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INVITED REVIEW

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UPADACITINIB IN ACTION: EFFICACY AND SAFETY IN THE TREATMENT OF RHEUMATOID ARTHRITIS, PSORIATIC ARTHRITIS, AND AXIAL SPONDYLOARTHRITIS

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Abstract

This review examines the efficacy, safety, and pharmacokinetics of upadacitinib (UPA) for treating rheumatoid arthritis (RA), psoriatic arthritis (PsA), and axial spondyloarthritis (axSpA). This review analyzes the results of multiple clinical trials and provides a comprehensive overview of UPA's effectiveness in improving disease activity, reducing symptoms, and preventing joint damage. The review also highlights the safety profile of UPA, including the increased risk of herpes zoster, non-melanoma skin cancer, and elevated creatine phosphokinase levels. In addition, the review discusses the pharmacokinetics of UPA, emphasizing its rapid absorption and limited plasma protein binding. Overall, UPA appears to be a promising therapeutic option for patients with RA, PsA, and axSpA, particularly those with inadequate response to other therapies.

Keywords: Upadacitinib, rheumatoid arthritis, psoriatic arthritis, axial spondyloarthritis

INTRODUCTION

Recent technological advancements have revolutionized our understanding and management of inflammatory rheumatic conditions. Among these breakthroughs, Janus kinases (JAKs) have emerged as pivotal components in signal transduction pathways, providing promising avenues for treating these diseases. The JAK enzyme family, comprising cytoplasmic protein tyrosine kinases (TYKs), has revealed new therapeutic possibilities for addressing unmet needs for treating inflammatory rheumatic diseases (1-3).

The JAK family consists of four members: JAK1, JAK2, JAK3, and TYK2. These kinases bind to transmembrane cytokine receptors, initiating downstream signaling cascades that ultimately activate transcription factors such as signal transducer and activator of transcription (STAT) proteins. JAKs play a role in various physiological processes, including immune defense, hematopoiesis, and development. Dysregulation of JAK activity has been implicated in the pathogenesis of various diseases, particularly immune-mediateddiseases. The JAK/STAT pathway plays a critical role in such diseases because cytokine signaling considerably impacts their development and progression (1-3).

Upadacitinib (UPA), or ABT-494, is an oral JAK inhibitor and targeted synthetic disease-modifying antirheumatic drug (tsDMARD) with selective activity toward JAK1 over JAK2, JAK3, and TYK2 (4). It is the first JAK1-selective inhibitor developed on the basis of the hypothesis that JAK1 inhibition would result in fewer adverse effects. Cellular assays have confirmed its selectivity, with UPA demonstrating >40-fold greater selectivity for JAK1 than for JAK2, 130-fold greater selectivity for JAK1 than

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for JAK3, and 190-fold greater selectivity for JAK1 than for TYK2 (4). Both the Food and Drug Administration (FDA) and European Medical Agency (EMA) have approved UPA for the treatment of rheumatoid arthritis (RA) and psoriatic arthritis (PsA). In addition, the FDA and EMA have approved it for treating ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-AxSpA) (5).

In this review, we provide a comprehensive overview of UPA application for treating RA, AS, and axSpA, with a focus on its efficacy and safety profile.

Rheumatoid Arthritis

RA is a chronic autoimmune disorder that primarily affects synovial joints, causing inflammation, progressive joint damage, deformity, and functional impairment. This systemic condition affects approximately 0.5-1% of the global population, with a higher prevalence in women than in men. Although the exact cause remains uncertain, the development of RA involves a complex interplay of genetic, environmental, and hormonal factors.

Patients with RA often experience joint pain, stiffness, and swelling, which significantly affect their quality of life and daily activities. In addition, the disease may involve extra-articular tissues, leading to complications such as rheumatoid nodules, vasculitis, and organ involvement. Early diagnosis and aggressive treatment are crucial to control inflammation, alleviate symptoms, and prevent joint damage. Initial treatment typically involves conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), which demonstrate a 60-70% drug survival rate at one year of treatment (6,7). However, approximately one-third of patients require the use of biological or tsDMARDs to achieve better disease control.

The efficacy of UPA in RA was assessed in two Phase 2 studies, BALANCE I and BALANCE II, which involved patients with moderate to severe RA and lasted 12 weeks each (8,9).

BALANCE I included 276 patients with RA on stable methotrexate (MTX) doses who had an inadequate response to at least one anti-tumor necrosis factor agent (TNF-IR) (8). They were randomized to receive immediate-release ABT-494 (UPA) at 3, 6, 12, or 18 mg twice daily or a matching placebo. The primary endpoint, American College of Rheumatology (ACR)20 response (20% improvement per the ACR criteria), at week 12 showed rates of 53%, 58%, 71%, 67%, and 34%, respectively, with all active treatment doses being significant compared with placebo (8). Secondary endpoints included ACR50 and ACR70, which demonstrated significance for all doses except the 3 mg bid dose. Additional secondary endpoints, low disease activity (LDA) based on disease activity score (DAS)28-C-reaktif protein (CRP) ≤3.2 and clinical disease activity index (CDAI) ≤10, revealed that only the 12 mg bid dose was significant for DAS28-CRP ≤3.2, while none of the doses were significant for CDAI ≤10. Remission rates based on DAS28-CRP <2.6 and CDAI ≤2.8 showed significance only for the 12 mg bid dose and none of the doses, respectively (8).

BALANCE II involved 300 active RA patients with inadequate responses to MTX (MTX-IR), who received immediate-release UPA at various doses or placebo while maintaining stable MTX doses (9). ACR20, ACR50, and ACR70 response rates were significant for all doses compared with placebo, except for the 12 mg bid dose in ACR70. LDA based on DAS28 ≤3.2 and CDAI ≤10 were significant at all doses compared with placebo. Remission rates for DAS28 <2.6 were significant for all doses except the 24 mg once daily, while none of the doses reached significance based on CDAI ≤2.8 (9). The most common adverse events (AEs) included headache, nausea, upper respiratory tract infection (URTI), and urinary tract infection. Infection rates increased with higher UPA doses, but none were severe. In patients with inadequate responses or intolerance to anti-TNF agents, the addition of UPA to MTX led to rapid, dose-dependent improvements in RA signs and symptoms (9). Table 1 summarizes the primary and secondary endpoints of both studies.

In BALANCE I, significant findings were observed for ACR20, ACR50, and ACR70 response rates with active treatment doses (except 3 mg bid), indicating improvement compared with placebo. Significant results were also observed for LDA (DAS28-CRP ≤3.2) with the 12 mg bid dose. No significant differences were found for CDAI ≤10 or remission rates based on CDAI ≤2.8. In BALANCE II, all doses (except 12 mg bid) showed significant improvements in ACR20, ACR50, and LDA (DAS28 ≤3.2 and CDAI ≤10) compared with placebo. ACR70 response rates were significant for all doses except 12 mg bid. Remission rates based on DAS28 <2.6 were significant for all doses except 24 mg once daily (QD). However, no significant differences were found for remission rates based on CDAI ≤2.8.

The BALANCE studies provided a solid foundation for advancing to Phase III trials, as both studies assessed efficacy and found no safety concerns. In BALANCE I, a dosage of 6 mg of UPA taken twice daily demonstrated near-maximum efficacy. The BALANCE II study revealed an additional benefit with a dosage of 12 mg taken twice daily. Based on these results, daily equivalent doses of 15 mg and 30 mg of UPA in the extended-release form, administered once daily, were selected for Phase III studies (10).

UPA has been evaluated in the SELECT Phase III RA program, which includes six multicenter, randomized, double-blind, placebo-controlled studies. Five of these studies were conducted

Table 1. Summary of primary and secondary endpoints in the BALANCE-I and BALANCE-II studies at 12 weeks

Dose	ACR20	ACR50	ACR70	DAS28-CRP ≤3.2	CDAI ≤10	DAS28-CRP <2.6	CDAI ≤2.8
BALANCE I							
Placebo	34	16	4	25	25	13	7
3 mg bid	53	24	13	33	27	24	9
6 mg bid	58	36	26	36	31	26	11
12 mg bid	71	42	22	49	40	33	13
18 mg bid	67	38	22	42	40	27	16
BALANCE II							
Placebo	46	18	6	20	20	14	6
3 mg bid	62	38	22	48	40	36	4
6 mg bid	68	46	28	52	38	36	12
12 mg bid	80	50	16	46	40	34	14
18 mg bid	64	40	26	46	46	40	6
24 mg QD	76	39	22	41	35	22	14

ACR: American College of Rheumatology, CDAI: Clinical disease activity index, DAS-28: Disease activity score 28, CRP: C-reaktif protein, QD: Once daily

in patients with MTX-IR or other csDMARDs. In four of these studies, UPA was tested in combination with either MTX or csDMARDs. Two of these studies were placebo-controlled trials without active comparators [SELECT-NEXT in a csDMARD-inadequate response (IR) population and SELECT-BEYOND in a biological DMARD-IR population] (11,12), whereas the other two studies included an active comparator (SELECT-COMPARE in a MTX-IR population and SELECT-CHOICE in a biological DMARD-IR population) (13,14). Another study was conducted with UPA as monotherapy in patients with an inadequate response to MTX, known as the SELECT-MONOTHERAPY trial (15). The final study, the SELECT-EARLY trial, was conducted in MTX-naive patients, in whom UPA was evaluated as monotherapy (16). Table 2 summarizes the key domains of the SELECT studies.

The SELECT-NEXT trial focused on the csDMARD-IR population and found that UPA 15 mg and 30 mg both led to significant improvements in ACR20 response rates, with 64% and 66% response rates, respectively, at week 12 (11). Additionally, both doses of UPA resulted in a DAS28-CRP ≤3.2 response rate of 48%, which was higher than the 17% response rate seen in the placebo group. It is important to note that patients in this trial were permitted to continue their background csDMARD therapy (11). In the SELECT-BEYOND trial, which targeted the biological disease-modifying antirheumatic drug (bDMARD)-IR population, UPA 15 mg and 30 mg demonstrated higher ACR20 response rates of 65% and 56%, respectively, at week 12 compared with the placebo group's 28% response rate (12). Similarly, the percentages of patients achieving DAS28-CRP ≤3.2 with UPA 15 mg and 30 mg were 43% and 42%, respectively, compared with only 14% in the placebo group. Patients in this trial continued their stable csDMARD therapy (12). The SELECT-COMPARE trial focused on the MTX-IR population and compared UPA 15 mg with adalimumab (ADA) 40 mg and placebo (13). At week 12, UPA 15 mg exhibited a strong ACR20 response rate of 71% and a DAS28-CRP ≤3.2 response rate of 45%, outperforming ADA 40 mg, which had lower response rates of 63% and 29%, respectively. In comparison, the placebo group showed the lowest response rates, with an ACR20 response rate of 36% and a DAS28-CRP ≤3.2 response rate of 15% at week 12. All patients in this trial received background MTX (13).

In the SELECT-CHOICE trial, which lasted 24 weeks, patients were treated with either oral UPA 15 mg once daily or intravenous ABA, along with stable synthetic DMARDs (14). At week 12, the ACR 20 response rate was higher in the UPA group (76%) than in the ABA group (66%), and this trend continued at week 24 (79% vs. 74%, respectively). In terms of DAS28-CRP ≤3.2 response rates, UPA was superior to ABA at both the 12-week mark (50% vs. 29%) and the 24-week mark (63% vs. 48%) (14).

In the SELECT-MONOTHERAPY trial, patients with active RA despite stable MTX were assigned to receive UPA 15 or 30 mg once daily or to continue MTX at their previous dose (15). The group that received UPA 15 mg had a 68% ACR20 response and 45% DAS28-CRP ≤3.2 response at week 14, whereas the UPA 30 mg group showed a 71% ACR20 response and 53% DAS28-CRP ≤3.2 response at the same time point. Comparatively, in the

Table 2. Summary of phase III clinical trials evaluating upadacitinib for the treatment of RA (11-16)

Study name	Study design	Population	Background therapy	Upadacitinib arms	Comparator	The type of treatment	Sample size	Primary endpoint
Next	12-week, multicenter, randomized, double-blind study	csDMARD-IR	csDMARD	15 mg QD, 30 mg QD	Placebo	Combination	661	ACR20 at week 12; DAS28-CRP ≤3.2 at week 12
Beyond	12-week, multicenter, randomized, double-blind study	bDMARD-IR	csDMARD	15 mg QD, 30 mg QD	Placebo	Combination	499	ACR20 at week 12; DAS28-CRP ≤3.2 at week 12
Compare	26-week, multicenter, randomized, double-blind study	MTX -IR	MTX	15 mg QD	Placebo	Combination	1629	ACR20 at week 12; DAS28-CRP >2.6 at week 12
Choice	24-week, multicenter, randomized, double-blind study	bDMARD-IR	csDMARD	15 mg QD, 30 mg QD	ADA 40 mg/2 weeks	Combination	612	Change in DAS28-CRP levels at week 12 (non-inferiority)
Monotherapy	14-week, multicenter, randomized, double-blind study	MTX -IR	Not applicable	15 mg QD	MTX	Monotherapy	648	ACR20 at week 14; DAS28-CRP ≤3.2 at week 14
Early	48-week, multicenter, randomized, double-blind study	Naive or limited exposure to MTX	Not applicable	15 mg QD	Not applicable	Monotherapy	947	ACR50 at week 12; DAS28-CRP ≥2.6 at week 24

RA: Rheumatoid arthritis, csDMARD: Conventional synthetic disease-modifying antirheumatic drugs, IR: Inadequate responses, ACR: American College of Rheumatology, DAS-28: Disease activity score 28, CRP: C-reaktif protein, bDMARD: Biological disease-modifying antirheumatic drug, MTX: Methotrexate, ADA: Adalimumab, QD: Once daily

same trial, the group that continued MTX treatment had a 42% ACR20 response and a 20% DAS28-CRP ≤3.2 response at week 14 (15).

The SELECT-EARLY trial aimed to evaluate the efficacy of UPA as monotherapy in patients with predominantly early RA who were either new to or had limited exposure to MTX (16). The trial comprised a 48-week active comparator-controlled period, followed by a long-term extension period of up to 4 years. The results showed that the ACR20 response rates at week 12 were higher in patients receiving UPA at both doses (76% and 77% for UPA 15 and UPA 30, respectively) than in those receiving MTX (54%). Similarly, the DAS28-CRP ≤3.2 response rates at week 12 were also higher in the UPA groups (53% and 55% for UPA 15 and UPA 30, respectively) than in the MTX group (28%). Both endpoints were statistically significant in the UPA groups compared with MTX (16).

The SELECT-SUNRISE trial was a dose-ranging study conducted in Japan and involved patients who were previously on stable csDMARDs (17). They were randomly assigned to receive UPA 7.5, 15, or 30 mg once daily or a matching placebo for a 12-week double-blind period. The primary endpoint of the trial was to measure the ACR20 response. At week 12, a higher percentage of patients receiving UPA at all doses (7.5 mg, 15 mg, and 30 mg) achieved the ACR20 response compared with those receiving placebo (76%, 84%, and 80% vs. 43%). The DAS28-CRP ≤3.2 response rates at week 12 were also significantly higher in patients receiving UPA (53%, 69%, and 72%) than in those receiving placebo (18%) (17). Following the initial 12-week study, patients were enrolled in a blinded extension period. Recently, the 84-week results of this extension study were reported (18). During this period, placebo patients were randomly assigned to UPA 7.5, 15, or 30 mg doses, whereas former UPA patients

continued the same dose scheme. The ACR20 response rates for patients initially randomized to UPA demonstrated continued improvement or maintenance over time up to week 84. In contrast, patients initially randomized to placebo showed improvements in ACR20 response after switching to UPA at week 12. At week 84, ACR20 response rates were 85.7%, 77.6%, and 58.0% for patients continuing UPA 7.5 mg, 15, and 30 mg, respectively. These response rates were similar for patients who had switched to UPA at week 12. Similar trends were observed in patients who achieved DAS28-CRP ≤3.2 response rates at 84 weeks. In summary, patients who switched from placebo to UPA at week 12 showed efficacy improvements up to week 84 that were comparable to those observed in patients initially randomized to UPA (18). Table 3 summarizes the key outcome variables for each of the SELECT trials.

In the SELECT-NEXT trial, both doses of UPA demonstrated significant improvements in each outcome variable compared with placebo. In SELECT-BEYOND, all outcome variables except for ACR70 with UPA 15 mg were significantly better than those with placebo. In SELECT-COMPARE, UPA outperformed ADA and placebo in each outcome variable at both time points. In SELECT-CHOICE, no significant differences were found between UPA and ABA for each outcome variable at both time points, except for the remission rate based on DAS28 at week 12, which favored UPA over ABA. In SELECT-MONOTHERAPY, both UPA doses significantly outperformed MTX for each outcome variable. Finally, in SELECT-EARLY, both UPA doses showed significant improvements at both time points for all variables compared with placebo. It is noteworthy that CDAI LDA and remission rates were only presented for week 24.

The SELECT-EARLY and SELECT-COMPARE trials evaluated radiographic progression in patients with RA receiving UPA (19). The results showed that UPA monotherapy or in combination with background MTX was more effective than MTX monotherapy in inhibiting the progression of structural joint damage in MTX-naive patients with RA. In MTX-IR patients with RA, UPA plus MTX

Table 3. Key outcome variables for SELECT phase III trials (11-16)

Dose	ACR20	ACR50	ACR70	DAS28-CRP ≤3.2	CDAI ≤10	DAS28-CRP <2.6	CDAI ≤2.8
SELECT NEXT, % of patients achieving response at 12 weeks							
Placebo	36	15	6	17	19	10	3
15 mg	64	38	21	48	40	31	9
30 mg	66	43	27	48	42	28	12
SELECT BEYOND, % of patients achieving response at 12 weeks							
Placebo	28	20	11	14	14		
15 mg	65	34	12	43	32		
30 mg	56	36	23	42	34		
SELECT COMPARE, % of patients achieving response (weeks 12 and 26 respectively)							
Placebo	36, 36	15, 21	5	14, 18	16, 22	6, 9	3, 6
UPA	71, 67	45, 54	25	45, 55	40, 53	29, 41	13, 23
ADA	63, 57	29, 42	13	29, 39	30, 38	18, 27	8, 14
SELECT CHOICE, % of patients achieving response (weeks 12 and 26 respectively)							
UPA	76, 79	46, 59	21, 37	50, 63	41, 58	30, 46	8, 21
ABA	66, 74	34, 49	14, 26	29, 48	35, 52	13, 31	3, 14
SELECT MONOTHERAPY, % of patients achieving response at 14 weeks							
15 mg	68	42	23	45	35	28	13
30 mg	71	52	33	53	47	41	19
MTX	41	15	3	19	25	8	1
SELECT EARLY, % of patients achieving response (weeks 12 and 24 respectively)							
15 mg	77, 79	52, 60	32, 45	53, 60	56	48, 48	28
30 mg	75, 78	56, 66	37, 50	55, 65	61	50, 50	29
MTX	54, 59	28, 33	14, 19	28, 32	38	18, 18	11

ACR: American College of Rheumatology, DAS-28: Disease activity score 28, CRP: C-reaktif protein, CDAI: Clinical disease activity index, UPA: Upadacitinib, ADA: Adalimumab, ABA: Abatacept, MTX: Methotrexate

was more effective in inhibiting the progression of structural joint damage than placebo plus MTX, with a mean change from baseline in the modified total Sharp score (mTSS) of 0.28 for UPA plus MTX compared with 1.73 for placebo plus MTX at week 48 ($p<0.05$). The mean change from baseline in mTSS was 0.39 for ADA plus MTX. Furthermore, significantly reduced progression of joint space narrowing and erosion scores with UPA plus MTX vs. placebo plus MTX were observed at 6 months and 1 year ($p<0.05$). Overall, these results suggest that UPA may be an effective treatment option for preventing the progression of joint damage in patients with RA (19).

In conclusion, studies evaluating the efficacy and safety of UPA for treating RA have provided valuable insights into its potential as a therapeutic option. UPA has demonstrated significant improvements in various outcome variables, including ACR response rates, disease activity scores, and radiographic progression, compared with placebo and other active comparators. The BALANCE studies, as well as the SELECT Phase III trials, have consistently shown that UPA, either as monotherapy or in combination with conventional synthetic or biological DMARDs, effectively reduces disease activity and improves patient outcomes. Notably, UPA exhibited dose-dependent efficacy, with the 15 and 30 mg daily doses generally demonstrating superior results. Furthermore, these studies have established the safety profile of UPA, with manageable AEs and no significant safety concerns. The positive results from these trials provide a solid foundation for considering UPA as a valuable treatment option for patients with RA, particularly those who have an inadequate response to other therapies.

Psoriatic Arthritis

PsA is a chronic inflammatory rheumatic disease characterized by joint inflammation and skin lesions. Although it often occurs in individuals with pre-existing psoriasis, it can also manifest independently. Despite extensive research, the exact cause of PsA remains unknown. However, emerging evidence suggests that the JAK/STAT pathway plays a critical role in PsA pathogenesis. The JAK/STAT pathway is responsible for regulating immune responses and inflammatory processes, making it an intriguing target for therapeutic interventions. As a result, JAK inhibitors have emerged as promising and innovative therapies for PsA, offering new possibilities for managing this complex condition (20). Currently, several studies have shown the efficacy of these treatments in PsA. The EMA approved UPA for treating active PsA in patients who are intolerant to DMARDs or have had an inadequate response to one or more DMARDs or conventional therapy. The SELECT-PsA1 trial, a randomized, double-blind, placebo-controlled phase 3 study, involved 1704 patients with PsA (21). Participants were eligible if they were 18 years or older, diagnosed with PsA, and had an inadequate response to at least one non-biologic DMARD. The study compared the efficacy of UPA 15 or 30 mg once daily with placebo or ADA 40 mg every other week. Patients with prior exposure to biological therapies or JAK inhibitors were excluded. The primary endpoint was an ACR20 response with UPA versus placebo at week 12. At this point, both UPA doses exhibited non-inferiority to ADA and superiority to placebo, with ACR20 response rates of 70.6% and 78.5% for UPA 15 mg and 30 mg, respectively, compared with 36.2% for placebo and 65% for ADA ($p<0.001$ for both UPA doses vs. placebo) (21). ACR50 response rates were 13.2% for placebo, 37.5% for ADA, 37.5% for UPA 15 mg, and 51.8% for UPA 30 mg. ACR70 response rates at week 12 were 15.6% for UPA 15 mg, 25.3% for UPA 30 mg, 13.8% for ADA, and 2.4% for placebo. At week 24, ACR20 response rates were 45.2% for placebo, 67.1% for ADA, 73.4% for UPA 15 mg, and 78.5% for UPA 30 mg. ACR50 response rates were 18.9% for placebo, 44.3% for ADA, 52.4% for UPA 15 mg, and 60.5% for UPA 30 mg. ACR70 response rates were 5.2% for placebo, 22.6% for ADA, 28.7% for UPA 15 mg, and 36.4% for UPA 30 mg (21).

The SELECT-PSA1 trial results include findings from 1- and 2-year follow-up periods (22,23). During the 56-week study, approximately 17% of the patients discontinued treatment, with 20% of them ceasing due to insufficient efficacy. Notably, patients who switched from placebo to active drugs experienced response rate improvements similar to those who started with active drugs (22). Efficacy was evaluated by measuring ACR20, 50, and 70 response rates for three different drugs at week 56: UPA 15 mg (73.7%, 57.1%, and 35.2%, respectively), UPA 30 mg (74.4%, 60.4%, and 39.7%, respectively), and ADA (68.5%, 51.3%, and 31.2%, respectively) (22). In the second year, these rates wereas follows: UPA 15 mg (69%, 53.6%, and 38%, respectively), UPA 30 mg (69.5%, 59.3%, and 43.5%, respectively), and ADA (63.4%, 47.1%, and 29.4%, respectively) (23). Regarding enthesitis resolution, 59.3%, 57.8%, and 54% of patients receiving UPA 15, UPA 30, and ADA 40 mg, respectively, experienced improvement by week 56, while 53.3%, 52.2%, and 49.1% did so by week 104. Regarding dactylitis, 75%, 74.8%, and 74% of patients achieved resolution by week 56, and 69.9%, 71.7%, and 72.4% achieved resolution by week 104, respectively (23).

The SELECT-PsA2 trial was conducted with 641 patients to assess the effectiveness of once-daily UPA 15or 30 mg compared with placebo in patients with PsA who were refractory or intolerant to biological DMARDs (24). Eligible patients were 18 years or older with active PsA, had a diagnosis of PsA with symptom onset for at least 6 months, had a history or current plaque psoriasis, had at least three swollen and tender joints at baseline, and had an inadequate response or intolerance to at least one biological DMARD. The primary endpoint was the ACR20 response at week 12. Both UPA doses demonstrated superior efficacy to placebo in achieving ACR20 response at week 12, with response rates of

56.9% and 63.8% for UPA 15 and 30 mg, respectively, compared with 24.1% for placebo ($p<0.05$ for both UPA doses vs. placebo). At week 24, the response rates for ACR20, 50, and 70 wereas follows: UPA 15 mg (59.2%, 38.4%, and 19.4%, respectively), UPA 30 mg (61.5%, 36.2%, and 23.9%, respectively), and placebo (20.3%, 9.4%, and 0.9%, respectively). Both UPA doses were statistically significant compared with placebo. Other secondary endpoints at week 24, such as improvement in enthesitis [Leeds Enthesitis Index (LEI); UPA 15 mg 43%, UPA 30 mg 45%, and placebo 15%] and dactylitis [Leeds Dactylitis Index (LDI); UPA 15 mg 58%, UPA 30 mg 68%, and placebo 28%], were also significant compared with placebo (24).

