E-ISSN: 2980-1559

https://qrheumatol.com/

Volume 3 | Issue 1

RHEUMATOLOGY QUARTERLY

RQ
Rheumatology Quarterly

March
2025

galenos yayınevi

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

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

The journal is published online.

Owner: Galenos Publishing House

Responsible Manager: Sekib Sokolovic

galenos yayınevi

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

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

CONTENTS

ORIGINAL ARTICLES

CASE REPORT AND LITERATURE REVIEW

ORIGINAL ARTICLE

Rheumatology Quarterly

DOI: 10.4274/qrheumatol.galenos.2025.05706
Rheumatol Q 2025;3(1):1-5

THE CLINICAL FEATURES OF ARTHRITIS IN BEHÇET'S DISEASE

Cem Kıvanç Kırcı[1], Metin Özgen[2], Demet Yalçın Kehribar[3], Özlem Kırcı[4]

[1]Ondokuz Mayıs University Faculty of Medicine, Department of Internal Medicine, Samsun, Türkiye
[2]İzmir Ekonomi University Medical Point Hospital, Department of Rheumatology, İzmir, Türkiye
[3]Dokuz Eylül University Faculty of Medicine, Department of Internal Medicine, İzmir, Türkiye
[4]Samsun Training and Research Hospital, Clinic of Family Medicine, Samsun, Türkiye

Abstract

Aim: This study aims to explore the clinical, laboratory, and systemic differences between Behçet's disease (BD) patients with arthritis and those without, focusing on how arthritis influences disease progression and treatment strategies.

Material and Methods: A retrospective, observational study was conducted on 881 patients diagnosed with BD according to the International Study Group criteria. Patients were categorized into two groups: those with arthritis (n=233) and those without (n=648). Clinical findings, laboratory markers [C-reactive protein (CRP), erythrocyte sedimentation rate (ESR)], and systemic manifestations, including neurological and vascular complications, were compared between the groups. Statistical analyses were performed to identify significant differences.

Results: Patients with arthritis exhibited higher systemic inflammation, as evidenced by elevated ESR (37.6±23.9 vs. 31.1±23.9, p=0.000) and CRP (25.9±32.2 vs. 18.6±34.6, p=0.006) at baseline. Family history of BD was more prevalent in the arthritis group (15% vs. 10%, p=0.041). Neurological involvement was significantly higher in the non-arthritis group (11% vs. 4%, p=0.002), as were vascular complications, including: pulmonary artery aneurysms (2%, p=0.043) in the non-arthritis group and arterial thrombosis (5% vs. 1%, p=0.025). Patients with arthritis were more likely to receive corticosteroid therapy (36% vs. 21%, p=0.019), while pulse corticosteroid use was higher in the non-arthritis group (9% vs. 4%, p=0.008).

Conclusion: BD patients with arthritis demonstrate heightened systemic inflammation, a stronger genetic predisposition, and greater reliance on corticosteroids. In contrast, those without arthritis have higher rates of severe systemic complications, including neurological and vascular involvement. These findings emphasize the importance of individualized management strategies tailored to the presence or absence of arthritis, addressing the diverse clinical spectrum of BD.

Keywords: Behçet's disease, arthritis, systemic inflammation, vascular complications, neurological involvement, individualized management

Address for Correspondence: Özlem Kırcı, Samsun Training and Research Hospital, Clinic of Family Medicine, Samsun, Türkiye
E-mail: drkirciozlem@gmail.com **ORCID ID:** orcid.org/0000-0002-6184-2039
Received: 10.01.2025 **Accepted:** 18.02.2025 **Publication Date:** 21.03.2025

Cite this article as: Kırcı CK, Özgen M, Yalçın Kehribar D, Kırcı Ö. The clinical features of arthritis in Behçet's disease. Rheumatol Q. 2025;3(1):1-5

INTRODUCTION

Behçet's disease (BD) is a chronic, multisystem inflammatory disorder that typically presents with recurrent oral and genital ulcers, uveitis, and various systemic manifestations such as arthritis, neurological, vascular, and gastrointestinal involvement (1). First described by the Turkish dermatologist Hulusi Behçet in 1937, BD predominantly affects individuals from countries along the "Silk Road," such as Türkiye, Japan, and Iran. Despite extensive research, the exact pathogenesis of BD remains poorly understood, although both genetic predisposition and environmental factors are believed to play key roles in its development (2). The disease's heterogeneous nature, coupled with its multi-organ involvement, makes it a challenging condition to diagnose and treat. In the absence of a definitive diagnostic test, diagnosis is primarily clinical, and management involves a multidisciplinary approach to control inflammation and manage symptoms (3).

Arthritis is one of the most common manifestations of BD, affecting approximately 40% to 60% of patients (4). It is typically a non-deforming, inflammatory condition that can affect various joints, with the knee joint being the most frequently involved (5). However, not all BD patients experience arthritis, and its presence or absence may influence the disease's clinical course and treatment strategies. Several studies have shown that BD patients with arthritis tend to have higher levels of systemic inflammation, as measured by elevated C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) (6). In addition, arthritis may be associated with other systemic complications, including vascular and neurological involvement, which may affect prognosis. Untreated ocular, vascular, nervous system, and gastrointestinal tract involvement may lead to serious damage and even death (7,8).

BD also presents with a range of other systemic manifestations, such as vascular complications, including arterial thrombosis and pulmonary artery aneurysms, which contribute significantly to morbidity and mortality in BD patients (9). Vascular involvement can be seen in 50% of patients with BD, mostly as superficial and deep vein thrombosis (10). Neurological involvement can occur in 5.3% to 59% of cases of BD and can cause serious complications such as central nervous system vasculitis and meningoencephalitis, which are associated with poor outcomes (11). Given the broad spectrum of organ involvement in BD, it is essential to understand how the presence or absence of arthritis impacts the severity and progression of these complications.

This study aims to compare the clinical features, laboratory findings, and systemic manifestations between BD patients with and without arthritis. By identifying potential differences between these two groups, the study seeks to enhance our understanding of how arthritis influences the course of BD, contributing to more personalized and effective management strategies. Understanding these differences could also improve early diagnosis and prognostic prediction for patients with BD.

MATERIAL AND METHODS

This retrospective, observational study was conducted at our Rheumatology Clinic between February 1, 2013, and December 31, 2023, and included 881 patients diagnosed with BD. The approval was obtained from the Ondokuz Mayıs University Local Ethics Committee (approval number: B30.2.OMD.0.20.08/488-536, dated: 14.11.2023) and was conducted in accordance with the tenets set forth in the Helsinki Declaration. Signed informed consent forms were obtained from the patients participating in the study. The study aimed to compare the clinical features, laboratory findings, and systemic manifestations between BD patients with arthritis and those without arthritis.

The inclusion criteria were patients aged 18 years and older who had a confirmed diagnosis of BD, as defined by the ISG criteria (12). Patients with other chronic inflammatory diseases or those with incomplete medical records were excluded from the study. A detailed review of patient medical records was performed, gathering demographic information, clinical findings, and laboratory results, including CRP, ESR, and other relevant markers. The presence of arthritis was determined by clinical examination and radiographic imaging. Patients were categorized into two groups: those with arthritis and those without arthritis.

Data on additional systemic manifestations, including neurological, vascular, and gastrointestinal involvement, were also collected. Family history of BD, corticosteroid use history, and current medications were recorded. The laboratory values of ESR and CRP were measured at baseline and after treatment, and comparisons were made between the two groups.

Statistical Analysis

Statistical analyses were performed using IBM Statistical Package for the Social Sciences for Windows Version 25.0. Descriptive statistics, such as means, standard deviations, and frequencies, were calculated for demographic and clinical characteristics. Comparisons between groups were made using independent t-tests for continuous variables and chi-square tests for categorical variables. A p-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 881 BD patients were included in the study, consisting of 434 females (49%) and 447 males (51%). Of these, 233 (26.4%) patients had arthritis, while 648 (73.6%) did not. The mean age of

patients with arthritis was 41.7±11.5 years, while the mean age of patients without arthritis was 39.3±11.6 years. The average age at diagnosis was 31.3±9.7 years in the arthritis group and 30.3±9.9 years in the non-arthritis group (Table 1).

Significant differences were found between the two groups in terms of laboratory markers. The ESR was significantly higher in the arthritis group (37.6±23.9) compared to the non-arthritis group (31.1±23.9) (p<0.001). Similarly, the mean CRP level was higher in the arthritis group (25.9±32.2) than in the non-arthritis group (18.6±34.6) (p=0.006). However, after treatment, there were no significant differences in ESR or CRP levels between the groups.

Family history of BD was more prevalent in the arthritis group (15%) than in the non-arthritis group (10%) (p=0.041). Neurological involvement was significantly more common in the non-arthritis group, with 11% of patients in this group showing neurological manifestations, compared to only 4% in the arthritis group (p=0.002).

Vascular complications also showed significant differences between the groups. Pulmonary artery aneurysm was found only in the non-arthritis group (2%, p=0.043); and arterial thrombosis was more common in the non-arthritis group (5%) compared to the arthritis group (1%) (p=0.025).

Regarding medication use, corticosteroid therapy was more commonly used in the arthritis group, with 36% of patients currently using corticosteroids compared to 21% in the non-arthritis group (p=0.019). Pulse corticosteroid therapy, however, was more frequently used in the non-arthritis group (9% vs. 4%, p=0.008). There were no significant differences between the groups regarding the use of other immunosuppressive medications, such as colchicine, azathioprine, and methotrexate.

The most commonly affected joint in patients with arthritis was the knee, with 124 patients (53%) exhibiting knee involvement. Among these, 71 patients (30%) had unilateral knee involvement, and 53 patients (23%) had bilateral knee involvement. The least affected joint was the elbow, with only 14 patients (6%) reporting involvement (Table 2).

Table 1. Comparison of demographic characteristics, laboratory values and clinical features of cases with and without arthritis

	Arthritis present (n=233)	No arthritis (n=648)	p-value
Age (years)	41.7±11.5	39.3±11.6	0.007
Gender (female/male)	105/128 (45/55%)	329/319 (51/49%)	0.078
Age at diagnosis	31.3±9.7	30.3±9.9	0.167
ESR before treatment (mm/h)	37.6±23.9	31.1±23.9	0.000
ESR after treatment (mm/h)	23.5±18.4	23.4±18.0	0.960
CRP before treatment (mg/L)	25.9±32.2	18.6±34.6	0.006
CRP after treatment (mg/L)	7.7±12.3	7.2±13.6	0.646
Family history	34 (15%)	65 (10%)	0.041
Neurological involvement	9 (4%)	68 (11%)	0.002
Pulmonary artery aneurysm	0 (0%)	12 (2%)	0.043
Arterial thrombosis	3 (1%)	30 (5%)	0.025

ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein

Table 2. Locations of joints affected in cases of arthritis

Joint	No involvement	Unilateral involvement	Bilateral involvement
Knee	109 (47%)	71 (30%)	53 (23%)
Ankle	139 (60%)	43 (18%)	51 (22%)
Wrist	169 (72%)	32 (14%)	32 (14%)
Elbow	219 (94%)	7 (3%)	7 (3%)
Hip	211 (91%)	12 (5%)	10 (4%)
Sacroiliac	211 (91%)	22 (9%)	0
Hand joints	198 (85%)	35 15(%)	0

DISCUSSION

This study aimed to investigate the clinical and demographic differences between patients diagnosed with BD who presented with arthritis and those who did not. The results highlighted significant differences in several clinical aspects, such as age at diagnosis, laboratory values, family history, and the occurrence of specific complications, which are consistent with findings from previous studies on BD. These differences provide valuable insights into the disease's systemic manifestations and may guide clinical management.

One of the notable findings of this study was the slight difference in age between patients with arthritis and those without. The mean age of onset for arthritis was 31.3 years, which is consistent with earlier reports that suggest a delayed onset of arthritis in BD compared to other symptoms, such as, oral ulcers or ocular involvement (6). Previous studies have suggested that BD-associated arthritis tends to present later in the disease course, which may reflect a more advanced or aggressive disease state (12). This observation may prompt clinicians to monitor for arthritis as the disease progresses, particularly in those with early BD manifestations. In the study conducted in Greece, oligoarthritis was found in 20.0% and 41.6% of male and female patients, respectively, and a significant difference was found between the sexes (13). In our study, arthritis findings were detected in 27% of the patients, and no significant difference was found between male and female genders.

Regarding laboratory markers, sedimentation rate and CRP levels were higher in patients with arthritis, indicating a more pronounced inflammatory response, similar to the findings of Alibaz-Oner et al. (8). The significantly elevated sedimentation rate (37.6±23.9) and CRP levels (25.9±32.2) in patients with arthritis suggest that these individuals experience greater systemic inflammation, which aligns with previous reports that describe elevated inflammatory markers in BD patients with joint involvement (14).

However, the lack of significant difference in these markers after treatment highlights the effectiveness of current therapies in controlling systemic inflammation across both groups, as previously observed in studies on BD management (15).

The family history of BD was more prevalent in patients with arthritis (15%) than in those without (10%), a finding that is consistent with earlier research suggesting a genetic predisposition to more severe forms of BD, including the development of arthritis (16,17).

A family history has been linked to an increased risk of systemic manifestations in BD, such as arthritis, which may reflect the underlying genetic factors that contribute to both disease severity and the tendency to develop multisystem involvement (8). This suggests that family history could be a useful marker for predicting the risk of arthritis in BD patients, though further genetic studies are needed to better understand this relationship.

The study found that neurological complications were more common in patients without arthritis (11%) compared to those with arthritis (4%). This is in line with earlier studies that reported a higher prevalence of neurological involvement in BD patients without joint symptoms (18). Neurological manifestations, including central nervous system involvement, are considered to be one of the most severe complications of BD, and their higher frequency in patients without arthritis may reflect different disease mechanisms at play in those without joint involvement. Therefore, careful monitoring for neurological complications is crucial in all BD patients, particularly those with milder joint symptoms or those in the early stages of the disease.

The study also identified a significant difference in vascular complications between the two groups. Pulmonary artery aneurysm was found exclusively in the non-arthritis group, while arterial thrombosis was more common in the non-arthritis group. These findings corroborate previous studies, such as those by Baskar et al. (9), which suggested that vascular involvement, particularly arterial thrombosis and aneurysms, tends to be more prevalent in patients without arthritis. The underlying pathophysiological mechanisms of BD-related vascular complications are complex and multifactorial, but they might be more pronounced in patients with fewer joint involvement, suggesting different disease phenotypes. This highlights the need for careful vascular screening in BD patients, especially in those without arthritis.

In terms of corticosteroid use, the results demonstrated that patients with arthritis were more likely to be treated with corticosteroids (36%) compared to those without arthritis (21%). This finding is consistent with the clinical experience that arthritis in BD often requires more intensive treatment, potentially due to its impact on larger joints or its role in causing significant disability (19).

Conversely, pulse corticosteroid use was higher in the non-arthritis group (9% compared to 4%), which may reflect the acute flare of BD or involvement of other organ systems, as pulse steroids are often employed in cases of severe systemic involvement or vascular complications. The higher frequency of corticosteroid therapy in the arthritis group may indicate that joint involvement is a key determinant in treatment decisions, aligning with previous research on the therapeutic approach for BD patients with arthritis (20).

Finally, the use of other immunosuppressive medications, such as colchicine, azathioprine, and methotrexate, did not show

significant differences between the two groups. This suggests that the decision to initiate these therapies is likely driven by disease severity and multisystem involvement rather than the presence or absence of arthritis, as noted also in studies by Gül et al. (4). It is interesting to note that despite the lack of significant differences in drug use, the choice of therapy in BD often involves a multidisciplinary approach, tailored to the patient's individual needs, and clinical manifestations, including the presence of systemic involvement such as gastrointestinal or neurological issues.

Study Limitations

Limitations of this study include its retrospective design, which may introduce selection bias and limit causal inferences. The reliance on medical records may result in incomplete data, particularly for systemic manifestations. Additionally, the study was conducted at a single center, which may limit the generalizability of the findings. Future prospective, multicenter studies are needed to validate these results and explore the mechanisms underlying the observed differences.

CONCLUSION

In conclusion, this study provides important insights into the clinical differences between BD patients with and without arthritis. Patients with arthritis tended to exhibit higher systemic inflammation, a stronger family history, and more intensive corticosteroid use. In contrast, those without arthritis experienced more neurological and vascular complications, highlighting the diverse clinical spectrum of BD. These findings underscore the importance of individualized treatment strategies that consider both the systemic nature of BD and the presence or absence of specific manifestations such as arthritis.

Ethics

Ethics Committee Approval: The approval was obtained from the Ondokuz Mayıs University Local Ethics Committee (approval number: B30.2.OMD.0.20.08/488- 536, dated: 14.11.2023).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: C.K.K., M.Ö., D.Y.K., Ö.K., Concept: C.K.K., M.Ö., D.Y.K., Ö.K., Design: C.K.K., M.Ö., D.Y.K., Ö.K., Data Collection or Processing: C.K.K., M.Ö., D.Y.K., Ö.K., Analysis or Interpretation: C.K.K., M.Ö., D.Y.K., Ö.K., Writing: C.K.K., M.Ö., D.Y.K., Ö.K.

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

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

REFERENCES

1. Emmi G, Bettiol A, Hatemi G, et al. Behçet's syndrome. Lancet. 2024;403:1093-108.
2. Akbaba TH, Ekici M, Çolpak Aİ, et al. Behçet's syndrome: recent advances to aid diagnosis. Clin Exp Med. 2023;23:4079-90.
3. Lavalle S, Caruso S, Foti R, et al. Behçet's disease, pathogenesis, clinical features, and treatment approaches: a comprehensive review. Medicina. 2024;60:562.
4. Gül A, Samarkos M, Zouboulis C, et al. Behçet's disease: clinical features and management. Rheumatol Int. 2004.
5. Levy Y, Vaiopoulos G, Samarkos M, et al. Behçet's disease: epidemiology, pathogenesis, and treatment. Clin Rheumatol. 2008.
6. Frostegård J, Najafi A, Kooshki AM, et al. Immunological and inflammatory markers in Behçet's disease. Ann Rheum Dis. 1998.
7. Esatoglu SN, Ozguler Y, Hatemi G. Disease and treatment-specific complications of Behçet syndrome. Curr Rheumatol Rep. 2024;26:1-11.
8. Alibaz-Oner F, Moradi S, Masoumi M, et al. Behçet's disease and arthritis: a review. J Clin Rheumatol. 2011.
9. Baskar A, Vaiopoulos A, Kapsimali V, et al. Vascular complications in Behçet's disease: a review. Vasc Dis Manag. 2010.
10. Bettiol A, Alibaz-Oner F, Direskeneli H, et al. Vascular Behçet syndrome: from pathogenesis to treatment. Nat Rev Rheumatol. 2023;19:111-26.
11. Belfeki N, Ghriss N, Fourati M, et al. Neuro-Behçet's disease: a review. Rev Med Interne. 2024.
12. Davatchi F, Assaad-Khalil S, Calamia K, et al. The International Criteria for Behçet's Disease (ICBD): a collaborative study of 27 countries on the sensitivity and specificity of the new criteria. J Eur Acad Dermatol Venereol. 2014;28:338-47.
13. Vaiopoulos A, Kapsimali V, Kanakis M, et al. The frequency of arthritis in Adamantiades-Behçet's disease in Greek patients. J Eur Acad Dermatol Venereol. 2019;33:416-20.
14. Parsaei A, Moradi S, Masoumi M, et al. Predictive value of erythrocyte sedimentation rate and C-reactive protein in Behçet's disease activity and manifestations: a cross-sectional study. BMC Rheumatol. 2022;6:9.
15. Hasseli R, Ghriss N, Fourati M, et al. The genetics of Behçet's disease. J Invest Dermatol. 2008.
16. Zouboulis CC, Leclercq D, Saadoun D, et al. The genetics of Behçet's disease. J Invest Dermatol. 2008.
17. Kavak S, Moradi S, Masoumi M, et al. Treatment strategies for Behçet's disease. Arthritis Rheum. 2003.
18. Yazici H, Samarkos M, Zouboulis C, et al. Neurological involvement in Behçet's disease: a review. Rheumatology. 2007.
19. Yazici H, Vaiopoulos G, Samarkos M, et al. Treatment strategies for Behçet's disease. Arthritis Rheum. 2003.
20. Kahin S, Najafi A, Kooshki AM, et al. Corticosteroid use in Behçet's disease: a clinical overview. J Rheumatol. 2014.

