow-up to our rheumatology department between January 2014 and December 2023 were retrospectively analyzed. The diagnosis of FMF was established using the Eurofever/PRINTO classification criteria (11). Approval for the study was obtained from the Ondokuz Mayıs University Clinical Research Ethics Committee (approval number: 2023/207, date: 28.08.2023). This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all participants, and their confidentiality was maintained throughout the study.

Patient data were accessed using our university hospital information system "MIA" and telephone interviews. A total of 183 patients aged 18 years and older were included in the study. Data on patient demographics, clinical histories (hospital and outpatient records), laboratory results, and medication reports were reviewed.

Patient Selection and Data Collection

While determining clinical and demographic characteristics, the entire cohort of 183 patients was considered. The analyzed variables included age, age at symptom onset, age at diagnosis, gender, genotype, initial attack frequency, family history of FMF, the presence of FMF-related complications such as proteinuria and amyloidosis, symptoms including abdominal pain, chest pain, joint pain, arthritis, erysipelas-like erythema, calf pain, associated diseases, colchicine therapy, biological agent use, and comorbid conditions. Based on established clinical guidelines, proteinuria was defined as urinary protein excretion of 500 mg/day or higher. The inclusion criteria were a diagnosis of FMF, being over 18 years old, and having the M694V homozygous mutation. Patients with insufficient data records, malignancies, or chronic infections were not included in the study. Colchicine resistance is defined according to the 2016 European Alliance of Associations for Rheumatology recommendations, as the persistence of one or more attacks per month despite adherence to an adequate dose of colchicine for at least six months, or the presence of ongoing subclinical inflammation (elevated C-reactive protein or serum amyloid A) between attacks.

Statistical Analysis

IBM SPSS Statistics 25.0 software for Windows (IBM Corp., Armonk, NY, USA) was used for data analysis. Continuous variables are reported as mean ± standard deviation, while categorical data, including demographic and clinical characteristics, are expressed as frequencies and percentages. The Student's t-test was applied to variables with a normal distribution when making comparisons between genders. Statistical significance was defined as a p-value of less than 0.05 across all analyses.

RESULTS

Clinical Features

Among 183 patients with M694V homozygous mutation and a diagnosis of FMF, the most common symptom was abdominal pain, reported by 147 patients (88%). Other symptoms included

joint pain (78%), arthritis (46%), chest pain (33.3%), erysipelas-like lesions (32%), and calf pain (28%). Proteinuria and amyloidosis were detected in 22.4% and 7.1% of patients, respectively. In the study, the mean follow-up duration was 13.3±9.7 years (min 2 years-max 48 years) and the median age at death was 48 years (min 19 years-max 64 years). Detailed clinical findings are summarized in Table 1.

Ages of Symptom Onset and Diagnosis

In this cohort, the reported age of symptom onset was 14.1±11.2 years, and the age of diagnosis was 20.0±14.1 years. The mean time interval from symptom onset to diagnosis was 5.9±4.8 years. In this cohort, the mean age of symptom onset was 12.9 years in females and 8.5 years in males (p=0.146). Similarly, the mean age of diagnosis was 21.0 years in females and 19.1 years in males (p=0.364).

Attack Frequency

The average annual attack frequency for FMF-diagnosed patients with the M694V homozygous mutation is approximately 2.75 attacks per year; among them, 44.3% reported no attacks. The maximum recorded attack frequency was 24 attacks per year in two patients. Approximately 12% of the patients currently report having an attack frequency of more than once per month. There was no significant difference in attack frequency between genders (p=0.442).

Family History

A total of 123 patients reported having a first-degree relative with FMF.

Comorbid Conditions

Comorbidities were observed in 24% (45) of patients, though the percentage of each comorbid disease observed is separately detailed elsewhere. The most common accompanying disease are: spondyloarthritis (n=17), rheumatoid arthritis (n=7), Behçet's disease (n=5), systemic lupus erythematosus (n=3), inflammatory bowel disease (n=2), and others. Seven patients also had a history of acute rheumatic fever.

Table 1. Clinical findings of FMF-diagnosed patients with M694V homozygous mutation (n=168)

Clinical finding	Present (n)
Abdominal pain	147 (88%)
Chest pain	65 (39%)
Arthralgia	131 (78%)
Arthritis	78 (46%)
Erysipelas-like erythema	53 (32%)
Calf pain	47 (28%)
Amyloidosis	13 (8%)
Proteinuria	41 (24%)
FMF: Familial Mediterranean fever	

Diagnosis and Treatment

The majority of diagnoses were based on clinical symptoms supported by genetic testing. Among 177 patients with available data, 94.5% were on colchicine treatment. Biological agents, particularly IL-1 antagonists (21.8%) and tumor necrosis factor-α inhibitors (3.7%), were used in patients with additional inflammatory or autoimmune conditions.

Surgical History

Surgical interventions were documented in 17.5% of patients, including appendectomies (14.7%), cholecystectomies (1.6%), and splenectomies (1.6%).

Mortality

Eight patients (4.4%) died during follow-up. Among them, five had amyloidosis. Causes of death included complications related to amyloidosis, renal failure, infection, and malignancy. Four patients had undergone renal transplantation.

DISCUSSION

FMF is a prototype autoinflammatory disorder resulting from mutations in the *MEFV* gene. This study evaluates the clinical characteristics of patients who are homozygous for the M694V mutation, one of the most severe and clinically significant variants of *MEFV* responsible for FMF. The study provides valuable insights into the phenotype-genotype relationship and the challenges associated with the treatment of these patients by examining key clinical features, comorbidities, and treatment patterns. In this M694V homozygous cohort, abdominal pain (88%) and joint pain (78%) emerge as the primary symptoms, consistent with previous studies highlighting these features as prominent signs of FMF (12). The high prevalence of erysipelas-like erythema (32%) and calf pain (28%) in the dermatologic and musculoskeletal systems, indicates the significance of these symptoms in the disease spectrum, especially in M694V homozygous patients (1). Early symptom onset (mean age: 14.1 years) and late diagnosis (mean age: 20.0 years) emphasize the disease burden due to delays in diagnosis (13).

In this study, the annual attack frequency in M694V homozygous FMF patients was 2.75 attacks per year on average, with considerable variability observed among patients. Nearly half of the patients in the M694V homozygous cohort reported

no attacks, while a small subgroup experienced frequent recurrences (>12 attacks/year), suggesting suboptimal disease control or colchicine resistance (14). These findings are in line with reports linking M694V homozygosity to more severe disease and frequent, intense inflammatory episodes (15). Additionally, the significant variability in attack frequency among patients with the same genotype provides valuable insight into the genotype-phenotype relationship. The reason why some patients with the same genetic mutation experience no attacks while others have frequent attacks remains unclear, highlighting the need for further research. It is evident that factors beyond the *MEFV* gene influence disease activity. Additional studies are required to better understand the genotype-phenotype correlation in FMF.

A serious complication of FMF, amyloidosis, was detected in 7% of M694V homozygous patients, consistent with global estimates for untreated or inadequately managed FMF cases (16). Proteinuria was observed in 22.4% of patients, emphasizing the importance of routine kidney monitoring in this population. These findings reflect the known relationship between M694V homozygosity and an increased risk of amyloidosis, due to persistent subclinical inflammation and inadequate control of the IL-1β pathway (17). Early initiation of colchicine therapy significantly reduces the risk of amyloidosis; however, even in treated patients, amyloidosis may persist, highlighting the need for alternative treatments in colchicine-resistant cases (18).

In the M694V homozygous FMF cohort, 21.8% of patients used biological agents, particularly IL-1 inhibitors, reflecting the increased awareness of colchicine resistance. These agents have shown promising results in managing refractory cases, particularly in reducing attack frequency and preventing amyloidosis (19). However, barriers such as treatment costs, accessibility, and potential side effects limit their widespread use. Overcoming these barriers requires cost-effectiveness studies and patient education programs (20).

This study also identified a high prevalence of comorbidities at 24%, including ankylosing spondylitis, systemic lupus erythematosus, and inflammatory bowel disease, among other autoinflammatory and autoimmune disorders. This underscores the genetic susceptibility and shared inflammatory pathways between FMF and other immune-mediated diseases (21). These comorbidities often complicate treatment and highlight the need for comprehensive, individualized treatment approaches (22). Additionally, no significant differences were found between sexes in terms of attack frequency, symptom onset age, or diagnosis age, indicating that disease expression is generally similar in both males and females (23). However, the observed variability in clinical presentations even among patients with the same genotype supports the role of epigenetic and environmental factors in modulating FMF phenotypes (24-27). These findings emphasize the importance of studying these regulators to better understand disease heterogeneity and improve prognostic accuracy.

Study Limitations

Several limitations should be considered when interpreting these findings. First, the retrospective design may introduce selection bias, and there may be missing information in patient records and interviews. Second, the single-center study design limits the generalizability of the findings to larger populations. Another limitation is the lack of a comparison non-homozygous M694V group, which could have provided clearer insight into the effects of the homozygous M694V mutation on disease phenotype and facilitated a deeper understanding of the genotype-phenotype relationship. The clinical features of arthritis were not evaluated, which is also a limitation of our study.

CONCLUSION

This study comprehensively evaluated the clinical characteristics, comorbidities, and treatment outcomes of M694V homozygous FMF patients. The findings highlight the severe disease phenotype associated with this genotype, characterized by frequent attacks, early symptom onset, and a high-risk of amyloidosis. While colchicine remains the cornerstone of FMF management, the increasing use of IL-1 inhibitors underscores the need for personalized treatment strategies to address colchicine resistance and refractory cases.

Key takeaways from this study include the significant variability in symptom presentation and attack frequency among patients with shared genetic profiles, in FMF. This highlights the critical role of additional genetic, epigenetic, and environmental factors in modulating FMF expression. Furthermore, despite the higher use of biological treatments in M694V homozygous FMF patients, the high prevalence of comorbidities emphasizes the need for treatment and monitoring approaches tailored to the mutation status of these patients.

Ethics

Ethics Committee Approval: Approval for the study was obtained from the Ondokuz Mayıs University Clinical Research Ethics Committee (approval number: 2023/207, date: 28.08.2023). This study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Informed Consent: Written informed consent was obtained from all participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.Ç., D.Y.K., M.Ö., Concept: A.Ç., D.Y.K., Design: A.Ç., D.Y.K., M.Ö., Data Collection or Processing: A.Ç., D.Y.K., Analysis or Interpretation: A.Ç., L.S.B., M.Ö., Literature Search: A.Ç., D.Y.K., M.Ö., Writing: A.Ç., L.S.B., D.Y.K., M.Ö.

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SERIAL QUANTIFERON-TB TEST SCREENING IN RHEUMATOLOGY PATIENTS DURING TUMOR NECROSIS FACTOR ALPHA INHIBITORS TREATMENT

Cansu Akleylek[1], İbrahim Halil Sever[2], Safiye Koçulu Demir[3], Canan Akman[2], Neslihan Yılmaz[1]

[1]Demiroğlu Science University Faculty of Medicine, Department of Rheumatology, İstanbul, Türkiye
[2]Demiroğlu Science University Faculty of Medicine, Department of Radiology, İstanbul, Türkiye
[3]Demiroğlu Science University Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, İstanbul, Türkiye

Abstract

Aim: Screening for latent tuberculosis infection (LTBI) prior to biological therapy are recommended. Although our country is in the moderate risk category for tuberculosis infection, our national data regarding the seroconversion rate of the tuberculosis test during the use of these drugs remains unclear. The aim of this study was to evaluate the risk of emerging LTBI in our patients during treatment with tumor necrosis factor-alpha inhibitors.

Material and Methods: This study included 81 patients with rheumatic diseases who had negative baseline QuantiFERON-TB test. All patients were evaluated by a serial QuantiFERON-TB test during their treatments. The primary endpoint was to reveal the LTBI risk by serial testing, while secondary endpoints were to determine the factors associated with seroconversion.

Results: A total of 81 patients were evaluated with serial QuantiFERON-TB testing for an average of 28.3 months. During the follow-up, positive conversion of QuantiFERON-TB was detected in 6 (7.4%) of 81 patients. In multivariate analysis, aging was found to be the only independent risk factor for positive seroconversion rate (p=0.01).

