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Evaluation of Subclinical Peripheral Neuropathy in Ankylosing Spondylitis Patients on Biological Treatment

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ABSTRACT

Background: Ankylosing spondylitis (AS) is a chronic autoimmune inflammatory disease affecting the axial skeleton. For patients with persistent symptoms, biological therapy mainly tumor necrosis factor (TNF) inhibitors and interleukin (IL)-17 inhibitors have proved efficacy in controlling disease progression. However, Peripheral neurological side effects have been reported. **Objective:** This work aimed to investigate the effect of biological agents, including anti-TNF-α and anti-IL 17, on peripheral nerves in patients with ankylosing spondylitis (AS).

Patients and Methods: This prospective study included 30 biologic-naïve patients with AS, with no neuropathic symptoms or signs. A nerve conduction study (NCS) was performed for each patient at baseline and then after duration of follow-up (12 months). Biological therapy was administered to the patients during this period, including anti-TNF-a agents (5 etanercept, 6 adalimumab, and 5 golimumab) and IL-17 inhibitors (14 secukinumab). Patients were subjected to clinical examination, activity score: Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), and lab evaluation. NCS was performed where motor and sensory latencies, amplitude, and conduction velocities were recorded and compared before and after treatment.

Results: There was a statistically significant increase in motor and sensory latencies in all recorded nerves after treatment, however, these latencies remained within normal physiological ranges. No significant changes were observed in other parameters including amplitude, conduction velocity, or f-waves.

Conclusion: It could be concluded that biological therapies, like TNF-α and IL-17 inhibitors, have significantly advanced AS treatment. However, rare neurological side effects, such as demyelinating events, need careful monitoring. Our findings and existing literature highlight the importance of assessing neurological involvement throughout treatment to actively manage adverse effects and improve patient outcomes.

Keywords: Ankylosing spondylitis, Peripheral neuropathy, Biological therapy, TNF-α inhibitors, IL 17 inhibitors, Demyelinating.

INTRODUCTION

In the world, up to 1.4% of adults suffer with axial spondyloarthritis, a chronic inflammatory disease (CID) [(1)]. Axial spondyloarthritis, also known as ankylosing spondylitis (AS), is characterized by peripheral arthritis, enthesitis, and inflammation of the spine and sacroiliac joints. It often leads to progressive spinal ankylosis. Common extra-articular manifestations include psoriasis, inflammatory bowel disease, and anterior uveitis. AS affects both radiographic and non-radiographic patients [(2)].

Ankylosing spondylitis (AS), also known as radiographic axial spondyloarthritis, is characterized by structural deterioration to the sacroiliac joints that may be seen on radiographs. Due to gradual, irreversible structural damage and ongoing axial and extra-axial inflammation, this illness, which frequently manifests early in infancy, can result in severe morbidity and functional deterioration. Compared to the general population, patients with AS have higher rates of unemployment, work impairment, and death, as well as a lower quality of life [(3)]. Current guidelines for managing ankylosing spondylitis recommend a combination of nonpharmacological approaches and non-steroidal anti-inflammatory drugs (NSAIDs) as the first line of therapy. However, NSAIDs are not always well tolerated and may be inadequate in controlling symptoms for some patients [(4)]. Methotrexate and sulfasalazine are examples of conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs). While they are generally ineffective in treating axial symptoms, they may be beneficial in managing peripheral symptoms that accompany axial disease [(5, 6)].

Patients who continue to exhibit disease activity after receiving standard therapy are advised to be treated with biological disease-modifying anti-rheumatic medications (bDMARDs) [(4)].

Biological drugs play a major role in many aspects of immune response regulation and T-cell-mediated cascades. Tumor necrotizing factor alpha (Anti TNF-a) and Interleukin 17 (IL-17) inhibitors are the most significant improvement in the treatment of AS and have become increasingly used, however, there have been several reports of peripheral demyelinating events in patients receiving these agents [(7)]. The pathogenesis of neuropathies, according to the authors, remains unclear as it involves complex mechanisms such as the destruction of peripheral nerve myelin by humoral and T-cell immune responses, nerve ischemia caused by vasculitis, and the disruption of axon signaling support [(8)].