ORIGINAL ARTICLE

Rheumatology Quarterly

DOI: 10.4274/qrheumatol.galenos.2025.72692
Rheumatol Q 2025;3(1):6-11

THE ROLE OF CHEMOKINES IN FIBROMYALGIA

Tuba Tülay Koca[1], Muhammed Seyithanoğlu[2], Fırat Sakınmaz[1]

[1]Kahramanmaraş Sütçü İmam University Faculty of Medicine, Department of Physical Medicine and Rehabilitation, Kahramanmaraş, Türkiye
[2]Kahramanmaraş Sütçü İmam University Faculty of Medicine, Department of Biochemistry, Kahramanmaraş, Türkiye

Abstract

Aim: Chemokines are cytokines that cause chemotaxis to leukocytes and stem cells in inflammation and homeostasis. Fibromyalgia (FM) is characterized by widespread chronic pain and somatic symptoms. The role of immun mediators in the pathogenesis of FM is the topic of recent researches and current evidence supports that chemokines are important in the syndrome's pathogenesis. In our study, the importance of some chemokines and their receptors in FM and their relationship with pain and disease severity are analyzed.

Material and Methods: This is a cross-sectional analytic study. Our study included 40 female patients with FM (American College of Rheumatology, 2016) and 40 healthy controls matched for age and body mass index (BMI). C-C motif chemokine receptor 3, chemokine (C-C motif) 4 (CCL4), and macrophage-derived chemokine (MDC) levels were measured in the blood samples of the participants using the enzyme-linked immunosorbent assay. Pain and disease severity in FM patients were evaluated with a visual analog scale (VAS, 0-10 cm) and Fibromyalgia Impact Questionnaire (FIQ), respectively.

Results: The groups were similar in terms of age (p=0.19) and BMI values (p=0.109). C-reactive protein (p=0.013), MDC (p=0.016), and CCL4 (p=0.026) values were higher in the FM group. The mean VAS of the FM group was 7.5±2.5 cm, while the FIQ was 61.1±14.9.

Conclusion: MDC and CCL4 chemokines can be used as helpful parameters in diagnosing FM with moderate sensitivity and specificity. High levels of chemokines in the FM group support the role of chemokines in the etiopathogenesis of disease through immunomodulation in the nervous system.

Keywords: Fibromyalgia, chemokine, CCR3, CCL4, MDC

INTRODUCTION

Chemokines constitute a family of cytokines. With the rapid development of research in recent years, these 50 separate members serve as mediators that play a regulatory role in normal biological and pathological processes. Chemokine receptors are G-protein-dependent structures that transmit intracellular signals. The immune system's response to inflammatory events such as antigenic and autoimmune reactions depends on the chemokines directing and activating leukocytes at the right time (1,2). As a result of chemokines binding to the appropriate receptor, cells stimulated by signal transmission lead to tissue damage, inflammation, or migration to the required area (chemotaxis) (3).

Address for Correspondence: Tuba Tülay Koca, Kahramanmaraş Sütçü İmam University Faculty of Medicine, Department of Physical Medicine and Rehabilitation, Kahramanmaraş, Türkiye
E-mail: tuba_baglan@yahoo.com **ORCID ID:** orcid.org/0000-0002-4596-858X
Received: 20.11.2024 **Accepted:** 06.01.2025 **Publication Date:** 21.03.2025
Cite this article as: Koca TT, Seyithanoğlu M, Sakınmaz F. The role of chemokines in fibromyalgia. Rheumatol Q. 2025;3(1):6-11

The settlement of leukocytes in tissues constitutes an important step in inflammation and the host response to infectious situations. In summary, chemokines are cytokines that induce chemotaxis of leukocytes and stem cells in inflammation and homeostasis (3-6). There are several chemokine subfamilies (e.g., CXC, CC, C, and CX3C) defined according to the positioning of cysteine residues (7,8).

Disability due to chronic pain is common worldwide. We know that our immune system has a role in the pathogenesis of many pain syndromes. Involvement of the immune system may occur with autoantibodies, as in rheumatoid arthritis, or with cytokines, chemokines, and other inflammatory mediators. Immune cells (T cells, B cells, autoantibodies, microglia) play a role in immune-mediated pain. By elucidating this relationship, targets for treatment can be developed or optimized in diseases such as fibromyalgia (FM) that present with chronic pain (9).

FM is a multifaceted disease, and its clinical presentation includes comorbidities. Each comorbidity is a separate condition. Genetic, environmental, neurohormonal factors, and pathophysiological factors including inflammation are held responsible for the background of the disease. New data are obtained every day regarding the etiopathogenesis of FM. Cytokines and chemokines, lipid mediators, oxidative stress, and plasma-derived factors, support the existence of inflammatory/immunological pathways in FM development (9). It has been shown that the levels of some inflammatory cytokines, such as (IL-1RA, IL-6, and IL-8), and some chemokines have increased in recent years (9-11). In our study, the role of some chemokines and receptors [C-C motif chemokine receptor 3(CCR3), Chemokine 4 (CCL4), macrophage-derived chemokine (MDC)] and their relationship with pain and disease severity was analyzed.

MATERIAL AND METHODS

Study Design and Data Source

Our study was planned as cross-sectional. Forty female patients with FM (American College of Rheumatology, 2016) and 40 healthy volunteers with similar age and BMI distribution were included in the study. Pain and disease severity in FM patients were evaluated with a visual analog scale (VAS, 0-10 cm) and fibromyalgia impact questionnaire (FIQ) (12), respectively. Blood samples were taken during outpatient admission.

After centrifugation for 10 minutes, it was stored at temperatures below -80 degrees Celsius. Those with a history of chronic inflammatory rheumatic disease, infection, malignancy, hypothalamic-pituitary axis pathology, cognitive disorder, neurological disease, psychiatric disease, acute trauma, and surgical procedures were excluded from the study.

Biochemical Analysis

In blood samples from both groups, chemokine, and receptor levels; CCR-3, MDC, and CCL-4 were calculated using an enzyme-linked immunosorbent assay (ELISA) method according to the manufacturer's protocol (13-15). The kits were provided by Wuhan Fine Biotech (Wuhan, China). The characteristics of the kits are listed in Table 1. C-reactive protein (CRP, cut-off: 0-5) and erythrocyte sedimentation rate (ESR, cut-off: 0-30) values from the archive files of the patients within the last 3 months were checked and recorded for exclusion criteria. Patients with active infection were excluded.

Statistical Analysis

It was performed using the Statistical Package for Social Sciences (SPSS ver. 20), and $p<0.05$ were considered statistically difference. Normal distribution of the data was determined using the Shapiro-Wilk, the Kolmogorov-Smirnov test, and histogram columns. Numerical data with normal distribution are given as mean ± standard deviation; those with non-normal distribution are given as median (minimum/maximum). Independent Samples t-test was used to compare two groups. The Spearman correlation test was used.

A receiver operating characteristic (ROC) curve was applied for MDC and CCL4 diagnostic tests, and the threshold value for these values was manually selected based on both the highest sensitivity and the highest 1-1 specificity.

RESULTS

Forty female FM with a mean age of 46.1±9.8 years and 40 healthy control females with a mean age of 42.8±12.8 years were included in our study (p=0.19). BMI values were similar

Table 1. The characteristics of the kits

Kit name	Catalog number	Intra assay CV	Inter-assay CV	Detection range	Sensitivity
CCR3	EH2089	<8%	<10%	0.313-20 ng/mL	0.188 ng/mL
MDC	EH0223	<8%	<10%	62.5-4000 pg/mL	37.5 pg/mL
CCL4	EH0067	<8%	<10%	31.25-2000 pg/mL	18.75 pg/mL

CCR3: C-C chemokine receptor type 3, MDC: Macrophage derived chemokine, CCL4: C-C motif chemokine 4, CV: Coefficient of variation

in both groups (p=0.109). CRP (p=0.013), MDC (p=0.016), and CCL4 (p=0.026) levels were higher in patients with FM (Figure 1A, B). The mean VAS value of the FM group was 7.5±2.5 cm, while the FIQ value was 61.1±14.9. A comparison of the group data is summarized in Table 2.

In the correlation analysis, the VAS value was positively correlated with ESR (p=0.019) and FIQ (p<0.01). The CCL4 value was positively correlated with age (p=0.037), MDC (p=0.003), and BMI (p=0.003). Age and BMI (p=0.037) were found to be positively correlated. None of the 3 chemokines and receptor levels were not found to correlate with ESR and CRP. Only positive values are shown in Table 3.

In ROC analysis for the serum MDC levels was statistically significant (area under the ROC curve: 0.681, confidence interval: 0.562-0.800, p=0.005). High values indicated FM, with a threshold of >442,9 sensitivity of 67%, and specificity of 60% (Figure 2A). ROC analysis for the serum CCL4 levels was statistically significant (area under the ROC curve: 0.644, confidence interval: 0.522-0.766, p=0.026). High values indicated FM, with a threshold of >190,1 sensitivity of 62.5%, and specificity of 60% (Figure 2B).

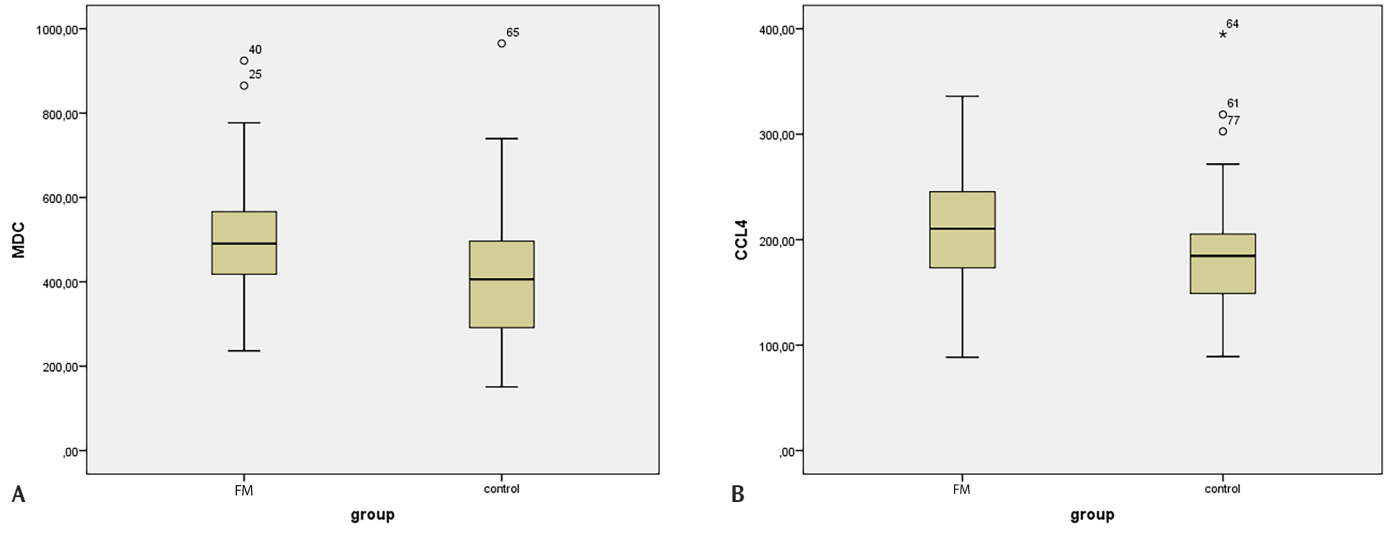

Figure 1. MDC (A) and CCL4 (B) levels in the study groups
MDC: Macrophage-derived chemokine, CCL4: C-C motif chemokine 4, FM: Fibromyalgia

Table 2. Comparison of parameters of groups

	FM (n=40) Mean ± SD/Med., (min.-max.)	Control (n=40) Mean ± SD/Med., (min.-max.)	p-value
Age (year)	46.1±9.8	42.8±12.8	0.19
BMI (kg/m^2)	26.9±4.2	25.2±5.17	0.109
ESR (mm/h)	11±8.3	11.1±9.1	0.95
CRP (g/dL)	3.2 (1.4-31)	3 (1-13)	0.013**
VAS (0-10 cm)	7.5±2.5	-	
FIQ	61.1±14.9	-	
CCR3 (ng/mL)	2.7±0.9	2.9±2.4	0.75
MDC (pg/mL)	506.6±145.4	419.2±172.0	0.016*
CCL4 (pg/mL)	210.46 (88.51-336)	184.6 (89.15-394.84)	0.026**

*Independent Samples t-test, **Mann-Whitney U test, p<0.05, statistically significance. FM: Fibromyalgia syndrome, BMI: Body mass index, FIQ: Fibromyalgia impact questionnaire, VAS: Visual Analog Scale, ESR: Erythrocyte sedimentation rate, CRP: C- reactive protein, CCR3: C-C chemokine receptor type 3, CCL4: C-C motif chemokine 4, MDC: Macrophage derived chemokine, Med.: Median, min.-max.: Minimum-maximum, SD: Standard deviation

Table 3. Inter-parameter correlation analysis

	r	p***
Age-CCL4	0.234	0.037***
Age-BMI	0.289	0.011***
VAS-ESR	0.380	0.019***
VAS-FIQ	0.764	<0.01***
ESR-CRP	0,380	0.019***
MDC-CCL4	0.330	0.003***
CCL4-BMI	0.329	0.003***

***Spearman's correlation analysis, p<0.05, stastitically significance. Only positive results were shown in Table 3. BMI: Body mass index, FIQ: Fibromyalgia impact questionnaire, VAS: Visual analog scale, ESR: Erythrocyte sedimentation rate, CRP: C- reactive protein, CCR3: C-C chemokine receptor type 3, CCL4: C-C motif chemokine 4, MDC: Macrophage derived chemokine

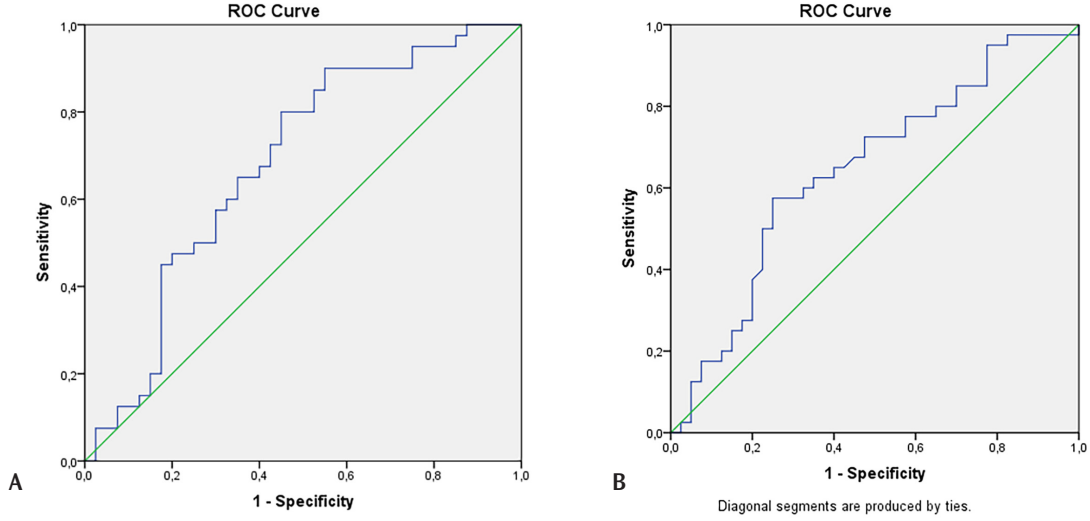

Figure 2. ROC analysis of MDC (A) and CCl4 (B) for fibromyalgia
ROC: Receiver operating characteristic, MDC: Macrophage derived chemokine

DISCUSSION

The etiology of FM is not well understood and we do not have hematochemical or instrumental tests for its diagnosis yet. Key features in the FM clinic include widespread pain and tenderness, sleep disturbance, fatigue, cognitive problems and psychological distress. Inadequate processing of pain and other sensory inputs occurs in the nervous system and is explained by sensitization. FM is classified as a central sensitivity syndrome. There is sufficient evidence supporting neurogenic inflammation in peripheral and central tissues (9-11). With the effect of both the inherent and acquired immunity, chemokines, cytokines, and various neuropeptides are involved in the process. These explain clinical findings such as swelling and dysesthesia, and may affect central symptoms including fatigue and cognitive changes. Emotional or stress-related psychological mechanisms may trigger neurogenic inflammation in FM (16).

Chemokines have important roles in many biological processes occurring in the body. The chemokine superfamily includes many ligands and receptors. However, this idea has changed after understanding the key roles of chemokine subgroups in the cellular network organization and functions that shape the immune system (17,18). Chemokines are effective in leukocyte-endothelial cell relations, T and B cell maturation, immune control, formation of tolerance and immunity, T-B cell transmission, and the formation of the primary immune response. In addition, they play a role in dendritic cell functions, T cell differentiation and functions, effector T cell response in inflammatory diseases, mucosal immunity, and events that suppress the host immune response by various viruses, including HIV-1 (17). Apart from inflammation, it has biological activities such as angiogenesis, hematopoiesis, and an increased host response to tumors (19). They act in the brain not only

as immunomodulators but also as potential modulators of neurotransmission and neuroendocrine regulation (20).

Today, the etiopathogenesis of the different clinical findings seen in FM remains to be elucidated. Both the central and peripheral nervous systems have an effect on disease development. Although the disease was classified as non-inflammatory before, we see that the immune system is also involved in the pathogenesis. Current data suggest that central nervous system dysfunction, which causes pain, mood, and sleep disturbances observed in FM, may be related to immune system changes (21).

FM is characterized by increased systemic inflammatory biomarkers and innate cellular response. Increased chemokines and proinflammatory cytokines in serum are thought to contribute to systemic inflammation (22). In our study, CRP, MDC, and CCL4 levels were significantly higher in the FM group than in the healthy group. Additionally, MDC and CCL4 were positively correlated with each other. We found that CCL4 values increase with advanced age and high BMI. Our study supports the idea that changes occur in the immune-inflammatory pathways in FM. Current studies focus on chemokines and cytokines that regulate pathogenesis in physiological and pathological conditions. When we look at similar studies in the literature, García et al. (23) found that monocytes from patients with FM are deregulated, releasing higher amounts of eotaxin, MDC, and growth-regulated-oncogene than healthy controls.

In meta-analysis by Andrés-Rodríguez et al. (24), an imbalance between upregulated pro-inflammatory and immune-regulatory cytokines was observed. In another study by Andrés-Rodríguez et al. (25) they observed that the mindfulness-based stress reduction method reduces the disease severity by affecting cytokines and chemokines (IL-6, IL-10, CXCL8) associated with psychological symptoms in FM. They found that this technique provides clinical benefits by regulating immune-inflammatory pathways. In our study, disease severity parameters (VAS, FIQ) were not related to MDC, CCL4, and CCR3. Chemokines, chemokine receptors, and CRP were high in the FM group, regardless of disease severity (FIQ). Only the VAS value was positively correlated with ESR. The correlation between ESR and VAS values in the study can be explained by the fact that pain complaints are more common in those with higher ESR values, and vice versa. We may say that neuroimmune processes take part in FM symptoms.