Conclusion: In this study, which we conducted in a population where tuberculosis infection is relatively common, QuantiFERON-TB test seroconversion rate was found to be 7.4% during treatment with inhibitors. Five out of six patients who developed seroconversion were in the ankylosing spondylitis group. These results emphasize the importance of annual LTBI screening in both rheumatoid arthritis and spondyloarthritis patients receiving biological therapy.

Keywords: Latent tuberculosis, quantiferon-plus, rheumatic diseases, tumor necrosis factor-alpha inhibitors

INTRODUCTION

Tuberculosis (TB) infection, which has a geographically heterogeneous distribution, is especially common in developing countries (1-3). According to epidemiological data, Türkiye is in the moderate-risk category for TB, with an annual incidence of 14.6 per 100,000 and latent TB infection (LTBI) prevalence of ~25% (4). Although the immune system is generally effective in keeping the infection in the latent stage, approximately 5-10% of people are at risk of developing active TB over time. Rheumatic diseases are among the high-risk group for the development of active TB due to both immune dysfunction and the use of immunosuppressive therapies. Tumor necrosis factor-alpha

Address for Correspondence: Cansu Akleylek, MD, Demiroğlu Science University Faculty of Medicine, Department of Rheumatology, İstanbul, Türkiye
E-mail: cansuakleylek@gmail.com **ORCID ID:** orcid.org/0000-0002-4703-6903
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(TNF-α) inhibitors, which are widely and effectively used in the treatment of rheumatic diseases, are among the leading drugs that cause LTBI reactivation. Therefore, the guidelines recommend that patients be evaluated for both active and latent TB before treatment with these agents (5,6).

De novo TB infection is another significant problem that occurs during the use of immunosuppressive agents, especially in areas with high TB prevalence. It is reported in the literature that the seroconversion rate of LTBI tests is 4-14% after starting TNF-α treatment (7-11). Although the clinical significance of LTBI screening tests' seroconversion is not clear, data from countries with moderate-high TB incidence suggest that a positive test conversion may precede development of clinical TB activation. Therefore, according to the 2012 American College of Rheumatology recommendations, annual LTBI screening is recommended for rheumatoid arthritis (RA) patients who are at high risk of encountering TB while using biological therapy (5). However, clear recommendations for other rheumatic diseases are not available, and the optimal screening strategy for LTBI is still questioned due to the uncertainty regarding the performance of tests in immunosuppressed patients.

Tuberculin skin tests (TST) or interferon-gamma (IFN-γ) release assays (IGRAs) are used in LTBI screening. It is known that the specificity of TST decreases, especially in individuals vaccinated with Bacillus Calmette-Guérin (BCG), patients using immunosuppressive therapy, or with non-TB mycobacterial infections. Since TST lacks sensitivity and specificity, novel screening tools, the IGRAs, have been introduced. IGRAs are a method of detecting and quantifying IFN-γ response of T lymphocytes to specific antigens for mycobacterium TB, without directly detecting the presence of the bacterium. In this way, the reliability of determining whether the individual has been exposed to bacteria before is improved. The 4th generation IGRA, QuantiFERON-TB Gold Plus (QFT-plus) test, contains the antigens early-secreted antigenic target-6 (ESAT-6) and culture filtrate protein-10 (CFP-10) that are not encoded by non-tuberculous mycobacteria, and is approved by the Food and Drug Administration and is currently in use (12,13).

In our country, which is in the moderate to high-risk category for TB infection and where national BCG vaccination is carried out, the Ministry of Health recommends annual testing. However, our national data on the IGRAs conversion rate in individuals using biological drugs are unclear. Therefore, in this study, we aimed to assess the risk of LTBI development and to determine the factors associated with seroconversion rates under TNF-α treatments.

MATERIAL AND METHODS

In this study, 113 patients treated with TNF-α inhibitors for rheumatic disease at a rheumatology clinic at a tertiary university hospital between January 2017 and June 2022 were included. A written informed consent was obtained from each patient. All patients enrolled were diagnosed with RA, ankylosing spondylitis (AS), psoriatic arthritis (PsA) and Behçet's disease based on standard criteria (14-17). Data regarding the patients' demographic information, concomitant medications, biologic treatment types, and disease duration were retrieved from patients' medical files.

IGRA test, which is recommended by Centers for Disease Control and Prevention guidelines to increase diagnostic sensitivity in those who received BCG vaccination, was preferred to reveal LTBI in this study (18). We performed the QFT-plus (Cellestis, Australia) test, which measures the responses to ESAT-6, CFP-10, and TB 7.7 proteins in all the participants of the study. QFT-plus results were considered positive, negative, or indeterminate according to manufacturer's recommendations. Chest X-rays were assessed by two radiologists for the presence of any signs of active TB infection.

The QFT-plus test results of a total of 113 patients at the beginning of the biological therapy were retrospectively scanned from patient files, and 28 (24.7%) cases thought to have LTBI because the test results were positive were identified. Four cases whose results were indeterminate were excluded. The patients who had a negative baseline QFT-plus test (n=81), were followed prospectively, and control QFT tests were requested at intervals of 13.8-30 months at outpatient clinic admissions. Eighty-one patients (>18 years of age) with more than 1 year of follow-up who had at least 2 QFT-plus test results were included in the study. The primary endpoints included investigating the positive seroconversion rate of serial QFT-plus testing. The secondary endpoints included revealing factors affecting this outcome and rates of treatment-associated active TB infection.

Ethical Statement

This study was approved by the Demiroğlu Science University Clinical Research Ethics Committee (approval number: 2022-15-04, date: 02.08.2022) and was conducted in accordance with the Declaration of Helsinki.

Statistical Analysis

Parametric variables were expressed as mean ± standard deviation, and non-parametric variables as median [interquartile range (IQR)]. Discontinuous variables were given as percentages. The Fisher exact test, univariate regression, and multivariate

logistic regression analyses were used to reveal independent risk factors (age, gender, underlying disease, etc.) associated with the positive conversion of QFT-plus test outcome. The Mann-Whitney U test was used to compare non-normally distributed continuous variables between groups with and without positive seroconversion according to the QFT-plus test. We considered a p-value less than 0.05 to be statistically significant. Statistical analyses were performed using the SPSS version 21.0 (IBM Corp. Armonk, NY, USA).

RESULTS

In this study, a total of 113 patients were evaluated, and the LTBI rate was identified in 24.7%, based on the QFT-plus test. A total of 81 patients (67-spondyloarthritis, 11-RA, 3-Behçet's disease) were treated with TNF-α inhibitors with a negative baseline QFT-plus result were serially screened using the QFT-plus test. Of these patients, the median age was 42 (IQR=34-54.5) years and the median TNF-α inhibitors therapy duration was 44 (IQR=24.5-63.5) months. The most frequently used agent among biological treatments was etanercept (n=25). Overall, 23 patients were treated with adalimumab, 6 with infliximab, 12 with certolizumab, 15 with golimumab, and 18 patients were also receiving concomitant immunosuppressant therapy. The demographics and clinical characteristics of the patients are summarized in Tables 1 and 2.

The QFT-plus test was repeated in all patients at intervals of at least 12 months after the initial measurement, and the patients were followed for an average of 28.3 (IQR=16.6-46.9) months. At the end point, all patients underwent a second QFT-plus test, and 37 of them, additionally, underwent a third test. The median time interval between the QFT-plus tests was 19 (IQR=13.8-30) months. Positive conversion was detected in 6 of 81 patients (7.4%): 5 with AS and 1 with RA, in the serial QFT-plus test, and all of this seroconversion was detected within the first

Table 1. The baseline demographic characteristics of the patients

	Total (n=81)	Converters (n=6)	Non-converters (n=75)	p-value
Age, median (IQR), years	42 (34-54.5)	59.5 (50.5-65)	40 (33-50)	<0.01
Female sex n (%)	35 (43.2)	4 (66.6)	31 (41.3)	NS
Diagnosis n (%) Ankylosing spondylitis Rheumatoid arthritis Psoriatic arthritis Behçet's disease	 54 (66.6) 11 (13.5) 13 (16) 3 (3.7)	 5 (83.3) 1 (16.7) 0 0	 49 (65.3) 10 (13.3) 13 (17.3) 3 (4)	 NS NS
Drugs administered, n (%) Adalimumab Etanercept Infliximab Golimumab Certolizumab	 23 (28.3) 25 (20.8) 6 (7.4) 15 (18.5) 12 (14.8)	 1 (16.6) 2 (33.3) 0 2 (33.3) 1 (16.6)	 22 (29.3) 23 (20.6) 6 (8) 13 (17.3) 11 (14.6)	
Concomitant csDMARD, n (%)	18 (22.2)	1 (16.6)	17 (22.6)	NS

csDMARD: Conventional synthetic disease-modifying antirheumatic drug, IQR: Interquartile range, NS: Not significant

Table 2. Clinical characteristics of 81 patients treated with TNF-α inhibitors

	Total (n=81)	Converters (n=6)	Non-converters (n=75)	p-value
Disease duration, median (IQR), months	96 (60-120)	78 (51-138)	96 (60-120)	NS
Cumulative exposure time to TNF-α inhibitors median (IQR), months	44 (24.5-63.5)	31 (15.7-53.2)	47 (26-64)	NS
Follow-up duration based on the QFT-plus test median (IQR), months	28.3 (16.6-46.9)	20 (13-30)	31.8 (17-47.3)	NS
Time interval between QFT tests, median (IQR), months	19 (13.8-30)	20 (13-30)	17.9 (13.5-30)	NS

IQR: Interquartile range, NS: Not significant, QFT: QuantiFERON, TNF-α: Tumor necrosis factor-alpha

24 months (mean 18.9±5.4). Isoniazid prophylaxis was started, and biological agent treatment was continued in these patients who had no signs of active TB. Table 3 shows the demographics and clinical characteristics of patients with QFT-plus positive conversion.

Chest radiographs of all patients were evaluated for active TB, such as cavitary lesions, consolidation, nodules, hilar lymphadenopathy, pleural effusion, and miliary TB. In both physical examinations and chest X-ray assessments, no evidence of active TB infection was found in the study patients during the follow-up.

Univariate analysis showed that age was significantly associated with the positive seroconversion rate of the QFT-plus test. All variables included in the univariate analysis were also entered into the multivariate analysis, and age was found to be a single independent factor in the multivariable analysis [odds ratio =1.1 (95% confidence interval =1.02-1.2), p=0.01] (Table 4).

DISCUSSION

TB continues to be a global health problem, although its incidence and mortality have been reported to be decreasing both in the world and in Türkiye. Immunosuppressive medications used in rheumatic diseases, especially TNF-α inhibitors, are known to increase the risk of active TB development. It has been reported that this risk is approximately 12 times higher in TNF-α inhibitor users than in the general population (19). Therefore, it is recommended to perform active and LTBI screening in all patients who will start TNF-α inhibitors and to repeat the test during treatment due to the risk of *de novo* infection in patients living in areas with a high incidence of TB. Although Türkiye is classified in the moderate risk category for TB, national data on LTBI during monitoring biological treatment is insufficiently available (4).

