

## Telmisartan-Induced Myotoxicity in Patients with Essential Hypertension

### Esansiyel Hipertansiyonlu Hastalarda Telmisartan Kaynaklı Miyotoksisite

#### ABSTRACT

Drug-related muscular adverse effects are relatively common among certain groups of drugs, such as statins and steroids. However, these adverse effects are less well-known for angiotensin receptor blockers (ARBs). It is proposed that telmisartan and irbesartan may cause myotoxicity via increased Peroxisome Proliferator-Activated Receptor gamma (PPAR-gamma) activity. Herein, we present two hypertensive patients in whom telmisartan-induced myotoxicity was observed. Therefore, physicians should be aware that telmisartan, along with some other ARBs, can also cause myopathy. Possible drug-drug interactions should be considered in cases of concomitant prescription of these agents with other myopathic drugs.

**Keywords:** Angiotensin receptor blocker, myotoxicity, telmisartan

#### ÖZET

İlaça bağlı kas yan etkileri, statinler ve steroidler gibi bazı ilaç grupları arasında nispeten yaygındır. Bununla birlikte, bu yan etkiler, anjiyotensin reseptör blokerleri (ARB'ler) için iyi bilinmemektedir. Telmisartan ve irbesartanın PPAR-gama aktivitesi artışı yoluyla miyotoksisiteye neden olabileceği öne sürülmüştür. Bu yazıda telmisartan kaynaklı miyotoksisite görülen 2 hipertansif hastayı sunduk. Hekimler telmisartan ve diğer bazı ARB'lerin de miyopatiye neden olabileceğini unutmamalıdır. Bu ajanların diğer miyopatik ilaçlarla birlikte reçetelenmesi durumunda olası ilaç-ilaç etkileşimleri göz önünde bulundurulmalıdır.

**Anahtar Kelimeler:** Anjiyotensin reseptör blokeri, miyotoksisite, telmisartan

Various drugs used in clinical medicine can cause myotoxicity, ranging from asymptomatic myopathy to rhabdomyolysis and severe myopathy that cause morbidity and even mortality. Drug-induced myotoxicity may occur through several mechanisms, including alterations at the myocyte cellular level, triggering of inflammatory and immune reactions, or causing electrolyte and nutritional disorders in myocytes. Known drugs that often cause myotoxicity include lipid-lowering drugs (e.g., statins, fibrates), antiretroviral drugs (e.g., zidovudine), immunosuppressants (e.g., steroids), rheumatological agents (e.g., colchicine, hydroxychloroquine), and antifungal agents (e.g., voriconazole).<sup>1</sup> However, data about the muscular side effects of angiotensin receptor blockers (ARBs) is scarce. Some ARBs are known to be associated with myalgia and elevated creatinine kinase (CK) levels, with varying incidences (1-10%). No cross-reactivity has been reported between various ARBs regarding myotoxicity side effects.<sup>2</sup> Herein, we present two patients with essential hypertension in whom telmisartan-induced myotoxicity was observed. We obtained verbal and written informed consent from both patients.

#### Case 1

A 69-year-old female patient, with a known diagnosis of essential hypertension and receiving telmisartan 80 mg daily, was admitted to our outpatient clinic with back and knee pain, and malaise. These symptoms had started two weeks after initiating telmisartan treatment and persisted for the last three years, intensifying in recent weeks. Her electrocardiogram and echocardiography results were normal. Her complete blood count, thyroid hormone panel, blood biochemistry levels, rheumatological markers, erythrocyte sedimentation rate, and C-Reactive Protein (CRP) were normal, except

#### CASE REPORT OLGU SUNUMU

Süleyman Cihan Kara <sup>ID</sup>

Uğur Canpolat <sup>ID</sup>

<sup>1</sup>Department of Cardiology, Hacettepe University Faculty of Medicine, Ankara, Türkiye

**Corresponding author:**

Uğur Canpolat

✉ dr\_u\_canpolat@yahoo.com

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her total CK level was 1228 IU/L (normal range < 145 IU/L). A detailed evaluation for other causes of myotoxicity, including musculoskeletal pathologies and potential medications other than telmisartan, was conducted. Her complaints completely improved after switching from telmisartan 80 mg once a day to olmesartan 40 mg once a day. One week after switching, her total CK level returned to the normal level at 105 IU/L. A causality analysis using Naranjo's algorithm (total score of 7) and the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) scale indicated that the adverse drug reaction was "Probable" with telmisartan.<sup>3</sup>