By week 56, approximately 25% of the patients had to discontinue medication due to various factors, primarily AEs. Approximately 19% of these discontinuations resulted from insufficient efficacy (25). At the same time, the proportion of patients achieving ACR20/50/70 was 59.7%, 40.8%, and 24.2% for UPA 15 mg and 59.2%, 38.5%, and 26.6% for UPA 30 mg, respectively. Responses at week 56 for both placebo-to-UPA groups were similar to those who received UPA from the beginning. In patients with dactylitis at baseline, complete resolution (LDI =0) was observed in 50.9% and 58.0% of patients treated with UPA 15 mg and 30 mg, respectively, by week 56. Additionally, for those with enthesitis at baseline, complete resolution (LEI =0) was achieved in 42.9% and 42.8% of patients for the 15 and 30 mg dosages, respectively (25).

In both SELECT-PsA 1 and SELECT-PsA 2 studies, axial involvement was also assessed (26). At baseline, the determination of axial involvement was made by the investigator's judgment (yes or no), considering all available clinical information such as duration and characteristics of back pain, age of onset, and any previous lab investigations or imaging, if accessible. Axial involvement was present in 30.9% of patients in SELECT-PsA 1 and 35.7% in SELECT-PsA 2. In SELECT-PsA 1, Ankylosing spondylitis disease activity score inactive disease (ASDAS ID) was achieved in higher percentages by week 12 for UPA 15 mg and ADA compared with placebo (23%, 29.9%, and 6.2%, respectively), as well as by week 24 (41.7%, 35.4%, and 13.1%, respectively). In SELECT-PsA 2, ASDAS ID was attained in 17.1% and 28.9% of UPA 15 mg patients by weeks 12 and 24, whereas for placebo, the percentages were 6.7% and 2.7%, respectively (26).

In summary, based on the controlled trials (Table 4), UPA at both doses proved effective in managing PsA. In addition to improving

Table 4. Key outcome variables for SELECT PsA-1 and SELECT PsA-2 phase III trials (21-26)

Dose	ACR20	ACR50	ACR70	ASDAS ID
SELECT PsA-1, % of patients achieving response (weeks 12 and 24 respectively)				
Placebo	36.2/45.2	13.2/18.9	2.4/5.2	6.2/13.1
15 mg	70.6/73.4	37.5/52.4	15.6/28.7	23/41.7
30 mg	78.5/78.5	51.8/60.5	25.3/36.4	
ADA	65/67.1	37.5/44.3	13.8/22.6	29.9/35.4
SELECT PsA-1, % of patients achieving response at one to two year follow up periods (weeks 56 and the second year respectively)				
15 mg	73.7/69	57.1/53.6	35.2/38	
30 mg	74.4/69.5	60.4/59.3	39.7/43.5	
ADA	68.5/63.4	51.3/41.7	31.2/29.4	
SELECT PsA-2, % of patients achieving response at 12 week				
Placebo	35.1			6.7
15 mg	56.9			17.1
30 mg	63.8			
SELECT PsA-2, % of patients achieving response at 24 week				
placebo	20.3	9.4	0.9	2.7
15 mg	59.2	38.4	19.4	28.9
30 mg	61.5	36.2	23.9	
SELECT PsA-2, % of patients achieving response at 56 week				
15 mg	59.7	40.8	24.2	
30 mg	59.2	38.5	26.6	

PsA: Psoriatic arthritis, ACR: American college of rheumatology, ASDAS ID: Ankylosing spondylitis disease activity score inactive disease, ADA: Adalimumab

arthritis symptoms, significant responses were observed across various domains, including enthesitis, dactylitis, and axial disease.

Axial Spondyloarthritis

UPA is effective in treating both AS and nr-axSpA patients with axSpA. The SELEXT-AXIS-1 trial, a placebo-controlled study, was conducted on patients with active AS who were unresponsive to NSAIDs (27). Exclusion criteria included previous exposure to any JAK inhibitor or biological therapy. Participants were randomized to receive either UPA 15 mg or placebo for 14 weeks. At week 14, a significantly higher percentage of patients in the UPA group achieved an Assessment of Spondylarhtritis International Society (ASAS)40 response compared with the placebo group (52% vs. 26%). Additionally, a greater proportion of patients in the UPA group reached ASDAS LDA (49% vs. 11%) and ASDAS inactive disease (16% vs. 0%) compared with those receiving the placebo. Furthermore, Spondyloarthritis Sesearch Concertium of Canada (SPARCC) magnetic resonance imaging (MRI) spine and sacroiliac joint scores showed greater improvement from baseline to week 14 in patients treated with UPA than in those given the placebo (27).

Of the 187 patients, 178 (95%) completed week 14 on the study drug and proceeded to the open-label extension (28). The most common reasons for discontinuation between weeks 14 and 64 were lack of efficacy (5.6%) and AEs (2.2%). Comparable proportions of patients in both groups (continuous UPA or placebo-to-UPA) achieved ASAS40 response or ASDAS indicating LDA at week 64. The primary efficacy endpoint of ASAS40, initially at 52% at week 14, continued to increase in the continuous group, reaching 72% by week 64. A similar pattern of improvement was observed for ASDAS LDA (70%), ASDAS ID (34%), and ASAS partial remission (40%) (28). The recently published second-year results of the study revealed that 144 patients (77%) completed week 104 (29). Between weeks 64 and 104, the rates of lack of efficacy and AEs were 0.7% and 4.1%, respectively. In the continuous UPA group, at week 104, ASAS40 was 66%, ASDAS LDA 62%, and ASDAS ID 33%. The mean baseline mSASSS was 8.1±11.6 units, with a mean change of 0.7 [95% confidence intervale (CI): 0.3 to 1.1] after two years. In the continuous UPA group, the mean (95% CI) decrease from baseline to week 14 in the SPARCC MRI spine inflammation score was -7.2 (-10.2 to -4.2), which was sustained through week 104 [-7.3 (-10.8 to -3.7)]. Similar results were observed in the SPARCC MRI sacroiliac joint inflammation score, with a mean decrease from baseline to week 14 of -6.1 (-8.5 to -3.7) and a consistent reduction through week 104 [-5.3 (-7.6 to -3.1)] (29).

The SELECT-AXIS 2 study employed a master protocol and a common screening platform to determine patient eligibility for two separate phase 3, randomized, double-blind, placebo-controlled multicenter trials: bDMARD-IR AS and active nr-axSpA resistant to NSAIDs (30,31). The bDMARD-IR AS study aimed to assess the efficacy and safety of once-daily UPA 15 mg versus placebo, with the primary endpoint being ASAS40 response at week 14 (30). The majority of participants had prior exposure to one TNF inhibitors (TNFi) (74%), followed by one interleukin (IL)-17i (13%). ASAS40 response at week 14 was observed in 45% of the UPA group compared with 18% in the placebo group. UPA also demonstrated superior ASAS40 treatment effects in subgroups of patients who had received either one (46% vs. 20%) or two (36% vs. 4%) prior bDMARDs, as well as in those with previous exposure to TNFi (47% vs. 22%) or IL-17i (37% vs. 4%). In addition, UPA improved objective inflammation markers, as indicated by hsCRP and SPARCC MRI spine and sacroiliac joint inflammation scores. ASDAS LDA rates were 44% vs. 10%, and ASDAS-ID rates were 13% vs. 2%, both in favor of UPA (30).

In the nr-axSpA study, participants were required to exhibit at least one objective sign of active inflammation during the screening phase, as evidenced by MRI of the sacroiliac joints or high-sensitivity CRP levels above the upper limit of normal. Patients must have had an inadequate response to at least two NSAIDs or demonstrated intolerance or contraindication for NSAIDs. Enrollment permitted previous treatment with one bDMARD for a minimum of 20% and a maximum of 35% of participants who had discontinued the prior bDMARD because of lack of efficacy (after ≥12 weeks at an adequate dose) or intolerance (31). The primary endpoint was the proportion of patients who achieved an ASAS40 response at week 14. ASAS40 responses were observed in 45% of the UPA group and 23% of the placebo group, whereas ASAS partial remission rates were 19% and 8%, respectively. Comparing baseline and 14-week SPARCC MRI scores for the spine and sacroiliac joint, the UPA group showed reductions of -0.79 and -2.49, whereas the placebo group experienced increases of 0.34 and 0.57 units, respectively (31).

In summary, the SELECT-AXIS studies demonstrated the benefits of UPA in patients with AS and nr-axSpA (Table 5), regardless of whether they were biologic-naïve or had previous experience with biological treatments.

Table 5. Key outcome variables for SELECT AXIS-1 and SELECT AXIS-2 phase III trials (27-31)

Dose	ASAS40	ASDAS LDA	ASDAS ID	ASAS PR
SELECT AXIS-1, % of patients achieving response at 14 weeks				
Placebo	26	11	0	
15 mg	52	49	16	
SELECT AXIS-1, % of patients achieving response (weeks 64 and 104 respectively)				
15 mg	72/66	70/62	34/33	40/40
SELECT AXIS-2 (bDMARD-IR AS study), % of patients achieving response at 14 weeks				
Placebo	18	10	2	6.7
15 mg	45	44	13	17.1
SELECT AXIS-2 (nr-axSpA study), % of patients achieving response at 14 weeks				
placebo	23			8
15 mg	45			19

ASAS: Assessment of Spondylarhtritis International Society,ASDAS: Ankylosing spondylitis disease activity score, LDA: Low disease activity, ID: Inactive disease, PR: Partial remission, bDMARD: Biologic disease-modifying antirheumatic drug, IR: Inadequate responses, AS: Spondylitis, nr-axSpA: Non-radiographib axial spondyloarthritis

Safety

The safety profile of UPA in RA has been investigated in various studies, including the SELECT phase III clinical studies and a systematic review and meta-analysis of JAK inhibitors (32,33). The SELECT trials found an increased risk of herpes zoster in patients receiving UPA compared with those receiving ADA, with hazard ratios of 2.997 (vs. MTX) and 3.221 (vs. ADA). The integrated safety analysis reported acceptable safety profiles with no new risks compared with other JAK inhibitors (32). In the systematic review and meta-analysis, JAK inhibitors, including UPA, were significantly associated with an increased risk of AEs [relative risk (RR) 1.09, 95% CI 1.05-1.13], herpes zoster (RR 2.57, 95% CI 1.43-4.62), and URTI (RR: 1.32, 95% CI: 1.07-1.63) compared with placebo. Both the 15 and 30 mg doses of UPA were linked to an increased risk of AEs (15 mg QD: RR 1.14, 95% CI 1.02-1.27; 30 mg QD: RR 1.15, 95% CI 1.02-1.30). The risk of herpes zoster was higher in patients receiving UPA, although the effect was not statistically significant (15 mg QD: RR: 1.41, 95% CI: 0.44-4.45; 30 mg QD: RR: 2.96, 95% CI: 0.59-14.83) (33).

In a safety study of UPA involving over 6,000 patients with RA, PsA, AS, and atopic dermatitis (AD), the overall occurrence of AEs was comparable between upadacitinib 15 mg QD and ADA 40 mg EOW among RA patients (205.5 vs. 203.6 events per 100 patient-years) (34). UPA showed a slightly lower rate of serious AEs (12.4 events per 100 patient-years) than ADA (13.7 events per 100 patient-years) in RA patients, whereas in PsA patients, both treatments had similar rates of serious AEs (11.1 vs. 9.0 events per 100 patient-years). The mortality rate was low and similar for both treatments in patients with RA (0.8 vs. 0.9 events per 100 patient-year). Patients with RA and PsA treated with UPA experienced higher incidences of herpes zoster (1.6-3.6 events per 100 patient-years), non-melanoma skin cancer (0-0.8 events per 100 patient-years), and increased creatine phosphokinase levels (4.4-7.9 events per 100 patient-years) compared with those on active comparators (34). The rates of serious infections, major cardiovascular events (MACE), venous thromboembolism, and malignancies were generally lower in patients with AS and AD. Acne rates rose only in AD patients (34). The study supports UPA as having an acceptable safety profile for treating RA, PsA, AS, and AD, with similar rates of malignancy (excluding non-melanoma skin cancer), MACE, and venous thromboembolism between UPA and active comparators (ADA and MTX). Known differences in the side effect profile of JAK inhibitors, such as increased rates of herpes zoster, elevated creatine phosphokinase levels, and NMSC, have also been observed (34).

Pharmacokinetics

Numerous investigations have explored the pharmacokinetics of UPA, including both human and in vitro studies (35,36). It is rapidly absorbed from the gastrointestinal tract, reaching peak concentration (C_{max}) within approximately 1 hour. The drug exhibits limited plasma protein binding, with less than 50% bound. Its primary metabolism involves the CYP3A4 enzyme. *In vitro* experiments have shown that it does not inhibit drug-metabolizing enzymes or transporters at clinically relevant concentrations (35,36). No significant QTc prolongation was associated with therapeutic doses. The average terminal

elimination half-life ranges from 8 to 14 hours. When examining the influence of food on its pharmacokinetics, Cmax decreased by 23%, but the area under the curve (AUC) remained unchanged compared with fasting conditions (36).

Regarding dose adjustments, the extended-release formulation has an average terminal elimination half-life of 9-14 hours. Dose modifications based on factors such as age, sex, body weight, race, and ethnicity are generally not required for most patients. Mild or moderate renal impairment does not necessitate dose adjustment, whereas severe renal impairment requires a recommended dose of 15 mg once daily. Similarly, individuals with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment do not require dose adjustment. However, the drug should not be administered to patients with severe hepatic impairment (Child-Pugh C). These considerations are particularly important for specific patient populations, including those with renal or hepatic failure (37).

In summary, these studies have shown that upadacitinib is associated with an increased risk of herpes zoster, non-melanoma skin cancer, and elevated creatine phosphokinase levels in patients with RA and PsA. However, the overall occurrence of AEs and serious AEs were generally comparable to those of active comparators, such as ADA and MTX. The rates of serious infections, MACE, venous thromboembolism, and malignancies were typically lower in patients with AS and AD. Collectively, these findings support an acceptable safety profile for Upadacitinib in treating RA, PsA, AS, and AD, while acknowledging known differences in the side effect profile of JAK inhibitors.

CONCLUSION

In conclusion, studies evaluating the efficacy and safety of UPA for treating RA, PsA, and axSpA have provided valuable insights into its potential as a therapeutic option. UPA has demonstrated significant improvements in various outcome variables, including ACR response rates, disease activity scores, and radiographic progression, compared with placebo and other active comparators. Studies have consistently shown that UPA, either as monotherapy or in combination with conventional synthetic or biological DMARDs, effectively reduces disease activity and improves patient outcomes. Furthermore, these studies have established the safety profile of UPA, with manageable AEs and no significant safety concerns. The positive results from these trials provide a solid foundation for considering UPA as a valuable treatment option for patients with RA, PsA, and axSpA, particularly those who have an inadequate response to other therapies.

Footnotes

Authorship Contributions

Surgical and Medical Practices: F.B., İ.S., Concept: F.B., İ.S., Design: F.B., İ.S., Literature Search: F.B., İ.S, Writing: F.B., İ.S.

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INVITED REVIEW

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TOFACITINIB: CURRENT CONSIDERATIONS IN THE MANAGEMENT OF IMMUNE INFLAMMATORY DISORDERS

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Abstract

Tofacitinib, the first member of targeted synthetic disease-modifying antirheumatic drugs, is an oral inhibitor of Janus kinases (JAK), preferentially JAK 1 and 3. It is an analog of adenosine triphospahte and inhibits several proinflammatory cytokines and pathways. Tofacitinib is rapidly absorbed and eliminated mainly via the liver. The efficacy of tofacitinib has been studied extensively in rheumatoid arthritis (RA) patients with different clinical scenarios. Tofacitinib is now approved in several countries for the treatment of RA, psoriatic arthritis, ankylosing spondylitis, polyarticular and systemic juvenile idiopathic arthritis, and ulcerative colitis. In addition, studies to assess the efficacy of tofacitinib in patients with several different indications are under consideration. Neutropenia, anemia, elevation of transaminase levels, hyperlipidemia, and increased risk of infections with several causes are well-known side effects. However, recent data from the ORAL Surveillance study shed light on the risk of cardiovascular events and malignancy. In that study, RA patients over 50 years with at least 1 cardiovascular risk factor were randomized to anti-tumor necrosis factor or tofacitinib, revealing increased cardiovascular event risk and malignancy (especially lung cancer and lymphoma) in the tofacitinib arm. Although post-hoc analysis of the dataset suggested a possible link between a history of cardiovascular disease and both cardiovascular and malignancy endpoints, the Food And Drug Administration and European Medical Agency announced black-box warnings for all JAK inhibitors covering all indications. Obviously, JAK inhibitors, the game changers of the last decade, need further evaluation, especially regarding safety issues.

Keywords: Tofacitinib, rheumatic diseases, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis

INTRODUCTION

The last three decades have been fruitful in treating inflammatory disorders such as rheumatoid arthritis (RA) and axial spondyloarthritis (1,2). Several pathways were targeted for this purpose, including the Janus kinase (JAK) pathway. At their first discovery, they were named "just another kinase" as they were discovered by polymerase chain reaction screening, and their role was not determined. As their potential and importance were discovered, they were named "Janus kinase" -the name of a ancient Roman god, because of their two near-identical phosphate-transferring domains (3). The JAK family consists of four types of intracellular, non-receptor tyrosine kinases (JAK 1-3 and TYK2), which are the bridges between cytokines and the JAK-STAT pathway. Several cytokines with very diverse actions use the JAK-signal transducer and activator of transcription (STAT) pathway to execute their "jobs" (4). JAK-STAT pathway dysregulation can result in several clinical manifestations: immune system-related diseases (RA, spondyloarthritis, immune

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deficiencies, etc.), cancer (melanoma, prostate cancer, breast cancer, etc.), and even COVID-19-related immune activation. Several JAK-STAT pathway inhibitors constitute an essential part of the armamentarium of rheumatologists (4).

In this review, from a rheumatological perspective, we will focus on the mechanism of action, pharmacological properties, safety, and efficacy of tofacitinib in rheumatic and non-rheumatic disorders.

Tofacitinib

General Information

Tofacitinib is an orally administered JAK inhibitor that belongs to the targeted synthetic disease-modifying antirheumatic drugs (DMARDs) family (2). In the last decade, tofacitinib has changed the clinical practice of physicians dealing with immune inflammatory disorders. However, recent data regarding the safety issues of tofacitinib (ORAL Surveillance) has spotted a big question mark on the current place of tofacitinib and other JAK inhibitors in the management of immune inflammatory disorders (5).

Pharmacodynamics

Mechanism of Action and Effects on the Cellular Level

Tofacitinib, which mimics adenosine triphospahte (ATP), reversibly and competitively binds to the ATP binding site and prevents the phosphorylation and activation of STATs (6). Biologic agents are generally directed against extracellular targets; however, tofacitinib acts at the intracellular level. Tofacitinib preferentially inhibits JAK-1 and JAK-3 over JAK-2 and TYK-2; however, with higher doses, this selectivity decreases (6). Inhibition of JAK 1 and 3 results in blockage of signal transduction for type I and II interferons (IFNs), interleukin 2, 4, 6, 7, 9, 15, and 21 (4,6,7). All these inhibitions inhibit cytokine- or growth factor-mediated gene expression, the activity of immune cells, mainly lymphocytes, and the suppression of inflammation.

In vitro studies of tofacitinib demonstrated the inhibition of lipopolysaccharide-induced inflammatory response, which is dependent on IFN-gamma, inhibition of anti-tumor necrosis factor (TNF), blockage of Th1, Th2, and Th17 differentiation, normalization of inflammatory cytokine levels, reduction in T-cell and macrophage infiltration, increase in receptor activator of nuclear factor kappaB ligand levels, and inhibition of osteoclast activation (6,8).

Neutrophil counts generally decrease within 3 months and generally remain within normal limits, and this effect is dose dependent. Lymphocyte counts modestly decrease; CD3+, CD4+, and CD8+ lymphocyte counts decrease very little in count. A decrease in T-cells is also reversible. However, natural killer cell counts decrease more prominently and in a dose-dependent manner. Treatment with tofacitinib was associated with dose-dependent increases in B-cell counts, possibly due to JAK3 inhibition, and immunoglobulin levels slightly decrease (7).

Tofacitinib rapidly decreases serum C-reactive protein (CRP) levels and remains stable throughout the treatment. Changes in CRP do not fully reverse within 2 weeks after discontinuation, suggesting a longer activity compared with the half-life.

Pharmacokinetics

Absorption and elimination of tofacitinib is rapid (peak plasma concentrations within 0.5-1 hour, half-life about 3 hours) and steady state concentrations are reached in 1-2 days after twice daily administration (9). Tofacitinib is well absorbed and similar with or without meals. Sex, body weight, ethnicity, and disease type psoriatic arthritis (PsA), (PsA, inflammatory bowel disease or RA) do not affect availability in a major way. In plasma, it binds to albumin (9). Clearence is approximately 70% hepatic and 30% renal; it is metabolized by cytochrome enzymes primarily mediated by CYP3A4. If glomerular filtration rate <50 mL/min, the dose should be reduced to half and dialysis does not clear tofacitinib. Mild hepatic impairment does not require dose reduction; however, in moderate hepatic impairment, the dose should be happened, and in severe impairment, tofacitinib should not be used (9).

Tofacitinib is available in the dosages of 2x10 mg, 2x5 mg or 1x11 mg [extanded relase (XR) form]. 2x10 mg dosage is not currently advised for safety concerns. The pharmacokinetic properties of 5 mg twice daily and extended-release forms are equivalent.

The recommended dosage for RA, ankylosing spondylitis (AS), PsA, psoriasis, and COVID-19 is 2x5 mg daily and for ulcerative colitis is 2x10 mg for 8 weeks than 2x5 mg for maintenance.

Effectiveness in Rheumatic Diseases

Rheumatoid Arthritis

Tofacitinib has been rigorously studied in patients with RA. Several randomized controlled randomised controlled trial (RCT) and real-life data have been published. RCTs have the same common title as “ORAL” studies:

ORAL start: Tofacitinib monotherapy was compared with methotrexate (MTX) in RA patients without a previous treatment. Tofatinib is more effective in reducing signs, symptoms, and radiographic progression (10).

ORAL solo: The efficacy of tofacitinib monotherapy was assessed and compared with placebo in convational syntetic DMARD (csDMARD) and biologic DMARD (bDMARD) resistant RA patients. All endpoints favored the tofacitinib arm. In addition, patients in the placebo arm who were crossed to tofacitinib after 3 months also achieved similar efficacy endpoints after an additional 3 months (11).

ORAL strategy: In MTX-unresponsive RA patients, the efficacy of tofacitinib monotherapy (2x5 mg), tofacitinib (2x5 mg) + MTX and adalimumab + MTX were compared. The efficacy of both tofacitinib and adalimumab with MTX combinations were non-inferior to each other at 6 months, and they were better than tofacitinib monotherapy (12).

ORAL shift: In this RCT, MTX-unresponsive RA patients were treated with tofacitinib XR for 24 weeks. Patients achieving low disease activity were then randomized to MTX withdrawal. After a 24-week period, overall disease activity was similar in both groups, suggesting that MTX can be safely withdrawn without a significant loss of efficacy (13).

ORAL standard: In MTX-unresponsive RA patients, the efficacy of tofacitinib (2x5 mg) + MTX, tofacitinib (2x10 mg) + MTX and adalimumab + MTX (as an active control) were compared. At the sixth month, the efficacy of all regimens was better than that of placebo, with numerically better in tofacitinib 2x10 mg dosage (14).

ORAL scan: In MTX-unresponsive RA patients, the effects of tofacitinib (2x5 mg) + MTX, tofacitinib (2x10 mg) + MTX were compared with placebo regarding radiographic progression. Although there was no significant difference in the changes in the modified total Sharp score (mTSS) values from baseline in the treatment arms, patients in both tofacitinib arms had lower changes in the mTSS value from baseline compared with the placebo arm. Subgroup analysis also revealed that patients with a higher risk of radiographic progression had much more benefit of tofacitinib than placebo (15).

ORAL sync: The efficacy of tofacitinib with csDMARD combinations (2x5 mg or 2x10 mg) was assessed and compared with placebo in cs/bDMARD-resistant RA patients. All endpoints favored the tofacitinib arm (16).

ORAL step: In anti-TNF-resistant RA patients, the efficacy of tofacitinib (2x5 mg) + MTX, tofacitinib (2x10 mg) + MTX were compared with placebo. All efficacy endpoints were better in tofacitinib arms; however, response rates were numerically lower compared with studies in which the efficacy of tofacitinib was assessed in MTX-unresponsive patients (17).

Besides all these RCTs, several study groups from different geographic areas have already been published and have shown parallel results both to each other and RCTs regarding the efficacy of tofacitinib (18-23). In addition, recent data suggest a possible role for tofacitinib in the management of RA-related interstitial lung disease (24,25).

Spondyloarthritis

Ankylosing spondylitis

For several years, anti-TNF antibodies and IL-17 inhibitors were the only bDMARDs used for the treatment of AS. Although several case reports and off-label use reports are available in the current literature, the results of the phase 3 trial will be published in 2021. In this phase 3, randomized, double-blinded, placebo-controlled trial, patients were randomized to tofacitinib 2x5 mg or placebo. At week 16, the assessment of spondylarhritis (ASAS)20 response rate (56.4% vs. 29.4%) and ASAS40 response rate (40.6% vs. 12.5%) were significantly higher in the tofacitinib arm with similar adverse event profile (26). In 2021, the Food And Drug Administration (FDA) approved tofacitinib for managing AS.

Psoriatic Arthritis

Targeting cytokines in the pathogenesis of PsA by tofacitinib has been studied in two randomized clinical trials. In OPAL Broden, tofacitinib had similar efficacy to adalimumab and tofacitinib in a cohort of patients who were anti-TNF naive and unresponsive to at least one csDMARD (27). In OPAL Beyond, tofacitinib was effective in active PsA patients who were unresponsive to anti-TNFs (28). In several countries, tofacitinib 2x5 mg has already been approved for the management of active PsA.