In our study, whose primary purpose was to evaluate new LTBI using serial IGRA in follow-up patients receiving TNF-α

Table 3. Clinical characteristics of six patients with QFT-plus positive conversion

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age/gender	58/F	49/M	61/F	51/F	77/M	61/F
Diagnosis	AS	AS	AS	AS	AS	RA
Disease duration, (months)	60	264	24	84	96	72
Drugs administered	ETA	CER	GOL	ADA	GOL	ETA
TNF-α inhibitor therapy duration, (months)	38	60	12	24	51	17
Interval between OFT-plus tests, (months)	24	24	12.7	17	23	13
Time of QFT-plus conversion, (months)	24	24	12.7	17	23	13

ADA: Adalimumab, AS: Ankylosing spondylitis, CER: Certolizumab, ETA: Etanercept, F: Female, GOL: Golimumab, M: Male, QFT: QuantiFERON, RA: Rheumatoid arthritis, TNF-α: Tumor necrosis factor-alpha

Table 4. Factors affecting QFT-plus conversion during biologic treatment

	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Age	1.112 (1.027-1.204)	0.009	1.1 (1.02-1.2)	0.01
Gender	1.41 (0.269-7.5)	0.68	-	
Diagnosis	0.47 (0.113-1.97)	0.3	-	
Drugs administered	1.06 (0.182-6.2)	0.94	-	
Concomitant csDMARDs	0.68 (0.075-6.24)	0.73	-	
Disease duration	0.99 (0.98-1.01)	0.86	-	
TNF-α inhibitors therapy duration	0.97 (0.93-1.01)	0.21	-	
Follow-up duration based on the QFT-plus test	0.96 (0.90-1.02)	0.17	-	

CI: Confidence interval, csDMARDs: Conventional synthetic disease-modifying antirheumatic drugs, NS: Not significant, QFT: QuantiFERON, TNF-α: Tumor necrosis factor-alpha

inhibitors, the positive conversion rate was found to be 7.4%. QFT test positivity and seroconversion risk vary according to regions, ethnicity, comorbidities, concomitant medications, and underlying diseases. Previous studies published in different populations reported that the seroconversion rate under TNF-α inhibitor treatment was 7.9% in AS patients and ranged from 3.7% to 13.6% in RA patients (9-11). Similarly, in studies including different rheumatic disease subsets, this rate varies between 6% and 14% (7,11,20,21). The variability of seroconversion rates in these studies is thought to be related to the use of different testing methods, follow-up times, host biological factors, and differences in TB risk rates between countries. As a matter of fact, it has been shown that the results vary depending on the method chosen, with the seroconversion rate 13-30% with TST, 10% with T-spot, and 4-14% with QFT-GIT (11,20-22). In addition, the low sensitivity of the QFT test in immunocompromised patients, and the potential suppression of IFN-γ release by immunosuppressive drugs may cause the variability seen in IGRA test results in these studies (23,24). Another important factor determining the LTBI seroconversion rate is the follow-up period. Although our study had a relatively short follow-up period of 28 months on average, all seroconversion cases were observed within the first 24 months. A similar study in RA patients in Italy reported TB test positivity in 13.6% of cases, with more than half of these cases occurring within the first two years (11). Although it is possible to add new LTBI cases as the follow-up period extends, the predominance of seroconversion in the first 2 years suggests the importance of close monitoring, especially in the initial 24 months of therapy.

The second aim of our study was to evaluate factors affecting QFT-plus seroconversion. Our results showed that the patient's age was the only independent factor and that the probability of QFT-plus conversion increased significantly with age. Similarly, in other previous studies, age was reported as the only factor determining seroconversion and increasing over the age of 50 (9,21). In only one study, Cuomo et al. (11) suggested that male sex is a second independent risk factor. In our study, no relationship could be determined with other possible factors such as disease subsets, type of biological drug, concomitantly used immunosuppressive agents, gender, disease duration and follow-up period. However, the limited number of patients with seroconversion is insufficient to draw conclusions on this issue.

Another important point is that most of the previous screening studies for LTBI were conducted in the RA group, as the risk of developing TB is thought to be higher due to both disease-related factors and the concomitant use of immunosuppressive drugs. Considering the high seroconversion rates of up to 13% in these data, it was predicted that disease subgroups might influence the results; however, no statistically significant differences were found in our multiple regression analyses (9,11,21). Five out of six patients who developed TB seroconversion were in the AS group in our study. This result may be related to the fact that the majority of our study population consists of AS patients. On the other hand, Kim et al. (8) have also shown that seroconversion occurs especially in AS patients, compared to other rheumatic diseases. Although the pathogenetic differences and the concomitant treatments (such as systemic steroids, immunosuppressive agents, etc.) between AS and RA can be confusing, these results suggest that patients with AS may also be at risk of TB seroconversion to at least the same extent as patients with RA (25-27). Therefore, monitoring for LTBI development in AS patients appears important, similar to the recommendations in RA guidelines.

Study Limitations

The main limitations of our study include a relatively small number of patients for subgroup analysis, variations in QFT re-test intervals, and a somewhat short follow-up period. However, considering that most LTBI cases occur in the first 2 years, the follow-up period can be considered sufficient.

CONCLUSION

In our study covering different rheumatological disease populations (AS, RA, PsA, and Behçet's disease) and treated with TNF-α inhibitors, the positive conversion rate in QFT-plus tests was found to be 7.4%, and age was determined as the only factor affecting this risk. The fact that most seroconversion was detected in AS patients emphasizes the importance of annual LTBI screening in all rheumatological diseases receiving biological therapy, and in RA as well. This situation emphasizes the need for personalized follow-up strategies not only among countries but also within different disease groups. However, larger studies with more extended follow-up periods are still needed to create clearer guidelines in this regard.

Ethics

Ethics Committee Approval: This study was approved by the Demiroğlu Science University Clinical Research Ethics Committee (approval number: 2022-15-04, date: 02.08.2022) and was conducted in accordance with the Declaration of Helsinki.

Informed Consent: A written informed consent was obtained from each patient.

Footnotes

Authorship Contributions

Surgical and Medical Practices: C.A., S.K.D., N.Y., Concept: C.A., N.Y., Design: C.A., İ.H.S., S.K.D., C.Akm., N.Y., Data Collection or Processing: C.A., İ.H.S., S.K.D., C.Akm., N.Y., Analysis or Interpretation: C.A., İ.H.S., S.K.D., C.Akm., N.Y., Literature Search: C.A., İ.H.S., C.Akm., N.Y., Writing: C.A., N.Y.

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BIOLOGICAL TREATMENT IN PATIENTS WITH REFRACTORY BEHÇET'S UVEITIS: A RETROSPECTIVE SINGLE-CENTRE STUDY

Dilbade Yıldız Ekinci[1], Lütfi Akyol[2]

[1]University of Health Sciences Türkiye, Diyarbakır Gazi Yaşargil Training and Research Hospital, Clinic of Ophthalmology, Diyarbakır, Türkiye
[2]University of Health Sciences Türkiye, Diyarbakır Gazi Yaşargil Training and Research Hospital, Clinic of Rheumatology, Diyarbakır, Türkiye

Abstract

Aim: This study aims to evaluate the examination findings and treatment outcomes of patients receiving biological therapy for Behçet's uveitis (BU) in a single center clinic.

Material and Methods: This retrospective, single-center study included patients diagnosed with BU who were treated with adalimumab (ADA) or infliximab (IFX). The demographic data of the patients, the medications used at the time of initial presentation, best-corrected visual acuity at the first and final examinations, findings of the anterior and posterior segments, presence of active uveitis, fundus fluorescein angiography (FFA) and optical coherence tomography findings, drug-related side effects, and medications used at the last visit were recorded.

Results: Thirty-four patients were included in the study. Seven (20.58%) were female and 27 (79.41%) were male. At initial presentation, 38.2% of the eyes had a pan-uveitis attack. Fifteen patients were receiving anti-tumor necrosis factor-alpha inhibitors at first visit. In the first FFA, disc staining and capillary leakage were detected in 47 eyes (69.1%), while 14 eyes (20.5%) showed disc staining alone. Sixteen (47.05%) patients received ADA as the first-line biologic agent, and 2 (5.8%) patients were started on IFX. At the final visit, the clinical remission rate was 85.2%, and the angiographic remission rate was 44.1%. Thirty patients (88.2%) were receiving biological therapy at the last visit.

Conclusion: Biological agents can be successfully used in cases of BU that complicated or resistant to conventional immunosuppressive therapy. FFA is the most important diagnostic tool for evaluating subclinical inflammation in patient follow-ups.

Keywords: Behçet's uveitis, refractory uveitis, adalimumab, infliximab

INTRODUCTION

Behçet's disease (BD) is a chronic, systemic vasculitis of unknown etiology, commonly seen in countries along the historical Silk Road. Its most frequent manifestations are oral aphthae and genital ulcers, with uveitis being a significant cause of ocular morbidity (1-3). Behçet's uveitis (BU) is a non-granulomatous uveitis characterized by flare-ups and remissions. Patients may present with anterior, posterior, or pan-uveitis. The most severe and important form of BU that leads to blindness is pan-uveitis. In this form, non-granulomatous anterior uveitis is accompanied

Address for Correspondence: Dilbade Yıldız Ekinci, Assoc. Prof., University of Health Sciences Türkiye, Diyarbakır Gazi Yaşargil Training and Research Hospital, Clinic of Ophthalmology, Diyarbakır, Türkiye
E-mail: dilbadeekinci@gmail.com **ORCID ID:** orcid.org/0000-0002-5535-264X
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by diffuse vitritis, retinal infiltrates, papillitis, periphlebitis, and occlusive retinal vasculitis. Macular edema, retinal and optic atrophy, cataracts, and glaucoma are the leading causes of vision loss. BU typically manifests as pan-uveitis in young males and is more frequent and severe than in females. Early diagnosis and treatment may prevent complications and blindness in a significant number of patients (3-5).

Fundus fluorescein angiography (FFA) and optical coherence tomography (OCT) are the most important imaging modalities for the follow-up and treatment of BU. The most typical BU finding in FFA is the fern-like leakage observed in the capillaries, which is correlated with disease activity. OCT may reveal macular findings and retinal nerve fiber defects at the posterior pole resulting from regressed retinitis (6-8).

The goal of BU treatment is to prevent acute flare-ups and recurrences, to achieve clinical and angiographic remission, and to prevent potential complications. Aggressive treatment is required to prevent blindness, especially in cases of pan-uveitis. In acute flare-ups, in addition to high-dose corticosteroid therapy, periocular and intravitreal corticosteroid injections are used, particularly in the presence of macular edema and unilateral severe uveitis. While systemic corticosteroids may treat acute flare-ups, they are insufficient for long-term remission, which is why conventional immunosuppressive or biological agents are employed in treatment (4,6,7,9-13). The most commonly used disease-modifying antirheumatic drugs (DMARDs) are azathioprine (AZA) and cyclosporine A (CSA). However, in complicated and resistant cases, interferon-alpha-2a (IFNα-2a), tumor necrosis factor-alpha (TNF-α) inhibitors such as adalimumab (ADA) and infliximab (IFX), are added to the treatment. In case of inefficacy of these anti-TNF agents, tocilizumab (TCZ), golimumab, and Janus kinase inhibitors may be used (13-16).

This study aims to assess the findings and outcomes of patients receiving biological therapy for BU at our institution.

MATERIAL AND METHODS

This retrospective, single-center study was approved by the Clinical Research Ethics Committee of the University of Health Sciences Türkiye, Diyarbakır Gazi Yaşargil Training and Research Hospital (approval number: 226, date: 11.10.2024) and conducted in accordance with the Declaration of Helsinki. The ethics committee disregarded the requirement to obtain patient consent due to the retrospective nature of the study. Patients diagnosed with BU who were treated with biological therapy, and followed jointly by the rheumatology and Behçet's-uveits departments, of our hospital between 2018 and 2024 were included in the study. The medical records of these patients were retrospectively reviewed. Demographic characteristics; age at diagnosis; presence of systemic comorbidities; follow-up duration; best-corrected visual acuity (BCVA) at the initial and final examinations using the Snellen chart; presence of glaucoma and cataracts; history of intraocular surgery; anterior chamber reaction and vitritis severity at baseline and final examination; as well as posterior segment findings, were recorded. The severity of anterior chamber reaction was classified according to the "standardization of uveitis nomenclature working group" criteria (17).

The medications used by the patients at the time of initial presentation, medications added during follow-up, and any drug-related side effects were documented. The findings from the first and last FFA and OCT examinations were reviewed to assess whether clinical and angiographic remission had been achieved.

The drugs and drug combinations and the treatment scheme to be applied to the patients were created by taking into account the patient's systemic findings and the severity of uveitis. The doses and frequency of application of the agents used are as follows:

1. AZA was administered at a dose of 2.5 mg/kg/day, and CSA at 3-5 mg/kg/day.

2. ADA was initiated with a subcutaneous loading dose of 80 mg, followed by 40 mg weekly for the first week, then 40 mg every 2 weeks. In patients who did not achieve clinical and angiographic remission after at least 3 months of ADA 40 mg every 2 weeks, the frequency was increased to once a week.