There is growing evidence that the peripheral nervous system and systemic inflammation are as effective as central mechanisms in the formation of widespread pain in FM (26). In the study by Khamisy-Farah et al. (27), high CRP, mean platelet volume, and platelet-lymphocyte ratio were observed in FM patients, along with a low lymphocyte count. Aktürk and Büyükavcı (28) observed that the neutrophil/lymphocyte ratio was high in the FM group. Systemic inflammatory response appears to be high in FM. In our study, we found the CRP value to be significantly higher in the FM group. CRP and ESR values were not correlated with chemokines.

In the meta-analysis conducted by O'Mahony et al. (29), high levels of pro-inflammatory and anti-inflammatory cytokines and eotaxin were detected in the peripheral blood of FM patients (30). In the study by García et al. (30) (n=17), inflammatory chemokines were found to be similar in the FM group and the control group. There is increasing evidence that proinflammatory cytokines and genetic variant connections in pain-related genes play a role in the development of FM and the severity of the disease (31,32). It is thought that the roles of FM-related central/peripheral neuroimmune processes in disease development and severity may be related to genes.

Many different mechanisms play a role in studies on the pathogenesis of FM. Also, chemokine levels are affected by factors, such as signaling, environmental influences, genetic predisposition, and various physiological and pathological conditions. Infections, tissue trauma, inflammatory conditions, immune signals, hormones, genetic factors, diet and lifestyle, environmental pollution, allergens, stress, age, and obesity can affect chemokine levels. It is difficult to explain clearly the mechanism by which chemokine levels are affected in FM patients. The study's limitations include the sample size and the omission of considering the use of medications that may affect the results.

CONCLUSION

A wide spectrum of symptoms seen in FM, including widespread pain, cognitive dysfunction, emotional distress, sleep disturbance, and chronic fatigue, appear to be related to central and peripheral neuroimmune pathways in the pathogenesis. The best-defined pathological mechanisms related to FM are changes in central pain pathways and emotional states that trigger or worsen symptoms. Studies in the last decade, to elucidate the etiopathogenesis of FM, reveal that inflammatory mediators, cytokines, peptides, and chemokines also have a role in the disease process. In our study, the high levels of CRP and chemokines (MDC and CCL4) in the FM group support the role of neuroimmune and inflammatory pathways in the pathogenesis of the disease. Elucidating the etiopathogenesis of FM will guide the management of different symptoms and the development of treatment approaches.

Ethics

Ethics Committee Approval: Our study was carried out by the Declaration of Helsinki and approved by Sütçü İmam University Faculty of Medicine Clinical Trials Ethics Committee (approval number: 02, protocol number: 86, dated: 14.02.2022).

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

Footnotes

Authorship Contributions

Concept: T.T.K., Design: T.T.K., Data Collection or Processing: F.S., Analysis or Interpretation: M.S., Literature Search: M.S., Writing: T.T.K.

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

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

REFERENCES

1. Lindley IJD, Westwick J, Kunkel SL. Nomenclature announcement-the chemokines. Immunol Today. 1993;14:24.
2. Campbell JD, Stinson MJ, Simons FE, HayGlass KT. Systemic chemokine and chemokine receptor responses are divergent in allergic versus non-allergic humans. Int Immunol. 2002;14:1255-62.
3. D'Ambrosio D, Panina-Bordignon P, Sinigaglia F. Chemokine receptors in inflammation: an overview. J Immunol Methods. 2003;273:3-13.
4. LusterAD. Chemokines-chemotactic cytokines that mediate inflammation. N Engl J Med. 1998;338:436-45.
5. Miller MC, Mayo KH. Chemokines from a structural perspective. Int J Mol Sci. 2017;18:2088.
6. Koca T, Koçyiğit B, Seyithanoğlu M, Berk E. The importance of G-protein coupled estrogen receptor in patients with fibromyalgia. Arch Rheumatol. 2019;34:419-25.
7. Matsushima K. Chemokines. Introduction. Springer semin immunopathol. 2000;22:321-8.
8. Inadera H, Matsushima K. [Chemokines and inflammation]. Nihon Ronen Igakkai Zasshi. 1999;36:82-9.
9. Totsch SK, Sorge RE. Immune system involvement in specific pain conditions. Mol Pain. 2017;13:1744806917724559.
10. Rodriguez-Pintó I, Agmon-Levin N, Howard A, Shoenfeld Y. Fibromyalgia and cytokines. Immunol Lett. 2014;161:200-3.
11. Coskun Benlidayi I. Role of inflammation in the pathogenesis and treatment of fibromyalgia. Rheumatol Int. 2019;39:781-91.
12. Sarmer S, Ergin S, Yavuzer G. The validity and reliability of the Turkish version of the fibromyalgia impact questionnaire. Rheumatol Int. 2000;20:9-12
13. National Center for Biotechnology Information. (n.d.). Gene: TP53. U.S. National Library of Medicine. Retrieved March 17, 2025. Avaliable from: https:/www.ncbi.nlm.nih.gov/gene/1232
14. Menten P, Wuyts A, Van Damme J. Macrophage inflammatory protein-1. Cytokine Growth Factor Rev. 2002;13:455-81.
15. Mantovani A, Gray PA, Van Damme J, Sozzani S. Macrophage-derived chemokine (MDC). J Leukoc Biol. 2000;68:400-4.
16. Littlejohn G, Guymer E. Neurogenic inflammation in fibromyalgia. Semin Immunopathol. 2018;40:291-300.
17. Zlotnik A, Yoshie O. The chemokine superfamily revisited. Immunity. 2012;36:705-16.
18. Nagasawa T. [Chemokines]. Nihon Rinsho. 2010;(68 Suppl 7):141-7.
19. Buc M, Bucova M. Chemokines. Bratisl Lek Listy. 2000;101:507-11.
20. Rostène W, Guyon A, Kular L, et al. Chemokines and chemokine receptors: new actors in neuroendocrine regulations. Front Neuroendocrinol. 2011;32:10-24.
21. Landis CA, Lentz MJ, Tsuji J, Buchwald D, Shaver JL. Pain, psychological variables, sleep quality, and natural killer cell activity in midlife women with and without fibromyalgia. Brain Behav Immun. 2004;18:304-13.
22. Banfi G, Diani M, Pigatto PD, Reali E. T Cell subpopulations in the physiopathology of fibromyalgia: evidence and perspectives. Int J Mol Sci. 2020;21:1186.
23. García JJ, Carvajal-Gil J, Guerrero-Bonmatty R. Altered release of chemokines by phagocytes from fibromyalgia patients: a pilot study. Innate Immun. 2016;22:3-8. Erratum in: Innate Immun. 2016;22:245.
24. Andrés-Rodríguez L, Borràs X, Feliu-Soler A, et al. Peripheral immune aberrations in fibromyalgia: a systematic review, meta-analysis and meta-regression. Brain Behav Immun. 2020;87:881-9.
25. Andrés-Rodríguez L, Borràs X, Feliu-Soler A, et al. Immune-inflammatory pathways and clinical changes in fibromyalgia patients treated with mindfulness-based stress reduction (MBSR): a randomized, controlled clinical trial. Brain Behav Immun. 2019;80:109-19.
26. Sluka KA, Clauw DJ. Neurobiology of fibromyalgia and chronic widespread pain. Neuroscience. 2016;338:114-29.
27. Khamisy-Farah R, Fund E, Raibman-Spector S, Adawi M. Inflammatory markers in the diagnosis of fibromyalgia. Isr Med Assoc J. 2021;23:801-4.
28. Aktürk S, Büyükavcı R. Evaluation of blood neutrophil-lymphocyte ratio and platelet distribution width as inflammatory markers in patients with fibromyalgia. Clin Rheumatol. 2017;36:1885-9.
29. O'Mahony LF, Srivastava A, Mehta P, Ciurtin C. Is fibromyalgia associated with a unique cytokine profile? A systematic review and meta-analysis. Rheumatology (Oxford). 2021;60:2602-14.
30. García JJ, Cidoncha A, Bote ME, Hinchado MD, Ortega E. Altered profile of chemokines in fibromyalgia patients. Ann Clin Biochem. 2014;51:576-81.
31. Marino Y, Arangia A, Cordaro M, et al. Analysis of the influence of IL-6 and the activation of the Jak/Stat3 pathway in fibromyalgia. Biomedicines. 2023;11:792.
32. Peck MM, Maram R, Mohamed A, et al. The ınfluence of pro-inflammatory cytokines and genetic variants in the development of fibromyalgia: a traditional review. Cureus. 2020;12:e10276.

ORIGINAL ARTICLE

Rheumatology Quarterly

DOI: 10.4274/qrheumatol.galenos.2025.07379
Rheumatol Q 2025;3(1):12-9

QUALITY AND READABILITY OF CHATGPT'S RESPONSES TO THE MOST FREQUENTLY SEARCHED WORDS ABOUT FIBROMYALGIA ON GOOGLE TRENDS

Alper Uysal[1], Ertürk Güntürk[2]

[1]Mersin City Training and Research Hospital, Clinic of Physical Medicine and Rehabilitation, Mersin, Türkiye
[2]Adana City Training and Research Hospital, Clinic of Physical Medicine and Rehabilitation, Adana, Türkiye

Abstract

Aim: We aimed to evaluate the quality and readability of ChatGPT's answers to frequently asked questions about fibromyalgia (FM).

Material and Methods: The most frequently searched terms related to FM were identified using Google Trends and entered into the ChatGPT-4 model in order of their rankings. The responses were categorized using the Ensuring Quality Information for Patients (EQIP) tool and evaluated based on quality and readability. Quality and readability were assessed with EQIP, the Flesch-Kincaid Grade Level (FKGL), and the Flesch-Kincaid Reading Ease (FKRE).

Results: According to Google Trends data, the search frequency for the term "FM" increased from 2004 to 2024, with a peak of 100% in March 2020. ChatGPT's responses were assessed in terms of both quality and readability, revealing notable shortcomings. The average scores for EQIP, FKGL, and FKRE were 39.89, 13.29, and 21.41, respectively. Furthermore, the statistical analysis among the four categories showed no significant variations in EQIP, FKGL, and FKRE scores.

Conclusion: Our study revealed significant deficiencies in the quality of ChatGPT's responses regarding FM. There is a need for more understandable and reliable information to improve communication in healthcare.

Keywords: Fibromyalgia, Google trends, ChatGPT, EQIP tool, Flesch-Kincaid Grade Level, Flesch-Kincaid Reading Ease

INTRODUCTION

Fibromyalgia (FM) is a relatively common chronic pain syndrome within the general population, with a global prevalence rate of approximately 2-3%. In addition to chronic widespread pain, the FM clinical profile is characterized by fatigue, sleep disturbances, cognitive impairment, autonomic dysfunction, somatic symptoms, and psychiatric disorders, all occurring without any underlying serious medical conditions (1). The pathogenesis of FM is incompletely understood; however, it is thought to involve a combination of genetic predisposition, stressful environmental factors, inflammatory processes, and central mechanisms such as pain centralization (2). The diagnosis of FM is made primarily based on clinical findings. Although physical examination and laboratory tests may not be definitive for diagnosis, they are

Address for Correspondence: Alper Uysal, Mersin City Training and Research Hospital, Clinic of Physical Medicine and Rehabilitation, Mersin, Türkiye
E-mail: alperuysal82@gmail.com **ORCID ID:** orcid.org/0000-0002-4114-1649
Received: 17.11.2024 **Accepted:** 06.01.2025 **Publication Date:** 21.03.2025

Cite this article as: Uysal A, Güntürk E. Quality and readability of ChatGPT's responses to the most frequently searched words about fibromyalgia on google trends. Rheumatol Q. 2025;3(1):12-9

crucial in excluding other conditions. The diagnosis is ultimately established through a detailed medical history (1,2). Patient education, physical exercise, pharmacological agents, and cognitive behavioral therapy are the four main components of the treatment (3).

The Internet has become an essential and irreplaceable resource for health-related information. It is now a significant source of information for patients with FM. The demand for information is heightened by the absence of specific diagnostic tools, evidence-based treatment recommendations for FM, and the ongoing debates surrounding the condition. Barriers to understanding specialized medical terminology and the chronic nature of FM further contribute to this increased demand (4). Research indicates that individuals living with FM frequently turn to the Internet to learn more about the disease and to support shared decision-making processes with their healthcare providers (4-6).

ChatGPT, developed by OpenAI (United States), is a highly advanced language model that leverages deep learning techniques to generate responses that closely mimic human language patterns. It is adept at understanding the subtleties and complexities of human communication, enabling it to produce contextually accurate and relevant responses across a wide range of topics (7).

In summary, FM exemplifies the challenges of patient education due to the lack of definitive diagnostic tests, the absence of universally accepted treatment guidelines, and widespread misconceptions about the condition. These factors often lead patients to seek information online, where the quality and accuracy of content vary greatly, and this may pose the risk of misinformation. FM was chosen as the focus disease for this study because it represents an especially relevant condition to evaluate the potential and limitations of AI-driven tools like ChatGPT in addressing global health information needs.

In this study, we aimed to evaluate the quality and readability of ChatGPT's answers to frequently asked questions about FM.

MATERIAL AND METHODS

This study, conducted on August 24, 2024, at the PM&R clinics of Mersin City Training and Research Hospital and Adana City Training and Research Hospital, was exempt from ethics committee approval as it only utilized online information and did not involve any human or animal participants. Consequently, no informed consent form was required. In compliance with the ethical principles of the Declaration of Helsinki, this study adheres to all required ethical standards. As no human or animal data were utilized, obtaining approval from an ethics committee was not necessary (8,9).

In this study, English was used as the primary language for conducting Google Trends analyses with the term "FM" generating ChatGPT responses, and evaluating these responses, using the Flesch-Kincaid Reading Ease (FKRE) and Flesch-Kincaid Grade Level (FKGL). This choice was made because English is a widely used international language, particularly in the fields of health, medicine, and scientific communication. By utilizing English terms, the study aimed to capture search behaviors from a broader audience across various regions and countries.

Before searches were made, all personal web browsing history was preemptively cleared to prevent interaction. The Google Trends tool was utilized to identify the top searched terms related to FM. Global searches under the health category, spanning from 2004 to August 25, 2024, were selected to determine top keywords associated with FM. The "most relevant" option was selected from the related questions section, while the "subregion" option was chosen from the geographical areas of interest section.

The top 25 searched terms were noted, encompassing a broad spectrum of topics in Google's online searches. Two terms "ms" and "me" identified during the process were excluded from the analysis as they were deemed irrelevant to the main context of FM-related searches.

The term "ICD-10 FM" was included as it appeared among the most frequently searched keywords on Google Trends. Although ICD-10 codes are primarily utilised by healthcare professionals, patients may also encounter these codes in their medical reports and seek to understand their meaning through online searches. Including this keyword ensured a comprehensive analysis of search behaviours and helped minimise selection bias, accurately reflecting the diversity of queries related to FM.

The identified keywords were entered into the ChatGPT-4 model sequentially, according to their rankings in Google Trends, and are presented in Table 1 in the same order.

Before evaluating ChatGPT's performance with the keywords, the web browsing history was cleared, and separate chat pages were opened for each keyword. This approach helped to prevent potential interactions. The responses generated by ChatGPT-4 were systematically catalogued to evaluate the quality of information, readability, and comprehensiveness.

The 23 keywords were divided into four categories according to the criteria specified in the "Ensuring Quality Information for Patients" tool (EQIP): condition or illness; drug, medication, or product; treatment or management; and diagnosis, testing, or procedures (Table 1). The EQIP tool takes into account various parameters, including clarity of information, writing quality, accuracy, reliability, and comprehensiveness. Each of the 20

Table 1. Keywords and the category of the topic based on EQIP

Rank	Keyword	Category of the topic based on EQIP
1	What are the symptoms of fibromyalgia	Condition or illness
2	Is fibromyalgia real	Condition or illness
3	What causes fibromyalgia	Condition or illness
4	Symptoms of fibromyalgia in women	Condition or illness
5	How is fibromyalgia diagnosed	Diagnosis, testing, or procedures
6	How to treat fibromyalgia	Treatment or management
7	Amitriptyline for fibromyalgia	Drug, medication, or product
8	Is fibromyalgia a disability	Condition or illness
9	Cymbalta for fibromyalgia	Drug, medication, or product
10	Fibromyalgia meds	Drug, medication, or product
11	Lyrica fibromyalgia	Drug, medication, or product
12	Define fibromyalgia	Condition or illness
13	Fibromyalgia in men	Condition or illness
14	Gabapentin for fibromyalgia	Drug, medication, or product
15	Lyrica for fibromyalgia	Drug, medication, or product
16	Naltrexone for fibromyalgia	Drug, medication, or product
17	Savella for fibromyalgia	Drug, medication, or product
18	Fibromyalgia flare	Condition or illness
19	Is fibromyalgia autoimmune	Condition or illness
20	Fibromyalgia and chest pain	Condition or illness
21	Is fibromyalgia hereditary	Condition or illness
22	ICD 10 fibromyalgia	Condition or illness
23	Allodynia	Condition or illness

EQIP: Ensuring Quality Information for Patients, ICD: International classification of diseases

parameters in the EQIP scale was assigned a score of 1 for a "yes" response, 0.5 for a "partial" response, and 0 for a "no" or "not applicable (N/A)" response. The scores for each parameter were then summed and divided by the total number of parameters. Finally, the resulting EQIP score was calculated and expressed as a percentage. According to EQIP scores, texts can be classified as well-written and high quality, (76% to 100%), good quality with minor problems, (51% to 75%), having serious quality issues, (26% to 50%), or having severe quality issues, (0% to 25%) (9,10). To minimize bias in the calculation of EQIP, the recorded responses were independently evaluated by two physical medicine and rehabilitation specialists in separate settings. In cases of discrepancy, the average values were taken.

The readability of the texts was analyzed using two key metrics: the FKGL and the FKRE. These parameters were employed to assess the complexity and accessibility of the text content.

The FKGL was determined through a series of specific calculations. Initially, the total number of words was divided by the total number of sentences, and this value was multiplied by 0.39. Subsequently, the total number of syllables was divided by the total number of words, with the resulting figure multiplied by 11.8. The results from these calculations were then added together, and finally, 15.59 was subtracted from the sum to yield the FKGL score. A lower grade level score signifies that the text is easier to understand, whereas a higher score indicates greater linguistic complexity and requires a more advanced level of comprehension.

The FKRE formula assesses a document's readability by first calculating the average sentence length, which is then multiplied by 1,015, and the average number of syllables per word, which is multiplied by 84.6. The difference between these two products is subtracted from 206,835 to yield the document's reading ease score. Higher scores reflect text that is easier to read, whereas a

score of 30 or below indicates that the content is likely suitable for a reading level appropriate for a college graduate (11).

Statistical Analysis

The statistical program used in the study was IBM SPSS Statistics for Windows, Version 22.0 (Armonk, NY, USA). The normality of continuous variables was assessed using the Kolmogorov-Smirnov test and histogram plots. Categorical variables were presented as numbers (n) and percentages (%). For continuous variables that followed a normal distribution, Independent Samples t-test was used for comparisons between two groups, while One-Way Analysis of Variance was employed for comparisons among four groups. For continuous variables that did not follow a normal distribution, comparisons among four groups were performed using the Kruskal-Wallis test. In cases where the Kruskal-Wallis test identified significant differences, pairwise comparisons were conducted using the Mann-Whitney U test. Groups with insufficient sample sizes (n=1) were excluded from the analysis. Bonferroni correction was not applied for pairwise comparisons, as only a single Mann-Whitney U test was conducted. Intrarater reliability for each researcher and interrater reliability between the researchers were analysed using Cohen's kappa coefficient for categorical data. A significance level of $p<0.05$ was considered statistically significant for all analyses.

