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RESEARCH ARTICLE



Effect of omalizumab treatment on peripheral nerves in patients with chronic spontaneous urticaria

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ABSTRACT

Aim: Chronic spontaneous urticaria (CSU) is characterised by itchy, red and raised lesions that appear as an attack without any cause and last for six weeks or longer. Omalizumab is a humanised monoclonal antibody that selectively binds to the Ce3 moiety of circulating IgE and is indicated for the treatment of resistant CSU. In this study, we aimed to investigate whether there was peripheral nervous system involvement in patients with chronic urticaria receiving omalizumab treatment.

Methods: Forty-seven patients who were treated with omalizumab for CSU were included in the study. Electrophysiological measurements were performed following a neurological examination before treatment and at three months after omalizumab treatment. In nerve conduction tests, eight different nerves were studied in four extremities (total 16 nerves). During these studies, two motor and two sensory nerves (median and ulnar) in the upper extremities, and two motor (tibial and common peroneal) and two sensory nerves (sural and superficial peroneal) in the lower extremities were analysed.

Results: No pathological electrophysiological findings supporting neuropathy were detected in any of the measurements performed before and after treatment. When the nerve conduction velocity, amplitude and latency values of all examined nerves were compared, no significant difference was found between the pre- and post-treatment values.

Conclusions: It can be considered that omalizumab has no effect on peripheral nerves, and it is a safe and well tolerated agent in terms of both peripheral nerves and neurological structure.

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Introduction

Chronic spontaneous urticaria (CSU) is characterised by itchy, red and raised lesions that appear as an attack without any cause and last for six weeks or longer. According to the international urticaria guidelines, the first choice in CSU treatment is second-generation H1 receptor blocker antihistamines at an appropriate dose. If there is no response to increasing doses, it is recommended to switch to one of the third-line treatments (such as omalizumab, cyclosporine, and leukotriene)¹. Omalizumab is a humanised monoclonal antibody that selectively binds to the Ce3 moiety of circulating IgE. Omalizumab reduces the release of allergic mediators by preventing IgE from binding to high-affinity receptors on mast cells and basophils^{2,3}. In addition, it induces eosinophil apoptosis and shows anti-allergic and anti-inflammatory activity by reducing the production of inflammatory cytokines⁴.

Peripheral nerves consist of long neuronal axon bundles with motor, sensory and autonomic functions originating from the central nervous system. The term peripheral neuropathy (PN) is used to describe the symmetrical and widespread damage of axons by the same pathophysiological processes⁵. The prevalence of PN in the general population is as high as 2.4%⁶. Diabetes mellitus is the most common cause of PN in the western population, with the prevalence

varying between 30 and 66% among diabetics⁷. Many conditions such as systemic diseases, toxic exposure, drugs, infections, and hereditary diseases may play a role in the aetiology of PN. The most common drugs associated with PN include amiodarone, chloroquine, hydralazine, lithium, metronidazole, phenytoin, isoniazid, statins, and vincristine⁸. It is unclear how omalizumab affects peripheral nerve function. It is thought that its properties such as increasing susceptibility to infections, changing growth factors and neuropeptides expressed in mast cells, and triggering autoimmune processes may have an effect on peripheral nerves⁹. In patients presenting with neurological signs or symptoms suggestive of PN, electroneuromyography and nerve conduction studies are extremely useful in confirming the diagnosis, making a differential diagnosis, determining the location and severity of involvement, and detecting pathophysiological findings¹⁰. In some recent studies, the presence of pathological effects of omalizumab treatment on peripheral nerves has been mentioned⁸.

There are some publications reporting peripheral nervous system involvement after monoclonal antibody therapy in some different diseases. However, the underlying mechanism has not yet been clearly elucidated¹¹. In this study, we aimed to investigate whether there was peripheral nervous system

involvement in patients with CSU receiving omalizumab treatment.