Safety in Rheumatic Diseases

Hyperlipidemia (although unclear clinical consequences), transaminitis, increased risk of infections (viral, bacterial, opportunistic; similar risk to anti-TNFs except herpes zoster which is reported higher in tofacitinib), neutropenia, anemia, and increased risk of gastrointestinal perforation have been reported in RCTs, long term extention studies, and real-life data (29).

Major “hot topic” adverse events related to tofacitinib are cardiovascular events and malignancies. Although former or some of the recent studies and meta-analyses suggested a low or decreased cardiac event risk, the ORAL Surveillance study dislodged our perception of tofacitinib (30,31). In this trial, patients over 50 years of age with at least 1 cardiovascular risk were randomized to anti-TNFs (etanercept or adalimumab)

or tofacitinib (2x5 mg or 2x10 mg). With the increased risk of pulmonary embolism reported in 2x10 mg arm, the dose was reduced to 2x5 mg in this arm. For this study, the non-inferiority margin was set to 1.8 in the confidence interval. Regarding major adverse cardiovascular event, Hazard ratio for tofacitinib 2x5 mg vs. anti-TNF was 1.24 (0.81-1.91) and that for tofacitinib 2x10 mg vs. anti-TNF was 1.43 (0.94-2.18). In 2x10 mg arm but not in the 2x5 mg arm, venous thromboembolism and overall mortality risk were higher than those in the anti-TNF arm. Similarly, an increased risk of lymphoma and lung cancer was reported in the ORAL Surveillance trial. Following the release of this data, the FDA and European Medical Agency (EMA) announced black box warnings. The EMA recommended that all JAK inhibitors in all indications should be used in the following patients if there is no available option: age ≥65 years, increased risk of major cardiovascular problems (such as heart attack or stroke), history of smoking, or increased cancer risk. Post-hoc analysis of the ORAL Surveillance study revealed that the increased risk of cardiovascular and malignancy risks were related to a history of atherosclerotic cardiovascular disease (32,33). Parallel to these recommendations, EULAR placed JAK inhibitors in the management of RA with first-line b/tsDMARD while considering special populations, as mentioned above (1).

Use in Other Diseases

Tofacitinib is approved for the management of moderate to severe ulcerative colitis in patients resistant to conventional treatment or bDMARDs (34).

Polyarticular juvenile idiopathic arthritis, sistemic juvenile idiopathic arthritis, Sjögren's syndrome, systemic sclerosis, Takayasu arteritis, atopic dermatitis, alopecia areata, psoriasis, polymyalgia rheumatica, Crohn's disease, pouchitis, cutaneous lupus erythematosus, kidney transplant, and COVID-19 are other conditions in which tofacitinib is being tried in different phase trials (4).

CONCLUSION

In conclusion, tofacitinib, the first member of the JAK inhibitor family, has changed the way of understanding and managing immune inflammatory disorders. However, recent safety data require further evaluation of current practice.

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INVITED REVIEW

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JAKINIBS IN SYSTEMIC LUPUS ERYTHEMATOSUS: CURRENT INSIGHTS AND FUTURE PROSPECTS

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Abstract

This review summarizes current research and data regarding the use of Janus kinase inhibitör (JAKinib) therapies in the treatment of systemic lupus erythematosus (SLE). SLE is a multisystemic inflammatory rheumatic disease that is considered the prototype of autoimmune diseases. The expanding body of knowledge concerning the disease's pathogenesis and advancements in drug technology have ushered in new treatment options and strategic approaches. JAK-signal transduction activator of transcription pathway activation is involved in the pathogenesis of several inflammatory diseases. JAKinibs were approved for the treatment of rheumatoid arthritis, psoriatic arthritis, psoriasis, alopecia, and ulcerative colitis. Jakinibs, emerge as a potential treatment option with the capacity to intervene in the pathogenesis of SLE. Their promise in SLE treatment lies in their ability to target the fundamental pathophysiological mechanisms underpinning this condition and regulate immune system responses. However, it is imperative to accumulate more comprehensive data regarding the clinical efficacy and safety of this innovative treatment approach. The thorough evaluation of this class of drugs through additional clinical trials and randomized controlled trials holds the potential to enhance the quality of life for SLE patients and positively influence the disease's course. In summary, it can be concluded that the search for new and effective treatments for SLE is ongoing, and JAKinibs are expected to play a crucial role in this quest.

Keywords: Systemic lupus erythematosus, JAKinibs, tofacitinib, baricitinib, upadacitinib, phase

INTRODUCTION

Systemic lupus erythematosus (SLE) is a multisystemic inflammatory rheumatic disease that is considered the prototype of autoimmune diseases. Complex genetic interactions, hormonal factors, and environmental triggers are involved in SLE pathogenesis. During the initial years following the characterization of this disease, high morbidity and mortality rates prevailed because of the limited availability of effective treatment options. The expanding body of knowledge concerning disease pathogenesis and advancements in drug technology have ushered in new treatment options and strategic approaches (1). Among the pivotal cytokines involved in the pathogenesis of SLE, type 1 interferon (IFN) plays a crucial role (2). A relatively recent addition to the therapeutic arsenal, Janus kinase inhibitors (Jakinibs) act by blocking the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway and have shown significant efficacy in treating various inflammatory rheumatic diseases, particularly rheumatoid arthritis (RA) (3). These orally administered molecules bind to type I and II cytokine receptors, inhibiting the intracellular response of cytokines and effectively modulating multiple cytokines implicated in the pathogenesis of SLE. Consequently, the use of Jakinibs for treating SLE has gained prominence recently (4). In this review, we summarize current research and

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data regarding the use of Jakinib therapies for treating SLE, providing valuable insights into this evolving field.

JAK/STAT Pathway in SLE Pathogenesis

SLE presents with various abnormalities in both innate and acquired immunity, contributing to the complex pathogenesis of autoimmune and autoinflammatory changes. Within this context, numerous proinflammatory cytokines exhibit irregularities in SLE, including type 1 IFN, interleukin (IL)-2, IL-4, IL-6, IL-13, IL-15, IL-17, IL-23, and IL-31 (5). These cytokines play a pivotal role in activating the JAK/STAT pathways in dendritic cells and initiating proliferation mechanisms in T and B lymphocytes. The use of jadinii treatment strategically intervenes by blocking the JAK/STAT pathway, setting in motion a series of intricate mechanisms. This blockade effectively inhibits the activation of B cells, forming the fundamental basis for the efficacy of these drugs for treating SLE.

JAK Inhibitors

Jakinibs, referred to as targeted synthetic (non-biological) disease-modifying antirheumatic drugs (tsDMARDs) within the field of rheumatology, play a pivotal role in the management of rheumatic disorders. DMARDs constitute a diverse class of therapeutic agents renowned for their dual capability to alleviate symptoms by directly intervening in the underlying pathogenic processes and to impede or slow the progression of the disease, thereby offering effective symptom control. Within this category, Jakinibs exert their influence by primarily targeting JAK proteins. JAKs constitute a family of tyrosine kinases that associate with the cytoplasmic domains of transmembrane type 1 and type 2 cytokine receptors. Upon ligand engagement, such as by cytokines or growth factors, JAKs bound to the receptor become activated, triggering receptor phosphorylation (6,7). Subsequently, this activation cascades into the phosphorylation of STATs, leading to their translocation into the nucleus. This intricate sequence of events culminates in the induction of cellular responses, encompassing processes such as proliferation, differentiation, migration, apoptosis, and immune modulation, orchestrated through the activation of various genes. The JAK family encompasses four isoforms, namely JAK1, JAK2, JAK3, and tyrosine kinase inhibitor 2 (TYK2), whereas the STAT family comprises seven distinct members. Different JAK complexes transduce specific cytokine signaling pathways. For instance, the JAK1-JAK3 complex, vital for lymphocyte proliferation and homeostasis, is stimulated by cytokines such as IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21, whereas IL-6 signaling is transduced by a combination of JAK1, JAK2, and TYK2 (6,7). Jakinibs, through their pharmacological action, bind to JAKs and interfere with their phosphorylation, thereby modulating the ensuing cellular responses, as previously elucidated. Notably, each Jakinib exhibits a distinct primary target and selectivity profile. Tofacitinib, baricitinib, ruxolitinib, brepocitinib, and ficitinib are considered non-selective in their actions. In contrast, filgotinib, upadacitinib, and solcitinib demonstrate a selective preference for JAK1, whereas decernotinib specifically targets JAK3. In addition, deucravacitinib exerts selective inhibition of TYK2, and R333 offers topical inhibition of JAK1-3/spleen tyrosine kinase (SYK) (7) (see Figure 1 for a visual representation).

Preclinical and Clinical Investigations of Jakinibs for SLE

Tofacitinib: Tofacitinib, a non-selective TYK that targets the JAK1-JAK3 pathway, has gained approval for the treatment of RA, psoriatic arthritis (PsA), and ulcerative colitis (8). In the context of lupus pathogenesis, tofacitinib has demonstrated its efficacy in reducing proinflammatory cytokines that play a pivotal role in the development of lupus (9,10). This reduction is achieved by the suppression of IFN-dependent JAK-STAT-related genes, as evidenced by the female lupus mouse model (MRL/lpr) that exhibits typical SLE features (11). Moreover, experimental studies have highlighted tofacitinib's potential benefits within the vascular system, attributed to its modulation of the innate and acquired immune systems, along with its positive impact on lipoprotein profiles (11,12). The reduction of antinuclear antibody (ANA), anti-dsDNA titers, and proteinuria has also been observed in these studies (11,13,14). A double-blind phase 1 safety study involving tofacitinib found that its use at a dosage of 5 mg twice daily was well-tolerated and safe among patients with SLE (15). Secondary results from this study suggested a potential association with increased high-density lipoprotein levels and a decrease in arterial stiffening via STAT4, which could contribute to the prevention of early atherosclerosis often seen in SLE (15). Case reports in the literature have outlined the efficacy of tofacitinib in SLE. Notably, its use in a case of RA (SLE complicated with RA) resistant to steroids and methotrexate led to decreased C-reactive protein (CRP) levels in the short term and a reduction in high anti-dsDNA titers and clinical lupus disease activity index in the long term. No side effects were reported during the study (16). In a similar study, tofacitinib at 10 mg daily showed success in managing skin, joint, and kidney involvement in two patients with RA who had not responded to multiple other drugs. It was also suggested as an alternative treatment option as a steroid-sparing agent (17). In a case series involving 10 patients with SLE, the addition of 10 mg/day tofacitinib to their existing immunosuppressive treatment effectively addressed clinical symptoms such as arthritis and rash, although no significant changes were observed in serological parameters (18). Other case

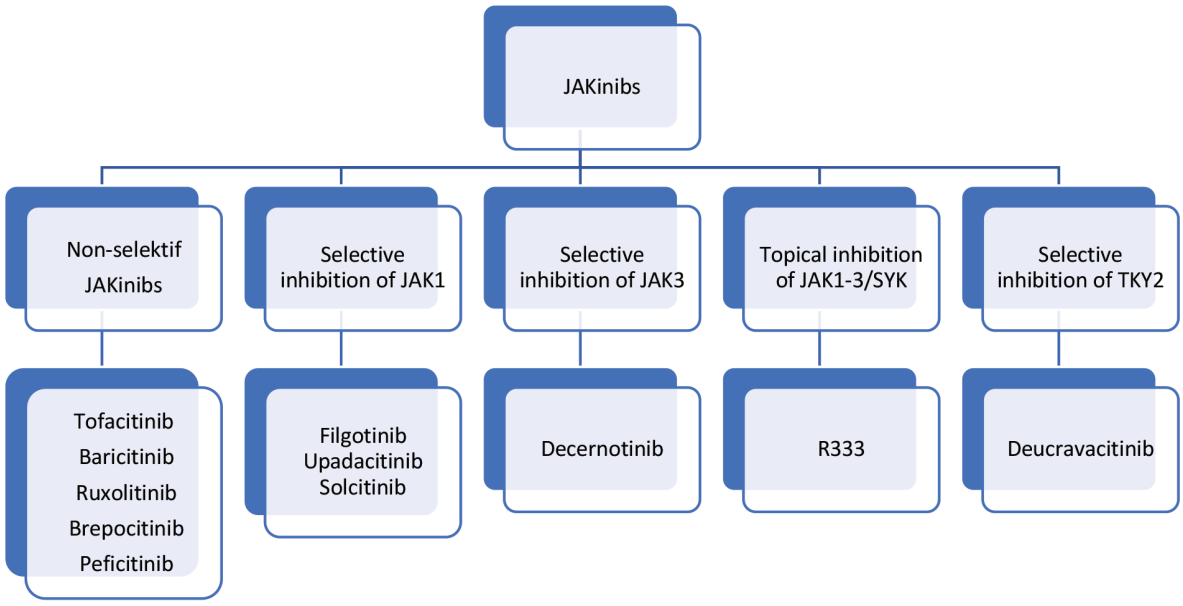

Figure 1. Jakinibs and their targets
JAK: Janus kinase, Jakinibs: JAK inhibitors, SYK: Spleen tyrosine kinase, TKY2: Tyrosine kinase 2

reports have illustrated complete remission in an SLE patient with Chillblain lesions resistant to standard treatments (19), decreased cutaneous lupus erythematosus (CLE) disease area and severity index (CLASI) scores in cases of CLE unresponsive to immunosuppressive therapy (20), remission of skin lesions in a patient with refractory bullous SLE (21), and successful treatment of resistant alopecia due to SLE with 10 mg/day tofacitinib for 2 years, all without reported side effects (22). Nevertheless, it is important to interpret these studies cautiously, given their small sample sizes and the limited number of controlled studies. Further data are needed to establish efficacy and safety profiles conclusively (see Table 1 for the clinical studies of Jakinibs).

Baricitinib: Baricitinib is a selective, reversible inhibitor of JAK1 and JAK2 (23), and it has obtained Food and Drug Administration (FDA) approval for use in active RA unresponsive to TNF inhibitors and alopecia areata. In a study conducted by Lee et al. (24) using a lupus mouse model (MRL/lpr), the effects of baricitinib on renal involvement in SLE were thoroughly explored. Over an 8-week investigation, baricitinib exhibited its effectiveness in averting renal inflammation by inhibiting abnormal B cell activation and reversing podocyte damage (24). Several publications have explored the clinical efficacy of baricitinib through case reviews. Notably, in a treatment-refractory patient presenting with frontal fibrosing alopecia in conjunction with subacute CLE (SCLE), nearly complete recovery was observed following 6 months of baricitinib treatment (25). Zhan et al. (26) reported the achievement of complete remission in a patient with Blaschkoid linear lupus erythematosus, an uncommon form of SCLE, through 4 mg daily baricitinib for 8 months. Fornaro et al. (27) obtained remission with an 8-week course of 4 mg baricitinib treatment in a patient who had developed a resistant papulosquamous rash in the context of SLE.

Subsequently, some controlled studies associated with baricitinib have been published. In a multicenter international double-blind, placebo-controlled phase 2 study conducted by Wallace et al. (28), SLE patients presenting with skin and joint involvement were randomized into three groups: 2 mg, 4 mg, and placebo. This 24-week study encompassed 315 patients, with the primary endpoint focusing on improvements in arthritis and rash as assessed by the SLE Disease Activity Index-2000 (SLEDAI-2K) index. The baricitinib 4 mg group outperformed the placebo group in relieving the signs and symptoms of active SLE (28). The study noted one case of deep vein thrombosis and six incidents of serious infections in the 4 mg baricitinib group, with no occurrences of mortality, malignancy, or major adverse cardiovascular events reported in any patient (28). In an analysis of the data from this study conducted by Dörner et al. (29), it was observed that patients with positive anti-dsDNA antibodies at baseline who were treated with 4 mg baricitinib exhibited a rapid, sustained, and significant reduction in antibody titers compared with the placebo group. In the SLE-BRAVE-I study, a multicenter, double-blind, randomized, placebo-controlled phase 3 investigation, active SLE patients were randomized into three arms: baricitinib 4 mg once daily, baricitinib 2 mg once

daily, and placebo, with a follow-up duration of 52 weeks (30). Among the 760 participants, the baricitinib 4-mg arm achieved the primary endpoint of the SLE Response Index-4 (SRI-4) at week 52. However, the study did not reach statistical significance in secondary endpoints such as glucocorticoid dose reduction and lupus low disease activity, falling short of expectations in terms of efficacy (30). In a 52-week, phase 3 placebo-controlled SLE-BRAVE-II study, which continued these investigations with 775 patients equally allocated to 4 and 2 mg doses of baricitinib and placebo, secondary endpoints such as SRI-4, the primary endpoint, and corticosteroid dose reduction were not attained, failing to support the notion of baricitinib as a prospective treatment for SLE patients (31). In summary, the efficacy of baricitinib in patients with SLE has not been conclusively established in controlled studies.

Ruxolitinib: Ruxolitinib, an oral TYK with a notable affinity for JAK1 and JAK2, has obtained FDA approval in various forms (5, 10, 15, 20, and 25 mg) for the treatment of myelofibrosis, hydroxyurea-refractory polycythemia vera, and steroid-refractory graft-versus-host disease (32,33). Preclinical studies have indicated significant improvements in the skin findings of MRL/lpr mice, a well-established animal model of lupus, following the administration of ruxolitinib (34). However, it is important to note that these studies did not show regression in autoantibody levels, lymphadenopathy, or splenomegaly (34). In another experimental investigation, ruxolitinib was reported to reduce the levels of cytokines such as CXCL10, CXCL9, and MxA, which are implicated in CLE, as observed in cutaneous lupus keratinocyte cultures and a 3D human epidermis model of cutaneous lupus (35). Wenzel et al. (36) demonstrated the efficacy of ruxolitinib in a case of treatment-refractory chilblain lupus and proposed that JAK/STAT inhibition holds promise as an approach for the treatment of cutaneous lesions.

Brepocitinib: Brepocitinib is a small-molecule TYK2/JAK1 inhibitor, and topical formulations are currently undergoing phase studies in atopic dermatitis (37). Notably, a Phase IIb study focusing on SLE, initiated in 2019, remains ongoing (38).

Filgotinib: Filgotinib, an oral small-molecule TYK with selective JAK1 inhibition, has gained approval in the European Union and Japan for the treatment of DMARD-refractory moderate to severe RA (39). In a Phase II randomized, double-blind, multicenter study conducted by Baker et al. (40), 32 biopsy-diagnosed lupus patients with membranous nephropathy were randomized 1:1 to receive filgotinib and lanraplenib, with a 52-week follow-up period. Despite patient dropouts for various reasons, 9 patients completed the study. The primary endpoint of the study was the regression in the amount of proteinuria at week 16. In the filgorinib arm, a notable average 50% reduction in 24-h urine protein was observed. Although the study sample size was limited, it was suggested that filgotinib may present

Table 1. Clinical studies conducted on Jakinibs for the treatment of SLE

Jakinibs	Type of lupus	Study ID, design	Number of patients	Study period	Dose of drug	Primary endpoint
Tofacitinib	SLE	NCT02535689, Phase 1 double blind	30	12 weeks	5 mg twice daily	SLEDAI/2K
Tofacitinib	CLE	NCT03288324, Phase 1b/2 open label	20	72 weeks	5 mg twice daily	CLASI-A
Baricitinib	SLE	Phase 2 controlled	315	24 weeks	2 mg, 4 mg	SLEDAI/2K
Baricitinib	SLE	Phase 2 controlled	315	24 weeks	2 mg, 4 mg	Titer of antidsDNA
Baricitinib	SLE	Phase 3 controlled BRAVE-I	760	52 weeks	2 mg, 4 mg	CLASI-A
Brepocitinib	SLE	Phase 2b double blind	349	52 weeks	15 mg, 30 mg	SRI4
Filgotinib	SLE	Phase 2 double blind	9	52 weeks	200mg	decrease in proteinuria
Filgotinib	CLE	Phase 2b double blind	47	12 weeks	200mg	CLASI-A
Upadacitinib	SLE	Phase 2 controlled	341	48 weeks	30mg	SRI4 10 mg – steroid dose
Solcitinib	SLE	Phase 2 controlled	50	12 weeks	50 mg, 100 mg, 200 mg	SLEDAI
Deucravacitinib	SLE	Phase 2 controlled	363	32 weeks	6 mg, 12 mg	SRI4

Jakinibs: JAK inhibitors, SLE: Systemic lupus erythematosus, ID: Identification, CLE: Cutaneous lupus erythematosus, SLEDAI/2K: Systemic lupus erythematosus disease activity index-2000, CLASI-A; Cutaneous lupus erythematosus disease area and severity index, SRI4: SLE response index

a novel treatment option for lupus-related renal involvement (40). Another Phase 2 study, in which patients with moderate to severe CLE were randomized one-to-one with filgotinib, lanraplenib, and placebo, assessed the primary endpoint as a 5-point improvement in the CLASI-A score. The nilotinib arm achieved this target in 69% of patients at week 12 (versus 50% in the placebo group and 56% in the lanraplenib group). No major side effects were reported during the study, indicating that the drug was well tolerated (41).

Upadacitinib: Upadacitinib, a JAK1-specific second-generation oral small molecule TYK, is used for treating various inflammatory rheumatism diseases such as RA and PsA (42). However, data regarding the use of upadacitinib in SLE are limited. In a case report, upadacitinib was noted to be effective in managing methotrexate-associated nodulosis, granuloma annulare, and arthritis in a female patient with SLE and Jaccoud arthropathy (43).

Solcitinib (GSK2586184): Solcitinib, a selective JAK1 inhibitor originally intended for the treatment of psoriasis and ulcerative colitis (44), faced a setback in a clinical trial intended to investigate its safety, tolerability, efficacy, and pharmacodynamic effects in patients with SLE. Unfortunately, the trial could not be completed because of drug-related drug rash with eosinophilia and systemic symptoms syndrome and elevated liver function tests. Following an analysis of the data from the study, it was determined that the use of this treatment in patients with SLE was not advisable (45,46).

Deucravacitinib: Deucravacitinib is an oral, selective TYK2 inhibitor that has received FDA approval for the treatment of moderate to severe plaque psoriasis (47). There are limited data on the use of this drug in SLE, with only one case report and one controlled study available. In the case of CLE resistant to treatments such as hydroxychloroquine, mycophenolate mofetil, and tacrolimus, complete lesion improvement was reported with a 4-month regimen of 6 mg/day deucravacitinib treatment. Notably, no adverse events were observed in this case (48). Additionally, in an international multicenter randomized trial involving 363 patients with active SLE, participants received deucra visitinib at doses of 3 mg and 6 mg twice daily or 12 mg once daily, with active treatment being compared with a placebo arm. The primary endpoint of the study was the SRI-4 response at week 32. The results indicated a higher number of patients achieving an SRI-4 response in the deucravacitinib arms (3 mg twice daily and 6 mg twice daily) than in the placebo group. While more improvements were observed in patients receiving a single daily dose of 12 mg compared with the placebo, this difference did not reach statistical significance. Importantly, no deaths, opportunistic infections, tuberculosis, or major adverse cardiovascular events were reported among the participants (49).

R333: R333 is a topical inhibitor targeting JAK1-3 and SYK that has been assessed in patients with discoid lupus erythematosus. In this study, 54 patients with discoid lupus erythematosus were randomly assigned to the R333 and placebo groups, and the evaluation of lesions was conducted using computerized planimetry at week 4 compared to baseline. This study did not yield significant results in terms of lesion activity and area change (50).

CONCLUSION

The treatment landscape for SLE remains marked by gaps and unmet needs. A crucial requirement persists for novel therapeutic approaches to effectively address the complexities of this disease. Jakinibs have emerged as a potential treatment option with the capacity to intervene in the pathogenesis of SLE. Their promise in SLE treatment lies in their ability to target the fundamental pathophysiological mechanisms underlying this condition and regulate immune system responses. However, it is imperative to accumulate more comprehensive data regarding the clinical efficacy and safety of this innovative treatment approach. Vital questions, including the identification of SLE patient subgroups that may benefit most from Jakinibs, understanding the potential side effects, long-term effects, and feasibility of combining them with other treatment modalities, demand answers. Nevertheless, the potential of Jakinibs for treating SLE remains a focus of future research. The thorough evaluation of this class of drugs through additional clinical trials and randomized controlled trials holds the potential to enhance the quality of life of patients with SLE and positively influence the disease course. In summary, the quest for new and effective treatment options for SLE continues, with Jakinibs poised to assume a pivotal role in this endeavor.

Footnotes

Authorship Contributions

Concept: T.D.Y., Design: T.D.Y., Data Collection or Processing: İ.S., Ananlysis or Interpretation: İ.S., Literature Search: T.D.Y., İ.S., Writing: T.D.Y., İ.S.

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INVITED REVIEW

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JANUS KINASE INHIBITORS IN THE TREATMENT OF SYSTEMIC VASCULITIDES

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Abstract

Glucocorticoids (GCs) are still the mainstay of treatment in systemic vasculitides. Immunosuppressive agents such as cyclophosphamide, rituximab, azathiopurine, and mycophenolate mofetil are chosen as steroid sparing agents according to the type of vasculitis. Biologic treatments such as tumor necrosis factor inhibitors and tocilizumab are used in particularly large vessel vasculitis (LVVs) for refractory patients. Janus kinase (JAK)-signal transduction activator of transcription (STAT) pathway activation is involved in the pathogenesis of several inflammatory diseases. JAK inhibitors were also approved for the treatment of rheumatoid arthritis (RA), psoriatic arthritis, and ulcerative colitis. However, there are very limited data including mostly case series and open studies with JAK inhibitor usage in systemic vasculitides. Current data mostly come from LVVs and some from Behçet's disease. In the light of current data, we are quite far from suggesting the common usage of JAK inhibitors in systemic vasculitides. JAK/STAT pathway inhibition also may cause severe complications in these group of patients treated with higher dose GC and more potent immunosuppressives compared to RA and ankylosing spondylitis. Although we have limited data showing the efficacy of the JAK inhibitors for systemic vasculitis treatment, they may be used in patients refractory to standard immunosuppresives. JAK inhibitors seem to be promising therapeutic agents, especially for treating LWs. There are ongoing controlled studies with tofacitinib and upadacitinib in TAK; upadacitinib and baricitinib in giant cell arteritis. Larger and controlled studies will clarify the efficacy and safety of JAK inhibitors in the treatment of systemic vasculitides.