RESULTS

The graph illustrates the temporal variation in search frequency for the term "FM" according to Google Trends data from 2004 to 2024 (Figure 1). In January 2004, the relative search interest for "FM" stood at 56%, while by August 2024, this interest had risen to 73%. Notably, the graph features a pronounced spike in March 2020, when the relative search interest reached 100%.

As depicted in the graph, Norway, Puerto Rico, and the United Kingdom are the top three countries where the term "FM" has been most frequently searched. Geographically, the highest search interest is concentrated in North America, Western and Northern European countries, and Australia (Figure 2).

Table 1 presents the 23 keywords obtained from Google Trends along with their corresponding categories as determined by the EQIP analysis.

The minimum, maximum, mean, and standard deviation values for EQIP, FKGL, and FKRE, as well as the percentages for the category of the topic based on EQIP, are presented in Table 2. Based on the EQIP analysis, the most frequently observed categories for this topic are "condition or illness," which accounts for 57%, and "drug, medication, or product," which represents 35% (Figure 3).

No statistically significant differences were found between Group 1 and Group 2 in terms of EQIP, FKGL, and FKRE values. In Groups 3 and 4, the standard deviation could not be calculated due to the response count being only one. Additionally, the statistical analysis across the four groups revealed no significant differences in EQIP, FKGL, and FKRE values (Table 3). The obtained kappa value (0.79) represents a high level of interrater reliability ($p<0.001$). The intrarater reliability analysis conducted after 109 days yielded kappa values of 0.87 for researcher 1 (Alper Uysal) and 0.85 for researcher 2 (Ertürk Güntürk), both statistically significant ($p<0.001$).

DISCUSSION

Our study revealed significant issues in the quality of responses provided by ChatGPT. The FKGL corresponded to a 13-year education level, while the FKRE score indicated that the texts were at a difficult readability level.

FM significantly impacts individuals' lives, often manifesting as chronic widespread pain, sleep disturbances or non-restorative sleep, physical exhaustion, and cognitive difficulties.

Figure 1. Temporal change in search frequency for the term "fibromyalgia"

This condition involves a range of somatic and psychological symptoms and is frequently accompanied by co-morbid illnesses such as functional somatic syndromes (for instance, irritable bowel syndrome), anxiety and depressive disorders, and rheumatic diseases. These symptoms and associated conditions can profoundly complicate daily living, substantially diminishing quality of life (2).

When analysing Google Trends data for the term "FM" from 2004 to 2024, a significant spike is observed in March 2020, with the relative search interest peaked at 100%. On 11 March 2020, the World Health Organization declared COVID-19 a global pandemic (12), and by 13 March 2020, Europe was reported as the new epicentre of the crisis (13). The spike in searches for FM during this period may be linked to the heightened anxiety,

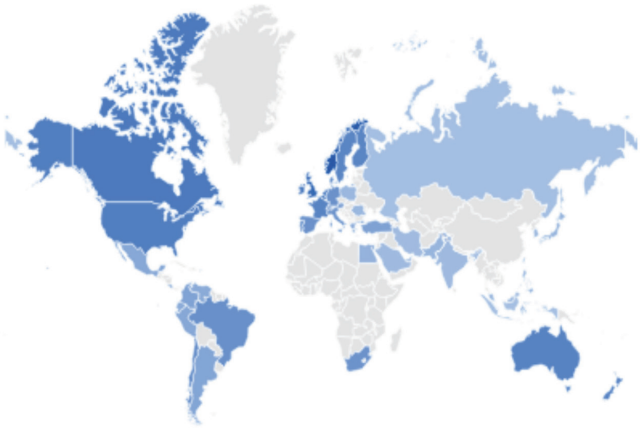

Figure 2. Global search interest in fibromyalgia: 2004-2023

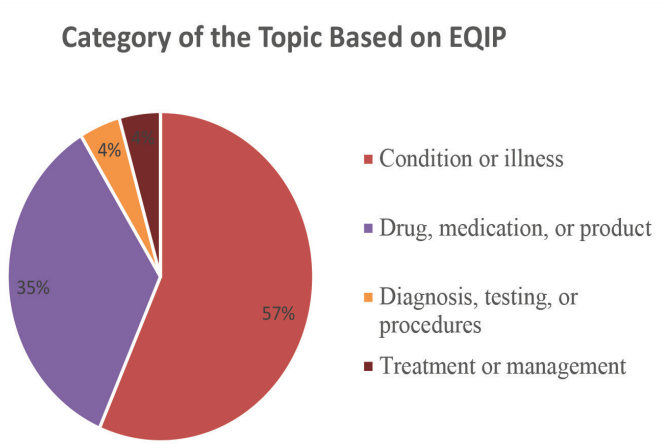

Figure 3. Category of the topic based on EQIP
EQIP: Ensuring Quality Information for Patients

Table 2. Quantitative properties of parameters

Parameters	Minimum	Maximum	Mean	Standart deviation	n
EQIP	25.00	56.25	39.89	6.20	23
FKGL	11.10	17.50	13.29	1.56	23
FKRE	5.84	39.90	21.41	9.37	23
Percantage					
Category of the topic based on EQIP	Condition or illness		57%		13
	Drug, medication, or product		35%		8
	Diagnosis, testing, or procedures		4%		1
	Treatment or management		4%		1

n: Number, EQIP: Ensuring Quality Information for Patients, FKGL: Flesch-Kincaid Grade Level, FKRE: Flesch-Kincaid Reading Ease

Table 3. Comparison of parameters between groups

	Group 1 (n=13)	Group 2 (n=8)	p*	Group 3 (n=1)	Group 4 (n=1)	p**
	Mean ± SD	Mean ± SD		Mean	Mean	
FKGL	13.62±1.72	12.86±1.29	0.298	11.60	14.30	0.457
FKRE	19.26±8.27	24.74±9.94	0.188	33.60	10.60	0.195
	Median (min.-max.)	Median (min.-max.)		Median	Median	
EQIP	37.50 (25.00-56.25)	44.38 (32.50-45.13)	0.059	34.38	43.75	0.136

*p-value for Group 1 and Group 2, **p-value for all groups, n: Number, SD: Standart deviation, EQIP: Ensuring Quality Information for Patients, FKGL: Flesch-Kincaid Grade Level, FKRE: Flesch-Kincaid Reading Ease, Min.-max.: Minimum-maximum

depression, and stress caused by the pandemic, which could have exacerbated FM symptoms. Notably, the surge in FM searches coincided with the rapid increase in COVID-19 cases, suggesting a possible correlation between the pandemic's impact on mental health and the worsening of FM symptoms. when evaluating this relationship, it is also important to consider Long COVID, which presents symptoms that closely resemble those of FM (14,15).

Despite such a complicated clinical picture, no cure currently exists for FM, so treatment is centred on improving the patient's ability to function while managing pain and other associated symptoms (16). Moreover, given the complicated aspects of FM, numerous myths and misconceptions abound. All of these leads patients to actively seek reliable information (17). Patients may wish to gain a deeper understanding of their condition and the available treatment options to actively engage in the decision-making process. An informed patient is better equipped to contribute meaningfully to decisions about their care and may experience reduced anxiety as a result. Conversely, without access to quality information, patients may struggle to discuss their findings coherently with their doctors and may be unable to make well-informed decisions (18,19). 72% of internet users seek medical information online (20). However, it is argued that the quality of web information is often poor and is presented in a way that increases the likelihood of misunderstanding (4,21). Basavakumar et al. (21) have shown that online resources concerning FM, including its etiology, symptoms, comorbidities, and management, are frequently incomplete, with content that may be difficult to access and susceptible to misinterpretation. Ozsoy-Unubol and Alanbay-Yagci (19) investigated the quality of online information on YouTube concerning FM. They found that, despite its variability, the content on the YouTube platform was generally of poor quality. Moreover, they suggested that this poor-quality information could mislead patients and potentially harm the doctor-patient relationship.

Previous research has highlighted that online resources for FM, including those on platforms like YouTube, are often incomplete or of poor quality (19,21). Such deficiencies can mislead patients and hinder effective communication with healthcare providers. Although ChatGPT provides information that is quickly and easily accessible, our findings suggest that the quality and clarity of its responses are insufficient to fully meet patient needs. For example, EQIP scores for ChatGPT responses were lower than the threshold for high-quality information.

The integration of ChatGPT into our daily experiences has led to its widespread adoption across various fields, including medicine. Beyond its use in medical education, research, and clinical practice, ChatGPT has also been employed in patient education and information (22).

In this context, studies have been conducted on various diseases, including osteoarthritis, cerebral palsy (CP), and osteoporosis (8,9,23). Ata et al. (8) assessed the reliability and utility of ChatGPT's responses concerning cerebral palsy and determined that it serves as a reliable, though partially useful, source of information. They emphasized the importance of patients and their families verifying the medical information obtained by consulting their healthcare providers. Erden et al. (9) assessed the quality, readability, and comprehensibility of the information provided by ChatGPT concerning osteoporosis. Their findings indicated that the quality and readability of ChatGPT's information were insufficient for effective health management. Yang et al. (23) determined that ChatGPT's responses do not always fully align with recommendations from evidence-based clinical practice guidelines, and they suggested that both healthcare professionals and patients should approach the guidance offered by AI platforms with measured expectations. They should recognize the current limitations in providing clinically sound advice. Consistent with existing literature on other diseases (8,9,23), our study revealed that the quality of responses provided by ChatGPT was insufficient. Additionally, we determined that the understandability of the content was categorized as difficult. We believe that the optimal approach to information transfer is to convey highly reliable information in a manner that is comprehensible to all segments of society.

In diseases like FM, where the etiopathogenesis, diagnosis, and treatment are complex, excessive reliance on medical information obtained through artificial intelligence and the internet could have adverse effects on patient health. While these tools offer quick and easy access to information, the principle that treatment should be tailored to the individual rather than the disease itself implies that general information may be insufficient or even inaccurate in complex and complicated cases (9,24).

This study aimed to evaluate ChatGPT's ability to generate globally relevant health-related responses by focusing on English-language keywords and international search trends. While regional trends are valuable, the study prioritized global applicability, leaving localized analyses for future research.

Future studies should explore keywords in other languages to understand how language and cultural differences influence the quality and accessibility of AI-generated healthcare content. This could help create more inclusive AI tools, addressing disparities in reliable health information for non-English-speaking populations.

The main limitations of the study are the exclusive focus on English terms, which could constrain the findings, and the

selection of only 23 keywords. Expanding the keyword lists and incorporating other languages in future studies could yield more comprehensive results.

CONCLUSION

Our study revealed significant deficiencies in the quality and clarity of FM-related responses generated by ChatGPT, and these deficiencies raise concerns about its suitability for effective health communication. Healthcare professionals should guide patients in interpreting AI-generated information and verifying it with evidence-based sources. AI developers must enhance readability and alignment with clinical guidelines, to improve reliability. Patients should critically evaluate online health content and consult healthcare providers for accurate advice. Refining algorithms is crucial to advancing the accuracy and accessibility of AI-generated responses for more effective health communication. Future research should examine non-English keywords to enhance AI tools' inclusivity and address health information disparities across different languages and cultures.

Ethics

Ethics Committee Approval: As no human or animal data were utilized, obtaining approval from an ethics committee was not necessary.

Informed Consent: No informed consent form was required.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.U., E.G., Concept: A.U., E.G., Design: A.U., E.G., Data Collection or Processing: A.U., E.G., Analysis or Interpretation: A.U., E.G., Writing: A.U., E.G.

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

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

REFERENCES

1. Sarzi-Puttini P, Giorgi V, Marotto D, Atzeni F. Fibromyalgia: an update on clinical characteristics, aetiopathogenesis and treatment. Nat Rev Rheumatol. 2020;16:645-60.
2. Häuser W, Ablin J, Fitzcharles MA, et al. Fibromyalgia. Nat Rev Dis Primers. 2015;1:15022.
3. Llàdser AN, Montesó-Curto P, López C, et al. Multidisciplinary rehabilitation treatments for patients with fibromyalgia: a systematic review. Eur J Phys Rehabil Med. 2022;5:76-84.
4. Daraz L, Macdermid JC, Wilkins S, Gibson J, Shaw L. The quality of websites addressing fibromyalgia: an assessment of quality and readability using standardised tools. BMJ Open. 2011;1:e000152.
5. Crooks VA. "I Go on the internet; I always, You know, check to See What's New": chronically Ill Women's use of online health information to shape and inform doctor-patient interactions in the space of care provision. ACME. 2006;5:50-69.
6. Daraz L. Information availability and needs of people living with fibromyalgia. Diss Abstr Int B Sci Eng. 2012:72.
7. Brown TB, Mann B, Ryder N, et al. Language Models are Few-Shot Learners. arXiv preprint. 2020;arXiv:2005.
8. Ata AM, Aras B, Yılmaz Taşdelen Ö, Çelik C, Çulha C. Evaluation of informative content on cerebral palsy in the era of artificial intelligence: the value of ChatGPT. Phys Occup Ther Pediatr. 2024;44:605-14.
9. Erden Y, Temel MH, Bağcıer F. Artificial intelligence insights into osteoporosis: assessing ChatGPT's information quality and readability. Arch Osteoporos. 2024;19:17.
10. Moult B, Franck LS, Brady H. Ensuring quality information for patients: development and preliminary validation of a new instrument to improve the quality of written health care information. Health Expect. 2004;7:165-75.
11. Boles CD, Liu Y, November-Rider D. Readability levels of dental patient education brochures. J Dent Hyg. 2016;90:28-34.
12. WHO T. WHO Director-General's opening remarks at the media briefing on COVID-19-11 March 2020. Geneva; 2020.
13. Carroll W, Strenger V, Eber E, et al. European and United Kingdom COVID-19 pandemic experience: the same but different. Paediatr Respir Rev. 2020;35:50-6.
14. Fialho MFP, Brum ES, Oliveira SM. Could the fibromyalgia syndrome be triggered or enhanced by COVID-19? inflammopharmacology. 2023;31:633-51.
15. Mariette X. Long COVID: a new word for naming fibromyalgia? Ann Rheum Dis. 2024;83:12-4.
16. Hoffman DL, Dukes EM. The health status burden of people with fibromyalgia: a review of studies that assessed health status with the SF-36 or the SF-12. Int J Clin Pract. 2008;62:115-26.
17. Bragazzi NL, Amital H, Adawi M, et al. What do people search online concerning the "elusive" fibromyalgia? Insights from a qualitative and quantitative analysis of Google Trends. Clin Rheumatol. 2017;36:1873-8.
18. Longtin Y, Sax H, Leape LL, Sheridan SE, Donaldson L, Pittet D. Patient participation: current knowledge and applicability to patient safety. Mayo Clin Proc. 2010;85:53-62.
19. Ozsoy-Unubol T, Alanbay-Yagci E. YouTube as a source of information on fibromyalgia. Int J Rheum Dis. 2021;24:197-202.
20. Fox S, Duggan M. Health online 2013. Health. 2013;2013:1-55.

21. Basavakumar D, Flegg M, Eccles J, Ghezzi P. Accuracy, completeness and accessibility of online information on fibromyalgia. Rheumatol Int. 2019;39:735-42.

22. Sallam M. ChatGPT utility in healthcare education, research, and practice: systematic review on the promising perspectives and valid concerns. Healthcare (Basel). 2023;11:887.

23. Yang J, Ardavanis KS, Slack KE, Fernando ND, Della Valle CJ, Hernandez NM. Chat Generative Pretrained Transformer (ChatGPT) and Bard: artificial ıntelligence does not yet provide clinically supported answers for hip and knee osteoarthritis. J Arthroplasty. 2024;39:1184-90.

24. Tinetti ME, Fried T. The end of the disease era. Am J Med. 2004;116:179-85.

ORIGINAL ARTICLE

Rheumatology Quarterly

DOI: 10.4274/qrheumatol.galenos.2025.47966
Rheumatol Q 2025;3(1):20-6

OESOPHAGEAL DILATATION ON CHEST HIGH-RESOLUTION COMPUTED TOMOGRAPHY IN SYSTEMIC SCLEROSIS

Atalay Doğru, Zübeyde Uğurlu

Süleyman Demirel University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Isparta, Türkiye

Abstract

Aim: The present study was conducted to determine the relationship between oesophageal diameter and disease findings in patients with systemic sclerosis.

Material and Methods: The study included 86 patients. A retrospective evaluation was performed on the demographic data, biochemical and serological tests, and chest high-resolution computed tomography (HRCT) images of the patients. The presence of dilatation was defined as a measurement of over 10 mm in width. The oesophageal area was calculated at the level of the widest measurement. The relationship between oesophageal dilatation and digital ulcer (DU), pulmonary involvement, and pulmonary hypertension was evaluated.

Results: The number of patients with supra-aortic and infra-aortic esophageal lateral, anteroposterior, and widest esophageal dilatation measurements above 10 mm was 49 (56.9%). The largest oesophageal area was found to be 173.6±90.7 mm^2. The prevalence of DUs did not differ significantly between the groups with and without oesophageal dilatation. Pulmonary hypertension was detected in 22 (44.9%) patients with oesophageal dilatation and was found to be significantly higher in those without oesophageal dilatation (p=0.04). The extent of pulmonary involvement was significantly higher in the group with oesophageal dilatation (p=0.003).

Conclusion: The oesophageal diameter has been demonstrated to be associated with pulmonary involvement. HRCT offers a valuable opportunity to assess the oesophagus. Further research is required to ascertain whether oesophageal diameter can be utilised in HRCT evaluations as a means of patient monitoring.

Keywords: Computed tomography, oesophageal dilatation, systemic sclerosis, pulmonary involvement

INTRODUCTION

Systemic sclerosis (SSc) is a rare connective tissue disease characterised by diffuse fibrosis of the skin and organs. The gastrointestinal system is affected in over 90% of patients. It shows a heterogeneous involvement and may occur at any stage of the disease course (1). The underlying pathophysiology of gastrointestinal system involvement, especially in the oesophagus, remains to be fully elucidated. The prevailing hypothesis suggests that neural dysfunction, muscle atrophy, vascular problems, and fibrosis are the primary factors contributing to the pathology of the disease (2-4). The findings from autopsy studies indicate that smooth muscle atrophy is a

Address for Correspondence: Atalay Doğru, Süleyman Demirel University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Isparta, Türkiye
E-mail: atalay_dogru@hotmail.com **ORCID ID:** orcid.org/0000-0002-9797-1182
Received: 09.02.2025 **Accepted:** 06.03.2025 **Publication Date:** 21.03.2025

Cite this article as: Doğru A, Uğurlu Z. Oesophageal dilatation on chest high-resolution computed tomography in systemic sclerosis. Rheumatol Q. 2025;3(1):20-6

predominant feature in oesophageal lesions, particularly within the circular layer. These findings suggest that this phenomenon is not associated with ischaemic and inflammatory conditions. The targeted destruction of smooth muscle cells by autoimmunity, in conjunction with neuromuscular structures like muscarinic receptor swhich play a pivotal role in smooth muscle stimulation and autonomic dysfunction, has been identified as a causative factor for smooth muscle atrophy. The loss of Interstitial Cells of Cajal (ICC) has also been identified. ICC provides smooth muscle pacemaker activity and is part of the sensory units of vagal afferents. The involvement of the vagus nerve, a component of the autonomous nervous system that plays a crucial regulatory role in oesophageal motility and sphincter function, has been identified as a contributing factor to SSc oesophageal involvement (5,6).