Material and methods

Forty-seven patients who were treated with omalizumab for CSU were included in the study. The age, gender and clinical data of all the patients were recorded. Urticaria lasting longer than six weeks, either alone or accompanied by angioedema, was considered as CSU. Omalizumab treatment was administered to the patients subcutaneously every four weeks with 300 mg dose adjusted depending on the serum IgE concentration and body weight of each patient, following with dosage protocol recommended in the package insert¹². Hematological, biochemical and serological tests, including complete blood count, liver and kidney functions, acute phase reactants, sedimentation rate, thyroid hormones, vitamin B12 level, and folic acid level were applied to all the patients. Patients with systemic diseases such as chronic renal failure, chronic liver failure, diabetes, hypothyroidism, and rheumatologic and connective tissue disease were excluded from the study. Further excluded were those with a hematological disease or malignancy, pregnant women, those with heart failure, vitamin B12 and folic acid deficiency, active infection, or alcohol abuse history, and those using any agents that could affect peripheral nerve conduction. Before and at three months after treatment, a detailed neurological and physical examination was performed in each patient by the same neurologist with at least 10 years of experience. The neurological symptoms and neurological examination findings of all patients were scored using the Toronto Clinical Neuropathy Score (TCNS), which is a frequently used scale that includes sensory and motor symptoms, lower extremity sensory and reflex examination findings. TCNS is a valid and reliable scale for the diagnosis and staging of both diabetic polyneuropathy and other polyneuropathies¹³. In addition, the Urticaria Activity Score (UAS) was used to evaluate disease severity¹⁴. The study was designed in accordance with the principles of the Declaration of Helsinki and approved by the local ethics committee.

Electrophysiological measurements

Electrophysiological measurements following a neurological examination were applied to the patients before and at three months after omalizumab treatment. Medelec Synergy instrument (Oxford Instruments, Surrey, UK) was used for measurements. Electrophysiological evaluations were based on the Diabetic Neuropathy Guidelines of the American Diabetes Association¹⁵. In nerve conduction tests, eight different nerves were studied in four extremities (16 nerves in total). During the nerve conduction studies, two motor and two sensory nerves (median and ulnar) in the upper extremities, and two motor (tibial and common peroneal) and two sensory nerves (sural and superficial peroneal) in the lower extremities were analysed. The amplitude of sensory nerve action potential (SNAP) was calculated by measuring it from peak to peak, and that of the compound muscle action

potential (CMAP) was measured from the beginning of the potential to the negative peak. The latency values were calculated as the time until the first deviation in the isoelectric line after the stimulus was given. Ring and surface electrodes were used to obtain SNAP and CMAP, respectively. The stimulation intensity was increased to the point when the action potential amplitude reached the highest and remained constant, and supramaximal stimulation was obtained. The skin temperature of the arm was kept constant above 32 °C by an infra-red lamp. Filtering was performed at 5 Hz–10 kHz for motor conduction and 20 Hz–2 kHz for sensory conduction. The stimulation time was maintained at 0.1 ms. In nerve conduction velocity measurements, orthodromic methods were employed for motor nerves and antidromic methods for sensory nerves. For each nerve, the pre- and post-treatment latency (ms), amplitude (mV for motor nerves and μ V for sensory nerves) and velocity (m/s) values were compared. Polyneuropathy was defined as the presence of abnormalities in the action potential amplitude detected on the electrophysiological examination, nerve conduction velocity, or both, in two or more extremities. The suspicion of a decrease in the amplitude of action potentials, axonal damage, and a slowdown in nerve conduction velocity were interpreted in favour of demyelination.