In this study, we investigated the effect of biological agents (anti-TNF alpha and anti-IL-17A) on peripheral nerves in patients with AS.

MATERIAL AND METHODS

This prospective study included a total of 30 biologic-naïve patients with ankylosing spondylitis

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(AS), attending at Physical Medicine, Rheumatology, and Rehabilitation outpatient clinic, Menoufia University Hospitals. This study was conducted over a six-month period, from November 2021 to May 2022.

Patients were diagnosed according to the Assessment of Spondylo Arthritis International Society (ASAS) classification criteria [9].

Patients were selected according to predefined inclusion and exclusion criteria, excluding those with a prior diagnosis of neuropathy, those currently receiving treatment for neuropathy, or those exhibiting any known polyneuropathy, neuropathic symptoms, or signs.

All patients were in the age group of 18 up to 50 years old, each participant underwent a nerve conduction study (NCS) at baseline, before initiation of treatment, and was then repeated after a 12-month follow-up period. During this period, the 30 patients received biological therapy, including anti-TNF-α agents (5 etanercept, 6 adalimumab, and 5 golimumab) and IL-17 inhibitors (14 secukinumab).

All patients underwent demographic data collection, including name, age, sex, special habits, occupation, and comprehensive history taking that covered symptom analysis, disease duration, medical history, and drug history.

The clinical assessment involved a general examination and a detailed local examination of the back, sacroiliac joints, and peripheral joints. Additionally, a thorough examination of peripheral joints was performed, evaluating for tenderness, swelling, deformities, and synovitis.

Patients also underwent several specific tests, including the Occiput to Wall test, chest expansion measurement, and the modified Schober's test to assess the spinal range of movement. Additionally, sacroiliac joint evaluation involved the FABER (Patrick's) Test, Gansel's test, distraction test, compression test, and sacral thrust test. Also, a neurological examination was done to assess motor and sensory functions.

Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores were calculated for each patient at baseline, during follow-up, and after treatment duration. It consisted of six questions focusing on symptoms and their severity over the past week [10]. A score of 4 or higher typically indicates active disease requiring further medical intervention. The BASDAI is valued for its simplicity and effectiveness in clinical practice and research settings [11].

Each patient underwent a laboratory evaluation that included a complete blood count (CBC), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) tests. Additionally, the assessment included measurement of Rheumatoid Factor (RF) and Human Leukocyte Antigen B27 (HLA-B27), as well as a glycemic panel. All patients were subjected to nerve conduction studies which were conducted at the Electrophysiology Unit within the Physical Medicine, Rheumatology, and Rehabilitation Department at the Faculty of Medicine, Menoufia University using the Nihon Kohden Neuropack M1 electromyography apparatus from Tokyo, Japan.

All NCSs were performed by the same investigator. And were all investigated using surface and ring electrodes (G1 and G2).

All patients underwent a series of nerve conduction studies, which included motor NCS for the median, ulnar, tibial, and peroneal nerves, measuring distal motor latency, amplitude of the compound motor action potential (CMAP), and motor conduction velocity. Sensory NCS was performed on the median, ulnar, and sural nerves, with parameters including sensory peak latency, amplitude, and sensory conduction velocity. Additionally, an F-wave study was conducted for the median and tibial nerves, assessing minimal latency and persistence. Studied nerves for each patient included: both median nerves (motor and sensory), right ulnar (motor and sensory), both tibial nerves, right peroneal and both sural nerves, as well as f-wave for right median and right tibial nerve [12].

***Ethical Consideration*:**

This study was ethically approved by the Ethics Committee, Faculty of Medicine, Menoufia University (approval No.: 11/2021PMRR39). Written informed consent of all the participants was obtained. The study protocol conformed to the Helsinki Declaration, the ethical norm of the World Medical Association for human testing.

Statistical analysis

Using an IBM-compatible computer and SPSS version 26.0, the gathered data was tabulated and examined. Two primary categories of statistical analysis were conducted. In descriptive statistics, the mean±, SD, and range were used for quantitative data, and numbers and percentages were used for qualitative data. The following tests were used for analytic statistics: the Student's t-test evaluated the association between two quantitative normally distributed variables; the Mann-Whitney U test examined associations between two quantitative non-normally distributed variables; the paired t-test compared readings of normally distributed data within the same group; the Wilcoxon signed-rank test compared readings of non-normally distributed data within the same group; and the McNemar test evaluated paired categorical data measured at two time points with two outcomes. The p-value was deemed statistically significant if it was less than 0.05.