Keywords: JAK inhibitors, treatment, vasculitis

INTRODUCTION

Vasculitides are chronic systemic inflammatory diseases characterized by inflammation of the blood vessel wall. The etiopathogenesis of vasculitis is poorly understood. Among different classification efforts, definition according to the involved vessel size is still the most widely accepted and used one (1). Other than involved vessel size, systemic vasculitis also differ in terms of epidemiology, clinical manifestations, treatment, and prognosis. Glucocorticoids are still the mainstay of treatment for systemic vasculitis. Immunosuppressive agents such as cyclophosphamide, rituximab, azathiopurine, and mycophenolate mofetil are chosen as steroid-sparing agents according to the vasculitis type. Biologic treatments, such as tumor necrosis factor inhibitors (TNFi) and tocilizumab, are used, especially in large vessel vasculitis (LVVs) for refractory patients.

Cytokine receptors are divided into several superfamilies according to their shared structural elements (2). Janus kinase (JAK) and signal transduction activator of transcription (STAT) are the main players of a cellular transduction pathway named JAK/STAT. The JAK/STAT pathway is an important pathway involved

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in intracellular signal transduction. Type I and II cytokines use this pathway. They are involved in many physiological and pathological processes. JAKs are members of the intracellular non-receptor protein tyrosine kinase family, and they are able to transfer a phosphate residue from adenosine triphosphate to another substrate. When binding to their membrane receptors, they are activated and phosphorylate STATs to form a phosphorylated (p)-STAT dimer that is capable of migrating into the nucleus and inducing DNA transcription. Four JAKs and seven STATs were identified. Different combinations among these isoforms of the JAK/STAT pathway determine the specificity of signal transduction. Many pro- and anti-inflammatory mediators [interleukin (IL)-2, IL-6, IL-21, IL-12, IL-35, interferon (IFN)-α, IFN-γ, IL-22, IL-10] and growth factors such as erythropoietin, granulocyte-colony stimulating factor, and granulocyte-monocyte-colony stimulating factorsignal through the JAK/STAT pathway (3). JAK/STAT pathway activation is involved in the pathogenesis of several inflammatory diseases. JAK inhibitors (JAKi) have also been approved for the treatment of rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis. Currently used JAKi are not selective for one specific isoform and mostly bind with different affinities to one or more subtypes. Different grades of affinity to different subtypes cause the lack of sensitivity and most frequent adverse effects such as cytopenia as a cause of JAK2 inhibition (2). Data supporting the role of the JAK/STAT pathway in vasculitis pathogenesis, the use of JAKi in systemic vasculitis are mostly focused on LVVs and Behçet's Disease (BD). In this review, we aimed to summarize the data of JAK inhibitor usage for treating systemic vasculitis.

Large Vessel Vasculitis

Giant cell arteritis (GCA) and Takayasu arteritis (TAK) are the main types of LVVs and are characterized by chronic granulomatous inflammation of the vessel wall (4). The pathophysiology of LVVs is poorly understood. However, Th1 and Th17 immune-mediated responses and an imbalance between Th17 and regulatory T (Treg) cells have been previously shown in LVVs. IFN-γ and IL-17 derived from Th1 and Th17 cells are the dominant cytokines (5-9). While $CD4^+$ T cells and macrophages are dominant in granulomatous lesions of GCA, $CD8^+$ T and natural killer cells are also involved in TAK (7). In GCA pathogenesis, most involved cytokines, such as IL-6, IL-12, IFN-γ, IL-17, and IL-23, signal via the JAK-STAT pathway (10). High levels of STAT1 expression were also shown in histopathological with experimentally induced vasculitis model of human temporal arteries grafted in immunodeficient mice (11). In another experimentally induced vasculitis model of GCA, STAT1 and STAT2-dependent target genes were found to be strongly upregulated, and tofacitinib (TOF) prevented adventitial microvascular angiogenesis, decreased hyperplastic intima outgrowth, and tissue-resident memory T-cells (12). In light of these data, it may be hypothesized that their pivotal role in TAK is also another LVVs.

There are only case reports and open studies showing the efficacy of JAKi in LVVs treatment. Li et al. (13) reported 5 refractory TAK patients treated with TOF. Four of the five patients responded well, and acute phase reactants were normalized. No adverse events were reported in the study. Régnier et al. (14) reported the efficacy of baricitinib in 2 patients and ruxolitinib in 1 patient with TAK. Baricitinib was reported as effective in a patient with refractory LVVs (including biologics) overlapping features of TAK and GCA (15). In a recent systematic review, 8 case reports of TAK patients treated with TOF were reviewed. Clinical response and normalization of acute phase response were achieved in 5 of 8 patients.

Angiography had been performed in 4 patients, and reported stable in all. Glucocorticoid dose could be decreased in 6 of 6 patients having the clinical data (16). In a prospective cohort including 53 active TAK patients, TOF and methotrexate (MTX) treatment were compared during follow-up period of 12 months. TOF was found superior to MTX for the achievement of complete remission, prevention of relapse, and tapering of the glucocorticoid dosage (17). In a recent open prospective study, the efficacy and safety of leflunomide (n=35) versus TOF (n=32) were compared in 67 active TAK patients. The observation period was 12 months. Leflunomide and TOF were found to be comparable regarding achieving remission, relapse rate, decrease in acute phase response, and GC dosage in TAK (18).

Sanada et al. (19) reported that upadacitinib was effective in patients with GCA and suggested that it may be a promising agent for remission induction and maintenance therapy in GCA. There are very few case reports with barrictinib reporting efficacy in refractory GCA patients (15,20). A recent Swedish case series including 15 GCA patients (14 baricitinib, 1 TOF) presented the real-life experience of JAKi treatment. All patients were unresponsive to glucocorticoid therapy alone or inappropriate for IL-6-blocking treatment. JAKi were well tolerated without any safety signals, and all patients remained on JAKi for ≥6 months. The mean duration of treatment was 19 months. Significant decreases in C-reactive protein levels and daily glucocorticoid dosage were found after JAKi treatment (21). Koster et al. (22) reported a prospective, open-label, pilot study of baricitinib in 15 GCA patients with a median of 1 (1-2) prior relapse. Fourteen patients completed 52 weeks of baricitinibtherapy. At the end of the study duration, 14/15 (93%) patients had ≥1 adverse event. The most frequent adverse event was infection not requiring

antibiotics (n=8). One patient discontinued baricitinib because of an adverse event. Only 1 of 14 (7%) patients experienced relapse during the study. The remaining patients discontinued glucocorticoid treatment and achieved remission during the study duration (22).

Behçet's Disease

Tulunay et al. (23) reported that the JAK1/STAT3 signaling pathway is activated in BD, possibly through the activation of Th1/Th17-type cytokines such as IL-2, IFN-γ, IL-6, IL-17, and IL-23. In a recent multi-ethnic GWAS study, *IFN-γ receptor-1 (IFNGR1)* gene was shown to be a susceptibility locus for BD (24). IFNGR1 encodes the binding subunit of the IFN-γ receptor, and the binding of IFN-γ stimulates the activation of the JAK-STAT pathway (24).

Transcriptome analysis also showed that Th17-related genes and type I IFN-inducible genes were upregulated and JAK/STAT signaling was activated through Th1/Th17 cytokines in patients with BD (25).

For severe and/or refractory BD, TNF-alpha inhibitors are suggested beyond glucocorticoids and immunosuppressant (26). However, there is still a subgroup of refractory BD patients unresponsive to TNFi. There are some data showing that JAKi may be promising agents, especially in this group of patients. In a case series with 13 (seven male and six female) patients, the efficacy and safety of TOF in refractory BD were recently reported. There were patients with active vascular/cardiac (n=5), gastrointestinal (n=6) and articular (n=2) involvements in this study. After a median follow-up of 8 (5.5-19) months, patients with cardiovascular and articular involvement achieved both clinical and radiological remission. The erythrocyte sedimentation rate and C-reactive protein level significantly decreased. However, among patients with gastrointestinal involvement, intestinal ulceration healed in one patient and persisted in 5 patients. This study reported that active BD patients with vascular and articular involvement responded well to TOF without any safety signal. However, active BD patients with gastrointestinal involvement responded poorly to TOF treatment (27).

Small Vessel Vasculitis

Granulomatosis with polyangiitis, microscopic polyangiitis (MPA), and eosinophilic granulomatosis polyangiitis (EGPA) are the anti-neutrophil cytoplasm antibody-associated vasculitides (AAV). AAVs are necrotizing small vessel vasculitis characterized by pulmonorenal involvement, ocular, ears-nose-throat, skin, gastrointestinal, and neurological involvement. It was previously shown that T cells and associated cytokines such as IL-6, IL-10, IL-12, IL-23, and type I IFNs play an important role in AAV pathogenesis via JAK/STAT pathway activation (28,29). Imatinib mesylate, which is a tyrosine kinase inhibitor, was recently reported to be effective in the treatment of a case with EGPA (30). Recently, a case series including 10 patients with AAV (6 with GPA, 3 with MPA and 1 with EGPA) reported the efficacy and safety of TOF. Complete remission was achieved in 9 of 10 patients. One patient achieved partial remission. There was no relapse during the follow-up of a median of 9.5 months. TOF was found effective in non-organ-threatening AAV patients without any safety signal (31).

Medium Vessel Vasculitis

There are very few data on the use of JAKi in medium vessel vasculitis treatment. Rimar et al. (32) reported a case with systemic polyarteritis nodosum (PAN) treated effectively with TOF in 2016. Zhu et al. (33) reported a refractory cutaneous PAN patient who responded well to TOF. Roy et al. (34) recently reported 4 cases with cutaneous PAN. In this report, 2 of 4 cases used TOF as the primary therapy without glucocorticoids after diagnosis. Remission was achieved in all four patients.

CONCLUSION

Because the JAK/STAT pathway is involved in most of the inflammatory processes in rheumatologic diseases, it is not surprising that JAKi may be effective in patients with refractory vasculitis. However, there are very limited data, including mostly case series and open studies with JAKi usage in systemic vasculitis. Current data mostly comes from LWs and some from. In the light of current data, we are quite far from suggesting the common usage of JAKi in systemic vasculitides. JAK/STAT pathway inhibition can cause severe complications in this group of patients treated with higher dose glucocorticoid and more potent immunosuppressives compared with RA and ankylosing spondylitis. The serious infection risk with JAKi is similar to that with TNFi. However, serious infection risk and herpes zoster development risk are higher with TOF than with TNFi. JAKi use ≥1 year was reported to be associated with increased venous thromboembolism (35). The increase in venous thrombosis risk should be kept in mind while managing patients with BD, which mainly involves venous vessels and leads to venous thrombosis. Surprisingly, there are few case reports of vasculitis induced after JAKi usage. Vasculitis developed after TOF usage in 2 cases and after ruxolitinib, which targets JAK1 and JAK2 (36-38). However, further research and more evidence are needed to assess whether there is a clear causality between vasculitis development and JAKi usage.

Although we have limited data showing the efficacy of JAKi for systemic vasculitis treatment, they may be used in patients refractory to standard immunosuppressives. JAKi appear to be promising therapeutic agents, especially for treating LWs. There are ongoing controlled studies with TOF and upadacitinib in TAK andupadacitinib and baricitinib in GCA. Larger and controlled studies will clarify the efficacy and safety of JAKi in the treatment of systemic vasculitis.

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INVITED REVIEW

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VASCULAR HEALTH IN BEHÇET'S DISEASE: THE ROLE OF UROTENSIN II AND SCLEROSTIN

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Abstract

Aim: Behçet's disease (BD) is characterized by the presence of skin and mucosal lesions, systemic inflammation, and vasculitis. The objective of this study was to examine changes in urotensin II (UII) and sclerostin levels in patients with BD and to assess their correlation with atherosclerosis.

Material and Methods: The study population comprised 32 patients with BD, 39 with systemic lupus erythematosus, and 30 healthy controls. A series of clinical examinations were conducted, and blood samples were obtained to analyze UII and sclerostin levels by enzyme-linked immunosorbent assay. The carotid intima-media thickness (cIMT) was evaluated using Doppler ultrasonography.

Results: UII levels were significantly elevated in the BD group compared with the other groups ($p<0.001$). Conversely, sclerostin levels were markedly diminished in the BD group ($p<0.001$). In the BD group, UII levels were positively correlated with cIMT ($r=0.513$, $p<0.001$), whereas sclerostin levels were negatively correlated with cIMT ($r=-0.270$, $p=0.020$).

Conclusion: Elevated UII and reduced sclerostin levels are crucial biomarkers of atherosclerosis risk in individuals with BD. These findings help to elucidate the cardiovascular complications associated with BD.

Keywords: Behcet disease, atherosclerosis, urotensin, sclerostin

INTRODUCTION

Behçet's disease (BD) is a multisystemic chronic inflammatory vasculitis characterized by skin and mucosal lesions. Although its etiopathogenesis is not fully understood, it involves major organs such as the eyes, joints, central nervous system, and gastrointestinal system. BD can affect any vessel and artery of any size. Endothelial dysfunction is a hallmark of BD and is considered an initial lesion in the development of atherosclerosis. Furthermore, the relationship between BD and atherosclerosis is emphasized by the observation that patients with BD frequently display elevated levels of inflammatory markers and endothelial progenitor cells, which are linked to disease activity and vascular complications (1). This inflammatory state not only exacerbates endothelial dysfunction but also promotes atherogenesis, suggesting that individuals with BD may be at increased risk of cardiovascular disease, including myocardial infarction and stroke (2).

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The presence of these vascular complications not only signifies a poor prognosis but also suggests a potential link between BD and increased cardiovascular risk, including atherosclerosis (3). For instance, the increased thickness of the epicardial adipose tissue and carotid intima-media thickness (cIMT) observed in patients with BD are indicative of heightened cardiovascular risk factors associated with atherosclerosis (4).

Urotensin II (UII) is a cyclic undecapeptide that has attracted considerable attention for its significant role in cardiovascular physiology and pathology, particularly in the context of atherosclerosis. The urotensinergic system, which encompasses the UII and its receptor (UTR), has been linked to several cardiovascular disorders, including atherosclerosis. In this context, UII has been shown to play a role in vascular remodeling and endothelial dysfunction. Some studies have shown that UII enhances human macrophage foam cell formation and vascular smooth muscle cell proliferation (5). There are studies reporting the association of this molecule with BD, diabetes, diabetic retinopathy, and systemic sclerosis. Sclerostin, a glycoprotein primarily secreted by osteocytes, plays a significant role in the regulation of bone metabolism and has emerged as a critical factor in vascular health, particularly with regard to atherosclerosis. Its primary function as an inhibitor of the Wnt signaling pathway has implications for both bone and vascular tissues, influencing processes such as cell proliferation, migration and calcification (6). The relationship between sclerostin and atherosclerosis is complex, and various mechanisms contribute to vascular calcification and cardiovascular risk (7).

The objective of this study was to determine the changes in UII and sclerostin levels and their correlation with atherosclerosis in patients with BD.

MATERIALS AND METHODS

The present study included patients diagnosed with BD and systemic lupus erythematosus (SLE) and healthy controls. The study was conducted in accordance with the ethical standards determined by the Fırat University Non-Interventional Research Ethics Committee and the Helsinki Declaration (approval no: 350179, date: 26/09/2019). Patients were provided with comprehensive information about the study and were included in the study only after providing informed consent to participate. All participants were evaluated comprehensively, including a clinical examination and medical history assessment.

cIMT measurements were conducted using Doppler ultrasonography. This non-invasive technique is widely employed for the early detection of atherosclerosis and cardiovascular diseases (8). cIMT was measured at the thickest points of both carotid arteries and evaluated independently by two experienced physicians. Plaque was defined as localized thickening of the cIMT compared to adjacent wall segments, with a thickness of at least 1.5 mm, protruding into the lumen, and consisting of calcified or non-calcified components. The cIMT of the right and left common carotid arteries was measured within a 1 cm segment proximal to the dilation of the carotid bulb. All measurements were performed manually on the static images obtained during sonographic scanning.

The levels of UII and sclerostin were quantified from blood samples collected from the patients. The measurement of UII and sclerostin was conducted using a specific and sensitive enzyme-linked immunosorbent assay kit, which was provided by a commercial source.

Statistical Analysis

Analyses were conducted using the SPSS 22 software package. Descriptive data are presented as n, % for categorical data, and mean ± standard deviation (mean ± SD) for continuous data. The chi-square test (pearson chi-square) was used to compare categorical variables between groups. The suitability of continuous variables for normal distribution was evaluated using the Kolmogorov-Smirnov test. The Student's t-test was used to compare normally distributed variables between the two groups, and the Mann-Whitney U test was used for non-normally distributed variables. One-way analysis of variance was used for more than two normally distributed variables, and the Kruskal-Wallis test for those not normally distributed. The Spearman correlation test was used to examine the relationship between continuous variables. A p-value of <0.05 was considered statistically significant.

RESULTS

Demographic Data and General Characteristics

A total of 101 participants were included in the study. Of the participants, 32 were diagnosed with BD, 39 with SLE, and 30 were healthy controls. No statistically significant differences were observed between the groups regarding gender and age (Table 1). A higher proportion of individuals with BD (28.1%) and SLE (15.4%) were smokers than the control group (0%). A significant difference was identified between the three groups in terms of smoking status ($p=0.004$). Additionally, notable discrepancies were observed in systolic ($p<0.001$) and diastolic ($p<0.001$) blood pressure between the groups. This disparity can be attributed to the divergence between the SLE and other groups (Table 1).

Laboratory Parameters

Significant differences in sedimentation values were observed between the groups. However, only the SLE and healthy control groups exhibited statistically significant differences (p=0.001). Significant differences were observed in C-reactive protein (p=0.002), urotensin (p=0.005) and sclerostin levels (p<0.001) between the groups. These differences were attributed to the comparison between the control group and the other two groups (Table 2).

Differences within the Different Behçet's Clinical Involvements A notable disparity was observed in UII concentrations among the different BD subgroups (p=0.001). The aforementioned discrepancy was identified between the articular and vascular groups, as well as between individuals in the mucocutaneous, uveitis, and neuro behçet groups. The UII levels of smokers were significantly higher than those of non-smokers (p=0.013). Additionally, a notable discrepancy was observed in sclerostin levels between the BD and non-BD groups. This disparity was attributed to the contrast between the vascular and mucocutaneous, uveitis, and neuro Behçet groups (p=0.023) (Table 3).

Table 1. Comparison of demographic data of the groups

	BD (n=32)	SLE (n=39)	HC (n=30)	p-value
Gender (Females), n (%)	14 (43.8)	26 (66.7)	18 (60)	0.143*
Mean age (years)	40.4±11.7	39.0±12.1	35.5±11.0	0.236**
BMI, kg/m^2	24.6±4.7	24.8±4.2	25.1±5.0	0.894**
SBP, mmHg	114.8±18.8^a	124.7±19.9^b	107.8±10.6^a	**<0.001****
DBP, mmHg	71.1±11.0^a	81.3±14.0^b	67.0±7.9^a	**<0.001****

*Chi-square analysis, **One-way analysis of variance (ANOVA) analysis was applied. ^{a,b}Group where the difference originated, BD: Behçet's disease, SLE: Systemic lupus erythematosus, HC: Healthy controls, BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure

Table 2. Comparison of laboratory parameters among the study groups

	BD (n=32)	SLE (n=39)	HC (n=30)	p-value
Total cholesterol (mg/dL)	173.4±39.4	181.3±49.8	169.0±32.5	0.516*
Triglyceride (mg/dL)	122.1±44.1	135.7±65.3	110.8±67.3	0.264*
LDL (mg/dL)	108.8±36.6	113.9±41.5	93.7±20.5	0.102*
HDL (mg/dL)	46.3±9.8	46.4±13.5	60.7±35.4	0.116**
ESR (mm/h)	19.0±18.6$^{a.b}$	28.2±21.0^a	11.8±8.7^b	**0.001***
CRP (mg/L)	5.2±5.6^a	7.6±9.1^a	3.9±1.7^b	**0.002****
GFR (mL/min)	86.2±15.3	88.7±5.1	90.0±.0	0.088**
Urotensin (ng/mL)	14.3±14.8^a	10.8±11.6^a	4.7±2.8^b	**0.005****
Sclerostin (ng/mL)	14.4±7.8^a	11.2±7.2^a	25.6±25.0^b	**<0.001***

*One-way ANOVA analysis, **Kruskal-Wallis test was performed. ^{a,b}Group where the difference originated, BD: Behcet disease, SLE: Systemic lupus erythematosus, HC: Healthy control, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, GFR: Glomerular filtration rate

Correlation Analysis

A significant positive correlation was observed between urotensin levels and several cardiovascular risk factors, including duration of diagnosis, systolic and diastolic pressure, right and left cIMT, Framingham vascular age, and vascular risk. A significant inverse correlation was observed between urotensin levels and the glomerular filtration rate (GFR). A significant negative correlation was identified between sclerostin and age, body mass index (BMI), systolic and diastolic pressure, right and left cIMT, total cholesterol, low-density lipoprotein (LDL) and Framingham vascular age.

A significant difference in UII levels among the BD groups was due to differences between the articular and vascular group and the mucocutaneous, uveitis, and neuro group (p=0.001). UII levels in smokers were significantly higher than in non-smokers (p=0.013). Sclerostin levels differed significantly among the BD groups, particularly between the vascular group and the mucocutaneous, uveitis, and neuro Behçet group (p=0.023). Sclerostin levels were significantly lower in those with a cardiovascular history (p=0.010) and those using mycophenolate mofetil (p=0.011). Sclerostin levels in those using TNF inhibitors were significantly higher than in those not using them (p=0.010).

Table 4 illustrates the correlation between urotensin and sclerostin levels and a number of other variables, including age, BMI, disease duration, blood pressure, and laboratory data. A positive correlation was observed between urotensin levels and

Table 3. Comparison of urotensin and sclerostin levels in patients with Behçet's disease

Clinical Involvements	Urotensin (ng/mL)		Sclerostin (ng/mL)	
	Mean ± SD	p-value*	Mean ± SD	p-value*
Mucocutaneosis (n=14)	7.2±6.3^a	**0.001***	15.0±7.1^a	**0.023****
Uveitis (n=6)	7.1±3.7^a		18.5±7.7^a	
Articular (n=5)	30.3±22.6^b		10.5±4$^{a.b}$	
Vascular (n=5)	30.9±7.9^b		7.8±2.5^b	
Neuro-Behçet's (n=2)	4.2±1.5^a		24.9±15.3^a	

*One-way ANOVA analysis. $^{a.b}$Group where the difference originated

Table 4. Correlation between urotensin and sclerostin levels

	Urotensin		Sclerostin	
	r*	p-value	r*	p-value
Mean age (years)	0.144	0.150	**-0.229**	**0.021**
BMI (kg/m)^2	0.110	0.273	**-0.231**	**0.020**
Duration of diagnosis (month)	**0.241**	**0.043**	-0.137	0.255
Systolic blood pressure	**0.273**	**0.006**	**-0.381**	**<0.001**
Diastolic blood pressure	**0.233**	**0.019**	**-0.362**	**<0.001**
Right cIMT (mm)	**0.513**	**<0.001**	**-0.27**	**0.020**
Left cIMT (mm)	**0.530**	**<0.001**	**-0.323**	**0.006**
Total cholesterol (mg/dL)	0.054	0.604	**-0.24**	**0.018**
Triglyceride (mg/dL)	-0.059	0.571	-0.038	0.712
LDL (mg/dL)	0.071	0.499	**-0.244**	**0.018**
HDL (mg/dL)	0.016	0.880	-0.079	0.459
ESR (mm/h)	0.037	0.711	-0.180	0.073
CRP (mg/L)	-0.095	0.346	-0.131	0.194
Glucose (mg/dL)	-0.153	0.203	0.002	0.988
Uric acid (mg/dL)	0.046	0.706	-0.045	0.708
GFR (mL/min)	**-0.243**	**0.014**	0.188	0.060
Duration of corticosteroid treatment (month)	0.092	0.473	-0.211	0.097

BMI: Body mass index, cIMT: Carotid intima-media thickness, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, GFR: Glomerular filtration rate

disease duration, systolic and diastolic blood pressure, right and left carotid intima thickness, Framingham vascular age, and vascular risk; a negative correlation was observed with GFR. A negative correlation was observed between sclerostin levels and age, BMI, systolic and diastolic blood pressure, right and left cIMT, total cholesterol, LDL, and Framingham vascular age.

DISCUSSION

The main pathological finding of BD is vasculitis, which affects vessels of all sizes in both the arterial and venous systems. Venous involvement is more frequent than arterial involvement (up to 80%). Vascular involvement is observed in up to 40% of Behçet patients, especially in young males, and is a significant cause of mortality and morbidity (9). BD is considered a natural model of thrombosis caused by inflammation, driven by an impaired immune-inflammatory response rather than traditional cardiovascular risk factors. Neutrophils promote thromboinflammation through various mechanisms, leading to platelet activation, endothelial dysfunction, and impaired fibrinolysis.

Endothelial dysfunction and neutrophilic vascular inflammation mediate thrombosis in patients with BD. High-resolution B-mode ultrasonography is commonly used to evaluate endothelial function. Arterial intima-media thickness is a sensitive marker of early atherosclerotic vessel wall changes, particularly in the main carotid artery (10). The hypothesis that inflammatory processes in BD can lead to endothelial dysfunction and increased arterial IMT has emerged. Previous studies on Turkish cohorts have shown increased cIMT in patients with BD compared with healthy controls (11).