Statistical analysis

The data obtained for the study were analysed using the Statistical Package for the Social Sciences (SPSS) for Windows, v. 22.0. In the analysis of data, number, percentage, mean and standard deviation values were used as descriptive statistical methods. The normality of data distribution was determined using a histogram and/or the Kolmogorov-Smirnov/Shapiro-Wilk test. The paired-samples *t*-test to compare quantitative normally distributed continuous data between the two groups. Pearson's correlation analysis was used to explore the relationship between UAS and electromyographic parameters. The relationship between the duration of illness, which did not show a normal distribution, and electromyographic parameters were evaluated using the Spearman correlation analysis. *P* values below 0.05 were considered statistically significant.

Results

The study included a total of 47 patients, 26 female (55.3%) and 21 male (44.7%), with a mean age of 39.93 ± 16.94 years. The clinical and sociodemographic data of the patients are summarised in Table 1. No pathological electrophysiological finding supporting neuropathy was detected in any of the measurements performed before and after treatment.

Table 2 summarises the sensory nerve conduction data of the patients before and after treatment. No significant difference was observed between the pre- and post-treatment nerve conduction velocity, amplitude and latency values of the bilateral median sensory nerves ($p = 0.054$, 0.325 , and 0.096 , respectively for the right side and $p = 0.564$, 0.312 , and 0.872 , respectively for the left side), bilateral ulnar sensory

Table 1. Clinical characteristics of the patients.

Mean age (years)	39.93 ± 16.94
Gender	
Male	21 (44.7%)
Female	26 (55.3%)
Mean disease duration (months)	11.36 ± 5.56
Mean Urticaria Activity Score	24.86 ± 6.80
Cumulative dose per patient (mg)	900

Table 2. Comparison of pre- and post-treatment latency, amplitude, and velocity values of the sensory nerves.

	Pre-treatment	Post-treatment	<i>p</i> value
Left ulnar nerve			
Velocity	60.01 ± 6.01	59.16 ± 5.08	0.421
Amplitude	37.55 ± 13.23	36.03 ± 14.77	0.332
Latency	1.92 ± 0.24	1.93 ± 0.20	0.749
Right ulnar nerve			
Velocity	60.28 ± 5.90	61.52 ± 5.60	0.227
Amplitude	36.26 ± 15.24	34.52 ± 15.19	0.356
Latency	1.91 ± 0.23	1.87 ± 0.21	0.168
Left median nerve			
Velocity	59.93 ± 9.00	59.42 ± 8.58	0.564
Amplitude	35.98 ± 16.38	38.20 ± 18.62	0.312
Latency	2.37 ± 0.42	2.36 ± 0.41	0.872
Right median nerve			
Velocity	60.77 ± 8.60	58.58 ± 7.25	0.054
Amplitude	40.08 ± 16.37	38.69 ± 15.13	0.325
Latency	2.32 ± 0.37	2.37 ± 0.38	0.096
Left sural nerve			
Velocity	57.05 ± 6.01	56.23 ± 5.94	0.432
Amplitude	20.98 ± 10.66	19.33 ± 7.93	0.279
Latency	2.33 ± 0.29	2.42 ± 0.32	0.052
Right sural nerve			
Velocity	58.60 ± 5.97	56.93 ± 5.75	0.159
Amplitude	20.59 ± 8.57	20.85 ± 8.54	0.872
Latency	2.30 ± 0.31	2.39 ± 0.37	0.132
Left superficial peroneal nerve			
Velocity	58.94 ± 7.01	57.52 ± 7.32	0.265
Amplitude	11.05 ± 6.39	11.78 ± 7.48	0.498
Latency	2.70 ± 0.49	2.84 ± 0.50	0.114
Right superficial peroneal nerve			
Velocity	58.96 ± 7.65	59.26 ± 7.86	0.848
Amplitude	11.74 ± 5.95	11.24 ± 5.94	0.615
Latency	2.74 ± 0.44	2.75 ± 0.46	0.939

Paired-samples *t*-test.

nerves ($p=0.227$, 0.356 , and 0.168 , respectively for the right and $p=0.421$, 0.332 , and 0.749 , respectively for the left), bilateral sural sensory nerves ($p=0.159$, 0.872 , and 0.132 , respectively for the right and $p=0.432$, 0.279 , 0.052 , respectively for the left), and bilateral superficial peroneal nerves ($p=0.848$, 0.615 , and 0.939 , respectively for the right and $p=0.265$, 0.498 , and 0.114 , respectively for the left).