SSc-related pulmonary involvement, characterized by pulmonary arterial hypertension and interstitial lung disease (ILD) is the most significant predictor of mortality. The prevalence of SSc-related pulmonary involvement is higher in the diffuse cutaneous form, with a 10-year mortality rate that exceeds 40%. Consequently, it is recommended that patients diagnosed with SSc be screened for ILD by high-resolution computed tomography (HRCT) (7,8). The presence of digital ulceration and pulmonary hypertension is recognised as a risk factor for the development and progression of ILD (9). An increase in oesophageal diameter is considered a risk factor for ILD progression and is associated with an increased risk of death. Increased oesophageal diameter has been demonstrated to result in impaired motility and microaspiration of gastric contents. The role of microaspiration in the initiation and progression of ILD has been a subject of research (7,10).

The oesophagus in SSc is dilated and exhibits a loss of function, contrary to the usual narrowing of the structure. HRCT, utilised for the assessment of ILD, frequently reveals dilated oesophagus, in SSc patients; however, this finding is often overshadowed by the evaluation of lung parenchyma. The present study was conducted with the objective of determining the relationship between oesophageal diameter and disease findings in patients with SSc.

MATERIAL AND METHODS

Study Population

The present cross-sectional, retrospective study comprised 86 patients aged 18 years and over who were followed up in the rheumatology clinic between 2019 and 2024 and had been diagnosed with SSc according to the 2013 American College of Rheumatology/European League Against Rheumatism Classification Criteria for SSc (11). All patients for whom laboratory and HRCT data were available were included in the study. Patients under 18 years of age and those with inaccessible or missing data were excluded from the study. The demographic data, biochemical and serological tests, echocardiography, pulmonary function tests, and HRCT images of the patients were evaluated retrospectively. The clinical information, including the number of hand and foot digital ulcers (DUs), was obtained by analysing the patient files. Patients were categorised as limited cutaneous or diffuse cutaneous according to the LeRoy classification system (12) after physical examination by an experienced rheumatologist.

The clinical definition of DUs is as follows: areas of the fingers with a visually noticeable depth and loss of continuity of epithelial cover. The severity of DU was determined by the number of new DUs reported by the physician during the clinical examination. The severity of DU was categorised as follows: 0-5 DUs were defined as mild, 6-10 DUs as moderate, and >10 DUs as severe (13,14).

The anti-nuclear antibody (ANA) test was conducted using the indirect immunofluorescence (IIF) method, with HEp-2 (HEp-2000) cells serving as the substrate. The screening dilution was set at 1/160. Values below 1/160 titre were evaluated as negative, 1/160-1/320 titre 1+, 1/320-1/640 titre 2+, 1/640-1/1280 titre 3+, and >1/1280 titre 4+.

Transthoracic echocardiography was conducted within the echocardiography laboratory of the department of Cardiology, utilising a high-resolution Philips IE 33 imaging system (Andover, Massachusetts, USA) with transducers arranged at varying frequencies (2.5-3.5 MHz). Tricuspid regurgitation velocity >2.8 m/s and pulmonary artery pressures (PAPs) ≥35 mmHg, as determined by transthoracic echocardiography, were identified as indicators of pulmonary hypertension. Right heart catheterisation (RHC) was then performed in these patients in accordance with a standard protocol. During RHC, mPAP and pulmonary capillary wedge pressure were measured by placing the catheter. Pulmonary hypertension was diagnosed when the mean arterial pulmonary pressure was >20 mmHg on RHC at rest (15).

The evaluation of lung involvement was conducted through the use of HRCT, pulmonary function tests, and diffusing capacity of the lungs for carbon monoxide (DLCO). Determination of lung involvement was conducted exclusively through HRCT by a radiologist with expertise in this domain. A pathological diagnosis (lung biopsy) was not undertaken. The classification of the subject is as follows: NSIP, UIP, or possible UIP, according to the image type on HRCT. Patients were selected for medical

treatment in accordance with the treatment algorithm using HRCT, as outlined in the Expert consensus on the management of SSc-associated ILD. Patients with greater than 20% lung parenchymal involvement, along with forced vital capacity (FVC) and/or DLCO levels below the lower limit of normal, and moderate to severe symptoms, were initiated on medical treatment. While the patients included in the study received medical treatment for ILD, determining whether there was lung involvement, the type of involvement was determined by HRCT findings. Patients who did not fulfil the treatment criteria were not considered to have lung involvement (8).

Ethics committee approval for this retrospective study was obtained from the Süleyman Demirel University Faculty of Medicine Ethics Committee (approval number: 2024/83/25, dated: 05.11.2024).

Esophageal Measurements on High-Resolution CT

HRCT scans were obtained in the supine position during full inspiration using a SOMATOM Definition AS (Siemens Medical Systems, Iselin, NJ). HRCT was performed from the lung apices to the lung bases. In the axial sections of HRCT, the oesophagus was divided into two regions: supra-aortic and infra-aortic, according to their position relative to the upper border of the aortic arch. The presence of dilatation was defined as a measurement of over 10 mm in width. Supra-aortic and infra-aortic, lateral, antero-posterior, and widest measurements were taken. The oesophageal area was calculated at the level of the widest measurement (Figure 1) (16).

Supra-aortic and infra-aortic measurements, as well as oesophageal area calculations, were performed separately by both authors. The results demonstrated substantial agreement (Fleiss's Kappa 0.68) among the supra-aortic and infra-aortic measurements, and the oesophageal area.

Statistical Analysis

The data obtained from the study were analysed using the IBM SPSS 29.0 software package (Statistical Package for the Social Sciences, IBM, USA). Descriptive statistics were employed to present categorical data as frequencies and percentages and proportional scale data as mean ± standard deviation. The Kolmogorov-Smirnov method, the Student's t-test, and chi-square analysis were utilized in the analysis. The Kolmogorov-Smirnov method was employed to test the normal distribution of continuous numerical data, with parametric methods subsequently used to conduct comparisons between groups and repeated measurements. The Student's t-test was employed to compare two independent groups, and the paired t-test was used to compare two repeated measures. Chi-square analysis was used to determine the relationships between categorical data. The study found that the p-value was considered significant when it was less than 0.05, with a Type-I error rate of 5% throughout the study. The maximum accepted value of the type 2 error (beta) was 0.20.

RESULTS

The study included 86 patients. It appears that the number of patients with supra-aortic and infra-aortic oesophageal lateral, anteroposterior, and widest oesophageal dilatation measurements above 10 mm was 49 (56.9%). Patients were divided into two groups: one with oesophageal dilatation and one without. In patients with oesophageal dilatation, supraaortic oesophagus's widest lateral measurement was 13.4±5.8 mm and infraaortic oesophagus's widest lateral measurement was 14.6±6.7 mm. The supraaortic oesophagus anterior-posterior measured 9.2±4.9 mm, whereas the infraaortic oesophagus anterior-posterior measured 8.3±4.6 mm. The largest oesophageal area was found to be 173.6±90.7 mm2 (Table 1). The mean age of the group with oesophageal dilatation was

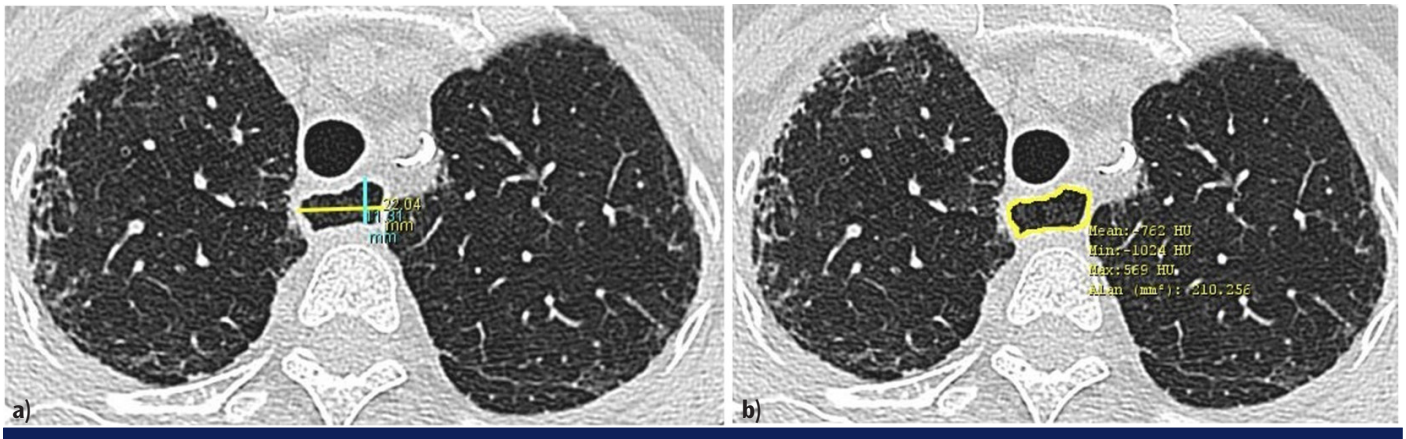

Figure 1. An example for measuring the largest oesophageal lateral and anteroposterior diameter (a) and maximal oesophageal area (b)

found to be significantly older than that of the group without oesophageal dilatation, with a statistically significant difference (p=0.04). Both groups were similar and had a preponderance of female patients and were similar. It appears that there is no significant difference between the two groups in terms of ANA titres and patterns. Anti-topoisomerase I (Anti Scl-70) and anti-centromere antibody positivity rates appeared to be similar. The rheumatoid factor positivity rate was 16 (32.7%) in the group with a dilated oesophagus and 5 (13.5%) in the group without a dilated oesophagus, indicating a statistically significant difference (Table 1).

An analysis of the clinical findings of patients with oesophageal dilatation revealed that the prevalence of DUs did not differ significantly between the study groups. When DUs were categorised, according to the scale employed, based on the number of lesions present, namely as Mild (1-5), Moderate (6-10), or Severe (>10), it was observed that the two groups exhibited comparable numbers and severity of DUs. Pulmonary hypertension was detected in 22 (44.9%) patients with oesophageal dilatation and was found to be statistically significantly higher in patients without oesophageal dilatation (p=0.04). When the number of patients with pulmonary involvement was analysed, the analysis showed that the degree of involvement was significantly higher in the group with oesophageal dilatation. The former group exhibited a prevalence of 32 (65%), while the latter group demonstrated a prevalence of 12 (32.4%) (p=0.003). Furthermore, the analysis of the specific types of pulmonary involvement revealed that NSIP was observed to be highly prevalent in both groups, being 93% in one group and 100% in the other, as illustrated in Table 2.

Binary logistic regression analysis revealed no statistically significant results concerning the factors influencing oesophageal

Table 1. Sociodemographic and laboratory data of the SSc patients

Variable	Oesophageal dilatation		p-value
	Yes (n=49)	No (n=37)	
Age, year	60.3±14.4	53.7±15.4	0.04*
Female, n	44 (89.8%)	35 (94.6%)	0.42
Age at diagnosis, year	51.4±15.6	46.9±14.7	0.08
Disease duration, months	110.6±75	82.7±63.5	0.07
ANA positive, n	48 (98%)	35 (94.6%)	0.40
ANA titer **<1/160 negative** **1/160-1/320 1+** **1/320-1/640 2+** **1/640-1/1280 3+** **>1/1280 4+**	 1 (2%) 5 (10.2%) 11 (22.4%) 19 (38.8%) 13 (26.5%)	 2 (5.4%) 3 (8.1%) 7 (18.9%) 17 (45.9%) 8 (21.6%)	0.88
ANA pattern **Speckled** **Homogenous** **Nucleolar** **Centromere** **Other**	 3 (6.1%) 15 (30.6%) 6 (12.2%) 21 (42.9%) 3 (6.1%)	 2 (5.4%) 11 (29.7%) 5 (13.5%) 16 (43.2%) 1 (2.7%)	0.96
SSc Subtypes **Diffuse cutaneous** **Limited cutaneous**	 26 (53.1%) 23 (46.9%)	 19 (51.4%) 18 (48.6%)	0.87
Anti-topoisomerase I (anti-Scl-70)	19 (38.8%)	10 (27%)	0.25
Anti-centromere	19 (38.8 %)	15 (40.5%)	0.86
RF positive, n	16 (32.7 %)	5 (13.5%)	**0.04***
Widest oesophageal diameter lateral, mm	14.61±6.79	-	
Widest oesophageal diameter, antero-posterior, mm	9.24±4.9	-	
Oesophageal area, mm²	173.6±90.7	-	

*: Significant at 0.05 level, calculated as mean ± standard deviation. NS: Not significant, SSc: Systemic sclerosis, ANA: Anti-nuclear antibody, RF: Rheumatoid factor

dilatation. However, when the factors affecting diffuse cutaneous SSc subtype were analysed, age and pulmonary involvement were found to be statistically significant [p-value 0.002 and <0.001, odds ratio: 0.934 (0.895-0.976), 31.003 (7.736-124.25), respectively] (Table 3).

DISCUSSION

In this study, we found that pulmonary hypertension and pulmonary involvement were more prevalent in SSc patients with oesophageal dilatation. Contrary to expectations, no correlation was found between dilatation and many other laboratory and clinical findings. As SSc is a fibroinflammatory disease, it is expected that laboratory data will not be normal in follow-up. However, a condition such as DUs, in which the role of vascular bed disorder and fibrosis in the pathophysiology is clear, would be expected to be associated with oesophageal dilatation. The relationship not being found in the study suggests that different factors are involved. The oesophagus is one of the organs frequently affected in SSc patients. In SSc patients presenting with GERD and dysmotility symptoms, a range of methods is employed to evaluate oesophageal involvement, including manometry, scintigraphy, and endoscopy. Consequently, a symptom-based screening procedure is performed in patients with gastrointestinal symptoms. However, all patients diagnosed with SSc are screened for lung involvement with HRCT because lung involvement is an important cause of mortality, and this screening also creates a good opportunity to evaluate the oesophagus even in asymptomatic patients. However, in clinical practice, the increase in oesophageal diameter is generally disregarded when evaluating the lung parenchyma, both at the time of initial diagnosis and during follow-up. However, since the early 2000s, it has been established that an increase in oesophageal diameter functions as a risk factor for ILD progression (9).

Table 2. Clinical findings of SSC patients according to Oesophageal dilatation

Variable	Oesophageal dilatation		p-value
	Yes (n=49)	No (n=37)	
Digital ulcer, n	30 (61.2 %)	16 (43.2%)	**0.09**
Number of digital ulcers **Mild (1-5)** **Moderate (6-10)** **Severe (>10)**	 22 (73.3 %) 6 (20 %) 2 (6.7 %)	 12 (75%) 3 (18.8%) 1 (6.2%)	0.99
Pulmonary hypertension, n	22 (44.9 %)	9 (24.3%)	**0.04***
Pulmonary involvement, n	32 (65 %)	12 (32.4%)	**0.003***
Pulmonary involvement type **NSIP** **UIP**	 30 (93.7 %) 2 (6.3 %)	 12 (100%) 0 (0%)	**0.01***

*: Significant at 0.05 level, calculated as mean ± standard deviation. NS: Not significant, NSIP: Non-specific interstitial pneumonia, UIP: Usual interstitial pneumonia

Table 3. Factors affecting diffuse cutaneous SSc subtype

Factors	Beta	p-value	OR (95% CI)
Age	-0.068	**0.002***	0.934 (0.895-0.976)
RF, positive	-1.187	0.103	0.305 (0.073-1.273)
Pulmonary involvement	3.434	**<0.001***	31.003 (7.736-124.25)
Constant	2.544	**0.029***	

Model is significant: chi-square =43.934; p<0.001; Nagelkerke R2=0.534. Limited cutaneous: reference category. *: Significant at 0.05 level according to Binary Logistic regression, OR: Odds ratio; CI: Confidence interval, SSc: Systemic sclerosis, RF: Rheumatoid factor

In a study conducted by Pandey et al. (17), with 50 SSc patients, the oesophagus was found to be dilated on HRCT in 58% of patients, and no age difference was observed between these patient groups. In a subsequent study involving 105 patients, the incidence of dilatation was found to be 62%, exhibiting a comparable trend. Furthermore, the study revealed that SSc subtypes, gender and serology were not associated with oesophageal dilatation (18). A further study, encompassing 54 SSc patients, revealed that oesophageal dilatation occurred in 69.2% of the subjects and was not associated with age (19). In contrast, the present study observed oesophageal dilatation in 56% of patients, consistent with existing literature. However, in contrast to the findings reported in the literature, it was observed that the mean age of patients with dilatation was higher than that of patients without dilatation. This may be attributable to the observation that progression is more prevalent in patients with advanced age of onset, as evidenced by other organ involvements, such as lung involvement. A more aggressive disease and increased organ involvement are typically observed in the diffuse cutaneous subtype when other laboratory characteristics are analysed. However, in this study, similar rates of oesophageal dilatation were observed in the limited and diffuse types. A similar observation was made in relation to ANA positivity titres and patterns. This finding may imply that oesophageal involvement is not determined by serology or subtype. However, further clarification is required through studies encompassing a larger number of patients.

DUs are a prevalent symptom in patients suffering from SSc, a condition in which vascular disease plays a pivotal role. These ulcers serve as indicators of not only the condition of the peripheral vascular bed but also the involvement of numerous organ systems. DUs have been observed to be associated with ILD, cardiac disease, and gastrointestinal involvement, particularly oesophageal involvement (20,21). It has been emphasized that esophageal motility disorder is observed, approximately 4.5 times more frequently in patients with DU (22). However, it should be noted that patients with esophageal symptoms (dysphagia, reflux) were evaluated in these studies. In the present study, it was observed that the prevalence of DUs was higher in the group with dilated oesophagus. However, this observation did not attain statistical significance. When ulcers were categorized as mild, moderate, and severe, similar findings were obtained in the two groups. Consistent with the findings of the present study, a lack of significant correlation was identified between the dilatation detected on HRCT and DU in the study by Vonk et al. (18). This finding suggests the possibility of etiopathogenetic factors other than vascular pathologies, playing a role in oesophageal dilatation.

A considerable number of studies have demonstrated a correlation between oesophageal dysfunction and the severity of ILD in SSc. Oesophageal dilatation is recognised as a risk factor for ILD progression. Moreover, studies have indicated that microaspiration of gastric content and GERD are associated with the onset and progression of ILD (23-25). In a study conducted by Salaffi et al. (26) with 126 SSc patients, the widest oesophageal dilatation was found to be 13.5 (±4.2) mm. It was emphasised that the severity of ILD increased as the oesophageal diameter increased on HRCT. Furthermore, a negative correlation was observed with DLCO.

Consequently, it has been emphasised that if the oesophagus is found dilated in patients with ILD in the early period of ILD diagnosis, it may be considered a risk factor, and early treatment may be initiated (26). In a further study of 270 SSc patients, the largest oesophageal diameter was found to be associated with more extensive radiographic ILD. In this study, the hypothesis that esophageal dysfunction increases with dilatation and leads to lung damage caused by aspiration of acid or gastric contents is defended, in accordance with other esophageal dilatation studies in the literature. It is thought that aspiration triggers the emergence of existing lung inflammation (27). In a study observing 75 early SSc patients over a period of one year, with the amount of oesophageal dilatation being measured concurrently, it was emphasised that worsening oesophageal diameter was a predictor of progression of lung fibrosis (28). In studies where oesophageal diameter and area were evaluated in conjunction, it was reported that both diameter and area were associated with the progression of ILD. However, the study did not ascertain whether pulmonary outcomes improved with symptomatic treatment (29,30). In the present study, it was established that oesophageal diameter was significantly larger in patients with pulmonary involvement and pulmonary hypertension. Consistent with the extant literature, the wider oesophageal diameter in patients with pulmonary involvement provides evidence to support the hypothesis that lung damage is caused by oesophageal dysfunction and aspiration of acid or gastric contents.