RESULTS

The cohort comprised 30 patients with a mean age of 30.57 years (SD ± 7.27), with 73.3% being male. Most participants were employed (70%) and had a mean disease duration of 15.33 months (SD ± 14.10). At baseline, 53.3% of the patients were not on any active DMARDs, while 46.7% were initiated on Secukinumab as their biological therapy, and the rest were on various anti-TNF therapies.

Clinical assessments revealed that 83.3% of patients had positive sacroiliac tests, and 50% exhibited peripheral arthritis before treatment. Following 12 months of biological therapy, significant clinical improvements were noted, including a reduction in BASDAI scores from a mean of 5.09 (SD ± 0.89) to 2.88 (SD ± 1.03) (W=4.79, P<0.001).

There were statistically significant improvements in the clinical evaluations following biological treatment. The Modified Schober's test score increased significantly, indicating enhanced spinal flexibility (P<0.001). The percentage of patients with positive sacroiliac (SI) tests also decreased significantly (P<0.001), also a notable reduction in the incidence of peripheral arthritis (P=0.008).

Furthermore, the BASDAI scores showed a statistically significant reduction (P<0.001), as in (Table 1).

Table (1): Pre and Post Biological Treatment Clinical Evaluation of Studied Patients (n=30)

Variable	Pre-treatment		Post-treatment		Test of significance	P value
	No.	%	No.	%		
Modified Schober test (cm)						
Mean ±SD	19.25 ±2.03		21.47 ±1.96		t=12.86	**<0.001***
Range	15-23		17-25			
SI tests						
Positive	25	83.3	12	40	Mc=11.08	**<0.001***
Negative	5	16.7	18	60		
Peripheral arthritis						
Positive	15	50	7	23.3	Mc=6.13	**0.008***
Negative	15	50	23	76.7		
BASDAI						
Mean ±SD	5.09 ±0.89		2.88 ±1.03		W=4.79	**<0.001***
Range	3.6-6.7		0.8-4.5			

*: Statistically significant, t: Paired t test, Mc: Mc-Nemar test, W: Wilcoxon signed rank, SD: standard deviation, No: number, cm: centimeter, SI: sacroiliac, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index.

The laboratory post-treatment findings demonstrated statistically significant reductions in ESR and CRP levels (both P<0.001), indicating a decrease in inflammatory activity. However, no statistically significant changes were observed in other hematological parameters such as hemoglobin levels, platelet counts, or white blood cell counts (Table 2).

Table (2): Pre and Post Biological Treatment Laboratory Findings of Studied Patients (n=30)

Variable	Pre-treatment	Post-treatment	Test of significance	P value
Hemoglobin (g/dL)				
Mean ±SD	11.55 ±1.79	11.52 ±1.75	t=1.49	0.147 (NS)
Platelets (10^3/mL)				
Mean ±SD	269.07 ±66.42	286.80 ±70.65	t=1.28	0.210 (NS)
WBCs (10^3/µL)				
Mean ±SD	6.23 ±1.41	6.36 ±1.55	t=0.55	0.587 (NS)
ESR (mm/hour)				
Mean ±SD	34.40 ±8.42	20.47 ±4.97	W=4.71	**<0.001***
CRP (mg/L)				
Mean ±SD	32.81 ±7.86	14.74 ±3.54	W=4.79	**<0.001***

*: Statistically significant, NS: Non-significant, t: Paired t test, W: Wilcoxon signed rank test, g/L: grams per liter, mL: milliliter, µL: microliter, mm/hour: millimeters per hour, mg/L: milligrams per liter, WBCs: white blood cells, ESR: erythrocyte sedimentation rate, CRP: c-reactive protein.