The motor nerve conduction data of the patients before and after treatment are given in Table 3. There was no significant difference between the pre- and post-treatment nerve conduction velocity, amplitude and distal motor latency values of bilateral median motor nerves ($p=0.675$, 0.244 , 0.460 , respectively for the right side and $p=0.886$, 0.356 , and 0.551 , respectively for the left side), bilateral ulnar motor nerves ($p=0.495$, 0.081 , and 0.338 , respectively for the right and $p=0.056$, 0.062 , and 0.603 , respectively for the left), bilateral common peroneal nerves ($p=0.054$, 0.679 , and 0.056 , respectively for the right and $p=0.217$, 0.384 , and 0.564 , respectively for the left), and bilateral tibial nerves ($p=0.339$, 0.133 , and 0.961 , respectively for the right and $p=0.153$, 0.256 , and 0.748 , respectively for the left).

Table 3. Comparison of pre- and post-treatment latency, amplitude, and velocity values of the motor components of the nerves.

	Pre-treatment	Post-treatment	<i>p</i> Value
Left ulnar nerve			
Velocity	61.87 ± 5.56	64.47 ± 5.61	0.056
Amplitude	10.40 ± 2.36	9.76 ± 2.07	0.062
Latency	2.24 ± 0.31	2.26 ± 0.30	0.603
Right ulnar nerve			
Velocity	63.14 ± 6.32	63.74 ± 5.62	0.495
Amplitude	10.84 ± 2.53	10.27 ± 2.46	0.081
Latency	2.30 ± 0.41	2.36 ± 0.44	0.338
Left median nerve			
Velocity	59.45 ± 5.12	59.59 ± 4.83	0.856
Amplitude	8.83 ± 2.78	9.08 ± 2.42	0.386
Latency	3.07 ± 0.66	3.04 ± 0.57	0.551
Right median nerve			
Velocity	59.34 ± 5.27	59.03 ± 4.13	0.675
Amplitude	8.89 ± 2.98	9.29 ± 2.60	0.244
Latency	3.01 ± 0.56	2.97 ± 0.47	0.460
Left peroneal nerve			
Velocity	51.66 ± 4.72	51.01 ± 4.77	0.217
Amplitude	3.81 ± 1.61	3.96 ± 1.75	0.384
Latency	3.70 ± 0.71	3.66 ± 0.74	0.564
Right peroneal nerve			
Velocity	53.14 ± 4.89	50.84 ± 4.16	0.054
Amplitude	4.00 ± 1.81	3.92 ± 1.73	0.679
Latency	3.73 ± 0.65	3.58 ± 0.57	0.056
Left tibial nerve			
Velocity	9.04 ± 3.51	8.53 ± 3.23	0.153
Amplitude	49.17 ± 4.04	48.48 ± 4.44	0.256
Latency	4.14 ± 0.67	4.17 ± 0.78	0.748
Right tibial nerve			
Velocity	48.81 ± 4.34	48.11 ± 4.46	0.333
Amplitude	8.24 ± 3.15	7.59 ± 2.65	0.139
Latency	4.17 ± 0.73	4.17 ± 0.69	0.961

Paired-samples *t*-test.

When the TCNS scores were compared before and after treatment, no significant difference was detected ($p=0.294$). There was also no significant correlation between disease duration and UAS and electrophysiological findings.