Study Limitations

The present study has some limitations. In this retrospective study, the lack of detailed data on lung involvement (FVC, DLCO, etc.) prevents the comparison of the level of involvement with oesophageal dilatation. Furthermore, the absence of parameters such as manometry, scintigraphy, or endoscopy for the evaluation of oesophageal dysfunction constitutes a significant limitation. The evaluation of oesophageal dilatation and progression of ILD with subsequent follow-up in this patient group is expected to provide valuable information. Finally, it is acknowledged that gastric pressure difference and medications (immunosuppressive and symptomatic treatment) may slightly change the oesophageal diameter during HRCT. A further limitation is the inability to compare oesophageal dilatation to the modified Rodman score, which significantly assesses skin fibrosis. Despite the study's limitations, it offers significant insights that will inform clinical practice and contribute to the existing body of literature.

CONCLUSION

HRCT performed to evaluate ILD, shows more esophageal dilatation than expected. HRCT particularly in newly diagnosed SSc patients, offers a valuable opportunity to assess the oesophagus. It offers numerous advantages over traditional methods, including cost-effectiveness and non-invasiveness. It is important to note that oesophageal diameter is associated with pulmonary involvement. Further studies are required to support the use of oesophageal diameter in HRCT evaluations as a parameter for patient follow-up.

Ethics

Ethics Committee Approval: Ethics committee approval for this retrospective study was obtained from the Süleyman Demirel University Faculty of Medicine Ethics Committee (approval number: 2024/83/25, dated: 05.11.2024).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: A.D., Design: A.D., Data Collection or Processing: A.D., Z.U., Analysis or Interpretation: A.D., Z.U., Literature Search: A.D., Z.U., Writing: A.D.

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

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

REFERENCES

1. Volkmann ER, Andréasson K, Smith V. Systemic sclerosis. Lancet. 2023;401:304-18.
2. Zampatti N, Garaiman A, Jordan S, et al. Performance of the UCLA Scleroderma Clinical Trials Consortium Gastrointestinal Tract 2.0 instrument as a clinical decision aid in the routine clinical care of patients with systemic sclerosis. Arthritis Res Ther. 2021;23:125.
3. Nassar M, Ghernautan V, Nso N, et al. Gastrointestinal involvement in systemic sclerosis: An updated review. Medicine (Baltimore). 2022;101:e31780.
4. Volkmann ER, McMahan Z. Gastrointestinal involvement in systemic sclerosis: pathogenesis, assessment and treatment. Curr Opin Rheumatol. 2022;34:328-36.
5. Roberts CG, Hummers LK, Ravich WJ, Wigley FM, Hutchins GM. A case-control study of the pathology of oesophageal disease in systemic sclerosis (scleroderma). Gut. 2006;55:1697-703.
6. Amaral TN, Peres FA, Lapa AT, Marques-Neto JF, Appenzeller S. Neurologic involvement in scleroderma: a systematic review. Semin Arthritis Rheum. 2013;43:335-47.
7. Bautista-Sanchez R, Khanna D. Systemic sclerosis-associated interstitial lung disease: How to manage in 2024? Rheumatol Immunol Res. 2024;5:157-65.
8. Rahaghi FF, Hsu VM, Kaner RJ, et al. Expert consensus on the management of systemic sclerosis-associated interstitial lung disease. Respir Res. 2023;24:6.
9. Perelas A, Silver RM, Arrossi AV, Highland KB. Systemic sclerosis-associated interstitial lung disease. Lancet Respir Med. 2020;8:304-20.
10. Winstone TA, Hague CJ, Soon J, et al. Oesophageal diameter is associated with severity but not progression of systemic sclerosis-associated interstitial lung disease. Respirology. 2018;23:921-6.
11. van den Hoogen F, Khanna D, Fransen J, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League Against Rheumatism Collaborative Initiative. 2013;72:1747-55.
12. LeRoy EC, Medsger TA Jr. Criteria for the classification of early systemic sclerosis. J Rheumatol. 2001;28:1573-6.
13. Cappelli L, Wigley FM. Management of Raynaud phenomenon and digital ulcers in scleroderma. Rheum Dis Clin N Am. 2015;41:419–38.
14. Morrisroe K, Stevens W, Sahhar J, et al. Digital ulcers in systemic sclerosis: their epidemiology, clinical characteristics, and associated clinical and economic burden. Arthritis Res Ther. 2019;21:299.
15. Simonneaul G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019;53:1801913.
16. Pitrez EH, Bredemeier M, Xavier RM, et al. Oesophageal dysmotility in systemic sclerosis: comparison of HRCT and scintigraphy. Br J Radiol. 2006;79:719-24.
17. Pandey AK, Wilcox P, Mayo JR, et al. Oesophageal dilatation on high-resolution CT chest in systemic sclerosis: what does it signify? J Med Imaging Radiat Oncol. 2011;55:551-5.
18. Vonk MC, van Die CE, Snoeren MM, et al. Oesophageal dilatation on high-resolution computed tomography scan of the lungs as a sign of scleroderma. Ann Rheum Dis. 2008;67:1317-21.
19. Karamanolis GP, Denaxas K, Panopoulos S, et al. Severe oesophageal disease and its associations with systemic sclerosis. Clin Exp Rheumatol. 2017;35:82-5.
20. Hughes M, Herrick AL. Digital ulcers in systemic sclerosis. Rheumatology (Oxford). 2017;56:14-25.
21. Sunderkötter C, Herrgott I, Brückner C, et al. Comparison of patients with and without digital ulcers in systemic sclerosis: detection of possible risk factors. Br J Dermatol. 2009;160:835-43.
22. Xu D, Li MT, Hou Y, et al. Clinical characteristics of systemic sclerosis patients with digital ulcers in China. Clin Exp Rheumatol. 2013;31:46-9.
23. Tobin RW, Pope CE 2nd, Pellegrini CA, Emond MJ, Sillery J, Raghu G. Increased prevalence of gastroesophageal reflux in patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 1998;158:1804-8.
24. Hoppo T, Komatsu Y, Jobe BA. Gastroesophageal reflux disease and patterns of reflux in patients with idiopathic pulmonary fibrosis using hypopharyngeal multichannel intraluminal impedance. Dis Esophagus. 2014;27:530-7.
25. Ruaro B, Pozzan R, Confalonieri P, et al. Gastroesophageal reflux disease in idiopathic pulmonary fibrosis: Viewer or actor? To treat or not to treat? Pharmaceuticals (Basel). 2022;15:1033.
26. Salaffi F, Di Carlo M, Carotti M, Fraticelli P, Gabrielli A, Giovagnoni A. Relationship between interstitial lung disease and oesophageal dilatation on chest high-resolution computed tomography in patients with systemic sclerosis: a cross-sectional study. Radiol Med. 2018;123:655-63.
27. Richardson C, Agrawal R, Lee J, et al. Esophageal dilatation and interstitial lung disease in systemic sclerosis: A cross-sectional study. Semin Arthritis Rheum. 2016;46:109-14.
28. Wangkaew S, Losuriya P, Euathrongchit J. Worsening of esophageal dilatation is associated with increase in a high-resolution computed tomography (HRCT) score in early systemic sclerosis-associated interstitial lung disease (SSc-ILD). Clin Rheumatol. 2021;40:955-63.
29. Volkmann ER, Tashkin DP, Leng M, Kim GHJ, Goldin J, Roth MD. Association of symptoms of gastroesophageal reflux, esophageal dilation, and progression of systemic sclerosis-related interstitial lung disease. Arthritis Care Res (Hoboken). 2023;75:1690-7.
30. Figueiredo AFSD, Costa JF, Matos AP, Ramalho M. Esophageal dilatation as a predictor of systemic sclerosis in patients with interstitial lung disease. Turk Thorac J. 2021;22:231-6.

CASE REPORT AND LITERATURE REVIEW

Rheumatology Quarterly

DOI: 10.4274/qrheumatol.galenos.2025.94914
Rheumatol Q 2025;3(1):27-36

ADDING NINTEDANIB TO IMMUNOSUPPRESSIVE THERAPY IN CONNECTIVE TISSUE RELATED INTERSTITIAL LUNG DISEASES; CASE SERIES BASED ON REAL-LIFE DATA FROM A SINGLE CENTRE

Burak Okyar[1], Nurhan Atilla[2], Gözde Yıldırım Çetin[1], Mehmet Cihan Karacaoğlu[3], Betül Kızıldağ[3], Bekir Torun[1], Esen Saba Öktem[1], Fatih Yıldız[1]

[1]Kahramanmaraş Sütçü İmam University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Kahramanmaraş, Türkiye
[2]Kahramanmaraş Sütçü İmam University, Department of Chest Disease, Kahramanmaraş, Türkiye
[3]Kahramanmaraş Sütçü İmam University, Department of Radiology, Kahramanmaraş, Türkiye

Abstract

Connective tissue-related interstitial lung disease (CTD-ILD) is a severe process that progresses in approximately 30% of patients. These patients may need aggressive treatment. Therefore, new treatment strategies are being developed. Anti-fibrotic agents used in idiopathic pulmonary fibrosis are now being used in patients with a diagnosis of CTD-ILD. In the systemic sclerosis safety and efficacy study, the use of nintedanib in systemic sclerosis-related interstitial lung disease was shown to slow the loss of forced vital capacity (FVC). It has been shown to slow the loss of FVC. We retrospectively analyzed four patients diagnosed with CTD-ILD who used nintedanib for one year. The first two cases were diagnosed with systemic sclerosis, the third case with primary Sjögren's disease, and the fourth case with anti-synthetase syndrome. FVC, carbon monoxide diffusion capacity, 6-minute walking test, and echocardiography data of the cases were obtained. High-resolution computerized tomography records available in the system were re-evaluated with semi-quantitative and quantitative methods (artificial intelligence). We added nintedanib to mycophenolate mofetil treatment in our first, second and fourth cases. In our third case, we added nintedanib to the rituximab treatment. No severe side effects were encountered due to the combined treatment. In our third case, the treatment was terminated due to progressive severe weight loss. Except for the third case, all patients showed improvement in the modified borg dyspnea indices. In our second case, both semi-quantitative and quantitative interstitial lung disease scores were regressed. CTD-ILD is a complex pathology that requires patient-specific evaluation and personalized treatment. Immunosuppressive therapy was modified in all our patients. Immunosuppressive therapy is vital in the treatment of CTD-ILD. Patients with progressive pulmonary fibrosis should receive adequate and effective doses of immunosuppressive therapy. Despite this, treatment should be modified in patients with progression. The addition of nintedanib may contribute to the treatment of these patients.

Keywords: Connetive tissue disease, interstitial lung disease, nintedanib

Address for Correspondence: Burak Okyar, Kahramanmaraş Sütçü İmam University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Kahramanmaraş, Türkiye
E-mail: okyarmd@gmail.com **ORCID ID:** orcid.org/0000-0002-9028-9930
Received: 03.11.2024 **Accepted:** 09.02.2025 **Publication Date:** 21.03.2025

Cite this article as: Okyar B, Atilla N, Yıldırım Çetin G, et al. Adding nintedanib to immunosuppressive therapy in connective tissue related interstitial lung diseases; case series based on real-life data from a single centre. Rheumatol Q. 2025;3(1):27-36

INTRODUCTION

Interstitial lung disease (ILD) may develop during connective tissue diseases (CTD). Most of these patients do not show any severe progression. However, about 30% of patients show a progressive and fatal course (1). Such patients may need aggressive and new treatment strategies. Nintedanib, which has anti-fibrotic properties, is one of these drugs. One of the causes of mortality in patients with CTD is ILD. Pulmonary function test [forced vital capacity (FVC)], carbon monoxide diffusion test (DLCO), and 6-minute walk test (6MWT) are important clinical parameters in the follow-up of patients with ILD (2).

Nintedanib is multiple tyrosine kinase inhibitor. Platelet-derived growth factor, fibroblast growth factor, and vascular endothelial growth factor show their effect by activating the receptor signaling cascade (3). It inhibits fibroblast proliferation and migration. TheSafety and Efficacy of Nintedanib in Systemic Sclerosis (SENCSIS) study consisted of patients diagnosed with Ssc-ILD. The INBUILD (Nintedanib in patients with progressive fibrosing ILD) study consisted of patients diagnosed with non-idiopathic pulmonary fibrosis (IPF) progressive pulmonary fibrosis. The FVC measurement in these patients has been shown to that nintedanib slows its loss (5,6). The INBUILD study identified other disease groups with progressive pulmonary fibrosis, such as hypersensitivity pneumonitis (26.1%), autoimmune disease-related ILDs (25.6%), idiopathic non-specific interstitial pneumonia (NSIP) (18.9%), and unclassifiable idiopathic interstitial pneumonia (17.2%). The INBUILD study showed a slowdown in FVC decline in ILDs with non-IPF pulmonary fibrosis, independent of groups (6).

Nintedanib has been shown to act as an anti-inflammatory and anti-fibrotic agent for scleroderma-related ILD and other CTD characterized by progressive pulmonary fibrosis ((7). Therefore, it has been used both in scleroderma-related ILD and in other CTD-ILD patients with progressive pulmonary fibrosis. In a study with 663 , those using nintedanib were divided into two groups, mycophenolate mofetil (MMF) and non- MMF treatment, and compared. In both groups, FVC decline was statistically significantly slower than that in the placebo group. Although the FVC decline was less in the group receiving MMF, it was statistically insignificant. However, it was concluded that this result may be due to the small number of patients (8).

Studies have shown the efficacy of nintedanib in patients with CTD-ILD. In addition, no serious side effects have been reported with immunosuppressive agents such as MMF. Therefore, we added nintedanib to the treatment of our patients, due to the progression of their existing pulmonary fibrosis.

In this article, we presented a total of four cases, two of whom were diagnosed with Ssc-ILD, one with primary Sjögren's disease-associated ILD, and one with the diagnosis of anti-synthetase syndrome-associated ILD (ASS-ILD), for whom nintedanib was initiated due to their progression despite adequate treatment. In our case series, all patients were under immunosuppressive therapy before nintedanib. MMF was added to the treatment of three patients, and nintedanib was added to the rituximab (RTX) treatment of one patient.

METHODOLOGY

Inclusion/Exclusion Criteria

Patients with progression of existing pulmonary fibrosis despite adequate duration and dose of immunosuppressive therapy were included. Patients who did not sign informed consent and did not want to share their data were excluded.

Clinical Analysis

Patients with a diagnosis of CTD-ILD who regularly used nintedanib for one year were retrospectively analyzed. For this purpose, physical examination findings, routine laboratory parameters, FVC, DLCO, 6MWT, and echocardiography were obtained at three-month follow-ups.

High Resolution Computerized Tomography (HRCT) Analysis

High resolution computerized tomography was done if the clinician considered it necessary based on clinical and laboratory findings that suggested disease progression, and HRCT data were screened and retrieved retrospectively. Images were obtained in the supine position at full inspiration without intravenous contrast material using a multi-detector computed tomography (CT) system (Aquilion ONE ViSION edition; Canon Medical Systems Corporation, Otawara, Japan) through helical scanning from the apex to the base of the lungs. Acquisition parameters were as follows: detector width, 80x0.5 mm; tube voltage (120 kV): tube current 250-300 mAs; slice thickness, 3 mm; slice interval, 1,5 mm; rotation duration, 0.35; pitch factor (PF) 1.388; and FOV variable, between 35-45 cm (e.g., 40*40 cm). A phantom with a 32-cm diameter representing the body of an adult was used, and mean CDTIvol and DLP values were 4.8 mGy and 182.7 mGycm, respectively.

Semiquantitative HRCT Analysis

All HRCT images were examined by two observers blinded to the clinical findings, pulmonary function test results, and quantitative measurements of the patients, and decisions were made by consensus. Differences between observers could not be evaluated due to the very limited number of patients.

Examinations were done with the lung window setting (window center, 500-600 HU; window width, 1600 HU), and evaluations were made using the ILD staging system described by Goh et al. (9) CT images were scored at five levels: origin of large vessels, carina, pulmonary venous junction, middle of the third and fifth segments, and just above the right hemidiaphragm. Disease involvement was estimated for each level in the nearest 5% of total area and multiples of 5% (Figures 1 and 2). Patients were assigned to two groups based on semiquantitative image analysis: patients with limited (<20%) and diffuse (>20%) ILD.

Quantitative HRCT Analysis

All images were analyzed using a workstation (Vitrea; Canon Medical Systems Corporation, Otawara, Japan) and software called "lung density analysis" by a single trained radiology resident. Owing to the nature of quantitative measurements, inter-observer agreement was not examined. Minimal user intervention was allowed when necessary to exclude pulmonary vessels, esophagus, trachea, and main bronchus. With threshold values previously used in patients with systemic sclerosis, the ratio of ILD volume to the total lung volume was calculated. The device calculated ILD volume and total lung volume in milliliters using voxels between -200 and -700 HU and voxels between -200 and -950 HU, respectively (10). An example of the measurements is shown in Figures 1 and 2 (Case 3).

CASE REPORTS

Case 1

A 59-year-old female was admitted to our clinic with Raynaud's phenomenon, sclerodactyly, esophageal dilatation in 2016. Antinuclear antibody (ANA) test findings were as follows: granular pattern positive and anti-Sc170 positive. The patient was diagnosed with SSc. HRCT findings were consistent with fibrotic NSIP. Treatment with nine courses of cyclophosphamide (CYC) 1000 mg/month was initiated, and MMF 2 g/day was used as the maintenance treatment. In February 2021, the following findings were considered ILD progression: progression on HRCT; FVC, 66% (1670 mL); diffusing capacity of lung for DLCO, 75% (5.47 mmol/kPa/min); and 6MWT, 140 m (<440m). Nintedanib 300 mg/day was added to the ongoing treatment. FVC was 95% (2400 ml) at the third month of nintedanib treatment, and at the sixth month FVC and DLCO were 83% (2030 ml) and 91% (6.58 mmol/kPa/min), respectively. Due to radiological progression on HRCT and a 10% decline in FVC, MMF 1 g/day and RTX 2 g/6-months were added, and the patient was followed with MMF, RTX, and nintedanib treatment. During the 6-month follow-up period, FVC decline stopped, the Modified Borg Dyspnea Index (MBDI) score decreased to 3 from 5, the 6MWT increased from 140 m to 280 m, and no desaturation was evident during the test procedure. During a 13-month follow-up, a transient elevation of transaminases (less than two times normal) was seen within the first three months, and they spontaneously returned to normal. The patient lost 6 kg during the first three months (less than 10% of total body weight), but weight loss stopped spontaneously. She had diarrhea (not more than three times a day) during the first three months, which was controlled with loperamide. The combination treatment with MMF, RTX, and nintedanib was well-tolerated without any side effects. The patient is still receiving the treatment and follow-up data is given in Tables 1 and 2. Semiquantitative measurements were not consistent with progression; however, quantitative measurements identified 5% progression of parenchymal involvement at one year.