## Case 2

A 63-year-old female patient had started taking telmisartan 80 mg per oral, once daily, for essential hypertension. After ten days of telmisartan medication, she was admitted with complaints of generalized myalgia and malaise. Her electrocardiography and echocardiography results were normal. Her biochemical tests, thyroid function tests, complete blood count, rheumatological markers, erythrocyte sedimentation rate, and CRP levels were within the normal range. However, her total CK level was significantly high at 975 IU/L (normal range < 145 IU/L). A detailed assessment of the potential causes of myotoxicity, including medications other than telmisartan, revealed no abnormalities. Her total CK level, obtained one week after switching from telmisartan to candesartan treatment, normalized and measured at 74 IU/L. Her complaints also completely improved after the discontinuation of telmisartan. A causality analysis using Naranjo's algorithm (total score of 7) and the WHO-UMC scale indicated that the adverse drug reaction was "Probable" with telmisartan.<sup>3</sup>

## Discussion

In this paper, we presented two patients with essential hypertension in whom telmisartan-induced myotoxicity was diagnosed. In the first case, the diagnosis of telmisartan-induced myotoxicity was delayed. After switching to olmesartan, both the complaints and elevated total CK levels improved. In the second case, the diagnosis of myotoxicity was made immediately after the administration of telmisartan, and symptoms improved after switching to candesartan. Both patients had no previous history of using any other medications or any disease that could cause myopathy.

Drug-related myotoxicity can be related to various drugs. Typically, symptoms such as muscle weakness, muscle pain, and elevated total CK levels occur after weeks or months of treatment initiation and diminish after discontinuation of the treatment. The diagnosis can be made by a typical history and ruling out other causes that induce myopathy, such as endocrine disorders (e.g., hypo/hyperthyroidism, hyperparathyroidism),

metabolic disorders, storage disorders, muscular dystrophies, and inflammatory disorders. A causality analysis using Naranjo's algorithm and the WHO-UMC scale can be performed for such adverse drug reactions.<sup>1,3</sup> Both scales revealed a "probable" causality between myotoxicity and telmisartan in our patients.

In previous studies, it has been claimed that angiotensin-II can cause myopathy by inhibiting protein synthesis and augmenting proteasome activity in myocytes. For this reason, some angiotensin-converting enzyme inhibitors, such as enalapril and ramipril, may also cause myopathy.<sup>4</sup> However, this mechanism was not applicable in our cases, as there was no myopathy observed with other ARBs (olmesartan and candesartan).

The ARBs may differ in their activity on the Peroxisome Proliferator-Activated Receptor gamma (PPAR-gamma) receptor. In a study performed on cell culture, telmisartan and irbesartan were found to cause PPAR-gamma activation by increasing its transcriptional activity, augmenting insulin sensitivity, and reducing the incidence of type 2 diabetes<sup>5</sup>, while olmesartan and valsartan did not affect PPAR-gamma.<sup>6</sup> Other medications that activate PPAR-gamma are thiazolidinediones, which are used to treat diabetes. In two case reports, Slim et al.<sup>7</sup> and Kennie et al.<sup>8</sup> showed that pioglitazone and rosiglitazone caused rhabdomyolysis and myopathy, respectively. Thus, this mechanism may explain the telmisartan-induced myopathy in our cases.

Telmisartan is uptaken by hepatocytes via the organic anion transporting polypeptide 1B (OATP), then metabolized in the liver by uridine glucuronyl transferase enzymes and *CYP2C9*. Afterward, telmisartan glucuronide is excreted into bile by the efflux protein superfamily of ABCs. Any genetic polymorphism or another drug that inhibits one of these steps can cause an accumulation of telmisartan and toxicity.<sup>9,10</sup> Meyer et al.<sup>11</sup> reported a case of myopathy associated with the concomitant use of fluvastatin and telmisartan. After the addition of telmisartan to treat newly developed hypertension in a patient already under treatment with fluvastatin for hyperlipidemia, an elevation in total CK levels was observed. Genetic tests concluded that a single nucleotide polymorphism in the *CYP2C9* enzyme caused reduced activity of the eliminating enzyme *CYP2C9*. They concluded that a combination of both pharmacogenomics and knowledge of drug-drug interactions helps in the better assessment of patients and achieving good outcomes through personalized medicine.