Our study revealed no difference in cIMT values between patients with BD and healthy controls. Differences in patient characteristics, such as disease duration and age, may influence these results (12). A study by Messedi et al. (11) indicated that cIMT is affected in patients with BD, regardless of symptoms, disease duration, or corticosteroid treatment, and is potentially linked to subclinical atherosclerotic changes.

This study evaluated the serum levels of two peptides involved in the vascular pathogenesis associated with atherosclerosis: UII and sclerostin. The U-II is a potent vasoconstrictor peptide that stimulates cell proliferation. Inflammation increases urotensin receptor expression, leading to endothelial and smooth muscle cell proliferation, foam cell formation, and chemotaxis. UII also produces reactive oxygen species in vascular smooth muscle cells, inducing proliferation and accelerating atherosclerosis (13).

UII receptor interaction stimulates calcium release in vascular smooth muscle cells, leading to cellular proliferation and activation of Ca2+-dependent kinases. Recent studies have suggested that UII adversely affects vascular remodeling by influencing vascular endothelial growth factor expression in adventitial fibroblasts (14). The upregulation of UII in endothelial cells within atherosclerotic plaques suggests that UII directly contributes to disease progression by promoting a pro-inflammatory and pro-thrombotic environment (15).

Our study found higher serum UII levels in patients with BD with vascular involvement than in the other subgroups. Additionally, cIMT was significantly increased in all patients with BD and positively correlated with serum UII levels. High UII levels in patients with articular involvement may be related to its role in synovial fibrosis (16).

Sclerostin, a Wnt pathway modulator, affects endothelial dysfunction, vascular smooth muscle cell (VSMC) proliferation, and intimal thickening. Wnt signaling's role in atherogenesis was first reported in families with coronary artery disease linked to *LRP6*

gene mutations (17). Studies have shown varying effects of Wnt levels on atherosclerotic plaques (18). The negative relationship between sclerostin and cIMT contradicts the findings of Morales-Santana et al. (19), possibly because of differences in patient groups. Agostino et al. also showed an inverse relationship in diabetic patients. Furthermore, sclerostin's function is not merely correlative; it actively participates in the modulation of VSMC behavior. Sclerostin downregulates matrix metalloproteinases and other factors involved in vascular remodeling, thereby influencing the progression of atherosclerosis (20). In conditions of low sclerostin, an increase in VSMC proliferation and migration has been observed, which can lead to structural changes in blood vessels that promote atherosclerosis (21). Conversely, in conditions of elevated sclerostin, the inhibition of Wnt signaling may result in the reduction of VSMC activity and the potential mitigation of vascular calcification (22). If high sclerostin levels have a protective vascular effect, further research is needed to elucidate the Wnt/β-catenin pathway's role in atherosclerosis. This study is the first to reveal the relationship between serum sclerostin levels and IMT.

The interplay between urotensin and sclerostin may also be influenced by the systemic inflammatory response. BD is characterized by elevated levels of pro-inflammatory cytokines that can affect both urotensin and sclerostin levels. For instance, inflammatory cytokines can stimulate the production of urotensin while downregulating sclerostin expression in osteocytes (23). This dual effect may create a feedback loop in which increased urotensin exacerbates endothelial dysfunction, while decreased sclerostin a limitation of this study is that it did not include patients who had not previously undergone any treatment.

The relationship between UII and sclerostin levels and cIMT in patients with BD offers insight into the underlying pathophysiology of this systemic inflammatory condition. BD is typified by vasculitis, which can result in significant vascular complications, including atherosclerosis and increased cIMT, which serve as markers of cardiovascular risk. The presence of elevated UII levels and decreased sclerostin levels has been documented in this patient population, suggesting a potential correlation with the vascular alterations observed in BD.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the ethical standards determined by the Fırat University Non-Interventional Research Ethics Committee and the Helsinki Declaration (approval no: 350179, date: 26/09/2019).

Informed Consent: Patients were provided with comprehensive information about the study and were included in the study only after providing informed consent to participate.

Footnotes

Authorship Contributions

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

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

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IMPACT OF COVID-19 ON GRANULOMATOSIS WITH POLYANGIITIS: A RETROSPECTIVE ANALYSIS OF INCIDENCE AND CLINICAL CHARACTERISTICS

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Abstract

Aim: This study aimed to evaluate the impact of the coronavirus disease-2019 (COVID-19) pandemic on the incidence and clinical characteristics of granulomatosis with polyangiitis (GPA) in patients diagnosed before and after the onset of the pandemic.

Material and Methods: A retrospective analysis was conducted on 67 patients diagnosed with GPA between 2012 and 2023, categorized into pre-pandemic (n=35) and post-pandemic (n=32) cohorts. Data on sociodemographic, laboratory, and clinical characteristics were collected and statistically analysed.

Results: The incidence of GPA increased from approximately 0.58 to 1.07 cases per 100,000 person-years post-pandemic. No statistically significant differences were observed in most clinical parameters, although a notable rise in alkaline phosphatase levels was identified (p=0.016). The demographic analysis revealed a higher prevalence of male patients in the post-pandemic group (p=0.020). Despite the increased incidence, mortality rates and clinical features remained stable between the two periods.

Conclusion: The findings suggest a significant association between the COVID-19 pandemic and the increased incidence of GPA, potentially linked to immune dysregulation triggered by severe acute respiratory syndrome coronavirus 2 infection. While the clinical management of GPA has remained effective, the need for heightened awareness of autoimmune conditions in the context of COVID-19 is emphasized, warranting further investigation into the long-term implications of viral infections on autoimmune diseases.

Keywords: Autoimmune disease, COVID-19, granulomatosis with polyangiitis, incidence

INTRODUCTION

The outbreak of coronavirus disease-2019 (COVID-19) due to severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) has had serious consequences on a global scale, including in people with chronic autoimmune diseases. Given the increased morbidity and mortality rates during the pandemic, concerns have been raised about the exacerbation of autoimmune diseases and the emergence of new autoimmune phenomena. Research suggests that SARS-CoV-2 infection may lead to various autoimmune diseases by triggering autoimmune responses through mechanisms such as molecular mimicry, epitope spreading, and immune dysregulation (1-5).

Recent studies suggest a possible link between SARS-CoV-2 and the development of granulomatosis with polyangiitis (GPA), a vasculitis associated with antineutrophil cytoplasmic antibody (ANCA). GPA is characterized by necrotizing granulomatous

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inflammation affecting small- to medium-sized blood vessels and is often associated with respiratory symptoms such as cough and hemoptysis (6,7). It has been hypothesized that hyperactivation of the immune system during the process of infection with the SARS-CoV-2 virus, which can potentially result in elevated levels of autoantibodies, may act as a mechanism that may initiate the onset of GPA in individuals who are genetically predisposed to such an outcome (6,8,9).

A review of the literature revealed numerous case reports documenting the occurrence of GPA in patients infected or vaccinated with SARS-CoV-2. Furthermore, there is evidence that if a patient receiving SARS-CoV-2 treatment develops GPA, it may present challenges in the treatment and management of the patient (7,10). As evidenced by case reports of ANCA-associated vasculitis following vaccination to prevent the development of SARS-CoV-2, the mechanism that initiates vasculitis formation may be linked to the vaccination itself (11,12).

The exact mechanism by which SARS-CoV-2 contributes to GPA is not known. However, the pandemic has caused a notable increase in autoimmune diseases, highlighting the need for healthcare professionals to be vigilant about the potential for SARS-CoV-2 to induce or exacerbate autoimmune diseases.

In conclusion, there is a need for studies that examine the sociodemographic, laboratory, clinical, and outcome characteristics of autoimmune diseases during the post-pandemic period. As the world continues to experience the effects of the pandemic, understanding these dynamics will be critical for improving patient care and outcomes in individuals with autoimmune diseases.

The aim of this study was to assess the impact of the pandemic on patients with GPA by comparing the sociodemographic, laboratory, and clinical characteristics of patients in our GPA cohort before and after the onset of the SARS-CoV-2 pandemic.

MATERIALS AND METHODS

The present study retrospectively examined patients diagnosed with GPA in the rheumatology department between 2012 and 2023. The patients were grouped according to the timing of their diagnosis before or after 11 March 2020, the start date of the SARS-CoV-2 pandemic in Turkey. After reviewing the patient files and hospital information system, cases that met the 2022 Acr/Eular criteria were identified and included in the study cohort of patients with granulomatous polyangiitis.

The sociodemographic data, laboratory results, and clinical involvement characteristics used in this study were sourced from the hospital automation system and patient files. The data employed in the statistical analyses were the baseline values recorded at the time of GPA diagnosis in both groups. A total of 67 patients were included in the study, comprising 35 cases diagnosed with GPA prior to the onset of the SARS-CoV-2 pandemic and 32 cases diagnosed with GPA subsequent to the onset of the pandemic.

This study was approved by the Fırat University Non-Interventional Research Ethics Committee (approval no.: 2024/12-21, date: 11.09.2024) and was conducted in accordance with the tenets set forth in the Helsinki Declaration. The retrospective nature of the study, combined with its ethical oversight, provides a solid foundation for the findings, allowing for insights into the ramifications of the SARS-CoV-2 pandemic on GPA cases.

Statistical Analysis

The data underwent statistical analysis using the appropriate tests to compare the two groups. Continuous variables were analyzed using either Welch's t-test or Student's t-test, while Levene's test was employed to assess the equality of variances. Chi-square tests were employed for categorical data, thereby ensuring a robust statistical framework for the analysis of differences in clinical characteristics and outcomes between the two cohorts.

RESULTS

The institution where the study was conducted was not a healthcare facility where patients with confirmed or suspected SARS-CoV-2 infection could receive inpatient or outpatient treatment or vaccination during the pandemic period. As a result, it was not possible to gather data regarding vaccination and infection status in patients with GPA diagnosed during the post-COVID-19 period. Nevertheless, the official data indicate that the rate of at least one vaccination dose in the region where the study was conducted was 71.4%, and that approximately 20% of the country's population was infected with the SARS-CoV-2 virus. Furthermore, the study region has not been affected by natural disasters or migration, which could have resulted in changes to the sociodemographic structure during the post-pandemic period.

The analysis indicates that the incidence of GPA increased from approximately 0.58 cases per 100,000 person-years in the pre-pandemic period to approximately 1.07 cases per 100,000 person-years in the post-pandemic period.

A comparative analysis of the clinical parameters and demographic characteristics of patients with GPA before and after the beginning of the SARS-CoV-2 outbreak is presented in Table 1.

The analysis of clinical parameters in patients with GPA revealed no statistically significant differences in most parameters when comparing the pre-COVID-19 period (n=35) to the post-COVID-19 period (n=32). The mean age of patients in the pre-COVID-19 group was 53.2±13.8 years, whereas that in the post-COVID-19 group, it was 49.0±14.8 years (p=0.246).

Among the laboratory parameters, c-ANCA (Enzyme-Linked Immunosorbent Assay (ELISA) levels showed a mean of 68.3±40.4 in the pre-COVID-19 group compared to 52.5±43.4 in the post-COVID-19 group (p=0.129). p-ANCA (ELISA) levels increased from 7.8±26.1 to 18.4±36.8 [minimum-maximum (min.-max.): 3-100, both] (p=0.183). Furthermore, no notable

Table 1. Comparative analysis of clinical parameters in GPA patients before and after the onset of the SARS-CoV-2 pandemic

	Pre-COVID-19 period (n=35)	Post-COVID-19 period (n=32)	p-value
Age (years)	53.2±13.8	49.0±14.8	0.246[x]
C-ANCA (ELISA) (AU/mL)	68.3±40.4	52.5±43.4	0.129[x]
P-ANCA (ELISA) (AU/mL)	3-100[b]	3-100[b]	0.183[a +]
CRP (mg/L)	96.4±62.5	106.0±75.8	0.570[x]
ESR (mm/h)	79.3±30.6	75.5±33.9	0.633[x]
GFR (mL/dk/1.73 m^2)	55.8±35.4	53.1±34.1	0.751[x]
Urea (mg/dL)	83.4±64.5	89.6±80.3	0.729[x]
Creatine (mg/dL)	2.05±1.93	2.62±2.76	0.324[x]
Uric acid (mg/dL)	1.7-9.8[b]	2.4–14.4[b]	0.407[a +]
Uric acid/creatine ratio	4.24±2.68	3.62±1.97	0.296[x]
Total protein (g/dL)	6.50±0.80	6.48±0.77	0.949[x]
Albumin (g/dL)	3.47±0.66	3.60±0.62	0.415[x]
T protein/alb ratio	1.91±0.29	1.83±0.29	0.314[x]
AST (U/L)	6-111[b]	12-285[b]	0.077[a +]
ALT (U/L)	2-142[b]	7-665[b]	0.112[a +]
GGT (U/L)	2-325[b]	6-549[b]	0.084[a +]
ALP (U/L)	19-144[b]	26-281[b]	**0.016**[a +]
LDH (u/L)	251.6±115.5	270.3±156.2	0.577[x]
Total biluribin (mg/dL)	0.47±0.22	0.68±0.94	0.206[x]
Direct biluribin (mg/dL)	0.1-0.4[b]	0.1-4.1[b]	0.240[a +]
Hemoglobin (g/dL)	10.4±2.53	10.3±2.57	0.885[x]
Haemotocrit (%)	32.1±7.94	31.4±8.00	0.719[x]
MCV (fL)	92.0±63.7	82.8±4.84	0.421[x]
Platelet (10e3/µL)	354.8±168.0	382.6±162.2	0.495[x]
Mpv (fL)	8.41±1.21	8.68±1.15	0.346[x]
WBC (10e3/µL)	10.9±4.32	11.1±5.11	0.861[x]
Neu (10e3/µL)	8.44±3.69	8.73±4.78	0.776[x]
Lym (10e3/µL)	1.49±0.73	1.40±0.64	0.581[x]
Neu/Lym ratio	8.66±9.71	8.20±7.50	0.833[x]
Overall duration of disease (Weeks)	242.1±198.6	240.9±205.9	0.980[x]
Time to mortality post-disease onset (Weeks)	8-148[b]	3-432[b]	0.503[a +]

[a]Levene's test is significant (p<0.05), suggesting a violation of the assumption of equal variances, [b]Minimum-maximum value, [+]Welch's test p-value, [x]Student's t-test, p-value, c-Anca: Antineutrophil cytoplasmic autoantibody, cytoplasmic, p-Anca: Perinuclear anti-neutrophil cytoplasmic antibodies, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, GFR: Glomerular filtration rate, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GGT: Gamma-glutamyl transferase, ALP: Alkaline phosphatase, MCV: Mean corpuscular volume, MPV: Mean platelet volume, WBC: White blood cells, Neu: Neutrophil, Lym: Lymphocyte

discrepancy was detected in terms of C-reactive protein levels, erythrocyte sedimentation rate, urea, creatinine, uric acid, uric acid/creatinine ratio, total protein, albumin, and protein/alb ratio.

Liver function tests indicated a significant elevation in alkaline phosphatase (ALP) levels from 78.4±29.5 to 110.5±66.3 (min.-max. 19-144, 26-281 respectively) (p=0.016). Other parameters, including complete blood count, showed no significant changes over the two periods.

The statistical analysis indicated that the overall duration of disease was comparable between the pre-COVID-19 group (242.1±198.6 weeks) and the post-COVID-19 group (240.9±205.9 weeks), with a p-value of 0.980, suggesting no statistically significant difference. In contrast, the time to mortality post-disease onset was notably longer in the post-COVID-19 group (94.6±147.3 weeks) (min.-max. 3-432 weeks) than in the pre-COVID-19 group (56.8±47.1 weeks) (min.-max. 8-148 weeks). However, this change was not statistically significant (p=0.503).

A comparative analysis of categorical demographic and laboratory parameters in GPA before and after the onset of the SARS-CoV-2 pandemic is presented in Table 2.

The demographic analysis indicated a significant difference in gender distribution, with a chi-square value of 5.43 (p=0.020), suggesting a higher prevalence of male patients in the post-COVID-19 group. No statistically significant difference was observed in the positivity rates of ANCA Immunofluorescence assay (IFA) (PR3 a/o MPO ANCA) between the two study periods (p=0.08). The analysis of ANCA (ELISA) status exhibited no relevant changes in the presence of c-ANCA and p-ANCA between the two periods (p=0.29, 0.27 respectively).

The spot urine protein:creatinine ratio analysis indicated no significant differences in the severity of proteinuria between the two periods (p=0.53).

A comparative analysis of the categorical clinical manifestations and outcome parameters in patients with GPA before and after the onset of the SARS-CoV-2 pandemic is presented in Table 3.

The clinical manifestations of GPA were evaluated, demonstrating no notable discrepancies in the occurrence of glomerulonephritis, pulmonary hemorrhage, non-cavitating pulmonary nodules, retro-orbital disease, episcleritis, nasal and paranasal disease, myositis, central nervous system, meningeal, cardiac, or mesenteric involvement from pre- to post-COVID-19 era.

However, the analysis of mortality rates indicated that 12 patients died in the pre-COVID-19 period compared with 8 in the post-COVID-19 period (p=0.407), suggesting no significant change in mortality rates. Moreover, the occurrence of life-threatening diseases and infections necessitating hospitalization does not exhibit a substantial change between the two intervals. (respectively p=0.987, p=0.853).

DISCUSSION

In this retrospective study of our cohort, we observed an increase in the incidence of GPA compared with the pre-pandemic period. Furthermore, we found that GPA was more common in

Table 2. Comparative analysis of demographic and laboratory parameters in in GPA patients before and after the onset of the SARS-CoV-2 pandemic

	COVID-19 period				
	Previously (n=35)	After (n=32)	χ^2	df	p-value
Male Female	13 (38%)	21 (62%)	5.43	1	0.020
	22 (66%)	11 (34%)			
Anca (IFA) + (PR3 a/o MPO) Anca (IFA) - (PR3 & MPO)	31 (88%)	4 (12%)	2.98	1	0.084
	23 (72%)	9 (28%)			
c-ANCA (ELISA) + c-ANCA (ELISA) -	28 (56%)	22 (44%)	1.12	1	0.29
	7 (41%)	10 (59%)			
p-ANCA (ELISA) + p-ANCA (ELISA) -	3 (30%)	7 (70%)	2.33	1	0.27
	32 (56%)	25 (44%)			
Normal&mild Spot urine protein/creatine ratio Modarate spot urine protein/creatine ratio Severe spot urine protein/creatine ratio	22 (56%)	17 (44%)	1.27	2	0.53
	5 (38%)	8 (62%)			
	8 (53%)	7 (47%)			

Anca (IFA); Antineutrophil cytoplasmic antibodies (Immunofluorescence assay), c-Anca; Antineutrophil cytoplasmic autoantibody, cytoplasmic, p-Anca; Perinuclear anti-neutrophil cytoplasmic antibodies, PR3; Proteinase 3, MPO; Myeloperoxidase, df; Degrees of freedom

Table 3. Comparative analysis of clinical manifestations and outcomes in GPA patients before and after the onset of the SARS-CoV-2 pandemic

	COVID-19 period				
	Previously (n=35)	After (n=37)	χ^2	df	p-value
Glomerulonephritis +	20 (50%)	20 (50%)	0.199	1	0.655
Glomerulonephritis -	15 (55%)	12 (45%)			
Pulmonary haemorrhage +	11 (55%)	9 (45%)	0.0871	1	0.768
Pulmonary haemorrhage -	24 (51%)	23 (49%)			
Meningeal involvement +	1 (50%)	1 (50%)	0.00414	1	0.949
Meningeal involvement -	34 (52%)	31 (48%)			
CNS involvement +	7 (46%)	8 (54%)	0.241	1	0.624
CNS involvement -	28 (54%)	24 (46%)			
Retro-orbital disease +	1 (50%)	1 (50%)	0.001	1	0.965
Retro-orbital disease -	34 (52%)	31 (48%)			
Cardiac involvement +	4 (57%)	3 (43%)	0.075	1	0.784
Cardiac involvement -	31 (52%)	29 (48%)			
Mesenteric involvement +	3 (50%)	3 (50%)	0.01	1	0.980
Mesenteric involvement -	32 (52%)	29 (48%)			
Nasal&paranasal disease +	16 (47%)	18 (53%)	0.742	1	0.389
Nasal&paranasal disease-	19 (57%)	14 (43%)			
Skin involvement +	8 (50%)	8 (50%)	0.04	1	0.83
Skin involvement -	27 (53%)	24 (47%)			
Myositis +	2 (100%)	0 (0.0%)			0.493[a]
Myositis -	33 (51%)	32 (49%)			
Non-cavitating pulmonary nodules +	23 (56%)	18 (44%)	0.631	1	0.427
Non-cavitating pulmonary nodules -	12 (46%)	14 (54%)			
Episcleritis +	2 (50%)	2 (50%)	0.008	1	0.926
Episcleritis -	33 (52%)	30 (48%)			
Life/organ threatening diseases +	24 (52%)	22 (48%)	2.48	1	0.987
Life/organ threatening diseases -	11 (52%)	10 (48%)			
Mortality +	12 (60%)	8 (40%)	0.688	1	0.407
Mortality -	23 (49%)	24 (51%)			
Infection requiring hospitalisation +	15 (54%)	13 (46%)	0.034	1	0.853
Infection requiring hospitalisation -	20 (51%)	19 (49%)			

[a]Fisher's exact test, p-value
CNS: Central nervous system, GPA: Granulomatosis with polyangiitis, SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2, df; Degrees of freedom

men during the post-pandemic period. Additionally, we did not observe a significant difference between the pre-pandemic and post-pandemic periods in terms of many clinical and laboratory parameters, including important parameters such as infection requiring hospitalization and mortality.

The elevated incidence observed in the present study may be attributable to an exaggerated and aberrant inflammatory response to SARS-CoV-2. It has been demonstrated that the SARS-CoV-2 virus can elevate the levels of inflammatory cytokines, including interleukin 6, 10, 17, 18, 22 and tumor necrosis

factor-alpha, in infected patients (13,14). In some cases, this exaggerated immune response manifests as a cytokine storm. This hypothesis is supported by several case reports that documented the development of GPA or the exacerbation of existing GPA in patients following a diagnosis of SARS-CoV-2 infection. This evidence suggests that the virus may act as a trigger for such autoimmune responses (6,7,15-17). The pandemic has also resulted in increased awareness and diagnosis of GPA, as healthcare systems have adapted to recognize and treat autoimmune conditions that are exacerbated by viral infections (18). Furthermore, the psychological distress and anxiety associated with the pandemic may exacerbate autoimmune conditions, underscoring the necessity for comprehensive care that addresses both physical and mental health (19,20).

Furthermore, it has been postulated that SARS-CoV-2 may precipitate vascular inflammation and vasculitis by directly affecting endothelial cells (21). The inflammatory response induced by SARS-CoV-2, which is typified by a cytokine storm, may additionally predispose individuals to autoimmune phenomena (15,22). The presence of antineutrophil cytoplasmic antibodies (ANCA) has been observed in some patients who have recovered from coronavirus SARS-CoV-2 infection, indicating that the virus may contribute to the dysregulation of the immune system (8,16).

It is possible that immunodysregulation caused by SARS-CoV-2 may increase the likelihood of GPA occurrence or exacerbate existing ones, as is the case in many rheumatic diseases (23). Additionally, several studies have indicated a rise in the prevalence of rheumatic disorders during the pandemic (24,25). For example, one study demonstrated an increase in the incidence of giant cell arteritis during the pandemic, indicating that the SARS-CoV-2 virus may have exacerbated the underlying pathogenetic mechanisms or triggered new cases (26).

In the context of our study, the fact that GPA was more common among male patients in the post-COVID-19 period than in the pre-COVID-19 period is another issue that needs to be discussed.

The male predominance in GPA cases according to COVID-19 may be due to natural differences in the immune response between the sexes and a stronger inflammatory response to viral infections in men. This observation is also consistent with the findings of the COVID-19 Global Rheumatology Alliance, which stated that male gender is an important risk factor for serious outcomes in rheumatic diseases during the pandemic (27,28).

The mean age of patients showed a slight decrease from the pre-COVID-19 period (53.2±13.8 years) to the post-COVID-19 period (49.0±14.8 years), although not statistically significant ($p=0.246$). The fact that patients with GPA were diagnosed at a younger age may be due to the fact that GPA has similar clinical features to SARS-CoV-2 and the effect of the pandemic on disease awareness (29).

The present study revealed no statistically significant difference in c-ANCA and p-ANCA (ELISA) levels (p-values of 0.129 and 0.183, respectively. This finding is consistent with the results of previous studies indicating that ANCA (ELISA) levels remain relatively stable in response to external stressors such as pandemics (30,31).

In this study, we observed that ALP values increased in patients with GPA in the post-COVID-19 period. This may be attributed to the higher male sex ratio of GPA patients in the post-COVID period. ALP levels are generally higher in men than in women for various physiological and hormonal reasons (32).

The lack of notable alterations in the majority of laboratory parameters indicates that the overall inflammatory profile remained unaltered, contrary to the hypothesis proposed in studies of a different nature (33).

Despite the observed increase in cases of GPA, the clinical features and outcomes have remained relatively stable. In the period following the pandemic, the clinical presentation pattern of GPA remained unchanged, with respiratory tract involvement and renal involvement being the most common (16,34). The prevalence of hospitalization among patients with GPA has remained consistent, indicating that the characteristics of the disease and the efficacy of established protocols for the management of severe cases have not undergone any significant alterations (35,36). The present study did not reveal any statistically significant increase in mortality rates among patients with GPA during the post-pandemic period. This indicates that although the incidence of COVID-19 is increasing, its overall management remains efficacious (37,38).