The motor nerve conduction studies for all examined nerves revealed a statistically significant increase in latency following treatment (P<0.001). However, there were no significant changes observed in amplitude or conduction velocity. Additionally, no statistically significant differences were found in the mean latencies or persistence percentages of F-wave studies for the median and tibial nerves between pre-treatment and post-treatment (Table 3).

Table (3): Pre and Post Biological Treatment Motor Nerve Conduction Studies (NCS) Among Studied Patients (n=30)

	Variable	Pre-treatment	Post-treatment	Test of significance	P value
	Right median nerve				
Latency (ms)	Mean ±SD Range	3.17 ±0.48 2.1-3.9	3.54 ±0.36 2.8-4.2	t=6.69	**<0.001***
Amplitude (mV)	Mean ±SD Range	11.00 ±2.97 5-18.8	10.97 ±2.96 5-18.8	t=1.68	0.103 (NS)
Conduction velocity (m/s)	Mean ±SD Range	63.53 ±9.61 50-84	62.70 ±8.07 52-82	t=1.19	0.244 (NS)
	Left median nerve				
Latency (ms)	Mean ±SD Range	3.24 ±0.37 2.3-2.88	3.57 ±0.33 2.9-4.2	t=8.38	**<0.001***
Amplitude (mV)	Mean ±SD Range	10.15 ±2.76 4.8-18	9.80 ±2.06 5.5-14	t=1.49	0.148 (NS)
Conduction velocity (m/s)	Mean ±SD Range	63.00 ±9.50 51-88	63.17 ±7.25 51-78	t=0.17	0.866 (NS)
	Right ulnar nerve				
Latency (ms)	Mean ±SD Range	2.42 ±0.34 1.8-3	2.67 ±0.29 2.1-3.1	t=9.12	**<0.001***
Amplitude (mV)	Mean ±SD Range	8.98 ±2.16 6-13.9	9.39 ±2.29 6.1-13.5	t=1.36	0.185 (NS)
Conduction velocity (m/s)	Mean ±SD Range	65.23 ±8.21 50-80	65.77 ±7.83 52-80	t=0.53	0.599 (NS)
	Right tibial nerve				
Latency (ms)	Mean ±SD Range	3.61 ±0.47 2.8-4.6	4.02 ±0.48 3.2-4.9	t=8.29	**<0.001***
Amplitude (mV)	Mean ±SD Range	10.11 ±3.71 5.1-17.3	9.84 ±2.99 5.5-15.8	t=0.99	0.330 (NS)
Conduction velocity (m/s)	Mean ±SD Range	51.03 ±6.72 41-66	50.93 ±6.46 41-66	t=0.57	0.573 (NS)
	Left tibial nerve				
Latency (ms)	Mean ±SD Range	3.64 ±0.52 2.7-4.9	4.03 ±0.49 3.1-5.3	t=7.83	**<0.001***
Amplitude (mV)	Mean ±SD Range	10.70 ±3.98 5.2-18.5	10.17 ±2.74 5.4-15.1	t=1.51	0.142 (NS)
Conduction velocity (m/s)	Mean ±SD Range	53.59 ±11.39 40-90	52.97 ±8.10 40-70	t=0.51	0.614 (NS)
	Right peroneal nerve				
Latency (ms)	Mean ±SD Range	3.62 ±0.53 2.5-4.8	4.30 ±0.53 3.2-5.1	t=8.98	**<0.001***
Amplitude (mV)	Mean ±SD Range	4.94 ±1.30 3.2-8.9	4.91 ±1.32 3.2-9.8	t=1.75	0.090 (NS)
Conduction velocity (m/s)	Mean ±SD Range	52.57 ±7.52 41-68	52.03 ±7.10 40-71	t=0.50	0.618 (NS)

*: Statistically significant, NS: Non-significant, t: Paired t test, SD: standard deviation, ms: millisecond, mV: millivolt, m/s: meters per second.

Similarly, sensory nerve conduction study for all the studied sensory nerves revealed a statistically significant increase in latency following treatment (P<0.001). However, there were no statistically significant changes in amplitude or conduction velocity (Table 4).