3. IFX was administered intravenously at a dose of 5 mg/kg in a 0, 2, and 6-week loading regimen followed by 4-6 week intervals. If remission was not achieved, the infusion frequency was adjusted to 4 weeks.

4. TCZ was administered as a subcutaneous injection at a dose of 162 mg per week.

Clinical remission was defined as the absence of active inflammation in the anterior chamber and vitreous without the need for topical or systemic corticosteroids for at least 3 months, with fundus examination showing no retinitis, retinal vasculitis, macular edema, or papillitis. Angiographic remission was defined as the absence of optic disc staining, macular leakage, and peripheral vascular leakage. Resistant uveitis was defined as the presence of acute flare-ups requiring topical or systemic corticosteroids despite at least one immunosuppressive therapy, recurrence during corticosteroid dose reduction, development of new complications related to uveitis, and continued or

worsening activation on angiography. Patients with resistant uveitis were started on biological therapy or had the frequency of their current biological therapy adjusted.

All patients were informed about the side effects of the drugs used. Patients receiving biological treatment were evaluated for malignancy, tuberculosis, syphilis, viral hepatitis, and multiple sclerosis before initiating therapy. A complete blood cell count, renal and hepatic function tests, and a chest X-ray was performed at the initial presentation and during follow-ups. Purified protein derivative (PPD) testing was performed at six month intervals. At each visit, patients were questioned about systemic symptoms regarding side effects. If side effects were detected, the responsible agent was discontinued and, if necessary, treatment for the side effects was applied.

Statistical Analysis

The normality of data distribution was assessed using the Kolmogorov-Smirnov test. The Mann-Whitney U test was used for comparisons of non-parametric data. Statistical analyses were performed using the Jamovi software (The Jamovi Project, 2024, version 2.5, Sydney, Australia). Welch's t-test was used to compare continuous variables between two groups. Changes in vision levels at initial and final visits were compared with the Wilcoxon test. The significance level was set at $p<0.05$.

RESULTS

A total of 68 eyes from 34 patients receiving biological therapy for BU were included in the study. Of the patients, 7 (20.58%) were female, and 27 (79.41%) were male. The average age at initial presentation was 31.85±7.66 years (range: 18-47), and the average age at diagnosis of BU was 24.74±6.66 years (range: 14-37). The mean follow-up duration was 32.82±21.97 months (ranging 3-78) (Table 1).

All patients had been diagnosed with uveitis prior to presenting to our clinic. At initial presentation, 30 (88.2%) patients had a diagnosis of BD, whereas 4 (11.8%) patients were diagnosed with BD and associated uveitis at our institution. One patient had Crohn's disease along with BD. All patients had a history of topical and systemic corticosteroid usage. One patient, previously undiagnosed with BD and was treated only with systemic corticosteroids, had a history of corticosteroid-induced diabetes.

Table 1. Data for male and female

	Female (n=7)	Male (n=27)	p-value
Age	33.50±10.6	30.27±7.85	0.528
Age of diagnosis	26.88±8.28	24.085±6.11	0.528
Total follow-up time (month)	53.00±15.55	34.07±22.21	0.393
Initial visual aquity	0.61±0.42	0.53±0.39	0.415
Final visual aquity	0.76±0.29	0.76±0.45	0.497

Initial Examination Findings

All patients had bilateral BU. The BCVA measured using the Snellen chart was 0.87 (range 0-1.0) at the first examination. Initial clinical findings were given in Table 2. In addition to the retinitis-panuveitis (Figure 1), 4 eyes (5.8%) had terminal-stage BU findings, while 2 eyes (2.9%) had retinal vein occlusion, 1 eye (1.4%) had glaucomatous optic atrophy, and 1 eye (1.4%) had inoperable retinal detachment. FFA at initial presentation revealed disc staining and capillary leakage in 47 (69.1%) eyes, and disc staining alone in 14 (20.5%) eyes. No angiographic activation was found in 6 (8.8%) eyes, as shown in the consort Figure 2. One

Table 2. Clinical findings at initial visit and at the last follow-up visit

Clinical findings	Initial visit (n=number of eyes)	Last follow-up visit	p-value
Anterior uveitis	28 (41.1%)	2 (2.9%)	<0.01
Glaucoma	2 (2.9%)	2 (2.9%)	1
Pseudophakia	7 (10.2%)	8 (11.7%)	>0.05
Cataract	10 (14.7%)	14 (20.5%)	>0.05
Diffuse vitritis	26 (38.2%)	10 (14.7%)	<0.01
Retinitis	26 (38.2%)	0 (0%)	<0.01
BCVA	0.87 (0-1)	0.92	0.01

BCVA: Best-corrected visual acuity

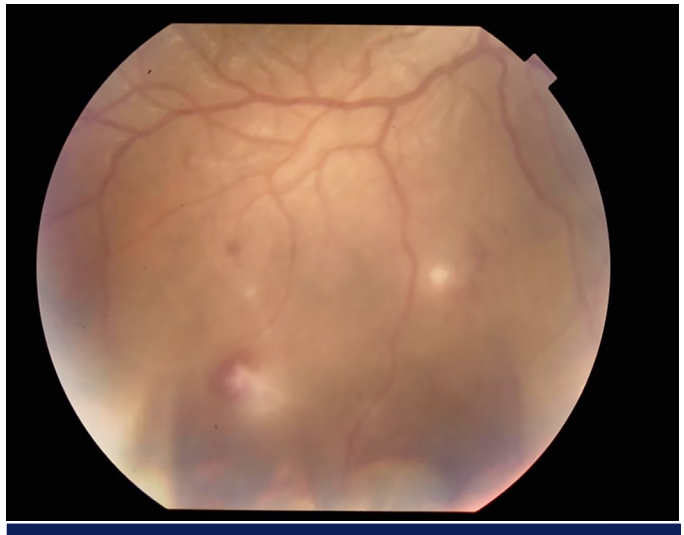

Figure 1. Hemorrhagic retinitis is observed in a 22-year-old male patient receiving azathioprine at 100 mg/day treatment

eye showed secondary optic nerve head neovascularization with fern-like leakage (Figure 3). In OCT, 5 (7.3%) eyes had epiretinal membrane (ERM), 2 (2.9%) had macular holes, 5 (7.3%) had foveal atrophy, and 7 (10.2%) had macular edema.

The medications used by the patients at the time of their first application are given in Table 3.

Follow-up Treatments

During follow-up, 7 (20.5%) patients received CSA, 8 (23.5%) patients received AZA, and 2 (5.8%) patients received both AZA and CSA. Sixteen (47.05%) patients with uveitis resistant to DMARDs were initially treated with ADA, while two (5.8%) received IFX. One patient on IFN was switched to ADA due to unavailability of the medication.

Five patients who were on ADA 40 mg every 2 weeks at the time of initial presentation did not achieve remission; therefore, the dosage was increased to weekly ADA. One patient on IFX developed an infusion reaction, and the other did not achieve remission; and therefore, both were switched to ADA. Due to recurrence, one patient on AZA, CSA, and ADA 40 mg every week was switched to IFX; and another patient on AZA and ADA 40 mg every week was switched to TCZ. One patient on IFX 5 mg/kg every 6 weeks and AZA had clinical and angiographic flare-ups; therefore the infusion frequency was increased to every 4 weeks, and CSA was added (Figure 4). Nine (26.4%) patients did not have any changes in their biological therapy (Table 3).

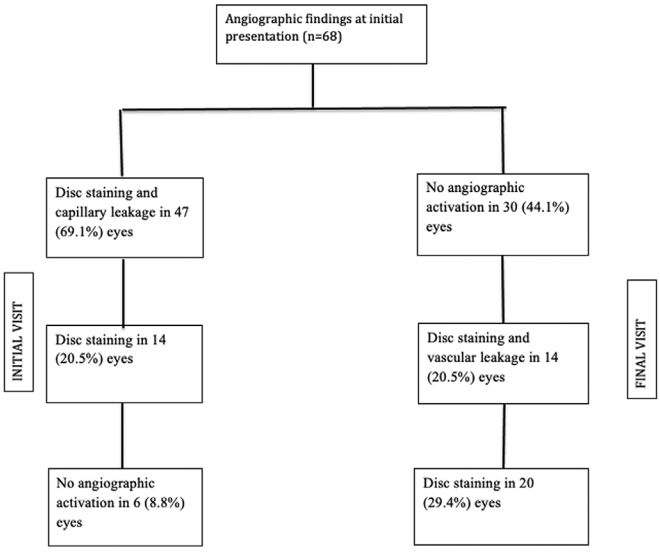

Figure 2. Consort flow diagram showing angiographic findings of the patients

Figure 3. Vascular leakage due to disc neovascularization and severe inflammation is observed under interferon therapy in a male patient

Final Examination Findings

At the final examination, the BCVA was 0.92 (0-1.0), showing a significant improvement from baseline (p=0.01). Clinical findings detected at the final visits are given in Table 2. At the final examination, 58 eyes (85.2%) of 29 patients were in clinical remission. FFA showed angiographic remission in 30 (44.1%) eyes from 15 patients (p=0.018). Disc staining and vascular leakage were observed in 14 (20.5%) eyes, and disc staining alone was noted in 20 (29.4%) eyes, leading to adjustments in treatment. OCT findings showed: of the eyes, 54 (79.4%) were normal, 4 (5.8%) had ERMs, 6 (8.8%) had foveal atrophy, 2 (2.9%) had macular holes, and 1 (1.4%) had central serous chorioretinopathy.

Demographic data, BCVA at initial and final examination, and clinical and angiographic remission rates by gender are given in Table 4.

Adverse Effects

Among patients receiving DMARDs, two CSA-treated patients experienced elevated blood pressure, and three developed

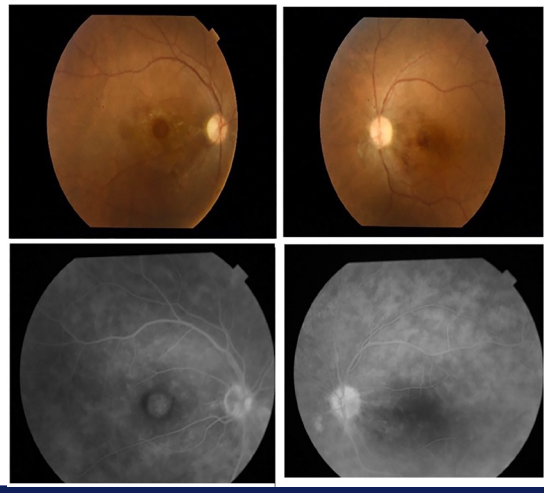

Figure 4. A 29-year-old male patient under infliximab 5 mg/kg/6 weeks and azathioprine 100 mg/day treatment has a hole in the macula in the right fundus photo; bilateral disc staining and vascular leakage in the posterior pole are observed in the taken angiography