Moreover, the impact of the SARS-CoV-2 pandemic on chronic systemic autoimmune disorders has been subjected to rigorous scrutiny in numerous scientific studies. For example, individuals with autoimmune rheumatic disorders who contracted the virus showed similar hospitalization and mortality rates to those without autoimmune disease, suggesting that underlying autoimmunity may not markedly worsen the prognosis of SARS-CoV-2 infection (35,39). This observation is consistent with the findings of previous studies that indicated no significant differences in the clinical features or outcomes of patients with systemic autoimmune diseases during the pandemic (35,36). The consistent application of management strategies and the use of immunosuppressive therapies, such as rituximab, likely contributed to the maintenance of stable outcomes for patients with GPA despite the increased incidence (34,40). Moreover, the healthcare system's response to the pandemic, including

the prioritization of patients with severe COVID-19, may have unintentionally sustained the standard of care for GPA patients, ensuring that they continued to receive appropriate treatment despite the overwhelming impact of the pandemic. Furthermore, the prevalence of comorbidities in patients with GPA, which could potentially complicate their clinical course, has remained relatively unchanged during the pandemic, contributing to the observed stability in mortality rates.

Study Limitations

This study is limited by several factors, including the inherent biases associated with retrospective data collection and the relatively small sample size. Furthermore, the institution where the study was conducted was not a designated health center for the follow-up, treatment, and vaccination of patients with the virus. This was due to decisions taken by the relevant authorities, which meant that data on SARS-CoV-2 infection status and vaccination levels against it were not included.

CONCLUSION

In conclusion, the incidence of granulomatous polyangiitis increased following the onset of the SARS-CoV-2 pandemic. Despite the observed increase in the incidence of GPA, the clinical features, hospitalization, and mortality rates have remained stable. This stability may reflect the effectiveness of current treatment protocols and the success of health systems in managing chronic conditions in the context of a global health crisis.

Ethics

Ethics Committee Approval: This study was approved by the Fırat University Non- Interventional Research Ethics Committee (approval no.: 2024/12-21, date: 11.09.2024) and was conducted in accordance with the tenets set forth in the Helsinki Declaration.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

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

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ETIOLOGY OF CARPAL TUNNEL SYNDROME

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Abstract

Aim: Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy resulting from compression of the median nerve at the wrist level. Increased intercarpal canal pressure plays an important role in the etiology of CTS. Although most cases are idiopathic, there may also be some systemic or local causes. The aim of this study was to evaluate the demographic and etiological characteristics of patients with CTS who applied to our electroneuromyography (ENMG) laboratory within 3 months.

Material and Methods: One hundred forty-nine patients (=298 hands) who were sent to our ENMG laboratory for ENMG evaluation and diagnosed with CTS were included in our study. Cases with cervical vertebral root lesions, thoracic outlet syndrome, polyneuropathy, trauma such as nerve injury, and cases with tumors and secondary CTS to pregnancy were excluded from the study.

Results: One hundred six (71.1%) of the cases in our study were women and 43 (28.9%) were men. The average age of the patients was 54.27±13.10, and the body mass index (BMI) was 27.92±3.98. BMI ≥30 was found in 47 (31.5%) of the patients. In our study, we found that housewives were the occupational group with the highest risk in terms of CTS (n=94, 63.1%). In this study, we found bilateral hand involvement in 93 (62.4%) patients. The most common condition was idiopathic CTS (n=81, 54.6%).

Conclusion: CTS is more common in postmenopausal women who work as housewives and is usually seen in the dominant hand. It was concluded that this study would be useful for the diagnosis of CTS.

Keywords: Carpal tunnel syndrome, etiology, electroneuromyography, demographic characteristics

INTRODUCTION

Carpal tunnel syndrome (CTS) is the most common type of entrapment neuropathy that occurs as a result of compression of the median nerve at the wrist level (1). The carpal tunnel (canalis carpi) is a fibro-osseous tunnel at the wrist level, limited by fibrous elements on the palmar side and osseous elements on the dorsal side (Figure 1) (2). CTS accounts for approximately 90% of entrapment neuropathies (3). CTS is more common in women. Approximately 50% of the cases are bilateral (3). The prevalence rate was approximately 3% in women and 2% in men (4). Increased intercarpal canal pressure plays an important role in the etiology of CTS (3).

CTS is usually diagnosed by history and physical examination. Electroneuromyography (ENMG) and ultrasonography (US) support the diagnosis of CTS. The use of US for the diagnosis of CTS is increasing. US can evaluate structural changes in the nerve (hypoechoic swelling of the nerve, loss of fascicular pattern), as well as other pathologies that cannot be detected by electrophysiological examinations (muscle hypertrophy, anatomical variations, tenosynovitis, tumors, etc.) (5). The

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median nerve enlargement (cross-sectional area ≥10 mm^2 at the level of the pisiform bone or tunnel entrance) on US is used to establish the diagnosis of CTS (6).

The Etiology of CTS

Although most cases are idiopathic, systemic or local causes may also occur.

Repetitive Trauma

It may be accompanied by occupational or hobby-related trauma. These include repetitive movements of the hand and wrist (carpenters, typewriter-computer use), continuous and repetitive gripping or pinching of tools and objects, work requiring forceful wrist movements, work that creates direct pressure on the carpal tunnel, and the use of vibrating hand tools (Table 1) (7).

Systemic Causes

These include diabetes mellitus (DM), hypothyroidism, acromegaly, amyloidosis, carcinomatosis, polymyalgia rheumatica, rheumatoid arthritis (RA), obesity, local trauma, pregnancy (may reach 25%), and breastfeeding, mucopolysaccharidosis, menopause, pyridoxine insufficiency, toxic shock syndrome, hemodialysis, chondrocalcinosis, and athetoid-dystonic cerebral palsy. The most common of these conditions are DM, RA, and obesity (Table 1) (8).

Local Causes

These include anomalies of muscles and tendons, tenosynovitis, persistent median artery (thrombosis, aneurysm or arteriovenous malformation), palmar infections, bleeding, masses (neurofibroma, hemangioma, lipoma, ganglion cyst, xanthoma, gouty tophaceous), wrist burns, familial or idiopathic thickening of the transverse carpal ligament, callus or malunion resulting from carpal bone fractures and colles fracture, dislocation of the intercarpal joint or wrist, and plaster compression (9-12). CTS occurs more frequently in individuals with congenital small carpal tunnel (Table 1).

In this study, we aimed to evaluate the demographic and etiological characteristics of patients with CTS who applied to our ENMG laboratory affiliated with University of Health Sciences Turkey, Elazığ Fethi Sekin City Hospital, Physical Therapy and Rehabilitation Clinic within 4 months.

MATERIALS AND METHODS

Before starting the study, approval was obtained from the Fırat University Non-Interventional Research Ethics Committee

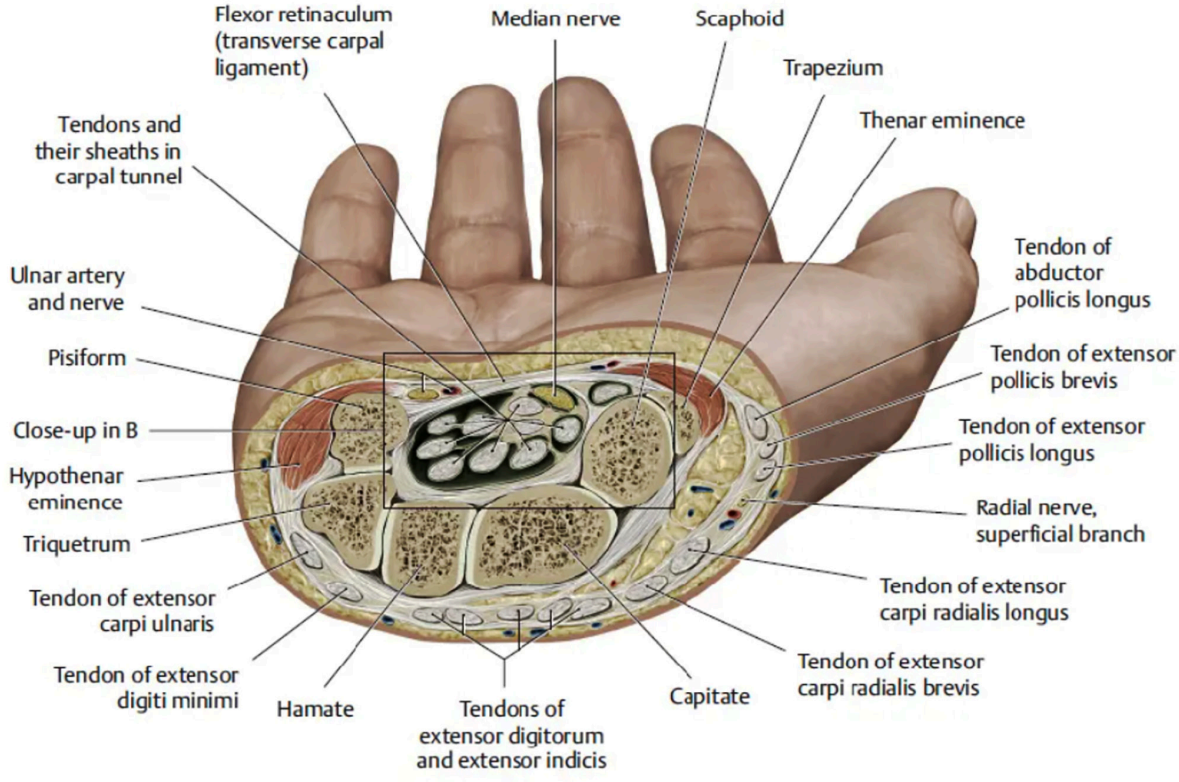

Figure 1. Cross-section of the right wrist at the level of the carpal tunnel

(approval number: 2024-23858, date: 25.04.2024) and the ability to work was confirmed. Written informed consent was obtained from the patients or their legal representatives.

One hundred forty-nine patients (=298 hands) who were sent to our ENMG laboratory for ENMG evaluation and diagnosed with CTS were included in our study. Patients who applied during a 4-month period between May 2024 and August 2024 were included in the study. Cases with cervical vertebra root lesions, thoracic outlet syndrome, polyneuropathy, trauma such as nerve injury, and cases with tumors and secondary CTS to pregnancy were excluded from the study. CTS diagnosis was made in patients who applied to our ENMG laboratory based on clinical findings, physical examination, and ENMG evaluation. During the examination, the results of the Tinnel and Phalen tests, which are auxiliary provocative tests, were evaluated as "positive" and "negative". For electroneuromyographic evaluation, a Medelek Synergy 2-channel ENMG device was used. After standardizing the extremity and ambient temperature, the median nerve peak sensory conduction velocity recorded from the 2nd finger was slower than 44 m/sec, and/or in the motor conduction study, when the distal motor latency (DML) was longer than 4.2 msec by stimulating the median nerve from the 5 cm wrist segment with recording from the abductor pollicis brevis muscle were evaluated as CTS (13). In median nerve sensory and mixed conduction studies, if the compound sensory action potential amplitude was normal and the conduction velocity was slowed, it was interpreted as mild CTS; if there was a prolongation of the median nerve DML in addition to these findings, it was interpreted as moderate CTS; if the compound sensory action potential could not be detected in sensory conduction studies and/or its amplitude was decreased and/or the compound muscle action potential amplitude was decreased in motor conduction studies, it was interpreted as severe CTS. All patients' age, gender, dominant and affected hand, height and weight, and presence of additional diseases that could cause entrapment neuropathy (DM hypo-hyperthyroidism, renal failure, and arthritis) were recorded. The height and weight of the subjects were measured and recorded, and body mass index (BMI) (kg/m^2) was calculated by dividing the individuals' weight by the square of their height.

Table 1. Etiology of carpal tunnel syndrome

A. Local causes **Inflammatory** • Tenosynovitis • Hypertrophic synovium **Trauma** • Colles fracture • Carpal bone dislocation **Tumors** • Hemangioma • Cyst • Ganglion • Lipoma • Neuroma **Anatomical abnormalities** • Thining of the transverse carpal ligament • Bone abnormalities • Accessory muscle • The persistent median artery	**C. Systemic causes** • Diabetes mellitus • Obesity • Hypothyroidism • Pregnancy • Menopause • Renal failure • Long-term hemodialysis • Alcoholism • Systemic lupus erythematous • Scleroderma • Dermatomyositis • Acromegaly • Multiple myeloma • Sarcoidosis • Leukemia • Hemophilia
B. Regional causes • Osteoarthritis • Rheumatoid arthritis • Amyloidosis • Gout	

Statistical Analysis

All statistical analyses were performed using the Statistical Packages for Social Sciences Version 22.0 for Microsoft Windows. Variables were presented in terms of mean ± standard deviation, and categorical variables were presented as number (n) and percentage (%).

RESULTS

In our study, 106 (71.1%) patients were female, and 43 (28.9%) were male. The average age of the patients was 54.27±13.10, and the BMI was 27.92±3.98. BMI ≥30 was found in 47 (31.5%) patients. Of the patients, 94 (63.1%) were housewives, 24 (16.1%) were civil servants, 13 (8.7%) were teachers, 10 (6.7%) were tradesmen, and 8 (5.4%) were farmers. While no additional disease was detected in 58 (38.9%) of the cases, hypertension was detected in 34 (22.8%), DM in 22 (14.7%), hypothyroidism in 13 (8.7%), asthma in 7 (4.7%), hyperlipidemia in 7 (4.7%), RA in 6 (4%) and chronic renal failure in 2 (1.3%). In total, 134 (89.9%) right-handed dominant cases were identified. Right hand involvement was found in 47 (31.5%) patients, left hand involvement in 9 (6%) patients, and bilateral hand involvement in 93 (62.4%) patients. The most common symptom in our patients was nocturnal hand paresthesia (124 patients-83%). Hypesthesia was detected in 35 (23.4%) patients, and thenar atrophy was detected in 14 (10%) patients on physical examination. The Tinnel test was performed in 97 (65.1%) patients and the Phalen-Phalen test in 82 (55%) patients. According to the ENMG results of the patients, 106 (71.1%) were mild CTS, 36 (24.2%) with moderate CTS, and 7 (4.7%) with severe CTS. The patient etiologies are presented in Table 2.

DISCUSSION

The most common entrapment neuropathy syndrome is CTS. In idiopathic cases, it is caused by microtrauma resulting from

Table 2. Etiology of CTS

Parameters (%)	CTS (n=149)
Idiopathic local causes	81 (54.6%)
Tenosynovitis	4 (2.7%)
Colles fracture	8 (5.3%)
Carpal bone dislocation	6 (4%)
Tumors (Ganglion cyst)	5 (3.3%)
Persistent median artery	1 (0.7%)
Thickening of the transverse carpal ligament	1 (0.7%)
Systemic causes	
Diabetes mellitus	22 (14.7%)
Hypothyroidism	13 (8.7%)
Rheumatoid arthritis	6 (4%)
Renal failure	2 (1.3%)

CTS: Carpal tunnel syndrome

chronic repetitive movements (3). The symptoms of CTS are burning, pain, and numbness in the hand (1st, 2nd, and 3rd fingers and the radial side of the 4th finger), which is consistent with the sensory distribution of the median nerve, and typically occur more frequently at night and during sleep. In late-stage cases, weakness develops in the thenar muscles, and thenar atrophy also develops secondary to denervation (14).

Maeda et al. (15) reported that CTS was seen at an average age of 49.3±8.6 years and the female/male ratio was 4/1. Yang et al. (16) conducted a population-based cohort study in Taiwan. They found that CTS was more common in women and in the 50-59 age group (16). The average age of the participants was 54 years, which is similar to the literature. The female/male ratio in CTS was 2/1-6/1 (17). Studies have reported that the frequency of estrogen receptors alpha and beta (ERα and ERβ) in the carpal tunnel is increased in women (18). These studies explain why CTS is higher in women. In our study, the female to male ratio was similar to that in the literature.

Bilateral involvement is common in CTS. The dominant hand is the most commonly used and the first affected hand in bilateral cases (3,8,14,19). This may be due to the more frequent use of the dominant hand and the smaller carpal tunnel diameter in the dominant hand. In our study, we found 134 (89.9%) patients who were right-handed dominantly, 47 (31.5%) of whom had right hand involvement, 9 (6%) had left hand involvement, and 93 (62.4%) had bilateral hand involvement. The hand-involvement results of our study were also consistent with the literature.

The most common symptom in our patients was nocturnal hand paresthesia (83%), which was found to be compatible with the literature (85%) (20). In a study conducted by Özgenel et al. (21), muscle atrophy and weakness were found in 8% of patients, and sensory loss was found in 24%. In our study, we detected thenar atrophy in 14 (10%) of our patients and hypesthesia in 35 (23.4%).

The Tinnel and Phalen provocative tests are widely used. However, conflicting results have been reported regarding the sensitivity and specificity of these two tests (22,23). In the literature, the sensitivity of the Tinnel test has been reported to be between 9% and 89% and that of the Phalen test between 10-74.5% (24-26). It has been stated that the reason for the variability in the results reported in the literature regarding the sensitivities of these tests may be due to differences in the application techniques (26). In our study, we found the sensitivity of the Tinnel test to be 65.1% and that of the Phalen test to be 55%. Our results indicate that the sensitivity of these two tests is not very high.

Electrophysiological examination is the most reliable method for diagnosing and determining CTS severity (3,14,26). The most commonly used parameters are median nerve sensory latency (SL) and DML. Some authors prefer peak sensory conduction velocity determined using peak SL, while others state that adding needle ENMG findings to nerve conduction velocity examinations is important in determining the severity of CTS (27). CTS is classified as mild, moderate, and severe using electrophysiological parameters to determine its severity (28). Sole (29) stated that ENMG provides the most reliable data for diagnosis, follow-up, and research purposes, but that the severity of patient symptoms should also be taken into consideration when planning treatment. According to the ENMG results, 106 (71.1%) patients presented with mild CTS, 36 (24.2%) with moderate CTS, and 7 (4.7%) with severe CTS.

It is known that repetitive microtraumas of the wrist, which are predicted to be the most common cause of idiopathic disease, are closely related to occupation. One of the known facts about CTS is that CTS is also defined among occupational diseases (14,30). The occupational distribution of 149 patients in our study included 94 housewives (63.1%), 24 civil servants (16.1%), 13 teachers (8.7%), 10 tradesmen (6.7%), and 8 farmers (5.4%). It seems reasonable to conclude that all patients in our study may have been exposed to repetitive movements and microtraumas during occupational practice. In their study examining the clinical effects of occupation and gender on idiopathic CTS, Mathew and John (31) found that the incidence of CTS was higher in housewives than in other occupations, and that the neurophysiological severity was higher. Among the patient groups included in our study, housewives were the most notable occupational group (n=94, 63.1%). The findings show that housewives are the most at-risk occupational group members in terms of CTS.

It has been suggested in the literature that the hydrostatic pressure resulting from the increase in fat tissue around the nerve in obesity causes a slowdown in median nerve sensory transmission. In the study conducted by Adebayo et al. (32) on the frequency and severity of obesity in CTS, the frequency of obesity (BMI >30 kg/m^2) and overweight (25.0-29.9 kg/m^2) was determined in patients with CTS. Similarly, in the study conducted by Moghtaderi et al. (33), BMI was found to be 30.6±5.8. Age, sex, and obesity have been found to be independent risk factors for CTS. In our study, we found the BMI to be 27.92±3.98 and 31.5% of our patients were obese. It was found to be compatible with the literature.

CTS is frequently observed in diseases such as DM, thyroid dysfunction, RA, osteoarthritis, connective tissue diseases, amyloidosis, various infectious and inflammatory diseases such as Lyme and sarcoidosis, and chronic renal failure (34). Studies have reported rates of DM at 15-33%, hypohyperthyroidism at 2-5%, and arthritis at 1-2.1% (35,36). In our study, we found DM at 14.7%, thyroid dysfunction at 8.7%, and arthritis at 4%.

Bony anomalies in the carpal canal narrow the canal diameter. Traumas such as Colles fractures, carpal fractures, and dislocations of the carpal bones and distal radius fractures can also lead to acute CTS (37). Altissimi et al. (38) found that CTS was observed in 31% of cases after Colles fractures. Tumors such as giant cell tumor of the tendon sheath, lipoma, lipofibromatous hamartoma, hemangioma, ganglioma, and osteoid osteoma have also been reported to cause CTS (37). In our study, we detected colles fractures in 8 (5.3%) patients, carpal bone dislocations in 6 (4%), and tumors (ganglion cyst) in 5 (3.3%). We thought that the reason why we detected fewer patients with colles fractures than in the study conducted by Altissimi et al. (38) might be related to the small number of patients in our study.

CONCLUSION

CTS is the most common and well-known compression neuropathy of the upper extremities. It is known that etiology-based treatment of CTS is of great importance in preventing the development of late-stage neurological deficits. In this study, our experiences with CTS regarding age, sex, predisposing factors, and accompanying diseases, symptoms, and physical examination findings are presented. It was concluded that the findings of this study would be useful in evaluating the diagnosis of CTS cases.

Ethics

Ethics Committee Approval: The study, approval was obtained from the Fırat University Non-Interventional Research Ethics Committee (approval number: 2024-23858, date: 25.04.2024).

Informed Consent: Written informed consent was obtained from the patients or their legal representatives.

Footnotes

Authorship Contributions

Concept: N.Y., Design: M.Ş.E., N.Y., Data Collection or Processing: M.Ş.E., N.Y., M.K., Analysis or Interpretation: M.Ş.E., N.Y., M.K., Literature Search: N.Y., M.K., Writing: N.Y., M.K.

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

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DO BIOLOGICAL THERAPIES HAVE ANY EFFECT ON NEUROPATHIC PAIN IN RHEUMATOID ARTHRITIS? WHAT ARE THE RELATED FACTORS?

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Abstract

Aim: The objective of this study was to investigate the frequency of neuropathic pain (NeP) in patients with rheumatoid arthritis (RA) who are receivers and non-receivers of biological treatment. The secondary objective of our study was to identify NeP-related factors in RA.

Material and Methods: This was a sectional case–control study that measured the frequency of NeP using painDETECT (pDETECT) in patients with RA being monitored in our rheumatology outpatient clinic and in the control group. In addition, along with the demographic data of the patients, the disease activity score in 28 joints calculated with C-reactive protein (DAS28-CRP), visual analog scale (VAS) pain, VAS fatigue, Beck depression index, Beck anxiety index, health assessment questionnaire, and RA quality of life index were used.

Results: A total of 105 patients with RA (60 biological, 45 conventional treatment) and 106 healthy controls were enrolled in the study. According to pDETECT, NeP was n=15 (7.1%), n=9 (4.3%), and n=13 (6.2%) in the Biological disease-modifying antirheumatic drugs (bDMARD), non-receivers, and control groups, respectively. There was no statistical difference between groups who were bDMARD receivers and non-receivers ($p>0.05$). There was a moderate positive correlation between pDETECT and RA duration ($r=0.363$), VAS pain score ($r=0.594$), VAS fatigue score ($r=0.589$), DAS28-CRP score ($r=0.489$), Beck depression index ($r=0.402$), Beck anxiety index ($r=0.606$), erythrocyte sedimentation rate (ESR) value ($r=0.226$), and tender joint count (TJC) ($r=0.367$) ($p<0.05$).

Conclusion: NeP is commonly observed in patients with RA, and treatment with bDMARDs did not change the frequency of NeP. A positive correlation was observed between NeP and RA disease duration, DAS28-CRP, VAS pain, VAS fatigue, Beck depression index, Beck anxiety index, ESR, and TJC. When measuring disease activity in patients with RA, NeP should not be ignored.

Keywords: Biological treatment, neuropathic pain, painDETECT, rheumatoid arthritis

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INTRODUCTION

Rheumatoid arthritis (RA) is one of the most common chronic inflammatories arthritides and leads to deformity and disability due to widespread joint involvement and damage. RA causes extra-articular involvement and systemic comorbidities and may shorten life span. In recent years, the use of biological medicines for RA has ensured a more efficient treatment of the disease (1). Approximately 90% of patients present to the physician with severe pain. Pain in RA manifests through different mechanisms, such as inflammatory, degenerative, central, and peripheral sensitization. Although conventional or biological or targeted disease-modifying agents [conventional disease-modifying antirheumatic drugs (cDMARDs)/biologic disease-modifying antirheumatic drugs (bDMARD)/ targeted synthetic disease modifying antirheumatic drugs (tsDMARD)] suppress the inflammatory activity, decreasing the progression of RA, they are often inadequate in relieving the pain entirely, which causes a decrease in the quality of life of patients (2,3).

Pain in RA is generally accepted as peripheral nociceptive pain originating from structures like synovium. The response of peripheral and central neurons increases in response to the inflammatory event and may continue after the inflammation resolves. This hypersensitivity may cause chronic pain originating from the central nervous system. This condition may manifest itself as increased neuropathic pain (NeP) in RA patients (4). Apart from central nervous system sensitization (nociplastic pain), NeP may manifest itself due to different causes like entrapment neuropathy, peripheral neuropathy, and small fiber neuropathy. The prevalence of NeP in rheumatoid diseases varies between 3% and 50% in different studies, and this proportion is higher than the NeP proportion in patients with chronic pain. The prevalence of NeP has been reported to be approximately 20% in RA (5). Pain due to NeP in patients with RA does not respond well to anti-inflammatory medicines and medicines like opioids. In addition, the presence of NeP may cause a higher manifestation of disease activity in RA (5,6).