Table (4): Pre and post biological treatment sensory NCS among studied patients (n=30)

Variable	Pre-treatment	Post-treatment	Test of significance	P value
Right median nerve				
Latency (ms) Mean ±SD Range	 2.55 ±0.39 1.45-3.2	 2.82 ±0.36 2.1-3.4	 t=8.94	 **<0.001***
Amplitude (µV) Mean ±SD Range	 42.57 ±13.44 23.8-88	 41.89 ±12.66 24-80	 t=0.64	 0.530 (NS)
Conduction velocity (m/s) Mean ±SD Range	 60.73 ±8.98 50-89	 59.73 ±7.46 50-83	 t=1.54	 0.135 (NS)
Left median nerve				
Latency (ms) Mean ±SD Range	 2.48 ±0.40 1.4-3.2	 2.72 ±0.33 2.1-3.3	 t=6.41	 **<0.001***
Amplitude (µV) Mean ±SD Range	 43.65 ±12.63 21-75	 40.18 ±12.38 24-66	 t=1.87	 0.071 (NS)
Conduction velocity (m/s) Mean ±SD Range	 62.12 ±10.60 49-92	 62.80 ±8.02 52-81	 t=0.61	 0.545 (NS)
Right ulnar nerve				
Latency (ms) Mean ±SD Range	 2.27 ±0.37 1.15-2.9	 2.55 ±0.31 1.9-3	 t=7.80	 **<0.001***
Amplitude (µV) Mean ±SD Range	 34.26 ±16.52 17-93	 34.21 ±14.72 21-90	 W=0.01	 0.992 (NS)
Conduction velocity (m/s) Mean ±SD Range	 61.67 ±11.56 50-95	 61.33 ±11.37 50-95	 t=1.78	 0.086 (NS)
Right sural nerve				
Latency (ms) Mean ±SD Range	 3.13 ±0.60 1.96-4.1	 3.48 ±0.53 2.4-4.3	 t=7.82	 **<0.001***
Amplitude (µV) Mean ±SD Range	 15.65 ±5.80 5.2-27	 15.64 ±5.00 7.8-28	 W=0.04	 0.967 (NS)
Conduction velocity (m/s) Mean ±SD Range	 54.57 ±6.32 47-69	 54.10 ±5.87 45-67	 t=0.44	 0.663 (NS)
Left sural nerve				
Latency (ms) Mean ±SD Range	 3.07 ±0.60 1.86-4.1	 3.47 0.51 2.3-4.3	 t=8.48	 **<0.001***
Amplitude (µV) Mean ±SD Range	 16.33 ±5.00 5.5-28	 16.02 ±4.81 7-26	 t=0.65	 0.520 (NS)
Conduction velocity (m/s) Mean ±SD Range	 54.93 ±6.60 43-75	 54.10 ±5.76 45-69	 t=0.83	 0.415 (NS)

*: Statistically significant, NS: Non-significant, t: Paired t test, W: Wilcoxon signed rank test, SD: standard deviation, ms: millisecond, µV: microvolt, m/s: meters per second.

Comparing the effects of Anti-IL-17 and Anti-TNF therapies, no statistically significant differences were found in nerve conduction parameters, including latency, amplitude, conduction velocity, and f-wave studies. This suggests that both types of biological treatments have a similar impact on nerve conduction (Table 5).

Table (5): Type of biological treatment in relation to motor NCS of studied patients (n=30)