Table 3. Medications used at the time of initial visit and at the last follow-up

Patient number	Medications used at the time of initial visit	Medications used at the last follow-up visit
1	AZA, CSA	-
2	AZA	AZA, ADA 40 mg/2 weeks
3	AZA	AZA, ADA 40 mg/2 weeks
4	AZA,ADA 40 mg/2 weeks	AZA, ADA 40 mg/1 week
5	AZA,ADA 40 mg/2 weeks	AZA, ADA 40 mg/1 week
6	-	AZA
7	AZA	AZA, CSA, ADA 40 mg/1week
8	AZA	AZA, ADA 40 mg/1 week
9	AZA, ADA 40 mg/2 weeks	AZA, TCZ 162 mg/1 week
10	AZA	AZA, ADA 40 mg/2 weeks
11	AZA	AZA
12	-	AZA, ADA 40 mg/2 weeks
13	-	AZA, ADA 40 mg/1 week
14	AZA	AZA, ADA 40 mg/1 week
15	AZA, ADA 40 mg/2 weeks	AZA, ADA 40 mg/2 weeks
16	AZA	AZA, ADA 40 mg/1 week
17	AZA, IFX 5 mg/kg/6 weeks	AZA, CSA, IFX 5 mg/kg/4 weeks
18	-	AZA, CSA, IFX 5 mg/kg/4 weeks
19	-	AZA, ADA 40 mg/2 weeks
20	AZA, CSA	AZA, ADA 40 mg/2 weeks
21	AZA, CSA	AZA, ADA 40 mg/2 weeks
22	AZA, ADA 40 mg/2 weeks	-
23	AZA, ADA 40 mg/2 weeks	ADA 40 mg/2 weeks
24	ADA 40 mg/2 weeks	AZA, ADA 40 mg/2 weeks
25	IFN	AZA, ADA 40 mg/2 weeks
26	ADA 40 mg/2 weeks	AZA, ADA 40 mg/2 weeks
27	AZA	AZA, CSA, ADA 40 mg/1 week
28	ADA 40 mg/2 weeks	AZA, ADA 40 mg/2 weeks
29	ADA 40 mg/2 weeks	ADA 40 mg/2 weeks
30	AZA, ADA 40 mg/2 weeks	AZA, ADA 40 mg/1 week
31	AZA, ADA 40 mg/2 weeks	AZA, ADA 40 mg/2 weeks
32	AZA, ADA 40 mg/2 weeks	AZA, ADA 40 mg/1 week
33	AZA, ADA 40 mg/2 weeks	AZA, ADA 40 mg/2 weeks
34	-	ADA 40 mg/2 weeks

AZA: Azathioprine, CSA: Cyclosporine, ADA: Adalimumab, IFN: Interferon, IFX: Infliximab, TCZ: Tocilizumab

Table 4. Distrubition of findings by gender

	Female	Male	p-value
Age	32.25	31.73	$0.082^{t\text{-test}}$
Age at the time of diagnosis	26.88	24.08	$0.39^{t\text{-test}}$
BCVA at initial visit	0.61	0.53	$0.65^{t\text{-test}}$
BCVA at final visit	0.76	0.76	$0.99^{t\text{-test}}$
Angiographic remission (n) (absent/present)	4/12	31/18	0.017^{x2}
Clinical remission (n) (absent/present)	0/16	10/42	0.134^{x2}

^{x2}: Chi-square test, $^{t\text{-test}}$: Welch t-test, BCVA: Best corrected visual acuity

neurotoxicity. Among AZA users, 2 patients developed hepatotoxicity, and 1 experienced drug intolerance, leading to discontinuation of the drugs. Of the two female patients who received ADA 40 mg/2 weeks and AZA 100 mg/day, one developed tuberculosis, and the other developed breast cancer. Their treatments were terminated. One patient underwent vitrectomy for rhegmatogenous retinal detachment, which resulted in foveal atrophy. Two patients receiving AZA and ADA 40 mg every 2 weeks had at least 2 years of clinical and angiographic remission; therefore, ADA therapy was discontinued, and AZA was continued without recurrence. Three patients on biological therapy received isoniazid, and 1 patient, who was a hepatitis B carrier, received antiviral prophylaxis.

The average duration of ADA therapy was 31.88±20.24 months (range 3-68). The average time to switch to weekly ADA administration was 27.41±26.3 months (range 3-98).

DISCUSSION

In our study evaluating the effectiveness of biological agents in BU, 79.4% of the patients were male, and the male-to-female ratio was 3.8. Although clinical remission rates were similar across genders, angiographic remission rates were higher in women. Studies conducted in our country have shown that ocular involvement is at least twice as common in males compared to females, and uveitis tends to be more aggressive in males (18-20). Considering that biological treatments are used in patients with aggressive disease courses, the high rate of biological agent use and the low angiographic remission rate prove that the disease has a worse prognosis in men.

BU is often diagnosed in the second or third decade of life, and the prognosis tends to be better in females and in cases of the disease with later onset. In our study, the age range at which the patients were diagnosed with BU was similar to that reported in the literature, with the second decade being most common (18-22). The average age at diagnosis was similar in females,

compared to males, and there was no difference between the initial and final BCVA. However, considering the small number of cases in our study, larger cohort studies are needed to obtain more definitive conclusions.

BU is also observed in the pediatric age group, with symptoms often starting in late childhood. Uveitis is more common in male children. The clinical manifestations usually present in the form of pan-uveitis, and aggressive immunosuppressive treatment is required for remission (22,23). In a study conducted by Tugal-Tutkun and Urgancıoğlu (22) in 2003, a high incidence of cataracts, maculopathy, and optic atrophy was reported in pediatric cases of BU, along with serious side effects from systemic steroids. Additionally, 22.7% of affected eyes had a BCVA of 0.1 or worse (21). In our study, two male patients were diagnosed with pediatric BU at the age of 14, and both developed frequent pan-uveitis flares despite being treated with AZA and systemic steroids. As a result, ADA 40 mg every 2 weeks was initiated in their treatment regimen. Remission was achieved in one patient with this treatment, while the other patient was switched to a combination of IFX 5 mg/kg, every month, along with AZA and CSA, which also resulted in remission. At the final examination, both patients had complete visual acuity and were in clinical remission. The anatomical and functional success achieved demonstrates the progress made in the treatment of BU with biological therapies in recent years, allowing for the prevention of blindness in these patients.

At the initial examination, all patients had bilateral uveitis based on clinical and angiographic findings. At the first consultation, 38% of the patients had a pan-uveitis attack. All these patients received 1 gram of intravenous steroids for 3 days, followed by a transition to the maintenance dose. Their immunosuppressive treatments were revised. At the final examination, there was a statistically significant increase in the average BCVA. In 16 eyes (23.5%), the initial BCVA was 0.1 or worse. After the treatment revision, BCVA improvement was achieved in only 7 of these eyes. In eyes where BCVA showed no improvement, major causes of blindness due to BU included optic atrophy, foveal atrophy, retinal detachment, and macular hole. These results emphasize the importance of initiating effective and aggressive treatment before permanent damage occurs in BU.

The classic angiographic finding in BU is fern-like capillary leakage, and the extent of this leakage correlates with the severity of the disease. The presence of optic disc leakage and capillary leakage in BU is an important prognostic indicator for active inflammation and recurrence (6,7,23). Kim et al. (24) demonstrated that the severity of retinal vascular leakage in FFA in BU patients, is associated with poor visual acuity as well as macular leakage and disc staining. The persistence of vascular leakage despite the decrease in attacks is an important sign that the treatment is still inadequate. In this patient group, the most important goal is to eliminate angiographic activation by strengthening the treatment to reduce recurrences and ocular morbidity. In our study, at the time of initial presentation, fern-like leakage and disc staining were present in 69.1% of eyes. At the final visit, although the clinical remission rate was 97.05%, the angiographic remission rate was only 44.1%. The lower angiographic remission rate compared to clinical remission suggests that the administered treatment needs to be reevaluated. Furthermore, these results support the idea that angiographic monitoring is an invaluable method in preventing uveitis recurrence and ocular morbidity.

It is known that the presence of ellipsoid zone damage and foveal thinning detected by OCT are associated with poor visual prognosis (23-25). In our study, at the final visit, OCT showed foveal thinning in 6 eyes and macular holes in 2 eyes. In all of these eyes, BCVA was 0.1 or worse, and no improvement in vision was observed during follow-up. Cystoid macular edema, which was observed in approximately 10% of the eyes at baseline, regressed with treatment. The ellipsoid zone remained intact, and BCVA increased.

In patients with aggressive uveitis, ADA and IFX are frequently used biological agents, and are the first-line treatment in selected cases. ADA is the only biologic agent approved by the United States Food and Drug Administration for the treatment of non-infectious uveitis is a humanized monoclonal antibody. For this reason, ADA is commonly the first-line biologic agent in clinical practice, for uveitis patients (6,13,26-31). On the other hand, IFX is known to be as effective as pulse steroid therapy and provides rapid inflammation control (32). A study comparing ADA and IFX as first-line biological therapies in resistant BU patients found that after one year, ADA-treated patients had better BCVA; however, IFX provided faster inflammation control. The study also showed that the continuation rate of ADA therapy was higher than that of the IFX group. The authors attributed this difference to the potential for infusion reactions due to the chimeric structure of IFX, the risk of anti-drug antibody formation, and the greater ease of ADA administration (13). In our clinic, at first presentation, 10 patients were receiving ADA 40 mg every 2 weeks in combination with AZA, 4 patients were receiving ADA 40 mg every 2 weeks alone, and 1 patient was on a combination of AZA and IFX 5 mg/kg every 6 weeks. Following clinical and angiographic evaluations, ADA was initiated in the treatment of 16 patients. IFX was initiated in 2 patients. In these patients, severe ocular complications and intense pan-uveitis

flare were present at first presentation, and our primary goal was to control the flare rapidly. Therefore, IFX was initially preferred among these 2 patients. However, in one patient, an infusion reaction occurred, and in the other, resistance developed, leading to a switch to ADA therapy.

The most undesirable side effects of anti-TNF agents are the development of malignancies and infectious diseases such as tuberculosis and hepatitis. In the follow-up of these patients, it is crucial to not only systematically query for symptoms but also to monitor viral markers, perform PPD tests, or QuantiFERON-TB Gold tests. Hematological malignancies are most commonly associated with these agents (33). In one female patient who started ADA and had a negative QuantiFERON-TB test, complaints of myalgia, fever, and night sweats developed after the second injection. Subsequent tests revealed the development of tuberculosis. The patient's current treatment was discontinued, and she was directed to tuberculosis treatment. In another patient who had been on ADA for at least 2 years, a suspicious mass was detected in the breast. A biopsy result confirmed malignancy, and the patient's treatment was terminated. Both patients were withdrawn from follow-up. These two cases highlight the importance of conducting a thorough systemic review at every visit, considering the extraocular symptoms and promptly initiating necessary consultations.

In our clinical practice, we aim to achieve not only clinical remission but also angiographic remission in patients with BD. We initiate treatment reduction after at least two years of remission in patients; instead of abruptly discontinuing biological agents, we reduce their frequency and continue with follow-ups. After an average follow-up period of 36 months, only two patients (5.8%) achieved two years of remission, during which biological agents were tapered and discontinued. The longest follow-up period was 78 months. The fact that such a small number of patients reached the target remission duration at the last visit indicates that the disease follows an aggressive course and requires long-term treatment.

Study Limitations

One of the limitations of our study is the small number of patients. This limitation reduces our ability to create subgroups for comparisons and affects the generalizability of the results we obtained. Additionally, the study being single-centered and retrospective in design is another limitation. Because the study was retrospective, clinical and angiographic examinations could not be performed at the same time schedule during follow-up. Both the small number of patients and the fact that angiography was not performed at fixed intervals prevent subgroup comparisons among biological agents. Multi-center studies with larger patient numbers are needed to perform more detailed statistical analysis and obtain more accurate results.

CONCLUSION

The present study supports the idea that remission may be achieved with biological agents in cases resistant to and complicated by DMARDs, and that an increase in the BCVA was observed. Although no recurrences were noted during follow-up, angiographic evaluation remains an important step in preventing blindness, as it helps detect subclinical inflammation that may persist or worsen, necessitating treatment adjustments.

Ethics

Ethics Committee Approval: This retrospective, single-center study was approved by the Clinical Research Ethics Committee of the University of Health Sciences Türkiye, Diyarbakır Gazi Yaşargil Training and Research Hospital (approval number: 226, date: 11.10.2024).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: D.Y.E., L.A., Concept: D.Y.E., L.A., Design: D.Y.E., L.A., Data Collection or Processing: D.Y.E., Analysis or Interpretation: D.Y.E., L.A., Literature Search: D.Y.E., Writing: D.Y.E.

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CERVICAL ZYGAPOPHYSEAL JOINT INVOLVEMENT IS ASSOCIATED WITH RADIOGRAPHIC DAMAGE AND IMPAIRED SPINAL MOBILITY IN AXIAL SPONDYLOARTHRITIS

Gülay Alp[1], Haluk Cinakli[2]

[1]Uşak University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Uşak, Türkiye
[2]Kırklareli Training and Research Hospital, Clinic of Rheumatology, Kırklareli, Türkiye

Abstract

Aim: To evaluate the clinical, functional, and radiographic implications of cervical facet joint [zygapophyseal joint (ZJ)] involvement and ankylosis in patients with axial spondyloarthritis (axSpA).