Biological therapies like anti-tumor necrosis factor alpha (tumor necrosis factor) used in the treatment of RA are effective in controlling disease activity and reducing pain. However, over the course of years, even though the inflammatory activity does not increase, the severity of the pain can intensify, and bDMARDs are inadequate in patients with RA who have high sensitivity to pain (6,7). However, in some studies, it has been demonstrated that medicines like anti-tumor necrosis factor (anti-TNF) can decrease peripheral NeP and hyperalgesia (8-10). Again, bDMARDs and tsDMARDs have been shown to decrease chronic pain in RA, however, with which mechanisms this happens and via which nociceptive, neuropathic, or oncoplastic pathways they demonstrate efficacy could not have been explained (11). Our objective in this study was to investigate whether there is a difference in NeP frequency between RA patients who receive bDMARDs and those who do not. Our secondary objective was to identify NeP-related factors in patients with RA in the investigated population.

MATERIALS AND METHODS

Our study was conducted between June 2021 and December 2021 and enrolled 105 patients who were monitored in the rheumatology outpatient clinic and had a diagnosis of RA according to the American College of Rheumatology (ACR)/ European League Against Rheumatism 2010 or ACR 1987 classification criteria and 106 healthy control group participants whose age and gender corresponded to the RA patients. This is a sectional case–control study in which patients aged >18 years who fulfilled the criteria and accepted to participate in the trial were recruited. Patients with neurological diseases, history of spinal surgery, and endocrinological diseases, such as diabetes mellitus (DM), that may cause NeP, who use drugs for NeP, pregnant women, patients with cancer, and patients with active infection were excluded from the study. Demographic data, clinical and laboratory data regarding the disease, tobacco use, additional diseases, medications used, and body mass index (BMI) were identified, and planned measurements with regard to the study were performed.

RA disease activity was calculated using disease activity score 28 (DAS28-CRP). Additionally, visual analog scale (VAS) pain score, VAS fatigue score, health assessment questionnaire (HAQ), RA quality of life index, Beck depression index, and Beck anxiety index were measured. The painDETECT (pDETECT) scoring system was used to assess NeP. As per pDETECT, 0-12, 13-18, and >18 were accepted as no NeP; the result was unidentified, but the NeP component was found and the NeP presence was observed.

Statistical Analysis

Compliance of data with normal distribution in the statistical method was evaluated with Kolmogorov-Smirnov test, and a normal distribution of data was detected. The independent t-test was used to compare two independent groups with normal distribution. Comparisons of more than two groups were made using the One-Way Analysis of Variance test. Correlations between variables were examined using Spearman's rho coefficient. Median ± standard deviation, minimum and maximum values were given for numeric variables as descriptive statistics, and number and percentage were given for categorical variables.

SPSS for Windows version 23.0 software package was used for statistical analyses, and $p<0.05$ was accepted as statistically significant.

The study was approved by the Hatay Mustafa Kemal University Non-Interventional Clinical Research Ethics Committee. Signed informed consent forms were obtained from the patients participating in the study. (approval number: 05, date: 01.07.2021).

RESULTS

One hundred-five patients diagnosed with RA who fulfilled the study criteria were enrolled in the study. Of these patients, 60 were bDMARD receivers and 45 were non-receivers. The average ages of the patients who were in the groups of receivers and non-receivers of bDMARD and the control group were 51.2 (min. 21–max. 77), 53.6 (min. 20–max. 77), and 46.8 (min. 24–max. 83), respectively, and there was no difference between the groups ($p>0.005$). 78% of the study participants were female and 22% were male; 22.3% were smokers; BMI values were 27.9, 27.6, and 27.1 in RA patients who received and did not receive biological medicine and in the control group, respectively. No significant difference was observed between the BMI averages in the groups. The demographic data of the patient and control groups are presented in Table 1. According to pDETECT, NeP was n=15 (7.1%) in the bDMARD group, n=9 (4.3%) in the group not receiving bDMARD, n=13 (6.2%) in the control group. There was no statistical difference between bDMARD and non-receivers ($p>0.05$) (Table 1).

Average values in patients who were receivers and non-receivers of bDMARD were observed as follows, respectively; disease duration 13.6 and 8.7, VAS pain 5.6 and 4.6, VAS fatigue 5.3 and 4.2, DAS28-CRP 3.4 and 3.3, CRP 13.5 and 11.6, swollen joint count 2.4 and 2.8, tender joint count (TJC) 3.5 and 3.2, erythrocyte sedimentation rate (ESR) in both groups 22.6, Beck anxiety index 15.9 and 15.3, Beck depression index 11.7 and 11.9, HAQ score 11.1 and 10.0, RA quality of life index 13.4 and 11.8. Compared with the control group, there was a significant difference in the average scores of the RA quality of life index ($p=0.000$), HAQ score ($p=0.003$), pDETECT ($p=0.000$), CRP ($p=0.008$), ESR ($p=0.007$), DAS28-CRP ($p=0.00$), VAS fatigue ($p=0.02$), and VAS pain ($p=0.00$). There were no significant differences between Beck's depression index ($p=0.094$) and BMI ($p=0.570$) (Table 2).

A moderate positive correlation was observed between pDETECT and RA duration ($r=0.363$), VAS pain score ($r=0.594$), VAS fatigue score ($r=0.589$), DAS28-CRP score ($r=0.489$), Beck depression index ($r=0.402$), Beck anxiety index ($r=0.606$), and ESR value ($r=0.226$). In addition, there was a moderate positive correlation between pDETECT and TJC, and TJC increased as the pDETECT score increased ($p<0.05$). A moderately negative correlation was observed between pDETECT and RA in terms of the number of medicines used ($r=-0.344$ and $p<0.05$). On the other hand, no significant difference was observed between BMI and pDETECT (Table 3).

DISCUSSION

In our study, we observed that whether or not taking bDMARD does not have any effect on RA patients. The frequency of NeP was 11.4% in patients with RA, and there was no difference between patients receiving bDMARDs and cDMARDs with regard to NeP ($p>0.05$). A positive correlation was observed between pDETECT scoring, which evaluates NeP, and RA disease duration, DAS28-CRP, VAS pain, VAS fatigue, Beck depression index, Beck anxiety index, ESR, and TJC. Interestingly, we observed a negative correlation between the total number of medicines used and pDETECT and did not observe any relationship between BMI and pDETECT.

Chronic pain is the leading cause of RA, and it can occur via different mechanisms. Pain in RA may arise from nociceptive pain originating from the synovium and periarticular tissues, pains such as NeP occurring via central or peripheral sensitization, or comorbid conditions like osteoarthritis or fibromyalgia or psychological causes (12). Although the pathogenesis of NeP is not entirely understood, it is a pain where the peripheral and central nervous systems are affected and is non-nociceptive and unrelated to peripheral articular damage. Medicines, comorbid conditions like DM and vasculitis, can also cause NeP (13). On the other hand, it has been established that cytokines such as tumour necrosis factor alpha (TNFα), interleukin 1, and interleukin 6, which play a role in the pathogenesis of RA, partake in the formation of NeP by being involved in peripheral and central sensitization mechanisms apart from inflammation and articular damage (14).

However, there are controversial studies regarding whether or not bDMARD treatments like anti-TNFα are effective against NeP. It has been demonstrated that TNFα blockade affects the pain sensitivity of the central nervous system, thereby reducing pain before the onset of the peripheral anti-inflammatory effect starts (15). In addition, it has been shown that TNFα blockade reduces pain with antinociceptive effects by impacting peripheral efferent C nerve fibers. This may explain why anti-TNFα medicines decrease pain rapidly before the anti-inflammatory effect starts in the joints (16). However, many studies have demonstrated that non-steroidal anti-inflammatory drugs do not have an effect on the treatment of NeP (17). A study conducted in 112 patients

Table 1. Demographic data of patients and control group

	bDMARD	non-bDMARD	Control	Total	p
Number of patients					
n	60	45	106	211	-
Age					
Average	51.2	53.6	46.9	49.5	0.47
Gender					
Female n (%)	53 (25.1)	39 (18.5)	73 (34.6)	165 (78.2)	0.004
Male n (%)	7 (3.3)	6 (2.8)	33 (15.6)	46 (21.8)	
Marital status					
Married n (%)	48 (22.7)	41 (19.4)	78 (37)	167 (79.1)	0.52
Single n (%)	12 (5.7)	4 (1.9)	28 (13.3)	44 (20.9)	
Educational status					
Below primary education n (%)	13 (6.2)	17 (8.1)	19 (9)	49 (23.2)	0.003
Primary education n (%)	44 (20.9)	23 (10.9)	61 (28.9)	128 (60.7)	
Undergraduate n (%)	2 (0.9)	5 (2.4)	25 (11.8)	32 (15.2)	
Postgraduate n (%)	1 (0.9)	0 (0)	1 (0.5)	2 (0.9)	
Smoking					
Yes n (%)	9 (4.3)	9 (4.3)	29 (13.7)	47 (22.3)	0.16
No n (%)	51 (24.2)	36 (17.1)	77 (36.5)	164 (77.7)	
BMI					
Average	27.9	27.6	27.1	27.4	0.85
Other medication					
Yes n (%)	22 (10.4)	23 (10.9)	28 (13.3)	73 (34.6)	0.013
No n (%)	38 (18)	22 (10.4)	78 (37)	138 (65.4)	
RF					
Positive n (%)	33 (15.5)	24 (11.4)	0 (0)	57 (27)	0.00
Negative n (%)	27 (12.8)	21 (10)	106 (50.2)	154 (73)	
Anti-CCP					
Positive n (%)	28 (13.3)	11 (5.2)	0 (0)	39 (18.5)	0.00
Negative n (%)	32 (15.2)	34 (16.1)	106 (50.2)	172 (81.5)	
Deformity					
Yes n (%)	17 (8.1)	7 (3.3)	0 (0)	24 (11.4)	0.00
No n (%)	43 (20.4)	38 (18)	106 (50.2)	187 (88.6)	
painDETECT					
No NeP	28 (13.3)	29 (13.7)	72 (34.1)	129 (61.1)	0.06
NeP unspecified	17 (8.1)	7 (3.3)	21 (10.0)	45 (21.3)	
NeP possible	15 (7.1)	9 (4.3)	13 (6.2)	37 (17.5)	

BMI: Body mass index, RF: Rheumatoid factor, Anti-CCP: Anti-cyclic citrullinated peptide, NeP: Neuropathic pain, bDMARD: Biological disease-modifying antirheumatic drugs

with RA showed that methotrexate, hydroxychloroquine, and leflunomide, which are cDMARDs, may be associated with NeP (18). In our study, we found that bDMARD or cDMARD use does not have any effect on NeP. In another study, the NeP frequency was observed as 38% and, similar to our study, it has been reported that cDMARD and bDMARD use does not have any effect on NeP (19). However, in this study, a lower number of patients used bDMARD, and the control group did not receive NeP. In another study that we conducted, we did not observe any relationship between NeP and anti-TNFα agents in patients with ankylosing spondylitis, again as in RA, but it was correlated with the NeP disease activity indicators (20).

It was previously reported that RA patients in whom a change of treatment is performed or treatment is intensified commonly exhibit NeP. NeP frequency is higher in patients with a poor quality of life index, disability, pain, fatigue, and anxiety (21). Similarly, in our study, NeP was also higher in patients with high HAQ scores, VAS pain, VAS fatigue, and the Beck anxiety index and Beck depression index. In addition, there was a positive correlation between the DAS28-CRP score and pDETECT.

Table 2. Clinical properties of the patients and control group

		n	Mean	SD	p
PainDETECT	Control group	106	8.03	7.61	0.00
	Receiver of biological medicine	60	13.90	5.81	
	Non-receiver of biological medicine	45	11.68	7.06	
	Total	211	10.48	7.45	
VAS pain	Control group	106	3.44	3.27	0.00
	Receiver of biological medicine	60	5.65	2.50	
	Non-receiver of biological medicine	45	4.62	2.77	
	Total	211	4.32	3.10	
VAS fatigue	Control group	106	3.70	3.14	0.02
	Receiver of biological medicine	60	5.38	2.57	
	Non-receiver of biological medicine	45	4.26	2.56	
	Total	211	4.30	2.95	
DAS28-CRP	Control group	106	2.65	1.14	0.00
	Receiver of biological medicine	60	3.46	1.26	
	Non-receiver of biological medicine	45	3.36	1.29	
	Total	211	3.03	1.26	
ESR	Control group	106	16.50	10.52	0.007
	Receiver of biological medicine	60	22.66	16.92	
	Non-receiver of biological medicine	45	22.64	16.94	
	Total	211	19.56	14.33	
CRP	Control group	106	6.82	8.22	0.008
	Receiver of biological medicine	60	13.59	19.37	
	Non-receiver of biological medicine	45	11.60	16.64	
	Total	211	9.76	14.37	
Beck anxiety index	Control group	106	11.37	10.70	0.01
	Receiver of biological medicine	60	15.93	10.52	
	Non-receiver of biological medicine	45	15.35	10.64	
	Total	211	13.52	10.81	
Beck depression index	Control group	106	9.25	8.77	0.09
	Receiver of biological medicine	60	11.75	8.38	
	Non-receiver of biological medicine	45	11.91	8.12	
	Total	211	10.53	8.58	
RA quality of life index	Control group	106	8.32	7.56	0.00
	Receiver of biological medicine	60	13.46	7.26	
	Non-receiver of biological medicine	45	11.80	8.06	
	Total	211	10.52	7.89	
HAQ score	Control group	106	6.39	8.55	0.003
	Receiver of biological medicine	60	11.18	10.44	
	Non-receiver of biological medicine	45	10.08	9.48	
	Total	211	8.54	9.53	

VAS: Visual analog scale, DAS28-CRP: Disease activity score in 28 joints calculated with C-reactive protein, ESR: Erythrocyte sedimentation rate, RA: Rheumatoid arthritis, HAQ: Health assessment questionnaire, SD: Standard deviation

Table 3. Correlation analysis of clinical and demographic properties of the patients and control group

		BMI	PainDETECT	HAQ	Beck depression index	VAS pain	RA disease duration	VAS fatigue	DAS28 CRP	Beck anxiety index	ESR	TJC	Number of drugs used for RA
BMI	**r**	1.00	0.02	0.02	-0.04	0.04	0.10	0.05	0.14	-0.03	0.99	0.59	0.90
	p		0.76	0.67	0.47	0.53	0.14	0.41	0.03	0.60	0.15	0.39	0.19
PainDETECT	**r**		1.00	0.60	0.40	0.59	0.56	0.59	0.48	0.60	0.22	0.36	0.34
	p			0.00	0.000	0.000	0.000	0.000	0.000	0.000	0.001	0.000	0.000
HAQ	**r**			1.00	0.56	0.52	0.30	0.46	0.51	0.52	0.23	0.34	-0.27
	p				0.00	0.00	0.00	0.00	0.00	0.00	0.001	0.00	0.00
Beck depression index	**r**				1.00	0.25	0.17	0.30	0.28	0.56	0.97	0.24	-0.21
	p					0.00	0.01	0.00	0.00	0.00	0.16	0.00	0.00
VAS pain	**r**					1.00	0.32	0.68	0.59	0.34	0.25	0.30	-0.25
	p						0.00	0.00	0.00	0.00	0.00	0.00	0.00
RA disease duration	r						1.00	0.27	0.33	0.26	0.17	0,69	-0.91
	p							0.00	0.00	0.00	0.01	0.00	0.00
VAS fatigue	**r**							1.00	0.42	0.44	0.21	0.20	-0.20
	p								0.00	0.00	0.00	0.003	0.003
DAS28 CRP	**r**								1.00	0.30	0.60	0.50	0.32
	p									0.00	0.00	0.00	0.00
Beck anxiety index	**r**									1.00	0.05	0.24	0.25
	p										0.45	0.00	0.00
ESR	r										1.00	0.18	-0.34
	p											0.008	0.01
TJC	**r**											1.00	-0.73
	p												0.00

BMI: Body mass index, HAQ: Health assessment questionnaire, VAS: Visual analog scale, RA: Rheumatoid arthritis, DAS28-CRP: Disease activity score in 28 joints calculated with C-reactive protein, ESR: Erythrocyte sedimentation rate, TJC: Tender joint count

This may cause a higher detection of DAS28-CRP, which is considered to demonstrate disease activity and hence inflammatory activity in RA patients with NeP. In our study, we observed that deformity had no effect on NeP. However, the number of patients with deformities was 24 (11.4%), which should be noted as low. A study conducted by Martins Rocha et al. (18) demonstrated, similar to our study, that structural damage has not been effective on NeP. In this study, it was also stated that the duration of the disease and anti-CCP therapy were not effective against NeP. In our study, although no relationship with anti-CCP was detected, NeP was found to be related to disease duration. In the studies carried out, NeP was more common in those in their 40s and 50s (22). Patient's age might be affecting this condition when the duration of the disease is being evaluated.

Although NeP has a similar frequency to that of RA in patients with connective tissue diseases such as systemic sclerosis, the patient load due to NeP is higher in patients with RA (23). Furthermore, NeP seems to affect remission success even in early RA patients (24). It should be noted that NeP may be affected by not only the primary disease but also the medicines used and conditions such as vitamin deficiency as well (25). In our study, we observed a negative correlation between increased medication use and NeP, but we did not investigate the relationship between vitamin deficiency and NeP.

Although the relationship between NeP and obesity is not clearly identified, NeP is unfavorably affected by weight gain unfavorably (26). In a study conducted by Ito et al. (27) in 300 patients with RA, a significant relationship was reported between

NeP and BMI, and because the study was conducted in the Japanese population, BMI was calculated as >22. In another study carried out by Ahmed et al. (7), again on RA patients, a significant association was observed between NeP and BMI, and here BMI was taken as >30. Interestingly, in our study, we did not observe any relationship between BMI and NeP. The BMI of the patients and control group were similar, and there was no difference. This result may be attributed to the fact that the BMI was approximately 27 kg/m^2 in our study. This should be re-studied in patients with higher BMI.

Study Limitations

The strengths of the study are that it compared the patients who received bDMARDs and cDMARD sand performed detailed measurements of disease activity, used anxiety and depression scales, and HAQ, as well as the RA quality of life index. Fibromyalgia and vitamin examinations were not performed. However, we used a control group with similar age and gender. Another limitation of this study was that we measured the efficacy of each medicine individually. It should also be noted that the sample size was relatively small. To this end, prospective monitoring of a high number of patients may lead to more detailed data on the medicines.

CONCLUSION

As a result, NeP is common in patients with RA, and treatment with bDMARDs does not change the frequency of NeP. The possibility of NeP is higher in RA patients with long disease duration, high disease activity scales, high pain and fatigue scores, high TJC, and anxiety and depression. When measuring disease activity, the presence of NeP should be investigated to increase the quality of life of patients with RA.

Ethics

Ethics Committee Approval: The study was approved by the Hatay Mustafa Kemal University Non-Interventional Clinical Research Ethics Committee (approval number: 05, date: 01.07.2021).

Informed Consent: Signed informed consent forms were obtained from the patients participating in the study.

Footnotes

Authorship Contributions

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

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

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CASE REPORT AND LITERATURE REVIEW

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FIVE CASES OF ACUTE ARTHRITIS: BRUCELLOSIS AND LITERATURE REVIEW

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Abstract

Brucellosis is a zoonotic disease frequently observed in regions where animal husbandry is intensive in Eastern and Southeast Anatolia. The most common transmission route is raw milk and unpasteurized dairy products. The condition can affect many organs and systems in the body, and clinical findings can vary depending on the location. This condition should be considered in the differential diagnosis of acute joint pain due to unknown causes. Early diagnosis of *Brucella* septic arthritis in endemic regions is important to prevent serious complications. Here, clinical, laboratory, and imaging data of five healthy patients with acute joint involvement who visited the outpatient clinic were presented with the support of visuals and literature.

Keywords: Brucellosis, endemic, arthritis, joint involvement

INTRODUCTION

Brucellosis is a zoonotic disease that is frequently observed in regions where animal husbandry is concentrated in Eastern and Southeast Anatolia. The most common route of transmission is through consumption of raw milk and unpasteurized dairy products obtained from animals infected with this gram-negative bacillus of the genus *Brucella* (1). After contamination, it first enters the reticuloendothelial system and spreads through the blood, causing various symptoms. The condition can affect many organs and systems, and clinical findings may vary depending on the location. It often presents as fever, fatigue, and non-specific widespread joint pain (2).

Osteoarticular involvement is a common finding in brucellosis. The most important clinical forms of osteoarticular arthritis are osteomyelitis, spondylitis, sacroiliitis, and peripheric arthritis. Soft tissue involvement around the joint may also cause tenosynovitis and bursitis. In addition, it can cause serious damage, such as the destruction of vertebrae and abscess formation in paravertebral muscle tissue (3).

Although the first symptoms are usually complaints such as fatigue, sweating, and fever, in the presence of low back pain, the pain character resembles enflammatory pain and can be confused with rheumatic diseases. This is still an increasing problem in differential diagnosis, especially in developing countries. It should be considered in patients with acute joint pain of unknown cause. This section presents five cases of brucellosis treated in an outpatient clinic with acute joint involvement.

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DETAILS OF CASE REPORTS

Case 1

Forty-six-year-old male patient with a history of continuous low back pain and weakness for two weeks. His back pain was worse at night and could not be relieved with simple painkillers. He also stated that he had been in pain throughout the day for the last month and had difficulty walking due to the pain. Since the onset of pain, he had lost about 3 kg of weight, along with a decrease in his appetite. He mentioned no fever or night sweats. He had no known disease, no history of drug use, and no family history. In the locomotor system examination, we observed pain and joint movement limitation in both hips. The Fabere test was positive on the left side. Laboratory findings included: white blood cell (WBC) count of 8.700/mm^3 (normal range: 3.500-11.000/mm^3), hemoglobin of 14.6 g/dL (normal range: 12.8-16.8 g/dL), C-reactive protein (CRP) of 29.9 mg/L (normal range: 0.1-5 mg/L), and erythrocyte sedimentation rate (ESR) of 55 mm/hour (normal range: 0-20 mm/hour). Rheumatic factor (RF), viral hepatitis B serology and anti-hepatitis C virus (anti-HCV) antibodies were negative. HLA-B27 was positive. Plain chest and pelvic X-ray results were normal. Magnetic resonance imaging (MRI) of the sacroiliac joint revealed similar changes; signal changes that may be compatible with bone marrow edema and enflammation were observed in the T2A series on the iliac and sacral bone faces, overlooking the left sacroiliac joint. The findings were in favor of active sacroiliitis on the left and spondylodiscitis on the Thoracolumbar MRI (Figure 1). After a detailed analysis, he mentioned that he probably had eaten unpasteurized products. The Rose Bengal screening test (RBT) was positive, so a *Brucella* tube agglutination test was performed. The serum standard tube agglutination titer was 1/320 (normal range: <1/160). He was referred to the infectious disease department, and the diagnosis of brucellosis was confirmed. The patient was treated with oral doxycycline and rifampicin for 8 weeks. Upon follow-up, the patient showed a significant decrease in low back pain, CRP levels returned to normal, and the *Brucella* agglutination test was positive at a 1/80 titer. A non-steroidal anti-enflammatory drug (NSAID) was administered on demand.

Case 2

A 22-year-old male patient presented with a history of left hip pain for 2 weeks. He was referred to the orthopedic clinic because of enflammation. The joint was tender with a restricted range of motion. He had no history of trauma or drug use. He also complained of fatigue and low-grade fever. He stated that he lived in a village, that there were livestock nearby, and that animal husbandry was performed. During the examination, his body temperature was elevated (37.8 ºC), and mild tenderness was noted over the right sacroiliac joint. The peripheral WBC count was 12.500 cells/mm^3, CRP level was 45.1 mg/L (normal range: 0.1-5 mg/L), and ESR was 76 mm/h (normal range: 0-20 mm/hour). RF, viral hepatitis serology (HBsAg and anti-HCV), and HLA-B27 were negative. MRI of the left hip showed effusion and

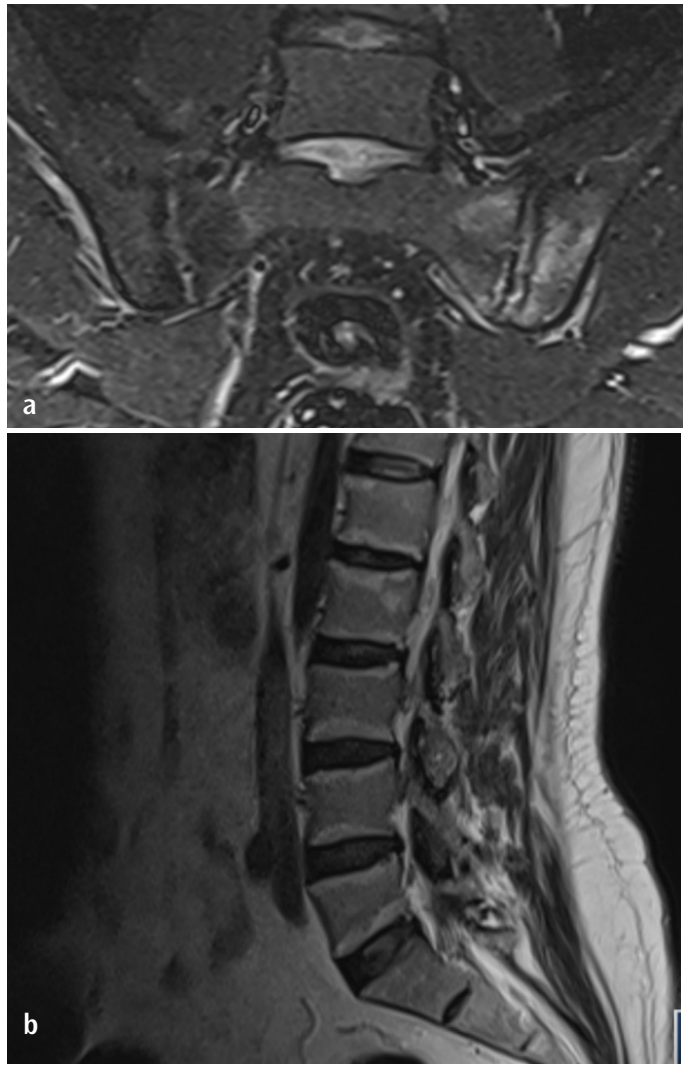

Figure 1. a) Sacroiliac MRI: Areas with millimetric cystic signal characteristics and slight irregularities were observed on the bone surfaces forming the sacroiliac joint on the right. On the left side, in addition to similar changes, signal changes that may be compatible with bone marrow edema and inflammation were observed in a T2A series of the iliac and sacral bone faces overlooking the sacroiliac joint. The findings were in favor of active sacroiliitis on the left. b) Thoracolomber MRI: T1 and T2 are compatible with fatty degeneration in the lower thoracic vertebra and lumbar vertebra, and edema in the lumbar vertebra corpus appears suspicious for spondylodiscitis
MRI: Magnetic resonance imaging

a widespread focal area of enhanced marrow signal intensity in the femur bone (Figure 2). The RBT was positive, and the Wright agglutination test was positive at a 1/640 titer. After evaluation with an infectious disease physician regarding the differential diagnosis, the patient was treated. He received three months of rifampicin and doxycycline and was fully recovered. The following treatment with short-term NSAIDs for joint pain, his symptoms and complaints improved dramatically. Sulfasalazine was administered at a dose of 2000 mg/day for 6 months.