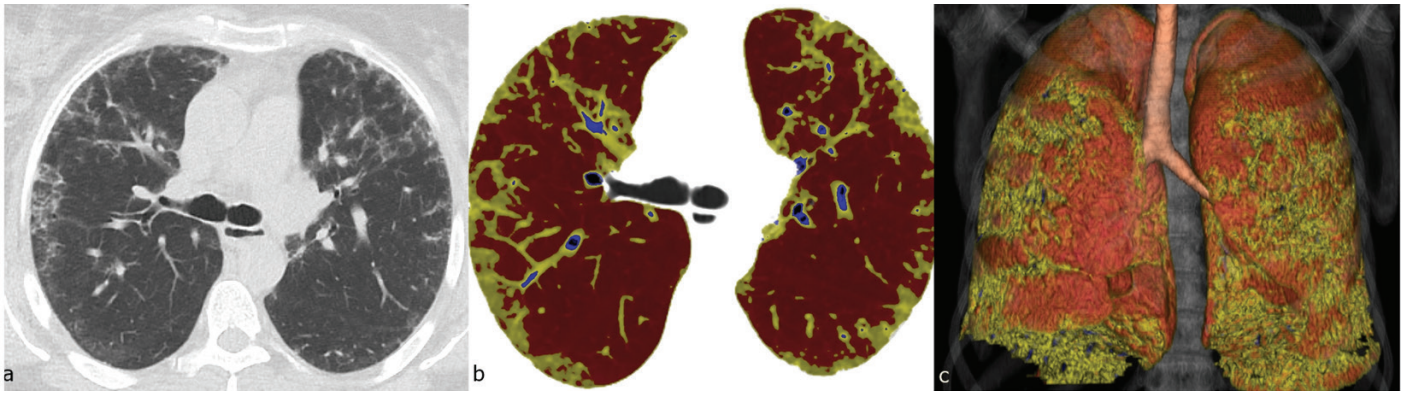

Figure 1. Involvement with peripherally located patchy fine reticulations is seen after treatment on axial HRCT section from carina level (Case 3) (a). In the quantitative analysis of the same section, threshold values corresponding to -200 to -700 HU are represented in yellow (b). Three-dimensional and color quantitative analysis of the same patient (c)

HRCT: High resolution computerized tomography

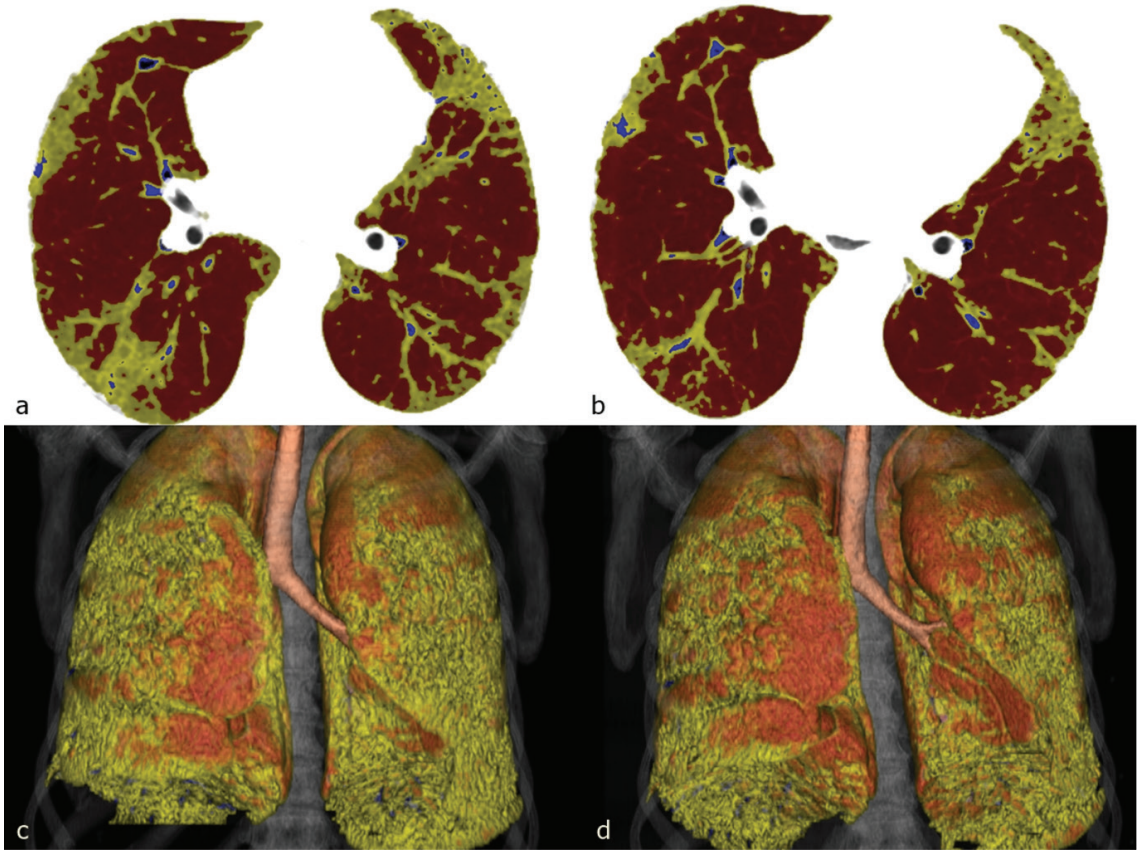

Figure 2. A visual reduction in the involvement after treatment is evident in the following images of Case 3: pre-treatment color axial section (a) and three-dimensional image (b), post-treatment axial section (c), and three-dimensional image (d). Threshold values between -200 and -700 HU corresponding to the involved regions are represented in yellow

Case 2

A 45-year-old female was admitted to our clinic in 2018 with Raynaud syndrome and digital swelling in both hands. She was diagnosed with Ssc and treatment was initiated based on the following findings: ANA homogenous (+), anti-Scl-70 (+), dilated capillaries and microhemorrhage on capillaroscopy, skin thickening beyond metacarpophalangeal joints, sclerodactyly, and Raynaud phenomenon. At that time, DLCO and FVC were 74% and 81%, respectively. On HRCT, >20% involvement was present, and findings were consistent with fibrotic NSIP. Twelve courses of CYC 1000 mg/month treatment were followed by MMF 2 g/day maintenance treatment. In February 2021, MBDI was 5 and the patient was evaluated for progression. DLCO, FVC, and 6MWT were 59% (5.02 mmol/kPa/min), 65% (2.06 L), and 300 m, respectively. HRCT revealed bilateral regions of ground glass appearance, primarily in the lower lung lobes, and increased reticular density in 32% of the lung. Based on these findings, the condition of the patient was considered progression and the treatment was continued with MMF 3 g/day and nintedanib 300 mg/day. At 6, 9, and 12 months, FVC was 75% (2360 mL), 75% (2390 mL), and 70% (2190 mL), respectively. DLCO was 82% (6.90 mmol/kPa/min) and 96% (7.99 mmol/kPa/min) at 6 and 12 months, respectively (Table 2). 6MWT increased but no desaturation was observed. In addition, the MBS dyspnea index score regressed (Table 1). On HRCT, both semiquantitative, (from 32% to 23%) and quantitative measurements (from 32.4% to 26%) demonstrated regression. No side effects were seen during the 12-month follow-up. The patient is continuing treatment with MMF 3 g/day and nintedanib 300 mg/day.

Case 3

A 43-year-old man was admitted to our clinic with non-productive cough, dyspnea on effort, sclerodactyly of the hands, and Raynaud phenomenon in 2010. He was diagnosed with primary Sjögren's disease-associated ILD based on the following findings: ANA (+), Anti-dsDNA (+), Anti-SSA (+), and usual interstitial pneumonia (UIP) pattern on HRCT. FVC and DLCO were 62%, (2420 mL) and 47%, respectively. Anti-Scl-70 and Jo-1 were negative. The patient received methylprednisolone 1 g/day for

three days, which was followed by 13 courses of CYC 1 g/month. Then, maintenance treatment was given with MMF 2 g/day. In 2014, the treatment was changed to RTX 2 g every 6 months since FVC was 74% (2780 ml) and DLCO was 47%, in addition to progression findings on HRCT. In 2020, maintenance treatment with MMF 2 g/day was re-initiated. Routine investigation findings in 2021, were suggestive of disease progression: progression of parenchymal involvement on HRCT; MBDI score, 6; FVC, 58% (2170 mL); DLCO, 46% (5.05 mmol/kPa/min) with desaturation on effort, and 46% parenchymal involvement on semiquantitative HRCT measurements. Nintedanib 300 mg/day was added, and the patient received it in combination with MMF for the first six months. The 6MWT could not be measured due to the oxygen need. During the first 6-month follow-up (Tables 1 and 2), no improvement was seen in dyspnea score, and oxygen need, although FVC was stable. Although semiquantitative measurements did not indicate significant parenchymal progression, quantitative measurements showed an increase in involvement. MMF treatment was changed to RTX treatment (1 g/6-month), due to clinical worsening. The patient lost weight during this period. Tables 1 and 2 show the 10-month follow-up data. No significant progression was seen in FVC. However, dyspnea and oxygen need increased. The patient lost 8 kg in 10 months (more than 10% of body weight). This continued. Nintedanib treatment was discontinued at the end of 10 months due to side effects. At that time, FVC and DLCO were 58% (2.21 L) and 32% (3.08 mmol/kPa/min), respectively. The patient started to gain weight after discontinuation of nintedanib, but symptoms persisted.

Case 4

A 29-year-old female was admitted to our clinic in 2014 with dyspnea on effort, Raynaud phenomenon, arthritis of both wrists, sclerodactyly, subcutaneous calcinosis at left elbow, and bibasilar velcro-type crackles. The patient was diagnosed with antisynthetase syndrome (ASS)-associated ILD based on the following findings: rheumatoid factor positivity, ANA (++) centromere pattern, anti dsDNA (++), anti-SSA (+), anti-Jo1

Table 1. Patient data

	Case 1	Case 2	Case 3	Case 4
Gender	Female	Female	Male	Female
Age	64	49	53	37
Additional disease	None	None	None	None
Diagnosis	SSc	SSc	Primary SjD	ASS
Antibodies	ANA ++ Anti-Scl-70 +	ANA +++ (Homogeneus) Anti-Scl-70 +	ANA ++ Anti-dsDNA + Anti-SSA +	ANA ++ (Centromer) Anti-dsDNA++ Anti-SSA: +++ Anti Jo1>100 (Normal value: <12 AU/mL)
Disease duration	6 (year)	4 (year)	12 (year)	8 (year)
Skin involvement	Diffuse	Limited	None	None
Interstitial lung involvement pattern	Fibrotic NSIP	Fibrotic NSIP	UIP	UIP
Previous immunosuppressive therapies	CYP RTX MMF	CYP MMF	CYP RTX MMF	CYP AZA Abatacept MMF
Current immunosuppressive therapy	MMF (2 g/day)	MMF (3 g/day)	RTX (1000 mg/6 months)	MMF (2 g/day)
Nintedanib duration (months)	13 months (300 mg/day)	12 months (300 mg/day)	10 months (300 mg/day)	12 months (300 mg/day)
Nintedanib continue	Yes	Yes	No	Yes

SSc: Systemic sclerosis, SjD: Sjögren's disease, ASS: Antisynthetase syndrome, ANA: Antinuclear antibody, Anti-Scl-70: Anti-topoisomerase I antibody, Anti-dsDNA: Anti-double stranded DNA antibody, Anti-SSA: Anti-Sjogren's-syndrome-relaeted antigen A, Anti-Jo1: Anti-histidyl-tRNA synthetase antibody, AU: Arbitrary unit, NSIP: Non-spesific intertisiel pneumonia, UIP: Usual intertisial pneumonia, CYP: Cyclophosphamide, RTX: Rituximab, MMF: Mycophenolate mofetil, AZA: Azathioprine, Anti-Sm: Anti-smith

>100 (<12 AU/mL), UIP pattern on HRCT. FVC and DLCO were 86% (2670 mL) and 73%, respectively. A ten-course of CYC (1 g/month) treatment was initiated and this was followed by azathioprine (AZT) 150 mg/day maintenance treatment. Due to the emergence of AZT-associated cytopenia during follow-up, the AZT dose was decreased to 100 mg/day, and abatacept 750 mg/month was added. However, a satisfactory response could not be achieved, and the maintenance treatment was changed to MMF 2 g/day. The condition of the patient was stable until the year 2021. In 2021, the following findings were suggestive of disease progression: FVC, 74% (2380 mL); DLCO, 59% (5.00 mmol/kPa/min); 6MWT, 280 m; and 15% increase in parenchymal involvement on semiquantitative HRCT measurements. Nintedanib 300 mg/day was added to the treatment. All follow-up data are given in Tables 1-3. At 6 months, a decrease in FVC and DLCO was evident, and the patient was diagnosed with pneumonia. Complaints improved following treatment; however, the treatment was changed as follows due to ground-glass appearance on HRCT: MMF 3 g/day, prednisolone 5 mg/day, and nintedanib 300 mg/day. At 9 months, FVC and DLCO improved (Table 2); no saturation was evident on the 6MWT test, but the distance was slightly reduced. The reduction in distance was attributed to bilateral knee osteoarthritis. Findings at 9 months were also maintained at 12 months, and a significant improvement of 6MWT was evident. A similar improvement was also seen in MBDI. No progression of parenchymal involvement was seen on semiquantitative HRCT measurements. However, quantitative measurements showed a 3% increase (Table 3) These findings were considered to be disease remission. No side effects were seen after the initiation of nintedanib except for

Table 2. Patient follow-up data

Case		FVC [% predicted (L)]	DLCO [% predicted (mmol/kPa/min.)]	6 min. walking test (meter)	Modified Borg Dyspnea Index	EKO (EF%-sPAB) (mmHg)
Case 1	Before nintedanib	66 [1.67]	75 [5.47]	140	5	65 - 15
	3rd month	95 [2.40]	None	None	None	None
	6th month	83 [2.03]	91 [6.58]	None	None	None
	9th month	84 [2.13]	None	280	None	None
	12th month	82 [2.05]	81 [5.79]	280	3	65-15
Case 2	Before nintedanib	65 [2.06]	64 [5.43]	300	5	65-20
	3rd month	None	None	None	None	None
	6th month	75 [2.36]	82 [6.90]	360	2	None
	9th month	75 [2.39]	None	None	None	None
	12th month	70 [2.19]	96 [7.99]	360	1	65-20
Case 3	Before nintedanib	56 [2.12]	46 [5.05]	None**	5	65-20
	3rd month	61 [2.33]	None	None	None	None
	6th month	58 [2.21]	None	None	5	None
	9th month	57 [2.16]	32 [3.08]	None	6	65-30
	12th month	58 [2.17]*	None	None	6	60-30
Case 4	Before nintedanib	74 [2.38]	59 [5.00]	280	4	65-25
	3rd month	74 [2.39]	40 [3.45]	310	4	None
	6th month	66 [2.13]	46 [3.94]	None	None	65-25
	9th month	70 [2.25]	54 [4.55]	280	3	None
	12th month	68 [2.22]	58 [4.87]	340	2	None

*Measurement after nintedanib was discontinued. **The walking test could not be performed in the patient who used continuous oxygen. FVC: Forced vital capacity, DLCO: Diffusing capacity of the lung for carbon monoxide, min.: Minute, EKO: Echocardiography, EF: Ejection fraction, sPAB: Systolic pulmonary artery pressure

Table 3. High resolution computed tomography measurements

Case	Before treatment		After treatment	
	Semiquantitative ILD score (%)	Quantitative ILD score (%)	Semiquantitative ILD score (%)	Quantitative ILD score (%)
Case 1	23%	17.30%	23% →	22.4% ↑
Case 2	32%	32.40%	23% ↓	26.0% ↓
Case 3	46%	37.10%	46% →	43.3% ↑
Case 4	15%	17.60%	15% →	20.1% ↑

ILD: Interstitial lung disease

mild diarrhea after one month and 4 kg weight loss during the first 6 months (less than 10% of body weight). Subsequently, weight loss stopped spontaneously. The patient is still receiving the same treatment with stable FVC and DLCO levels and without any serious side effects.

DISCUSSION

FVC, DLCO, 6MWT, and HRCT have important roles in ILD for long-term follow-up and predicting progression (11). In previous studies, limiting FVC decline has been shown to affect mortality directly (12). An annual FVC decline >10% and DLCO decline >15% are associated with a significant increase in mortality (13,14). The SENSCIS study used FVC decline in mL as a primary endpoint (5). In the present study, ILD diagnosis was made using clinical findings, serological tests, and HRCT findings in all patients. None of the patients required biopsies.

CTD-associated fibrosing ILD may respond well to immunosuppressive agents in the initial phase of treatment. As reported in the study by Tolle et al., disease progression may occur later despite an initial good response to treatment (15). Fibrosing-type ILD patients have a higher risk for progression and mortality (16). Disease progression is regulated by autoimmune, vascular, and fibrosing components in Ssc (17). That study did not report on the effects of MMF on remodeling and fibrosis (18). In another study, outcomes of five Ssc-ILD patients receiving RTX were as follows at one year: two patients, >10% regression; two patients, stable disease; and one patient, >10% progression (14). Nintedanib is a multiple tyrosine kinase inhibitor and prevents contraction of fibroblasts as well as their migration to the lungs. It prevents differentiation and migration of profibrotic fibrocytes. In addition, it reduces the transformation of fibroblasts to myofibroblasts in the lungs (19). Inhibition of inflammatory processes through T and B lymphocytes by MMF, through B lymphocytes by RTX, and the effect of nintedanib on fibrosis processes suggest that the combined use of these agents may act on the three components of disease progression in Ssc. In the present study, nintedanib was used in combination with immunosuppressive agents in all patients. Our study used the MMF/nintedanib combination in two patients (Cases 2 and 4). One patient received MMF/RTX/nintedanib (Case 1), and the other patient received MMF/nintedanib for the first 6 months, followed by 4 months of RTX/nintedanib (Case 3). In the SENSCIS study, no secondary parameter other than FVC improved. FVC was taken as the primary endpoint. In our cases, in addition to FVC, parameters such as DLCO, MBDI, and the 6MWT were also monitored. Close follow-up is essential in patients with the progression of pulmonary fibrosis and should not be limited to a single parameter. The cases we studied showed progression in pulmonary fibrosis, and we modified the immunosuppressive treatment of these patients. We tried to evaluate the progression with all the indicators without depending on a single parameter. In the SENSCIS study, patients with 10% pulmonary involvement were included (4). However, our cases have 15-46% pulmonary involvement, and their progression is expected to be much worse. Therefore, our cases may have different responses to treatment. In all our cases, even with the addition of nintedanib, immunosuppressive treatment was modified to prevent or slow progression. Therefore, the results obtained can never be attributed to nintedanib treatment alone.

In the Anti-Scl-70 (+) Ssc-ILD patient (Case 2), both semiquantitative and quantitative ILD scores regressed (Table 4). Lung parenchyma involvement was radiologically consistent with fibrotic NSIP. This patient showed up to a 5% improvement in FVC and a >10% improvement in DLCO. In addition, 6MWT and MBDI showed improvements. To the best of our knowledge, only one case has been reported to have improvement in parenchyma following nintedanib treatment. The 73-year-old female patient reported by Nishino et al. showed regression of parenchymal involvement after 8 months of nintedanib treatment. The patient was positive for anti-centromere, and HRCT images had prominent ground glass opacities radiologically consistent with NSIP (20). In our patient, there was more fibrotic involvement than ground glass areas, which differentiates it from other cases in the literature. However, it

is doubtful that this outcome directly resulted from nintedanib treatment. Case 2 received a higher MMF dose (3 g/day) than the other patients. Again the diagnosis of ILD associated with systemic sclerosis may have influenced this outcome. A more severe immunosuppression may also have led to this result. Further studies are needed in this respect. On the other hand, the combination of 3 g/day MMF treatment with nintedanib did not cause any serious side effects in our patient.