Discussion

The aim for personalised treatment methods in modern medicine has brought to the fore some approaches in the use of medical agents. At the centre of this approach is monoclonal antibodies used in the treatment of many diseases. Especially in the last three decades, monoclonal antibodies have been widely utilised in many oncological, hematological, allergic, rheumatological, dermatological and neurological diseases. However, there are only a limited number of studies investigating the effects of these agents on peripheral nerves. Publications examining the effect of omalizumab, an agent widely used in the treatment of CSU, on peripheral nerves are mostly in the form of case reports. In the current study, we present evidence that omalizumab has no pathological effect on peripheral nerves and is safe to use in terms of electrophysiological structure.

There are case reports in the literature discussing the effects of different monoclonal antibodies on both the central and peripheral nervous systems. Cases have been described to be associated with central and peripheral neurological system involvement, such as multiple sclerosis, optic neuritis, Guillain-Barré syndrome (GBS), Miller Fisher syndrome, and chronic inflammatory demyelinating

polyneuropathy caused by demyelination after monoclonal antibody treatments including infliximab and adalimumab acting as TNF alpha inhibitors^{16–18}. In addition, GBS cases related to the use of anti-CD 20 monoclonal antibody rituximab have been reported¹⁹. Among the 17 patients with Churg-Strauss who received omalizumab treatment, retro-bulbar optic neuritis was observed in two patients who did not respond to treatment and developed relapse, but it was considered that these symptoms were related to disease exacerbation, not directly induced by omalizumab. Despite this, the authors could not completely exclude the possibility of an adverse event associated with omalizumab²⁰.

We found only one study in the literature examining the effect of omalizumab treatment on peripheral nerves. In that study, the nerve conduction examinations of patients receiving omalizumab treatment were compared between the pre-treatment period and at three months after treatment. Although there was no pathological finding indicating neuropathic involvement as a result of this comparison, significant changes such as prolonged latencies, reduced amplitudes, and slowed conduction velocity were observed in some nerves after treatment compared to the pre-treatment values, and thus the authors concluded that treatment could affect peripheral nerves⁸. We used a similar method in our study but evaluated a higher number of motor and sensory peripheral nerves. Similar to the previous research, we detected no pathological finding indicating peripheral nerve involvement in the measured values and there was no significant change in the latency, amplitude and conduction velocity values of the peripheral nerves before and after treatment. Electrophysiological measurements can be affected by many factors. These include age, ethnicity, gender, physical conditions of the electrophysiology laboratory, extremity temperature measured, patient height and weight, and the difference in standard values among electrophysiology laboratories²¹. These factors may have contributed to the emergence of different results despite the use of similar methods with the aforementioned study. Our results led us to consider that omalizumab treatment is not a therapeutic agent that causes pathological effects on peripheral nerves.

It is known that omalizumab treatment has some neurological side effects. In a previous study, it was reported that the most common side effects of this treatment were headache and insomnia²². In addition, a total of nine reported cases of myasthenia gravis, of which two were ocular and seven were generalised, have been described⁹. It has also been reported that omalizumab causes musculoskeletal disorders such as arthralgia, myalgia, backache and low back pain²³. In our study, non-specific headache lasting one day was recorded in only two patients after the first dose of treatment, while no other neurological side effects were detected. Furthermore, we did not observe any side effect related to the musculoskeletal system in any of our patients.

Omalizumab has been shown to be a safe drug in numerous studies. However, it has also been associated with a number of serious side effects, such as anaphylaxis, susceptibility to parasitic infections, cardiovascular disease, and serum sickness²⁴. None of the patients included in our study had any allergic, infective or systemic side effect during their

follow-up, and there was no patient that discontinued treatment due to drug-related side effects. In this respect, we considered that omalizumab is a well-tolerated and safe treatment option.

Conclusion

To our knowledge, our study is the only work in the literature in which a total of 16 peripheral nerves in four extremities were examined before and after omalizumab treatment. Our results show that omalizumab does not have an effect on the latency, amplitude and velocity values of the peripheral nerves, and it is a safe and well-tolerated agent in terms of both peripheral nerves and neurological structure. However, prospective and multicenter studies involving more participants are needed to clarify controversial findings.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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