Variable	Anti-IL-17 (n=14)	Anti-TNF (n=16)	Test of significance	P value
	Mean ±SD	Mean ±SD		
Right median nerve				
Latency (ms)	3.43 ±0.34	3.65 ±0.35	t=1.74	0.094
Amplitude (mV)	11.04 ±2.34	10.91 ±3.49	t=0.12	0.903
Conduction velocity (m/s)	62.00 ±7.41	63.31 ±8.80	t=0.44	0.661
Left median nerve				
Latency (ms)	3.45 ±0.34	3.67 ±0.29	t=1.91	0.068
Amplitude (mV)	9.12 ±1.94	10.40 ±2.02	t=1.78	0.087
Conduction velocity (m/s)	61.78 ±5.55	64.38 ±8.46	t=1.00	0.325
Right ulnar nerve				
Latency (ms)	2.66 ±0.31	2.68 ±0.29	t=0.10	0.918
Amplitude (mV)	10.05 ±1.92	8.80 ±2.47	t=1.57	0.129
Conduction velocity (m/s)	64.07 ±6.98	67.25 ±8.44	t=1.13	0.269
Right tibial nerve				
Latency (ms)	3.99 ±0.46	4.04 ±0.51	t=0.27	0.790
Amplitude (mV)	10.06 ±2.54	9.64 ±3.41	U=0.25	0.803
Conduction velocity (m/s)	50.71 ±6.00	51.13 ±7.03	t=0.18	0.862
Left tibial nerve				
Latency (ms)	3.86 ±0.40	4.17 ±0.53	t=1.80	0.083
Amplitude (mV)	10.31 ±2.88	10.05 ±2.70	t=0.26	0.798
Conduction velocity (m/s)	52.64 ±7.70	53.25 ±8.68	t=0.20	0.841
Right peroneal nerve				
Latency (ms)	4.23 ±0.62	4.35 ±0.46	t=0.57	0.576
Amplitude (mV)	4.80 ±1.39	5.00 ±1.29	t=0.41	0.687
Conduction velocity (m/s)	52.71 ±7.35	51.44 ±7.06	t=0.48	0.633

*: Statistically significant, t: Student t test, U: Mann-Whitney U test, SD: standard deviation, ms: millisecond, mV: millivolt, m/s: meters per second, n: number, Anti-IL-17: anti-interleukin-17, Anti-TNF: anti-tumor necrosis factor.

DISCUSSION

The CID known as AS mostly affects the axial skeleton and causes the spine to become more rigid and fused [13]. It is a form of spondyloarthritis characterized by inflammation at the entheses [14]. AS predominantly affects young males and often presents with back pain, reduced spinal mobility, and sacroiliitis [15]. Over time, AS can lead to significant functional impairment and decreased quality of life [16]. The exact etiology remains unclear, though genetic factors, particularly the HLA-B27 allele, are strongly associated with the disease [17].

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the first-line treatment for active AS [5, 18]. For patients with persistent symptoms despite NSAIDs, biological drugs have majorly improved treatment options [19]. The use of biological therapies, including TNF-α inhibitors and IL-17A inhibitors, has revolutionized the treatment of spondyloarthropathies, providing more effective control of inflammation and disease progression [18].

In rheumatic diseases, these medications have infrequently been linked to neurological adverse effects. One of these is peripheral neurological adverse effects, which might lead to stopping the medication [20].

In this study, we investigated the effects of biological agents, particularly with TNF-α and IL-17A inhibitors on peripheral nerve function in patients with AS.

The demographic analysis of this study revealed a predominantly male and relatively young cohort, aligning with **Ibrahim *et al.* [21],** who reported a median age of 42 years and 86.6% male predominance in AS patients. This demographic distribution is typical of ankylosing spondylitis, where younger males are more commonly affected, potentially influencing the study's generalizability.

Biological treatment in our study led to a significant reduction in BASDAI scores, demonstrating symptomatic relief consistent with findings by **Capkin *et al.* [22] and Demirci *et al.* [23]** who also observed significant BASDAI score reductions following prolonged biological therapy. Additionally, post-treatment reductions in ESR and CRP levels mirrored

the inflammatory activity decreases reported in both **Ibrahim *et al.* [21] and Demirci *et al.* [23]** studies.

Motor and sensory nerve conduction studies revealed a significant increase in latency after treatment but remained within normative values, with no changes in amplitude or conduction velocity, indicating a potential demyelinating adverse effect of these biological therapies on peripheral motor and sensory nerve functions.

In a French study by **Seror *et al.* [24],** demyelinating effects were observed in 33 patients receiving anti-TNF-α therapy as part of a survey. The findings suggested that anti-TNF-α treatment may be associated with demyelinating side effects in the peripheral nervous system (17), it also estimated that peripheral demyelinating complications might occur more frequently than central demyelinating ones.

However, an earlier study **Bosch *et al.* [25]** found that peripheral nerve events are relatively rare in patients treated with monoclonal antibodies, compared to central nervous system (CNS) demyelinating disorders. **Kristensen *et al.*'s [26]** study stated that demyelination of the CNS or peripheral nervous system occurs with anti-TNF blockers with a prevalence ranging from 0.050 to 0.100%.