Material and Methods: This retrospective study included 132 patients diagnosed with axSpA. Cervical ZJ involvement and ankylosis were assessed using the De Vlam scoring method. Patients were stratified according to ZJ involvement (score ≥1) and complete ankylosis (score =3). Clinical, functional, and radiographic parameters were compared between groups. Multivariate linear regression was performed to identify independent associated factors, of impaired cervical mobility, as measured by cervical rotation.

Results: ZJ involvement was observed in 24 patients (18.3%), and ankylosis was observed in 11 (8.4%). Patients with ZJ involvement had significantly higher Bath Ankylosing Spondylitis Metrology Index scores, reduced cervical rotation, greater tragus-to-wall distance, and elevated cervical and total modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS). ZJ ankylosis was associated with male sex, hip involvement, cervical syndesmophytes, sacral enthesitis, and a higher prevalence of sacroiliac joint ankylosis. Notably, among patients with cervical ZJ involvement, 7/24 (29.2%; 5.3% of the overall cohort) had no anterior cervical damage (mSASSS=0). In multivariate analysis, both the De Vlam ZJ score (β=0.377, $p<0.001$) and cervical mSASSS (β=0.277, $p=0.012$) were independently associated with reduced cervical rotation.

Conclusion: Cervical ZJ involvement and ankylosis are associated with greater structural damage and reduced spinal mobility in axSpA. A subset of patients with ZJ ankylosis had no anterior cervical damage, highlighting the added diagnostic value of posterior structural assessment. Including posterior spinal evaluation may enhance functional assessment and improve prognostic accuracy.

Keywords: Axial spondyloarthritis, cervical spine, zygapophyseal joint, spinal mobility, functional limitation, radiographic damage

Address for Correspondence: Gülay Alp, MD, Uşak University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Uşak, Türkiye
E-mail: gulay_alp88@hotmail.com **ORCID ID:** orcid.org/0000-0003-1908-8439
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INTRODUCTION

Facet joints, also known as zygapophyseal joints (ZJ), are diarthrodial joints that, along with intervertebral discs, contribute to articulation between adjacent vertebrae and play a crucial role in spinal biomechanics. These joints facilitate load transmission and limit excessive motion, thereby maintaining spinal stability and integrity. As true synovial joints lined with hyaline cartilage, ZJs are commonly affected in degenerative conditions such as spinal osteoarthritis, particularly involving the posterior vertebral column.

In patients with axial spondyloarthritis (axSpA), ZJ involvement is common, especially in the thoracic spine (1). Current data suggest that facet joints may be affected early in the disease course. Altered spinal biomechanics, often due to syndesmophytes at the same vertebral level, may contribute to the development of ZJ fusion. Cervical ZJ involvement can lead to restricted neck motion, significantly affecting patients' quality of life. Pain originating from ZJ can vary based on the level of involvement. Lesions at the C2-C4 levels may result in occipital headaches (2), while C4-C6 involvement may cause pain in the upper trapezius region (3), while C6-C7 involvement may lead to pain in the scapular area. Lumbar ZJ-related pain is often referred to the sacroiliac region, hips, and thighs (4). Clinically, ZJ pain may mimic inflammatory back pain, presenting with morning stiffness and post-inactivity stiffness.

The modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) is the most widely used method to assess structural spinal damage in axSpA, evaluating erosion, sclerosis, squaring, and ankylosis in 24 anterior vertebral corners from C2 to L5, on lateral radiographs, yielding a total score ranging from 0 to 72 (5). However, this method focuses exclusively on anterior vertebral corner changes, failing to assess posterior structures such as the facet joints. Investigating the relationship between ZJ damage and mSASSS may enhance our understanding of spinal biomechanics and damage progression in axSpA. While anterior vertebral scoring remains standard, recent computed tomography (CT) studies have emphasised the significance of posterior structural lesions. Tan et al. (6) reported that facet joint lesions—including ankylosis, erosion, and joint space narrowing—can be detected in both early and advanced axSpA stages, regardless of radiographic classification. Despite these insights, the role of posterior spinal structures such as the cervical facet joints in contributing to clinical disability remains underexplored.

Previous studies have shown that ZJ ankylosis often occurs in vertebral segments with syndesmophytes (6). Syndesmophytes and ZJ fusion have been associated with reduced spinal mobility, including limitations in modified Schober's test and lateral thoracolumbar flexion. Radiographic evaluation of cervical vertebrae has been shown to correlate with disease activity and functional impairment in axSpA. In the study by Berbel-Arcobé et al. (7), cervical spine involvement was observed in 53.2% of patients. Compared with those without cervical damage, patients with cervical spine involvement were more frequently male, were older, had a higher body mass index (BMI), and were more often smokers. Among these, 38.1% had ZJ fusion, and overall ZJ involvement was reported in 29.1% of the entire cohort, including 5.9% with isolated posterior involvement (7). This condition was also associated with higher disease activity, worse functional scores, and greater structural damage. However, the relationship between cervical ZJ involvement and radiographic scores or functional limitation has not been fully elucidated.

Clinical observations indicate that many axSpA patients exhibit restricted cervical mobility despite having no visible anterior radiographic lesions. This raises the possibility that posterior structures, especially the cervical ZJs, may contribute to spinal dysfunction. This study aimed to investigate the association of cervical ZJ involvement and ankylosis with radiographic spinal damage and functional impairment in axSpA, and to identify clinical associations of ZJ involvement.

MATERIAL AND METHODS

This retrospective cross-sectional study was conducted at the Rheumatology Department of a tertiary care center. Demographic and clinical data, including age, sex, symptom, and disease duration, smoking status, education level, *HLA-B27* status, medication history (conventional synthetic disease-modifying antirheumatic drugs and biologic disease-modifying antirheumatic drugs), comorbidities, and presence of extra-musculoskeletal manifestations (e.g., uveitis, psoriasis, and inflammatory bowel disease), were also collected. Medical records of patients diagnosed with axSpA based on the 2009 Assessment of SpondyloArthritis International Society criteria and/or ankylosing spondylitis (AS) based on the modified New York criteria were reviewed (8,9). Eligible patients were between 18 and 65 years old and had available cervical and lumbar spine radiographs. To preserve cohort homogeneity, patients with other SpA subtypes (e.g., psoriatic arthritis, reactive arthritis) were excluded, restricting the analysis to AS and non-radiographic axSpA. Additional exclusion criteria were spinal malignancy, spinal infections, prior spinal surgery, and poor-quality radiographs.

Radiographic evaluation was performed retrospectively. Cervical spine radiographs were assessed for ZJ involvement, including ankylosis, joint space narrowing, erosion, and sclerosis. Cervical

ZJ damage was scored using the De Vlam method, which evaluates each ZJ from C2 to C7 on a 0 to 3 scale, where 0 signifies normal, 1 signifies joint space narrowing, 2 signifies partial ankylosis, and 3 signifies complete ankylosis, with a maximum total score of 15 (10). Structural spinal damage was quantified using the mSASSS, based on lateral radiographs of 24 vertebral corners from C2 to L5 (total score range 0-72). Cervical spine radiographs were independently evaluated by two experienced rheumatologists both of whom had prior training in spinal radiographic scoring. To assess interobserver reliability, a subset of 30 randomly selected radiographs was independently scored by both raters. Interobserver reliability was quantified using Cohen's kappa and interpreted according to the Landis-Koch classification (0.61-0.80: substantial; 0.81-1.00: almost perfect). The agreement for detecting ZJ involvement (De Vlam ≥1) was κ=0.85 (almost perfect), and the agreement for ZJ ankylosis (score =3) was κ=0.88 (almost perfect). These findings support the reliability and reproducibility of posterior cervical scoring in this study. In this study, cervical ZJ involvement was defined as any pathological finding affecting the facet joints, corresponding to a De Vlam score of 1 or higher. This includes joint space narrowing, partial ankylosis, and complete ankylosis. For further analyses, ZJ ankylosis was considered a distinct subgroup and was defined strictly as complete joint fusion, corresponding to a De Vlam score of 3.

Disease activity was evaluated using the Bath Ankylosing Spondylitis Disease Activity Index, which comprises six questions assessing fatigue, spinal pain, joint pain and swelling, enthesitis, and the severity and duration of morning stiffness. Each item is rated on a 0-10 visual analogue scale, and the final score is calculated as the mean of these six items, with higher scores indicating more active disease (11). Health-related quality of life was measured using the Ankylosing Spondylitis Quality of Life (ASQoL) questionnaire, a disease-specific instrument consisting of 18 dichotomous items (yes/no) that assess the impact of axSpA on physical, emotional, and social functioning (12). The total score ranges from 0 to 18, with higher scores indicating poorer quality of life. Functional limitations were assessed using the Bath Ankylosing Spondylitis Functional Index (BASFI) and the Bath Ankylosing Spondylitis Metrology Index (BASMI). BASFI consists of ten questions rated on a visual analogue scale (0-10), and BASMI includes cervical rotation, tragus-to-wall distance, lateral lumbar flexion, modified Schober's test, and intermalleolar distance, with final scores for each measure averaged (12).

Statistical Analysis

Statistical analyses included parametric and non-parametric tests to compare patients with and without cervical ZJ involvement (defined as any score ≥1 on the De Vlam scale) and those with and without cervical ZJ ankylosis (defined as a score of 3). Comparisons included demographic characteristics, radiographic scores (mSASSS), and functional parameters (BASMI, BASFI). Normality was assessed using the Shapiro-Wilk test. Depending on distributional assumptions, continuous variables were analysed using Student's t-test or Mann-Whitney U test, while categorical variables were assessed using chi-square or Fisher's exact test. Multivariate linear regression was performed to identify independent predictors of cervical mobility, using cervical rotation as the dependent variable. Confidence intervals were calculated using a 95% level based on standard errors from the regression model. A two-tailed p-value <0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA).

Ethics Approval

This retrospective study was approved by the Uşak University Non-Interventional Clinical Research Ethics Committee (approval number: 600-600-13, date: 20.03.2025). Written consent was not obtained due to the retrospective design of the study.

RESULTS

Out of 132 patients with axSpA, 24 (18.3%) had cervical facet joint (ZJ) involvement, defined as a De Vlam score ≥1, and 11 (8.4%) had ankylosis (score =3). Patients with ZJ involvement were slightly older (mean age: 44.0 vs. 39.1 years) and more often male (62.5% vs. 44.9%), although these differences were not statistically significant (Table 1). Symptom duration was also longer in the ZJ involvement group (median 10 vs. 8 years).

Patients with cervical ZJ involvement showed worse spinal mobility in unadjusted comparisons: BASMI 4.18 vs. 2.71 (p=0.002); cervical rotation 51.6 °C vs. 66.5 °C (mean difference -14.9 °C, p<0.001); tragus-to-wall distance 18.8 cm vs. 15.4 cm (p=0.001); and modified Schober 3.80 cm vs. 4.75 cm (p=0.019) (Table 2). In the ankylosis subgroup (De Vlam =3), decrements were larger: cervical rotation 43.9 °C vs. 65.4 °C (mean difference -21.5 °C, p<0.001) and BASMI 5.02 vs. 2.81 (p<0.001), with consistent differences across other mobility indices.