Case 3

A 42-year-old man was admitted with an 8-week history of left-sided back and buttock pain. His pain was not relieved by NSAID and progressively worsened over 4 weeks. He complained of listlessness, night sweating, and pain-restricting movements in bed and while walking. The morning stiffness lasted more than an hour. His left hip flexion was limited, and he was moderately tender to palpation at the right sacroiliac joint. The patient lived in a rural area and was engaged in animal husbandry. The blood results included an increased CRP level of 45.1 mg/L (normal range: 0.1-5 mg/L) and an increased ESR of 76 mm/hour (normal range: 0-20 mm/hour), and normal liver and renal function tests. RF, HBsAg and anti-HCV, and tuberculin skin tests were negative. HLA-B27 was positive. An X-ray examination of the hip was normal. MRI of the sacroiliac joint was performed in favor of active sacroiliitis, and the left hip showed enhanced marrow signal intensity and effusion (Figure 3a, b). The RBT for brucellosis was positive, and the Wright agglutination test was positive at 1/320 titers. The patient was initially treated with doxycycline and rifampicin for six weeks. The complaints of all patients decreased after treatment. CRP levels returned to normal, and the *Brucella* agglutination test was positive at a 1/40 titer after treatment.

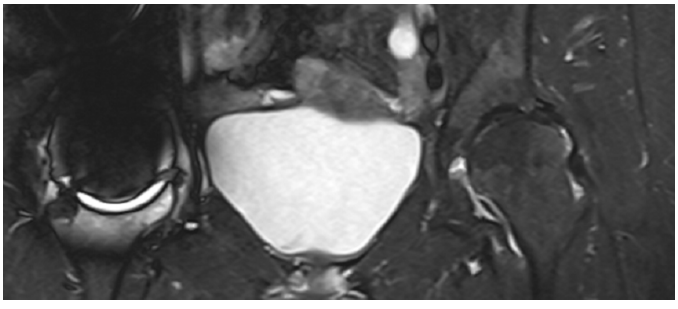

Figure 2. MRI of the left hip showing effusion and a widespread focal area of enhanced marrow signal intensity in the femur bone
MRI: Magnetic resonance imaging

Case 4

A 51-year-old female patient was admitted with a 3-week history of left knee pain. Her knee had worsened over the past 10 days and was swollen; she was unable to walk. The other complaints were listlessness, night sweating, and mild fever over the past 2 weeks. She had no known disease in her medical history. She mentioned that her son was a farmer in the village. The blood results included an increased CRP level of 18.2 mg/L (normal range: 0.1-5 mg/L), an increased ESR of 76 mm/h (normal range: 0-20 mm/hour), a normal WBC count of 13.300/mm^3, and renal function tests. RF and viral hepatitis serology (HBsAg and anti-HCV) were negative, HLA-B27 was negative, and the anti-tuberculosis antibody test was negative. She aspirated

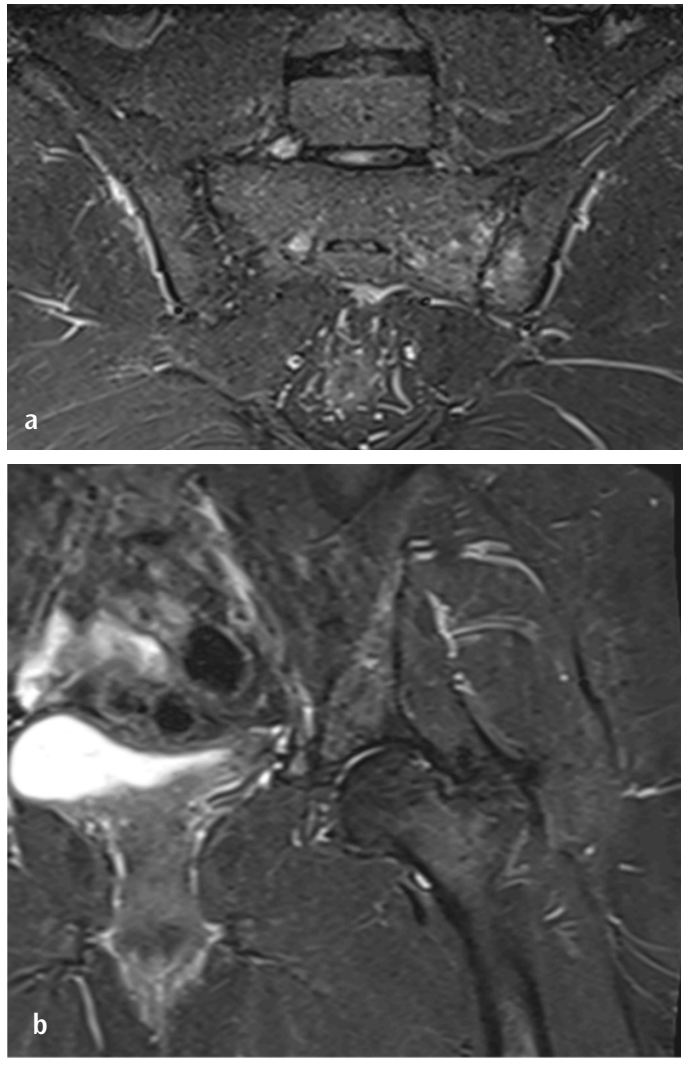

Figure 3. a) Active sacroiliitis is seen in the left iliac bone on T2WI, b) Magnetic resonance images of the left hip showing enhanced marrow signal intensity and effusion on T2WI
WI: Weighted imaging

the synovial fluid and sent a sample for culture. There was no bacterial growth in blood cultures, but *Brucella melitensis* was isolated in bursal aspiration fluid cultures on the fourth day of incubation. MRI of the left knee showed enhanced marrow signal intensity and effusion on T2WI (Figure 4). The RBT for brucellosis was positive, and the Wright agglutination test was positive at a 1/640 titer. The following treatment with NSAIDs, doxycycline, and rifampicin, her symptoms and complaints improved. Sulfasalazine was administered at 2000 mg/day for 6 months. *Brucella*'s agglutination test was positive at a 1/80 titer.

Case 5

A 52-year-old man was admitted with a 4-week history of right shoulder pain and night sweating. The patient reported occasional tactile fevers over the past 2 weeks. He mentioned that his son was a farmer, and he had kept a few animals. He was moderately tender, with right shoulder palpation. He could not move his shoulder in any direction. The morning stiffness lasted more than 2 hours. Laboratory studies revealed a mildly elevated ESR of 43 mm/hour, CRP of 36.8 mg/L, and WBC count of 11.800/mm^3. Normal liver and renal function tests. RF and viral hepatitis serology (HBsAg and anti-HCV) were negative. HLA-B27 was positive, but the anti-tuberculosis antibody test was negative. Imaging methods were also used for differential diagnosis. The patient's right shoulder MRI revealed findings consistent with effusion and tendinitis (Figure 5a, b). The RBT for brucellosis was positive, and the Wright agglutination test revealed positivity for 1/320. He was referred to the infectious disease department, and the diagnosis of brucellosis was confirmed. The patient was treated with oral doxycycline (200 mg) daily and rifampicin (300 mg) three times a day, combined with absolute bed rest for six weeks. Upon follow-up, the patient showed a significant decrease in lower back pain, CRP levels returned to normal, and the *Brucella* agglutination test was positive at a 1/40 titer. NSAIDs were administered on demand.

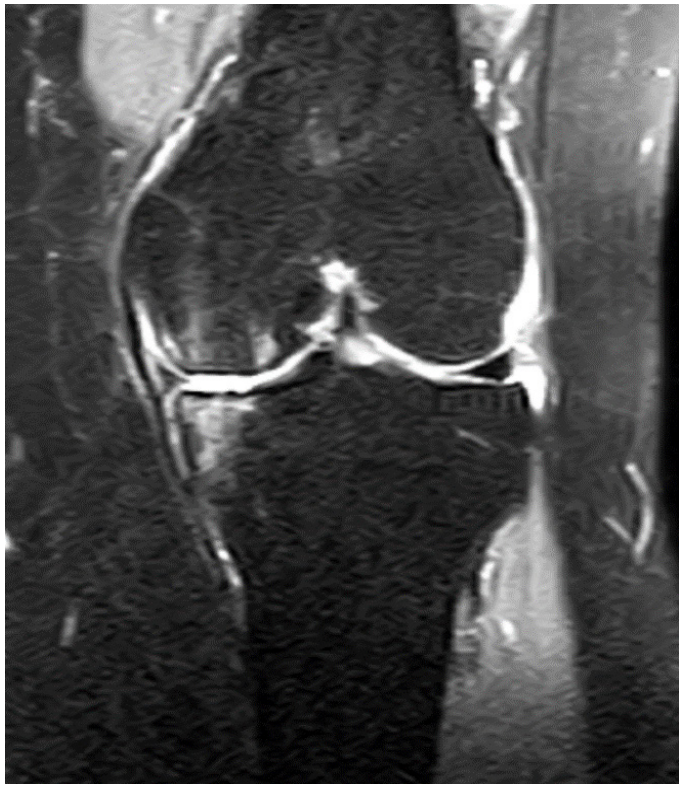

Figure 4. Magnetic resonance images of the left knee show increased joint fluid extending into the suprapatellar pouch. A millimetric Baker cyst is observed in the popliteal fossa

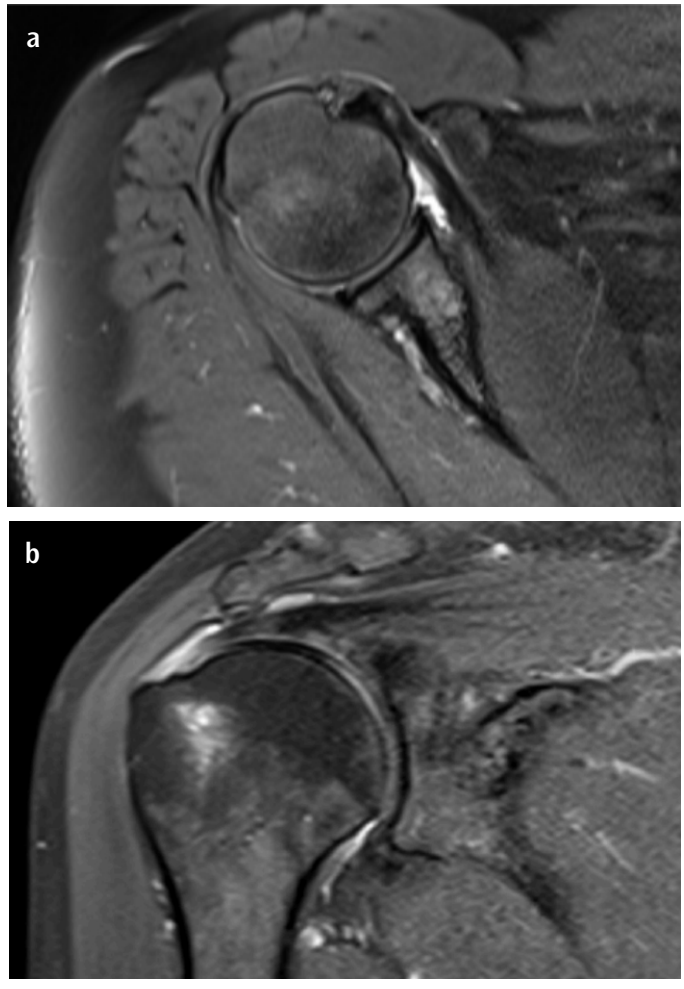

Figure 5. T2-weighted (a) sagittal and (b) coronal magnetic resonance images of right shoulder showing an increase in the subacromial subcoracoid bursa and intra-articular fluid in the bicipital groove (biceps tendinitis) and fluid around the subscapularis tendon (tendonitis)

DISCUSSION

In this study, five cases of acute joint involvement secondary to Brucella abortus infection were included. *Brucella* species (spp.) are highly virulent and cause acute and common infections in humans and animals. The most frequently isolated species of brucellosis worldwide is *B. melitensis*. The most common reservoirs are sheep and goats. Abortus is found especially in cattle. These gram-negative bacteria can persist in raw milk and other dairy products for a long time. They are inactivated by boiling and pasteurization (3,4).

This bacterium is known to cause neurological, cardiovascular, respiratory, and genitourinary infections and frequently causes musculoskeletal involvement (5).

Brucellosis is an important public health problem in Turkey, and various studies have shown that its prevalence varies between 1% and 7% in regions where it is endemic in Turkey. This study examined the situation in the Middle-Eastern Anatolia region. In different studies conducted in this region, cases were frequently (21.7%) reported in the Eastern Anatolia Region (6). In a prevalence study in Erzincan province, as seen in a study in the literature in 2007, RBT and *Brucella* antibodies were investigated with serological methods in 1715 people aged 15 and over in a non-probability sample in the province and its surroundings. Seropositivity was detected in 83 (4.83%) samples. RBT positivity was found to be 3.89% in the center and 8.55% in rural areas (7).

Serology and culture are required to definitively diagnose brucellosis. Although isolation of *Brucella* spp. from blood or other tissues is the gold standard for diagnosis, this approach makes diagnosis difficult due to the low rate of culture reproduction. In cases of joint involvement, isolating *Brucella* spp. in the relevant joint bursal aspiration fluid culture can be used for diagnosis. The most commonly used serological test is the serum agglutination test. Titers of 1:160 and above are considered significant in endemic areas. Routine blood markers, such as ESR and CRP, used to monitor infections are often high, but being normal does not rule out infection (3,8). In all cases, the serological values were high and returned to normal after optimal treatments as indicated in Table 1.

According to previous studies, osteoarticular involvement varies between 20% and 60%, and spondylitis due to spinal involvement is observed in 8-13% of cases. The most common musculoskeletal symptom of brucellosis is sacroiliitis, followed by peripheral arthritis (arthralgia), spondylitis, osteomyelitis, and bursitis (4,9). Sacroiliitis is usually unilateral, does not cause destruction, and responds to antibiotic treatment. Arthritis often presents as monoarthritis or asymmetric peripheral oligoarthritis. Peripheral *Brucella* arthritis usually affects large and weight-bearing hip, knee, and ankle joints. Generally, the onset of arthritis is acute and very painful, with redness, increased temperature, effusion, and limitations of movement in the affected joint. Arthritis is either infectious or reactive, and the frequency of arthritic development increases with increasing duration of infection. Peripheral arthritis responds to antibiotic therapy, but spontaneous recurrence may occur (10).

Table 1. Brief summary of the clinical and laboratory profiles of the five cases studied

Patient number	Age in years	Gender	Clinical history	Joint involved	CRP	Serology	HLA-B27	Treatments
Case 1	46	Male	Enflammatory back and lower back pain 1 h of morning stiffness, listlessness, and night sweats	Sacroiliac thoracolumbar vertebra	29.9 mg/dL	1/320	Positive	Doxy-rifampin acemetacin (120 mg)
Case 2	22	Male	Hip-groin pain difficulty walking and hip arthritis	L hip	45.1 mg/dL	1/640	-	Doxy/rifampicin naproksen 750 mg/day sle 2x2
Case 3	42	Male	Lower back pain, listlessness, night sweats	Sacroiliac	17 mg/dL	1/320	Positive	Doxy/rifampicin acemetacin 120 mg
Case 4	51	Female	Knee pain, knee arthritis, listlessness, night sweats	L knee	18.2 mg/dL	1/640	-	Doxy/rifampicin sle 2x2
Case 5	52	Male	Shoulder pain, limited movement arthritis, night sweats	R shoulder	36.8 mg/dL	1/320	Positive	Doxy/rifamicin

L: Left; R: Right; mg: Miligram, slz: Sulfosalazine, Doxy: Doxycycline, MRI: Magnetic resonance imaging, CRP: C-reactive protein

Recent publications have supported the view that there may be a genetic predisposition associated with the *HLA-B27* gene in the development of osteoarticular complications. There are cases of first- and co-occurrence of AS brucellosis that can be confused with non-radiographic Ax-spondyloarthropathy (SpA) in the same patient. The frequent occurrence of osteoarticular involvement should be kept in mind in terms of differential diagnosis, and it would be beneficial to evaluate patients with detailed examinations in this regard (11). In these cases, three patients were HLA-B27-positive. In both cases, the patients were given NSAIDs for a while.

Early bone changes are not evident on plain radiography, so MRI is important for early diagnosis. The differential diagnosis of infectious and inflammatory sacroiliitis is extremely important, as their treatments are very different. Early detection of sacroiliitis on MRI is important in the diagnosis of SpA, but the presence of sacroiliitis may cause overdiagnosis. While bilateral sacroiliitis is more common in spondyloarthritis, unilateral involvement involving soft tissue should be considered in septic cases in terms of differential diagnosis (12,13).

Because *Brucella* spondylitis and its associated damage can be confused with spinal tuberculosis (Pott disease), a history of tuberculosis should also be questioned in the differential diagnosis (14). The two cases mentioned here had active sacroiliitis and unilateral asymmetric involvement. Joint pain was completely resolved with a short-term NSAID administered after double antibiotic treatment.

The selection of the appropriate antibiotic combination should be based on the patient. In the triple regimen recommended by the World Health Organization, doxycycline (100 mg twice a day) plus rifampin (600 mg/day) plus streptomycin (1 g/day im 21 days) is recommended to be given for six months. After discontinuing streptomycin treatment at the end of three weeks, patients are switched to doxycycline and rifampin treatment only (3,15). The patients received dual medication (doxycycline and rifampicin treatment) for at least six weeks. In two cases (cases 2 and 4), additional sulfasalazine treatment (2000 mg/day) was administered for 6 months. NSAID treatment was administered in the necessary cases. No side effects were observed, and the patient's complaints about joint involvement and acute phase reactant levels decreased after treatment.

CONCLUSION

Brucellosis is considered an important health problem in Erzincan province. In patients with suspicion of brucellosis, occupational history, living space, and nutritional habits should be examined. To protect against Brucella infection, the blood, milk, or tissue fluids of infected animals should be avoided, animal products should be cooked well, and hygiene rules should be observed. Additionally, appropriate protective measures should be taken for at-risk professional groups (farmers, veterinarians, laboratory workers, etc.).

Because of the different treatments, early recognition of infectious arthritis is important and brucellosis should be considered in these endemic areas. It was prepared with the thought that the facts presented would contribute to the literature and raise awareness in this regard.

Ethics

Informed Consent: Written and oral consent was obtained from all patients included in the study.

Footnotes

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LETTER TO THE EDITOR

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RHEUMATOID FACTOR: WHAT GOOD FOR PEDIATRIC RHEUMATOLOGY?

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To editor:

Rheumatoid factor (RF) is an immunoglobulin M molecule directed against the fragment crystallizable portion of immunoglobulin G. It is mainly found in patients with rheumatoid arthritis, with approximately 80-90% of patients with rheumatoid arthritis testing positive for RF (1,2). Juvenile idiopathic arthritis (JIA) is the most common type of chronic arthritis in childhood. It is a diagnosis of exclusion, in which other causes of arthritis should be excluded, and arthritis should be present for at least 6 weeks. JIA has seven subtypes, and RF-positive polyarticular JIA comprises only 5% of children with JIA (3,4). RF positivity can also be found in other rheumatic diseases, such as Sjögren disease, systemic sclerosis, mixed connective tissue disease, cryoglobulinemia, and granulomatosis with polyangiitis. Additionally, RF may be present in infectious diseases like hepatitis B, hepatitis C, Epstein-Barr virus, and subacute bacterial endocarditis. Moreover, around 3-8% of healthy children may test positive for RF, especially after infection (1,2).

In pediatric rheumatology, no single diagnostic test is available for any disease. Laboratory tests are used to support the clinical diagnosis given to a patient after history taking and physical examination (1,2,5). Herein, we present 4 cases that were referred to pediatric rheumatology due to RF positivity with the provisional diagnosis of RF-positive polyarticular JIA and discuss the outcomes of the children. A summary of the cases is presented in Table 1.

A 15-year-old boy was referred to our pediatric rheumatology department for right knee pain with RF positivity [RF 138 IU/mL (normal: 0-14)]. The child had right knee pain for 2 weeks. He had febrile diarrhea for 7 days and had been taking antibiotics for 10 days a week before the symptoms started. The family did not report any rash, joint swelling, or fever during the visit. The child did not have arthritis in any joint but exhibited point tenderness in the superior medial part of the proximal tibia. Acute phase reactants were elevated [C-reactive protein (CRP): 88 mg/L (normal 0-5)], erythrocyte sedimentation rate (ESR): 65 mm/hr (normal: 0-15)]. The clinical picture was compatible with subacute osteomyelitis, and an orthopedic consultation was made. An X-ray of the right knee was normal, and magnetic resonance imaging revealed diffuse medullary edema (hyperintense on T2, hypointense on T1) in the upper two-thirds of the tibia with involvement of adjacent soft tissue. The child underwent surgery, and *Staphylococcus aureus* was isolated from the pus. He received antibiotic treatment for a month and was discharged without sequelae.

A 13-year-old girl was referred to pediatric rheumatology for joint pain in the hands for 2 months and RF positivity (RF: 52 IU/mL). She described pain in her hands and fingers with morning stiffness. Physical examination revealed arthritis in the bilateral wrists, elbows, 2nd and 3rd metacarpophalangeal and proximal

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Table 1. Demographics, laboratory features, and outcomes of the cases

	Age	Gender	Main complaint	Laboratory results	Referral diagnosis	Final diagnosis	Outcome
Case 1	15	M	Right knee pain for 2 weeks	RF: 138 IU/mL CRP: 88 mg/L ESR: 65 mm/hr	JIA	Subacute osteomyelitis	Complete healing with surgery and antibiotics
Case 2	13	F	Joint pain for 2 months	RF: 52 IU/mL CRP: 23 mg/L ESR: 42 mm/hr	JIA	JIA	Remission with methotrexate and prednisolone
Case 3	10	M	Recurring artralgia, swelling, and redness in the ankle joints for 2 years	RF: 25 IU/mL CRP 1.2 mg/L ESR: 8 mm/hr	JIA	FMF	Remission with colchicine treatment
Case 4	13	F	Joint pains for 2 years	RF: 36 IU/mL CRP: 0.6 mg/L ESR: 5 mm/hr	JIA	BJHS	Remission with physical therapy

M: Male, F: Female, RF: Rheumatoid factor, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, JIA: Juvenile idiopathic arthritis, FMF: Familial Mediterranean fever, BJHS: Benign joint hypermobility syndrome

interphalangeal joints. Acute phase reactants were elevated (CRP: 23.6 mg/L, ESR: 42 mm/hr). The clinical picture was compatible with RF-positive polyarticular JIA, and methotrexate (15 mg/m^2/week, sc) and prednisolone (1 mg/kg/day, po) were started. Prednisolone was administered for 6 weeks and was discontinued with gradual tapering. By the 3rd month of treatment, she had resolution of arthritis in all joints.

A 10-year-old boy was referred to pediatric rheumatology due to pain and swelling in the ankle joints and a positive RF test (RF: 25 IU/mL). He did not have arthritis in any joints at the time of referral. There was medical history of joint pain and swelling in the ankles over the past 2 years. The swellings, occurring on either the right or left ankle, were lasting for 5-7 days and recurring every 2-3 months, accompanied by redness around the ankle in some episodes. He had elevated CRP (40-60 mg/L) and ESR (35-65 mm/hr) levels during the arthritis attack. The clinical features were compatible with arthritis and erysipelas-like erythema attacks of familial Mediterranean fever. The family denied any prior episodes of recurrent fever and abdominal pain. *MEFV* gene analysis showed a homozygous M694V mutation, and colchicine treatment was started. The child has been taking colchicine for 3 years and has only experienced one episode of arthritis without any accompanying fever or abdominal pain.

A 14-year-old girl was referred to pediatric rheumatology due to joint pain and a positive RF test result (RF: 36 IU/mL). She had been experiencing joint pain for 2 years, without reporting any joint swelling or morning stiffness, but noted that the pain was more pronounced after exercise. On examination, she did not have arthritis but joint hypermobility. The clinical picture was compatible with benign joint hypermobility syndrome, and she was referred to the physical therapy unit. At the 6th month of follow-up, the RF test was negative.

As demonstrated in the present case series, pediatric rheumatologists do not rely solely on laboratory results for diagnosis. Laboratory tests should be ordered and interpreted in combination with patient history and physical examination findings.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.Ç., M.İ.N., Concept: M.Ç., M.İ.N., Design: M.Ç., M.İ.N., Data Collection or Processing: M.Ç., M.İ.N., Analysis or Interpretation: M.Ç., M.İ.N., Literature Search: M.Ç., M.İ.N., Writing: M.Ç.

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

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