Several studies have indicated that TNFα antagonists may cause CNS demyelination, including an increased risk of developing conditions such as multiple sclerosis, transverse myelitis, or optic neuritis [27, 28].

However, others asserted that TNFα antagonists can cause several peripheral neuropathies, such as Guillain-Barré syndrome, Miller-Fisher syndrome, axonal sensorimotor polyneuropathy, mononeuritis multiplex, chronic inflammatory demyelinating polyneuropathy, and multifocal motor neuropathy with conduction block [27, 28, 29, 30, 31].

49 cases of peripheral neuropathies associated with anti-TNF therapy were identified in a 2008 review. These cases included 20 instances of Guillain-Barré syndrome (GBS), 11 of multifocal motor neuropathy with conduction block, 6 of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), 5 of axonal polyneuropathy, 2 of Lewis-Sumner syndrome, and 1 case of humoral autoimmune disease induced by anti-TNF blockade [32].

Reports of only axonal neuropathy are limited in patients using anti-TNF-α however a study by **Bosch *et al.* [25]** stated that Anti-TNF-related peripheral neuropathies include various types of disorders including axonal polyneuropathy.

A study by **Nozaki *et al.* [29]** reported demyelinating polyneuropathy occurring solely during treatment with TNFα antagonists, presented by slowed motor conduction velocities, prolonged distal latencies, and conduction blocks by nerve conductions.

In the current study latencies were slightly increased in both motor and sensory studies however, reports of solely sensory polyneuropathy in patients using anti-TNF-α are limited [27].

One study by **Ekinci *et al.* [31]** found that while motor nerves were within acceptable bounds, sensory nerves were impacted in patients using anti-TNF-α medications. Also, **Kaltsonoudis *et al.* [30]** reported a case of sensory demyelination of both lower limb sensory fibers. In general neurological adverse events are rarely reported with biological therapies, a cross-sectional case-control study by **Watad *et al.* [33]** investigated the link between ankylosing spondylitis (AS) and major neurological disorders, including the potential protective effect of TNF inhibitors (TNFi), there is very limited data in the literature on the neurological adverse effects of IL-17A inhibitors. An article by **Milovanovic *et al.* [34]** talked about the potential benefits and protective mechanisms of IL-17A inhibitors against developing demyelinating disorders especially central. Also, **Havrdová *et al.* [35]** study results implied that blocking IL-17A with an antibody may actually reduce MRI lesion activity in MS.

These limited studies and results on the adverse effects of anti TNF and IL-17 on nerve functions might be consistent with our study as patients that started on these drugs did not have any neurological complications throughout the treatment or even after the end of the study duration. The statistically significant electrophysiological delay in motor and sensory latencies is still within the normative ranges. Also, our results showed that there was no difference between the impact of TNF-α and IL-17A inhibitors on nerve conduction studies.

LIMITATIONS

The variability in results may be influenced by some restrictions, which included several factors such as the short duration of follow-up and relatively small sample size.

Overall, while peripheral nerve involvement is considered rare in the literature, particularly with IL-17 inhibitors, additional multicenter trials with larger patient populations are needed.

CONCLUSION

It could be concluded that biological therapies, like TNF-α and IL-17 inhibitors, have significantly advanced AS treatment. However, rare neurological side effects, such as demyelinating events, need careful monitoring. Our findings and existing literature highlight the importance of assessing neurological involvement throughout treatment to actively manage adverse effects and improve patient outcomes.

Although peripheral nerve involvement with these therapies is rare, further multicenter studies with larger sample sizes are needed to better understand and confirm these effects.

RECOMMENDATION

Before starting biological therapy, it's important to assess patients for any existing neurological involvement. Regular follow-ups are necessary to monitor for any new neurological symptoms during treatment. If any adverse neurological events are detected, discontinuing the causing drug is considered to prevent further damage. More extensive research with larger patient groups and longer follow-up durations are needed to better understand the long-term neurological impacts of TNF-α and IL-17A inhibitors.

Availability of the data: The article incorporates the data used to substantiate the outcomes of this investigation.

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