It has also been found that some ARBs affect the activity of ABC proteins. This is why telmisartan can affect the concentration of drugs that are substrates of these proteins, such as digoxin.<sup>12</sup> Son et al.<sup>13</sup> presented a study in which the concentrations of both rosuvastatin and telmisartan were affected by coadministration, yet it was not enough to cause significant clinical results as these treatments were well tolerated. On the other hand, the interaction could become significant if combined with other drugs. In our cases, there was no evidence of drug-drug interaction; nonetheless, it should always be kept in mind that drug-drug interactions could augment myopathy or other side effects.

## Conclusion

In conclusion, telmisartan should be considered a probable cause of muscular side effects during the treatment of hypertensive

## ABBREVIATIONS

ARBs	Angiotensin receptor blockers
CK	Creatinine kinase
CRP	C-Reactive Protein
OATP	Organic anion transporting polypeptide
PPAR-gamma	Peroxisome Proliferator-Activated Receptor gamma
WHO-UMC	World Health Organization-Uppsala Monitoring Centre

patients. The potential for interaction with other drugs that cause myopathy should be kept in mind during concomitant prescription.

**Informed Consent:** Verbal and written informed consent was obtained from both patients.

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## References

- Valiyil R, Christopher-Stine L. Drug-related myopathies of which the clinician should be aware. *Curr Rheumatol Rep*. 2010;12(3):213-220. [CrossRef]
- Barvaliya MJ, Naik VN, Shah AC, Tripathi CR. Safety of olmesartan in a patient with telmisartan-induced myotoxicity: a case report. *Br J Clin Pharmacol*. 2015;79(6):1034-1036. [CrossRef]
- Shukla AK, Jhaj R, Misra S, Ahmed SN, Nanda M, Chaudhary D. Agreement between WHO-UMC causality scale and the Naranjo algorithm for causality assessment of adverse drug reactions. *J Family Med Prim Care*. 2021;10(9):3303-3308. [CrossRef]
- Peppers MP. Myalgia and arthralgia associated with enalapril and ramipril. *Am J Health Syst Pharm*. 1995;52(2):203-204. [CrossRef]
- Schupp M, Janke J, Clasen R, Unger T, Kintscher U. Angiotensin type 1 receptor blockers induce peroxisome proliferator-activated receptor-gamma activity. *Circulation*. 2004;109(17):2054-2057. [CrossRef]
- Erbe DV, Gartrell K, Zhang YL, et al. Molecular activation of PPARgamma by angiotensin II type 1-receptor antagonists. *Vascul Pharmacol*. 2006;45(3):154-162. [CrossRef]
- Slim R, Ben Salem C, Zamy M, Biour M. Pioglitazone-induced acute rhabdomyolysis. *Diabetes Care*. 2009;32(7):e84. Erratum in: *Diabetes Care*. 2010;33(6):1406. Zami, Michele [corrected to Zamy, Michele]. [CrossRef]
- Kennie N, Antoniou T, Berger P. Elevated creatine kinase and myalgia in a patient taking rosiglitazone. *Ann Pharmacother*. 2007;41(3):521-524. [CrossRef]
- Ishiguro N, Maeda K, Kishimoto W, et al. Predominant contribution of OATP1B3 to the hepatic uptake of telmisartan, an angiotensin II receptor antagonist, in humans. *Drug Metab Dispos*. 2006;34(7):1109-1115. [CrossRef]
- Weiss J, Sauer A, Divac N, et al. Interaction of angiotensin receptor type 1 blockers with ATP-binding cassette transporters. *Biopharm Drug Dispos*. 2010;31(2-3):150-161. [CrossRef]
- Meyer zu Schwabedissen HE, Siegmund W, Kroemer HK, Rollnik JD. Creatine kinase elevation caused by a combination of fluvastatin and telmisartan in a patient heterozygous for the CYP2C9\*3 and ABCC2 -24C > T variants: a case report. *BMC Res Notes*. 2014;7:688. [CrossRef]
- Schumacher T, Benndorf RA. ABC Transport Proteins in Cardiovascular Disease—A Brief Summary. *Molecules*. 2017;22(4):589. [CrossRef]
- Son M, Kim Y, Lee D, et al. Pharmacokinetic interaction between rosuvastatin and telmisartan in healthy Korean male volunteers: a randomized, open-label, two-period, crossover, multiple-dose study. *Clin Ther*. 2014;36(8):1147-1158. [CrossRef]