Structurally, cervical mSASSS was higher in patients with ZJ involvement (median 4 vs. 0), and cervical syndesmophytes were more common (62.5% vs. 14.2%). Hip involvement (41.7% vs. 18.7%) and sacroiliac ankylosis (37.5% vs. 9.3%) were also more frequent in this group. Although BASFI and ASQoL scores were numerically lower in patients with ZJ involvement, the differences were not statistically significant. Among patients with cervical ZJ involvement (De Vlam ≥1), 7/24 (29.2%) had a cervical mSASSS of 0, indicating no anterior cervical damage. This corresponds to 7/132 (5.3%) of the overall cohort. Within the ankylosis subset (De Vlam =3), 2/11 (18.2%) also had mSASSS=0 (2/132; 1.5% overall). Cervical facet joint ankylosis was present in 11 patients (8.4%), who had a longer symptom duration (median 16 vs. 7 years, p=0.107, not significant) and a significantly higher proportion of males (81.8% vs. 44.6%, p=0.018) (Table 3). These patients had significantly greater structural damage (median total mSASSS: 7.5 vs. 1) and reduced mobility (BASMI: 5.02 vs. 2.81; cervical rotation: 43.9 °C vs. 65.4 °C). Cervical syndesmophytes (81.9%) and hip involvement (54.5%) were particularly prominent in this subgroup (Table 4).

Spearman rank correlations showed that both the cervical facet (De Vlam ZJ) score and the cervical mSASSS were associated with several clinical/functional measures (Figure 1). Higher ZJ and mSASSS scores correlated with reduced cervical rotation (right: p=-0.23/-0.17, p=0.012/0.056; left: p=-0.24/-0.27, p=0.009/0.003; mean: p=-0.24/-0.23, p=0.008/0.010), greater tragus-to-wall distance (left: p=0.27/0.16, p=0.004/0.095), and lower modified Schober test (p=-0.16/-0.19, p=0.075/0.040). Correlations with lateral lumbar flexion were modest but significant in most comparisons (right: p=-0.18/-0.33, p=0.047/<0.001; left: p=-0.19/-0.40, p=0.040/<0.001). Intermalleolar distance showed small, non-significant associations (p=-0.05/-0.13, p>0.05).

Higher De Vlam ZJ scores [B=-2.397, 95% confidence interval (CI): -3.725 to -1.068, p<0.001] and cervical mSASSS scores (B=-1.007, 95% CI: -1.782 to -0.231, p=0.012) were independently associated with reduced cervical rotation in the multivariate

Table 1. Comparison of demographic, clinical, and treatment characteristics between axSpA patients with and without ZJ involvement (De Vlam score ≥1)

Variables	ZJ involvement (n=24)	No ZJ involvement (n=108)	p-value
Sex, male, n (%)	15 (62.5)	48 (44.4)	0.109
Age, years, mean ± SD	44.25±10.64	39.95±10.77	0.054
Smoker current, n (%)	10 (41.7)	46 (42.6)	0.934
Symptom duration, years, median (IQR)	10 (15)	8 (8)	0.754
Disease duration, years, median (IQR)	6 (7)	6 (10)	0.698
AxSpA type, r-axSpA, n (%)	14 (58.3)	63 (58.3)	0.820
HLA-B27 positive, n (%)	8 (44.4)	39 (50.6)	0.635
Spondlyloarthritis family history, n (%)	8 (33.3)	36 (33.6)	0.977
BMI, kg/m², mean ± SD	26.84±6.13	26.68±4.23	0.879
ESR mm/h, median (IQR)	8.5 (7)	8 (6)	0.256
History of enthesitis, n (%)	10 (41.7)	46 (42.6)	0.936
History of uveitis, n (%)	1 (4.2)	9 (8.3)	0.689
History of peripheral arthritis, n (%)	6 (25)	29 (26.9)	0.853
Psoriasis at baseline, n (%)	2 (4.5)	7 (9.3)	0.556
NSAID, current, n (%)	19 (79.2)	71 (65.7)	0.201
Biological therapy, n (%)	15 (62.5)	62 (57.4)	0.647
Comorbidity, at least one, n (%)	8 (33.3)	32 (29.6)	0.807
BASDAI, score, mean ± SD	3.76±2.03	4.43±2.36	0.111
BASFI, score, mean ± SD	3.40±1.69	2.75±2.45	0.823
ASQoL, score, mean ± SD	6.64±5.33	8.26±5.79	0.126

Data are presented as mean ± SD, median (IQR), or n (%).
axSpA: Axial spondyloarthritis, ZJ: Zygapophyseal joint, SD: Standard deviation, IQR: Interquartile range, BMI: Body mass index, ESR: Erythrocyte sedimentation rate, NSAID: Non-steroidal anti-inflammatory drug, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, ASQoL: Ankylosing Spondylitis Quality of Life, r-axSpA: Radiographic-axial spondyloarthritis

Table 2. Differences in functional measures and radiographic structural damage according to ZJ involvement (De Vlam score ≥1)

Variables	ZJ involvement (n=24)	No ZJ involvement (n=108)	p-value
BASMI total score, mean ± SD	4.18 (1.97)	2.71 (1.09)	**0.002**
Cervical rotation, mean ± SD	51.63 (19.9)	66.5 (14.9)	**<0.001**
Cervical rotation, right, mean ± SD, cm	51.70 (19.8)	64.75 (15.84)	**0.001**
Cervical rotation, left, mean ± SD, cm	51.05 (21.5)	67.75 (15.4)	**0.002**
Tragus-to-wall distance, mean ± SD, cm	18.80 (7.50)	15.4 (2.58)	**0.001**
Lateral lumbar flexion, right, mean ± SD, cm	13.55 (15.46)	19.72 (12.86)	0.086
Lateral lumbar flexion, left, mean ± SD, cm	12.96 (14.10)	18.87 (12.50)	**0.049**
Lateral lumbar flexion, mean ± SD, cm	13.40 (14.86)	19.56 (12.48)	0.086
Intermalleolar distance, mean ± SD, cm	96.6 (16.86)	102.18 (17.05)	0.111
Modified Schober's test, mean ± SD, cm	3.80 (2.22)	4.75 (1.59)	**0.019**
Sacroiliac ankylosis, n (%)	9 (37.5)	10 (9.3)	**<0.001**
Presence of cervical syndesmophyte, n (%)	14 (58.3)	15 (14)	**<0.001**
Presence of lumbar syndesmophyte, n (%)	7 (29.2)	13 (12.1)	**0.036**
Presence of symphysitis, n (%)	2 (8.3)	3 (2.8)	0.227
Sacral enthesitis, n (%)	5 (20.8)	10 (9.3)	0.148
Presence of hip involvement, n (%)	12 (50)	25 (23.1)	**0.008**
Cervical mSASSS, median (IQR)	4 (10)	0 (1)	**0.001**
Lumbar mSASSS, median (IQR)	1 (2)	0 (1)	**0.020**
Total mSASSS, median (IQR)	5 (11)	1 (2)	**<0.001**

Data are presented as mean ± SD, median (IQR), or n (%).
ZJ: Zygapophyseal joint, BASMI: Bath Ankylosing Spondylitis Metrology Index, SD: Standard deviation, mSASSS: Modified Stoke Ankylosing Spondylitis Spinal Score, IQR: Interquartile range

regression model (Table 5). Age, sex, and *HLA-B27* status were not found to be significant. Multicollinearity was not observed [variance inflation factors (VIFs) <1.4], supporting the independent contribution of posterior cervical damage to functional limitation in axSpA.

Binary ZJ involvement and ZJ ankylosis were not modeled multivariably due to limited events. These contrasts are presented as unadjusted mean differences.

DISCUSSION

This study highlights the clinical significance of cervical ZJ involvement in axSpA. We found that ZJ lesions were common and associated with impaired spinal mobility, supporting the notion that posterior spinal structures contribute substantially to functional limitation. Importantly, in multivariate regression, both the De Vlam ZJ score and cervical mSASSS were independently associated with reduced cervical rotation, indicating that posterior damage adds explanatory value beyond anterior vertebral scoring.

These findings support and extend previous reports on the clinical significance of cervical ZJ involvement in axSpA. In a 2024 study by Berbel-Arcobé et al. (7), cervical ZJ involvement was observed in 29.1% of patients, and ZJ fusion was present in 38.1% of those with cervical involvement. Notably, 20 patients (5.9% of the total cohort) exhibited isolated posterior involvement in the absence of anterior vertebral damage. Although the prevalence of ZJ ankylosis was lower in our cohort (8.4% vs. 20%), this difference may be attributed not only to a lower proportion of radiographic axSpA patients (58% vs. 91%) and a younger study population, but also to methodological differences, since Berbel-Arcobé et al. (7) reported ZJ fusion rates within the subgroup of patients with cervical involvement, whereas we reported prevalence across the entire cohort.

A meaningful subset lacked anterior cervical damage despite posterior ZJ lesions [7/24 (29.2%) within the ZJ-involvement group; 2/11 (18.2%) among those with complete ankylosis], supporting the added diagnostic value of posterior assessment. Compared with Berbel-Arcobé et al. (7), the overall proportion

Table 3. Comparison of demographic, clinical, and treatment characteristics between axSpA patients with and without cervical ZJ ankylosis (De Vlam score =3)

Variables	Facet joint ankylosis (n=11)	No ZJ ankylosis (n=121)	p-value
Sex, male, n (%)	9 (81.8)	54 (44.6)	**0.018**
Age, years, mean ± SD	44.82±10.8	39.98±10.81	0.158
Current smoker, n (%)	6 (54.5)	50 (41.3)	0.527
Smoker ever, n (%)	6 (54.5)	65 (54.2)	0.981
Symptom duration, years, median (IQR)	16 (14)	7 (8)	0.107
Disease duration, years, median (IQR)	8.5 (9)	6 (8)	0.414
AS type, r-axSpA, n (%)	9 (81.8)	68 (56.2)	0.120
HLA-B27 positive, n (%)	5 (62.5)	42 (48.3)	0.486
Spondlyloarthritis family history, n (%)	5 (45.5)	39 (32.5)	0.506
BMI, kg/m², mean ± SD	26.9±4.46	24.6±5.92	0.128
ESR mm/h, median (IQR)	10.5 (9)	8 (6)	0.117
CRP mg/L, median (IQR)	4.16 (9.01)	3.95 (6.13)	0.471
History of enthesitis, n (%)	2 (18.2)	54 (44.6)	0.116
History of peripheral arthritis, n (%)	2 (18.2)	32 (27.3)	0.727
History of uveitis, n (%)	1 (9.1)	9 (7.4)	0.595
Psoriasis at baseline, n (%)	2 (4.7)	29 (8.6)	0.556
NSAID, current, n (%)	8 (72.8)	82 (67.8)	1
Biological therapy, n (%)	9 (81.9)	68 (56.2)	0.120
Comorbidity, at least one, n (%)	2 (18.2)	38 (31.4)	0.503
BASDAI, score, mean ± SD	3.05±1.99	4.29±2.26	0.097
BASFI, score, mean ± SD	3.09±2.35	2.65±2.32	0.787
ASQoL, score, mean ± SD	6.33±6.46	7.79±5.62	0.460

Data are presented as mean ± SD, median (IQR), or n (%).
ZJ: Zygapophyseal joint, SD: Standard deviation, IQR: Interquartile range, BMI: Body mass index, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, NSAID: Non-steroidal anti-inflammatory drug, ASQoL: Ankylosing Spondylitis Quality of Life, axSpA: Axial spondyloarthritis, AS: Ankylosing spondylitis, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, r-axSpA: Radiographic-axial spondyloarthritis

of isolated posterior involvement was similar (5.3% vs. 5.9%), whereas the proportion within the ZJ-involvement subgroup was higher in our cohort (29.2% vs. 20.2%).

Mechanistically, posterior element pathology at the cervical ZJs—capsular thickening/ossification, joint-space narrowing, and ankylosis—restricts segmental rotation and extension. Hypertrophy/ossification of adjacent posterior ligaments further stiffens the posterior column and alters load transfer, leading to global motion loss even when anterior vertebral corners are normal on mSASSS. Pain-related muscle guarding may additionally reduce active range. These mechanisms are consistent with imaging data showing co-occurrence of posterior and bridging lesions and with studies demonstrating that posterior scoring adds information beyond anterior-focused indices (6,10,13,14). In unadjusted comparisons, cervical ZJ involvement was associated with a 15 °C lower cervical rotation, and ZJ ankylosis with a 22 °C lower rotation, alongside higher BASMI scores. While Berbel-Arcobé et al. (7) reported associations with male sex, smoking, and elevated BMI; these variables were not significant in patients with overall ZJ involvement in our cohort. However, male sex was significantly more frequent in the ankylosis subgroup, suggesting a potential sex-related predisposition to more advanced posterior damage.