In our second Anti-Scl-70 (+) Ssc-ILD patient (Case 1), MMF/nintedanib treatment provided encouraging results up to the first 6 months. However, the MMF dose was reduced and RTX was added due to the development of radiological progression at 6 months. MMF/RTX/nintedanib halted progression and resulted in clinical improvement. Semiquantitative ILD score on HRCT remained stable, whereas quantitative ILD score showed 5% progression. However, the case showed >10% and >5% improvement in FVC and DLCO, respectively. In addition, MBDI and 6MWT showed significant improvements. No severe side effects developed in the 12-month treatment period. This result appears to support the pathophysiologic process contributing to disease progression. In the study by Cutolo et al., nintedanib was shown to inhibit profibrotic activities of fibroblasts more effectively in Anti-Scl-70-positive ILD patients when compared to Anti-Scl-70-negative ILD patients (13). Increased αSMA and S100A4 gene and protein expressions were detected in fibrocytes of Anti-Scl-70-positive patients with ILD, but expressions were statistically less in Anti-Scl-70-negative patients. After nintedanib treatment, the expression of these genes and proteins was suppressed more in Anti-Scl-70-positive patients than in Anti-Scl-70-negative patients. This result suggested that nintedanib may be more effective in Anti-Scl-70-positive patients. The results of Case 2 can be explained by this mechanism. However, further studies with more patients are needed.

Our primary Sögren's disease-associated ILD patient (Case 3) exhibited a UIP pattern on radiological examination. MMF/nintedanib could not be continued for the first 6 months due to gastrointestinal side effects. RTX/nintedanib combination was administered for thenext four months. This was the patient with the highest ILD involvement score. No FVC decline was seen at the end of 10 months. However, a decline greater than 10% was evident in DLCO. In addition, MBDI increased (Table 2). During this period, the patient lost 8 kg (more than 10% of body weight). During follow-up, no progression was observed in the semiquantitative ILD score for parenchymal involvement; however, the quantitative score, showed approximately 6% progression (Table 3). Considering the case reported by Tuğsal et al. (14) with progression following RTX treatment higher ILD involvement scores may result in a worse treatment response, suggesting that adding antifibrotic agents when ILD involvement score is still low may lead to a more pronounced treatment benefit. Considering the above-mentioned pathophysiologic mechanisms, as well as the absence of improvement, support that nintedanib is more effective in Anti-Scl-70 (+) patients. Nevertheless, progression in lung parenchymal involvement slowed down, indicating treatment benefit. Despite the disappearance of weight loss following discontinuation of nintedanib, oxygen requirement continued at the same level.

Radiologically, the patient with Anti-Scl-70- ASS-ILD (Case 4) had UIP pattern involvement. The MMF/nintedanib combination was very well tolerated. The semiquantitative ILD score remained stable during the one-year follow-up, whereas a 2.5% increase was evident in the quantitative ILD score (Table 3). This was not considered progression. The patient developed pneumonia once in one-year follow-up; however, this was unlikely to be associated with nintedanib. It is well known that patients receiving a full dose of immunosuppressive treatment face a relatively high pneumonia risk. Despite a transient FVC decline after pneumonia, baseline FVC, and DLCO values could be achieved after increasing MMF dose and adding a steroid to the treatment. An improvement in MBDI was evident (Table 2). This ASS patient represents the first reported case in the literature of an ASS patient treated with the MMF-nintedanib combination.

The most common side effect in our patients was weight loss. Especially in case 3, there was a significant weight loss compared to other cases. This case had the highest semiquantitative and quantitative lung scores. The FVC value at the nintedanib baseline was the lowest. The weight loss in this particular case may have been due to relatively advanced pulmonary fibrosis, the combination of RTX and nintedanib, or the low baseline FVC while on nintedanib. This issue needs to be investigated by further studies.

In cases 1, 3, and 4, there are discrepancies between semiquantitative and quantitative measurements. In all three cases, semiquantitative measurements had no clear progression, whereas quantitative measurements showed a slight progression. Semiquantitative measurement requires an experienced radiological evaluation. By its very nature, it is a measurement technique that requires human experience. This causes variability in interpersonal scores. To address this issue, a study with more patients must clearly demonstrate the distinctions between quantitative and semiquantitative measurements.

No significant changes were seen in the modified Rodnan scores of the patients during the one-year follow-up. None of the patients developed digital ulcers, and no new cases of pulmonary or systemic hypertension were observed.

Diarrhea was the most common side effect with 75.7% incidence in the nintedanib arm of the SENSCIS safety and tolerability study, necessitating treatment discontinuation in 6.9% of the cases (21). Weight loss was seen in 11.8% of the patients in the nintedanib arm (5). Two of our patients developed diarrhea, and weight loss was the most important side effect in our series. Three out of four patients had significant weight loss, which stopped spontaneously in two of them (Case 1, Case 4). However, one patient lost 8 kg, and the loss continued gradually.

CONCLUCION

In conclusion, CTD-ILD is a complex condition requiring a multidisciplinary, patient-oriented, and individualized treatment approach. The management of immunosuppressive therapy in patients with CTD-ILD is complex and crucial. In patients with progression, nintedanib may be considered in addition to immunosuppressive treatment.

Ethics

Informed Consent: Patients who did not sign informed consent and did not want to share their data were excluded.

Footnotes

Authorship Contributions

Surgical and Medical Practicez: B.O., N.A., G.Y.Ç., M.C.K., B.K., B.T., E.S.Ö., F.Y., Concept: B.O., G.Y.Ç., B.T., F.Y., Design: B.O., N.A., G.Y.Ç., F.Y., Data Collection or Processing: B.O., N.A., G.Y.Ç., M.C.K., B.K., B.T., E.S.Ö., F.Y., Analysis or Interpretation: N.A., G.Y.Ç., E.S.Ö., F.Y., Literature Search: B.O., G.Y.Ç., E.S.Ö., F.Y., Writing: B.O., G.Y.Ç., F.Y.

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

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

REFERENCES

1. Kafle S, Magar MT, Patel P, et al. Systemic sclerosis-associated interstitial lung disease and nintedanib: a rare disease and a promising drug. Cureus. 2021;13:e16404.
2. Yamasaki Y, Kuwana M. Nintedanib for the treatment of systemic sclerosis-associated interstitial lung disease. Expert Rev Clin Immunol. 2020;16:547-60.
3. Ravanetti F, Ferrini E, Ragionieri L, et al. SSC-ILD mouse model induced by osmotic minipump delivered bleomycin: effect of nintedanib. Sci Rep. 2021;11:18513.
4. Martin-Lopez M, Carreira PE. Antifibrotics in systemic sclerosis. Best Pract Res Clin Rheumatol. 2021;35:101671.
5. Distler O, Highland KB, Gahlemann M, et al. Nintedanib for systemic sclerosis-associated interstitial lung disease. N Engl J Med. 2019;380:2518-28.
6. Wells AU, Flaherty KR, Brown KK, et al. Nintedanib in patients with progressive fibrosing interstitial lung diseases: subgroup analyses by interstitial lung disease diagnosis in the INBUILD trial. Lancet Respir Med. 2020;8:453-60.
7. Flaherty KR, Wells AU, Cottin V, et al. Nintedanib in progressive fibrosing interstitial lung diseases. N Engl J Med. 2019;381:1718-27.
8. Highland KB, Distler O, Kuwana M, et al. Efficacy and safety of nintedanib in patients with systemic sclerosis-associated interstitial lung disease treated with mycophenolate: a subgroup analysis of the SENSCIS trial. Lancet Respir Med. 2021;9:96-106.
9. Goh NS, Desai SR, Veeraraghavan S, et al. Interstitial lung disease in systemic sclerosis: a simple staging system. Am J Respir Crit Care Med. 2008;177:1248-54.
10. Salaffi F, Carotti M, Bosello S, et al. Computer-aided quantification of interstitial lung disease from high-resolution computed tomography images in systemic sclerosis: correlation with visual reader-based score and physiologic tests. Biomed Res Int. 2015;2015:834262.
11. Hambly N, Farooqi MM, Dvorkin-Gheva A, et al. Prevalence and characteristics of progressive fibrosing interstitial lung disease in a prospective registry. Eur Respir J. 2022;60:2102571.
12. Maher TM, Mayes MD, Kreuter M, et al. Effect of nintedanib on lung function in patients with systemic sclerosis–associated interstitial lung disease: further analyses of a randomized, double-blind, placebo-controlled trial. Arthritis Rheumatol. 2021;73:671-76.
13. Cutolo M, Gotelli E, Montagna P, et al. Nintedanib downregulates the transition of cultured systemic sclerosis fibrocytes into myofibroblasts and their pro-fibrotic activity. Arthritis Res Ther. 2023;25:134.
14. Tuğsal HY, Zengin B, Kenar G, et al. Rituximab on lung, skin, and joint involvement in patients with systemic sclerosis: a case series study and review of the literature. Int J Rheum Dis. 2022;25:755-68.
15. Tolle LB. Challenges in the diagnosis and management of patients with fibrosing interstitial lung disease. Case Rep Pulmonol. 2022;2022:9942432.
16. Brown KK, Martinez FJ, Walsh SLF, et al. The natural history of progressive fibrosing interstitial lung disease. Eur Respir J. 2020;55:2000085.
17. Gabrielli A, Avvedimento EV, Krieg T. Scleroderma. N Engl J Med. 2009;360:1989-2003.
18. Tashkin DP, Roth MD, Clements PJ, et al. Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): A randomised controlled, double-blind, parallel-group trial. Lancet Respir Med. 2016;4:708-19.
19. Wollin L, Distler JH, Denton CP, et al. Rationale for the evaluation of nintedanib as a treatment for systemic sclerosis-associated interstitial lung disease. J Scleroderma Relat Disord. 2019;4:212-8.

20. Nishino K, Sasatani Y, Ohara G, et al. Nintedanib-mediated improvement in CT imaging in pulmonary fibrosis associated with systemic scleroderma. Adv Respir Med. 2021;89:528-31.

21. Seibold JR, Maher TM, Highland KB, et al. Safety and tolerability of nintedanib in patients with systemic sclerosis-associated interstitial lung disease: data from the SENSCIS trial. Ann Rheum Dis. 2020;79:1478-84.

CASE REPORT AND LITERATURE REVIEW

Rheumatology Quarterly

DOI: 10.4274/qrheumatol.galenos.2025.63835
Rheumatol Q 2025;3(1):37-9

LEFLUNOMIDE USE IN THE PROPHYLACTIC TREATMENT OF GOUT

Gezmiş Kimyon

Hatay Mustafa Kemal University Faculty of Medicine, Department of Rheumatology, Hatay, Türkiye

Abstract

Gout is one of the most common inflammatory arthritides and is under-treated despite effective treatment options. Colchicine, non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids (CSs) are usually used for prophylactic treatment. Drugs used in prophylactic treatment may have some limitations. Colchicine, the most commonly used agent in prophylactic treatment, has a low level of evidence, while NSAIDs and CSs, which are recommended when colchicine cannot be used, have a very low level of evidence. There are unmet needs in the prophylactic treatment of gout. Our patient, a 69-year-old man, had his first episode of arthritis 19 years ago in the first metatarsophalangeal joint. The patient presented with classic gout attacks and no additional rheumatic disease findings. However, he could not use allopurinol and febuxostat, which are urate-lowering treatments; or colchicine, CSs, and NSAIDs used in prophylactic treatment, for various reasons. In the 12th year of the disease, he had an arthritis attack in his wrist. No gout attacks were detected for a long time after starting leflunomide (LEF). LEF appears effective for the treatment of some patients.

Keywords: Gout, leflunomide, prophylaxis, treatment

INTRODUCTION

Gout is one of the most prevalent inflammatory arthritic conditions, yet it remains undertreated despite the availability of effective therapeutic options. The most important reason for this is the under-initiation of urate-lowering therapy (ULT). However, the increased frequency of attacks after ULT is one of the major challenges in treating patients, and effective anti-inflammatory treatments should be developed (1). Guidelines for gout strongly recommend prophylactic treatment when starting ULT. Colchicine, non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids (CS) are usually used for prophylactic treatment (2). Comorbidities such as chronic renal failure, diabetes mellitus (DM), hypertension, ischemic heart disease, heart failure, often accompany gout patients. Therefore, drugs used in prophylactic treatment may have some limitations, especially in patients with comorbidities (3). Here we report a patient who underwent prophylactic gout treatment with leflunomide (LEF).

CASE PRESENTATION

A 69 years old male patient experienced his first episode of arthritis 19 years ago, affecting the first metatarsophalangeal (MTF) joint. His arthritis was typical of gout (podogra) with acute, red, monoarthritis attacks lasting 7-10 days. Serum uric acid (sUA) levels were between 8.3 to 9.7 mg/dL (normal sUA 3.5 to 7.2) measured at different times. Allopurinol, which was started as ULT for the patient who was using colchicine (1.2 mg/day bid) regularly and NSAIDs during an acute episode, was discontinued after 1 week of use because it caused skin rash. The patient had four to five gout attacks per year, but after the seventh year, he developed monoarthritis attacks in his ankles and knees.

Address for Correspondence: Gezmiş Kimyon, Hatay Mustafa Kemal University Faculty of Medicine, Department of Rheumatology, Hatay, Türkiye
E-mail: gkimyon@gmail.com **ORCID ID:** orcid.org/0000-0003-3775-639X
Received: 13.01.2025 **Accepted:** 24.02.2025 **Publication Date:** 21.03.2025

Cite this article as: Kimyon G. Leflunomide use in the prophylactic treatment of gout. Rheumatol Q. 2025;3(1):37-9

In the 12th year of the disease, he had an arthritis attack in his wrist. No tophi were detected on clinical examination or imaging. The patient had a family history of gout, as his father and brother had a history of the disease, but no additional rheumatic disease (including psoriatic arthritis) history or findings. Rheumatoid factor, anti-cyclic citrulline peptide, and HLA B27 were negative; a hand X-ray showed no findings suggestive of rheumatoid arthritis, and sacroiliac radiography was normal. Ultrasonography of the foot MTF showed a double contour appearance. Febuxostat (FEB), which was approved as the second ULT agent in Türkiye, was titrated and started in a patient experiencing 3-5 arthritis attacks per year on average, despite regular colchicine use. The sUA level decreased to 4.2 mg/dL within 2 months, but the frequency of attacks increased. For this reason, the patient was provided with regular NSAIDs; prednisolone was given as prophylactic treatment because the attacks continued. The patient whose attacks recurred under a CS dose of 10 mg/day was started on LEF for prophylactic treatment. CS was discontinued in the first month of treatment. The patient was followed up on FEB and LEF for 6 months and experienced no complaints. However, in the 12th month of FEB treatment, the patient underwent angioplasty and left anterior descending coronary artery stenting after angina. Meanwhile, the patient discontinued FEB and LEF medications and presented with ankle arthritis 6 months later. After the treatment of the attack, the patient refused the use of FEB. The sUA was 8.3 mg/dL. LEF and CS were initiated as prophylactic treatment, but CS was stopped in the first month of treatment due to elevated blood glucose levels and a diagnosis of DM. Colchicine was not used by the patient because it did not change the frequency of attacks. The patient who used clopidogrel for cardiac disease did not use diuretics, acetylsalicylic acid, fenofibrate, which may affect uric acid levels. Glomerular filtration rate was >90 mL/min/1.73 m^2 and sUA was between 7.4-8.2 mg/dL with no significant change in lifestyle and weight. The patient has been followed with LEF monotherapy for 33 months without an attack.

DISCUSSION

We present a patient whose gout attacks were successfully suppressed with LEF prophylaxis. ULT is the mainstay of management of gout. However, the factors that most affect the quality of life in gout patients are the number of attacks, the severity of attacks, and the pain between attacks (4). Therefore, prophylactic treatment for gout should be administered effectively to improve quality of life and treatment compliance.

However, the evidence supporting the efficacy of drugs used for prophylactic treatment remains limited. Colchicine, the most commonly used agent in prophylactic treatment, has a low level of evidence, while NSAIDs and CSs, which are recommended when colchicine cannot be used, have a very low level of evidence (5). The frequency of acute gout exacerbation was found to be 33.6% with treatment involving colchicine, which is the first recommended drug for prophylactic treatment (6). This suggests that other treatment options are needed for gout prophylaxis.

While colchicine is the first recommended drug in many guidelines for prophylactic treatment, there is no consensus on the drug to be preferred afterwards. The British Society guideline recommends colchicine first and then CS (7). In addition, anti-interleukin 1 therapies such as canakinumab and rilonacept are not the most recommended agents (8). On the other hand, colchicine is not always effective; NSAIDs have disadvantages such as renal dysfunction, and CS has disadvantages such as hyperglycemia. Canakinumab is a very expensive drug.

Gout consists of different clinical stages, and the course of arthritis may differ depending on the stage of the disease and the treatments administered. Moreover, it is known that there are differences in the pathogenesis of acute and chronic gout (9). To our knowledge, no comparative studies have evaluated the efficacy of prophylactic treatments administered during the early versus chronic stages of gout. Colchicine, NSAIDs, and CSs currently used in prophylactic treatment have the advantages of being short-acting and having a rapid onset of action. LEF, which we used in the chronic phase of gout in our patient, is a long-acting agent whose anti-inflammatory effect starts later but lasts longer. In addition, its use in renal failure and DM is an important advantage (10). Determining at which stage LEF therapy is effective and whether it is effective in the prophylactic treatment of gout may fulfill an important need in the management of gout.

However, concomitant calcium pyrophosphate dihydrate arthritis could not be excluded in the patient. Although there is no evidence of chondrocalcinosis on X-ray, this is because polarized light microscopy and dual energy computed tomography are not available to definitively distinguish crystals.

CONCLUSION

In summary, there are unmet needs in the prophylactic treatment of gout. LEF appears to be a potential therapeutic option for selected patients with contraindications to conventional prophylactic treatments. Gout is a disease with a high prevalence; the importance of planning studies on LEF in its prophylactic treatment is emphasized.

Ethics

Informed Consent: Informed consent form was obtained.

Footnotes

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

REFERENCES

1. Afinogenova Y, Danve A, Neogi T. Update on gout management: what is old and what is new. Curr Opin Rheumatol. 2022;34:118-24.
2. FitzGerald JD, Dalbeth N, Mikuls T, et al. 2020 American College of Rheumatology guideline for the management of gout. Arthritis Care Res (Hoboken). 2020;72:744-60.
3. Singh JA, Gaffo A. Gout epidemiology and comorbidities. Semin Arthritis Rheum. 2020;50:S11-6.
4. Chandratre P, Roddy E, Clarson L, et al. Health-related quality of life in gout: a systematic review. Rheumatology (Oxford). 2013;52:2031-40.
5. Neilson J, Bonnon A, Dickson A, et al. Gout: diagnosis and management-summary of NICE guidance. BMJ. 2022;378:o1754.
6. Borstad GC, Bryant LR, Abel MP, et al. Colchicine for prophylaxis of acute flares when initiating allopurinol for chronic gouty arthritis. J Rheumatol. 2004;31:2429-32.
7. Hui M, Carr A, Cameron S, Davenport G, et al. The British Society for Rheumatology guideline for the management of gout. Rheumatology (Oxford). 2017;56:1056-9.
8. Lee JJ, Lee JS, Chung MK, et al. Korean guidelines for the management of gout. Korean J Intern Med. 2023;38:641-50.
9. Ragab G, Elshahaly M, Bardin T. Gout: an old disease in a new perspective-a review. J Adv Res. 2017;8:495-511.
10. Russo PA, Wiese MD, Smith MD, et al. Leflunomide for inflammatory arthritis in end-stage renal disease on peritoneal dialysis: a pharmacokinetic and pharmacogenetic study. Ann Pharmacother. 2013;47:e15.