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Leflunomide-Induced Peripheral Neuropathy in a Patient with Rheumatoid Arthritis

Romatoid Artritli Bir Hastada Leflunomidle İlişkili Periferal Nöropati

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ABSTRACT

Leflunomide has been reported to be associated with the development of peripheral neuropathy in patients with rheumatoid arthritis. However, it is possible that this side effect has been underreported and underrecognized. We reported a case of leflunomide-induced peripheral neuropathy with the aim of raising awareness of this side effect. It was reported that cessation of leflunomide within 30 days of the arising symptoms enhances the likelihood of improvement or complete recovery. We should be aware of the possibility of peripheral neuropathy in patients using leflunomide. Early detection of symptoms and drug discontinuation may permit recovery.

Key Words: Leflunomide, peripheral neuropathy, rheumatoid arthritis

ÖZET

Leflunomid kullanımının romatoid artrit hastalarında periferal nöropati ile ilişkili olduğu bildirilmiştir. Ancak bu yan etkinin yeterince tanınmaması ve bildirilmemesi muhtemeldir. Bu yan etkinin farkındalığını arttırmak amacıyla leflunomid kullanımı ile ilişkili bir periferal nöropati olgusu sunduk. Semptomların başlamasından sonraki 30 gün içinde leflunomidin kesilmesinin tamamen iyileşme ihtimalini arttırdığı bildirilmiştir. Leflunomid kullanan hastalarda periferal nöropati ihtimalinin farkında olmalıyız. Semptomların erken tespiti ve ilacın kesilmesi iyileşmeyi sağlayabilir.

Anahtar Sözcükler: Leflunomid, periferal nöropati, romatoid artrit

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease of unknown cause. Symmetric polyarthritis is the hallmark of RA. Extra-articular manifestations of the disease include interstitial lung disease, rheumatoid nodules, ophthalmic involvement, and neurological manifestations, including various forms of neuropathy (1). The prevalence of peripheral neuropathy varies widely in studies. Two recent studies reported that the electrophysiological evidence of peripheral neuropathy in patients with RA was detected as 39.19% and 57.4% (1, 2). Sensory and sensorimotor neuropathies were reported as two frequent subtypes of neuropathy in rheumatoid patients. The presence of peripheral neuropathy in patients with RA contributes significantly to the functional limitation. However, clinicians usually overlook this problem. Leflunomide is one of the disease-modifying drugs (DMARDs) that are licensed for the treatment of RA. The approval of leflunomide in RA was based on data from double-blind, multicenter studies. Studies showed that leflunomide was superior to placebo and had similar efficacy as the other DMARDs (3, 4). It was also demonstrated that treatment with leflunomide slows radiological progression of RA (3-5). This drug is an isoxazole derivative. It is a prodrug. Its active metabolite, A77 1726,

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has immunosuppressive properties (3, 6). This drug has been reported to be associated with the development of peripheral neuropathy. However, it is possible that this side effect has been underreported and underrecognized. We reported a case of leflunomide-induced peripheral neuropathy with the aim of raising awareness of this side effect.

Case

A 78-year-old woman with a 28-month history of seropositive RA was started on 20 mg/day leflunomide (Arava; Sanofi, Cedex, France) after cessation of methotrexate, owing to severe nausea. Other medications included alendronate, calcium, meloxicam, and lansoprazole. Three weeks later, she reported back and radicular leg pain. The physical examination revealed limited range of motion in all 3 planes in the lumbar region and decreased sensation of the left leg and foot in a nondermatomal pattern. Lumbar magnetic resonance imaging (MRI) was planned. MRI revealed bilateral neural foraminal stenosis at the L4-5 level and spondylosis. She was diagnosed with neural foraminal stenosis and neuropathic pain. Pregabalin had been added to her treatment regimen. Her pain was decreased with medical treatment. Nine months later, she reported tingling and burning in the feet bilaterally for 2 months. She was not taking leflunomide for 1 month. Examination revealed decreased sensation of the 4th and 5th toes of the right foot. Deep tendon reflexes were normal. Her liver enzymes were mildly elevated. She had mild anemia (hemoglobin 10.8 g/dL). Her glucose level was 105 mg/dl, and the erythrocyte sedimentation rate and C-reactive protein levels were normal. Because the patient had neural foraminal stenosis, nerve conduction studies were planned as a diagnostic approach for the differential diagnosis. Nerve conduction studies showed sensorial polyneuropathy. Three months after discontinuation of the treatment, there was complete resolution of the neurological symptoms in her limbs. Nerve conduction studies were repeated 4 months later and showed normal results. Written informed consent was obtained from the patient who participated in this case.

Discussion

Identifying medication-induced neuropathy is crucial, because the neuropathy potentially can be reversed. Insidious onset of bilateral sensory changes has been reported in patients with RA using leflunomide. The onset of neuropathy usually occurs 3 to 6 months after drug use. Symptoms, including hypoesthesia, paresthesia, numbness, or painful burning sensations in the hands and feet, may appear sooner. It was reported that cessation of leflunomide within 30 days of the arising symptoms enhances the likelihood of improvement or complete recovery (7). However, the recovery is slow. The half-life of leflunomide is 15-18 days (4). Since this long half-life means that side effects may persist for several weeks after the drug cessation, cholestyramine wash-out was reported as a choice of treatment of neuropathy associated with leflunomide (8). In the present case, improvement of neuropathy after cessation of leflunomide supported the relationship between this drug and neuropathy. The present case recovered completely at the end of 3 months after the drug cessation.

Conclusion

It is crucial to know of the possibility of peripheral neuropathy in patients using leflunomide. Early detection of symptoms and drug discontinuation may permit recovery.

Informed Consent: Written informed consent was obtained from the patient who participated in this case.

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