A key methodological distinction is that we conducted a multivariate regression analysis in which both the De Vlam ZJ score and cervical mSASSS were found to be independent predictors of reduced cervical rotation. Notably, despite the anatomical and pathological overlap between anterior and posterior lesions, no significant multicollinearity was detected (VIFs <1.4). This suggests that posterior structural changes,

Table 4. Differences in functional measures and radiographic structural damage according to the presence of cervical ZJ ankylosis (De Vlam score =3)

Variables	ZJ ankylosis (n=11)	No ZJ ankylosis (n=120)	p-value
BASMI total, mean ± SD	5.02 (2.51)	2.85 (1.83)	**<0.001**
Cervical rotation, mean ± SD	43.9 (17.88)	65.43 (15.76)	**<0.001**
Cervical rotation, right, mean ± SD	46.2 (17.99)	63.7 (16.62)	**0.002**
Cervical rotation, left, mean ± SD	43.95 (17.80)	64.9 (15.62)	**<0.001**
Tragus-to-wall distance, mean ± SD, cm	21.50 (9.79)	15.76 (2.74)	**<0.001**
Lateral lumbar flexion, right, mean ± SD, cm	16.20 (22.67)	18.17 (12.47)	0.659
Lateral lumbar flexion, left, mean ± SD, cm	15.55 (21.13)	17.96 (12.19)	0.577
Lateral lumbar flexion, mean ± SD, cm	15.87 (21.85)	18.52 (12.75)	0.642
Modified Schober's test, mean ± SD, cm	3.05 (2.77)	4.71 (1.58)	0.093
Intermalleolar distance, mean ± SD, cm	93.70 (20.55)	99.57 (17.36)	0.316
Sacroiliac ankylosis, n (%)	8 (72.7)	11 (9.1)	**<0.001**
Presence of cervical syndesmophyte, n (%)	8 (72.7)	21 (17.5)	**<0.001**
Presence of lumbar syndesmophyte, n (%)	3 (27.3)	17 (14.2)	0.372
Presence of symphysitis, n (%)	2 (18.2)	5 (4.1)	0.106
Sacral enthesitis, n (%)	4 (36.4)	11 (9.1)	**0.023**
Presence of hip involvement, n (%)	8 (72.7)	29 (24)	**0.001**
Cervical mSASSS, median (IQR)	7 (17)	0 (1)	**0.006**
Lumbar mSASSS, median (IQR)	0.5 (12)	0 (2)	0.412
Total mSASSS, median (IQR)	7.5 (29)	1 (3)	**0.012**

Data are presented as mean ± SD, median (IQR), or n (%).
ZJ: Zygapophyseal joint, BASMI: Bath Ankylosing Spondylitis Metrology Index, SD: Standard deviation, mSASSS: Modified Stoke Ankylosing Spondylitis Spinal Score, IQR: Interquartile range

primarily facet joint damage, provide additional explanatory value for cervical mobility impairment in axSpA, beyond what is captured by anterior vertebral scoring alone.

The frequent co-occurrence of syndesmophytes and ZJ ankylosis in our cohort (72.7% vs. 17.5%) aligns with findings from Tan et al. (6), who used thoracolumbar CT to demonstrate that ZJ ankylosis commonly occurs alongside vertebral bridging lesions. Although the cross-sectional nature of our study precludes inference of causality, the predominance of syndesmophytes in patients with ZJ fusion lends support to the hypothesis that anterior and posterior structural damage may develop in close association at the same levels.

The study findings are consistent with a large longitudinal analysis involving 1,106 AS patients, which found that cervical facet joint ankylosis occurred as frequently as bridging syndesmophytes (17.8% vs. 16.8%), and often coexisted (13.5%). That study also found that patients with ZJ ankylosis had a higher disease burden, including elevated cervical mSASSS, more severe sacroiliitis, increased hip involvement, and a greater frequency of uveitis (13). Consistently, in our cohort, ZJ ankylosis was associated with greater functional impairment, as evidenced by higher BASMI scores, reduced cervical rotation, and increased tragus-to-wall distance. In addition, patients with ZJ ankylosis showed more severe structural damage, including higher cervical and total mSASSS scores, and more frequent sacroiliac ankylosis, cervical syndesmophytes, hip involvement, and sacral enthesitis. Together, these findings highlight the importance of evaluating posterior spinal elements, which may reflect more extensive structural damage in axSpA.

Longitudinal data from the same cohort also demonstrated reciprocal changes between anterior and posterior lesions: patients with bridging syndesmophytes showed faster increases in cervical ZJ scores, while those with ZJ ankylosis exhibited more rapid progression in cervical mSASSS (13). Our cross-sectional findings, are consistent with this concept, especially in patients with functional limitation despite low mSASSS values, highlighting cases where posterior damage may precede or exceed anterior lesions.

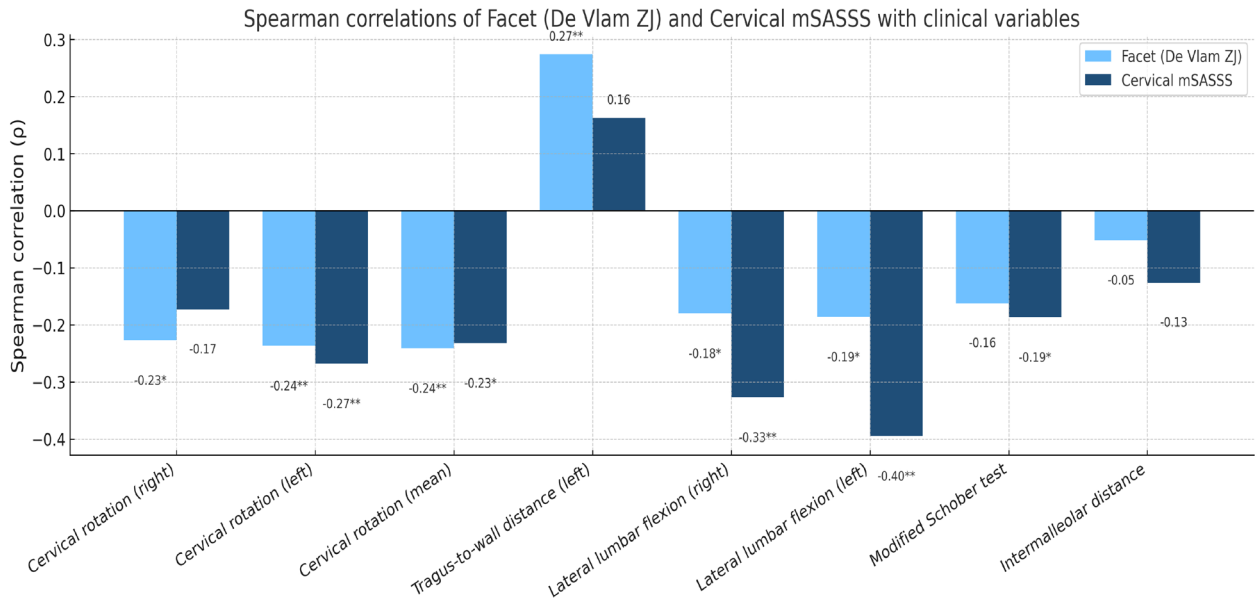

Figure 1. Spearman correlations (ρ) of posterior (cervical facet; De Vlam ZJ) and anterior (cervical mSASSS) structural scores with clinical/functional measures in axial spondyloarthritis (axSpA). Bars display ρ for cervical rotation (right/left/mean), tragus-to-wall distance (left only), lateral lumbar flexion (right/left), modified Schober test, and intermalleolar distance. Numeric labels on bars are r values.
*: p<0.05, **: p<0.01, ZJ: Zygapophyseal joint, axSpA: Axial spondyloarthritis, mSASSS: Modified Stoke Ankylosing Spondylitis Spinal Score

Table 5. Multivariate linear regression for determinants of cervical mobility in patients with axial spondyloarthritis

Variable	B	SE	Beta	p-value	95% CI (Lower)	95% CI (Upper)	Tolerance	VIF
De Vlam score	-2.397	0.668	-0.377	**<0.001**	-3.725	-1.068	0.762	1.312
Cervical mSASSS score	-1.007	0.390	-0.277	**0.012**	-1.782	-0.231	0.729	1.372
Male sex	0.305	0.161	0.179	0.062	-0.016	0.626	0.934	1.071
Age	1.637	3.357	0.048	0.627	-5.037	8.312	0.872	1.147
***HLA-B27* positivity**	5.240	3.368	0.153	0.123	-1.456	11.936	0.867	1.154

mSASSS: Modified Stoke Ankylosing Spondylitis Spinal Score, B: Unstandardised regression coefficient, CI: confidence interval, VIF: Variance inflation factor, SE: Standard error

Recent efforts to improve radiographic assessment have led to the development of the Combined Ankylosing Spondylitis Spine Score (CASSS), which incorporates both cervical mSASSS and ZJ scoring. CASSS has demonstrated greater sensitivity and consistency in tracking disease progression compared to mSASSS alone. In the study by Maas et al. (14), CASSS provided a more balanced representation of axial structural damage, supporting our observation that cervical ZJ ankylosis is independently associated with impaired spinal mobility.

Our findings support incorporating posterior cervical assessment into routine practice when anterior-focused scores are normal or low despite impaired mobility (e.g., high BASMI or reduced cervical rotation), when neck symptoms are disproportionate to anterior radiographic damage, and at baseline before longitudinal follow-up in established axSpA. Posterior scoring is also reasonable when syndesmophytes are present elsewhere or clinical-radiographic discordance is suspected, as it can uncover clinically relevant ZJ pathology that may be missed by anterior-only indices (6,7,13,14).

While the CASSS (cervical mSASSS + ZJ scoring) increases sensitivity to structural burden (14), its practical limitations include additional scoring time, need for reader training in facet-joint grading, and interobserver variability reported in some settings (7). Thus, a pragmatic approach is to apply CASSS at baseline and when clinical–radiographic discordance exists, reserving simpler indices for routine visits. Looking ahead, validated artificial

intelligence and machine-learning-based image analysis could streamline ZJ scoring and improve standardization, potentially enhancing the clinical feasibility of CASSS.

Study Limitations

Our study has several limitations. First, its retrospective and cross-sectional design precludes causal inference and limits our ability to evaluate disease progression over time. Second, the assessment of structural damage was based solely on conventional lateral spinal radiographs, which may lack sensitivity for detecting early or subtle lesions and does not allow evaluation of active inflammation, such as bone marrow oedema. Advanced imaging modalities, such as magnetic resonance imaging or CT, can provide a more comprehensive assessment of both inflammatory and structural changes, particularly in the posterior elements of the spine. Third, the relatively small number of patients with ZJ ankylosis (n=11) may limit the statistical power and generalizability of subgroup analyses. Despite these limitations, the inclusion of detailed functional measures, including BASFI and BASMI, strengthens the clinical validity of our findings. It supports the observed associations between posterior structural damage and spinal mobility impairment.

CONCLUSION

Cervical ZJ involvement and ankylosis are independently associated with reduced cervical mobility and increased structural damage in axSpA. Posterior lesions, which may be radiographically silent on anterior-focused scoring systems, provide additional prognostic information. These findings support the integration of posterior cervical assessments into routine imaging protocols to enhance the evaluation of functional limitation and radiographic severity in clinical practice.

Key Messages

- Cervical zygapophyseal joint involvement is associated with greater radiographic burden and impaired spinal mobility in axial spondyloarthritis.

- ZJ ankylosis is associated with significantly higher Bath Ankylosing Spondylitis Metrology Index scores, indicating more severe functional limitations.

- De Vlam scoring allows detection of posterior structural lesions not captured by modified Stoke Ankylosing Spondylitis Spinal Score.

Ethics

Ethics Committee Approval: This retrospective study was approved by the Uşak University Non-Interventional Clinical Research Ethics Committee (approval number: 600-600-13, date: 20.03.2025).

Informed Consent: Retrospective study.

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Footnotes

Authorship Contributions

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

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

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