Journal of Population Therapeutics & Clinical Pharmacology

Case Report
DOI: 10.15586/jptcp.v26i2.627

REVERSIBLE NEUROTROPHIC KERATOPATHY ASSOCIATED WITH ROSUVASTATIN THERAPY: A CASE REPORT

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Submitted: 18 July 2019. Accepted: 26 July 2019. Published: August 13, 2019.

ABSTRACT

Background
Rosuvastatin is a 3-hydroxy-3-methyl-glutaryl-CoA reductase enzyme inhibitor that is in wide use with few reported ocular adverse events.

Objectives
To report a case of bilateral neurotrophic keratopathy associated with rosuvastatin therapy that dramatically improved following drug discontinuation.

Case presentation
A 65-year-old female presented with painless diminution of vision in both eyes of gradual onset and progressive course for 1 month. She had recently started rosuvastatin therapy for hyperlipidemia. Examination revealed bilateral stage 2 neurotrophic keratopathy with impaired corneal sensation which was previously resistant to conservative ulcer treatment. Following discontinuation of rosuvastatin therapy, there was dramatic bilateral improvement in corneal sensation, size of the corneal ulcers, and visual acuity.

Conclusion
Rosuvastatin may result in reversible trigeminal nerve impairment and neurotrophic keratopathy.

Keywords: *cranial neuropathy; drug-induced ocular adverse event; neurotrophic keratopathy; rosuvastatin; trigeminal neuropathy*

J Popul Ther Clin Pharmacol Vol 26(2):e38–e42; August 13, 2019.

Statins are inhibitors of 3-hydroxy-3-methylglutaryl-CoA reductase enzyme that are widely used to lower serum cholesterol and reduce the risk of cardiovascular diseases.[1] Several statins are available on the market and include atorvastatin, fluvastatin, and rosuvastatin. These drugs are generally well tolerated, but may rarely cause side effects such as elevated liver transaminases or myopathy.[2] Few ocular side effects have been associated with their use and include diplopia and ptosis that are thought to be due to localized myositis affecting the extraocular muscles.[3–5] Other reports have shown an increased risk of peripheral neuropathy associated with statin use.[6,7]

Neurotrophic keratopathy is a rare condition in which there is impaired corneal epithelial healing due to absent or diminished corneal sensation. This occurs due to damage of the trigeminal nerve which normally innervates the cornea.[8] Damage may occur at any level of the nerve and reported causes include diabetes mellitus, multiple sclerosis, leprosy, and tumors compressing the trigeminal nerve or ganglion. It is classified into three stages according to the Mackie classification.[8,9] Stage 1 is characterized by punctate keratopathy, irregularity, and scarring of the stroma, while stage 2 is characterized by a superficial persistent epithelial defect with a smooth and rolled epithelial edge and Descemet's membrane folds, and stage 3 is characterized by stromal involvement with the ulcer that may progress to perforation and corneal melting.[9]

Reporting side effects that may be associated with statins use is important due to its wide and increasing use. We report a case of bilateral stage 2 neurotrophic keratopathy that was temporally associated with initiation of rosuvastatin therapy and that rapidly resolved following drug discontinuation.

REPORT OF A CASE

A 65-year-old female presented with painless diminution of vision in both eyes of gradual onset and progressive course for 1 month. Two weeks following the diminution of vision, she saw an ophthalmologist who diagnosed her as having bilateral corneal ulcers and prescribed her tear substitutes and topical antibiotic drops which did not result in any improvement. She had a history of hypertension controlled by a beta-blocker. She also suffered from dyslipidemia and started taking 10 mg rosuvastatin 2 months prior to the onset of visual complaints. She had no history of dry eyes, herpetic eye disease, or any other relevant ocular history. Examination revealed a corrected-distance visual acuity (CDVA) of 20/600 in both eyes. External ocular examination was normal and ocular motility was full bilaterally. Pupillary examination was normal. Anterior segment examination revealed large clean central corneal epithelial defects in both eyes that are extending to the limbus with smooth rolled edges and an associated ciliary injection with no signs of infiltration or infection consistent with stage 2 neurotrophic keratopathy (Figure 1A). Corneal sensation was severely diminished bilaterally. Anterior chamber examination was free in both eyes. A neurological examination was unremarkable. Magnetic resonance imaging of the brain did not reveal any abnormality. Because of the temporal association with the initiation of rosuvastatin therapy, a drug-related adverse event was suspected, and the patient was instructed to discontinue rosuvastatin therapy. Bilateral patching was also done, and 48 h following discontinuation of the drug there was marked improvement of the corneal epithelial defect bilaterally (Figure 1B). Patching was then substituted by therapeutic contact lenses, and a prophylactic topical antibiotic was added. One week later, her CDVA improved to 20/300 in the right eye and 20/80 in the left eye; there was complete healing of the corneal epithelial defect in the left eye (Figure 2) and further improvement of the epithelial defect in the right eye (Figure 1C) with partial recovery of corneal sensation. She was

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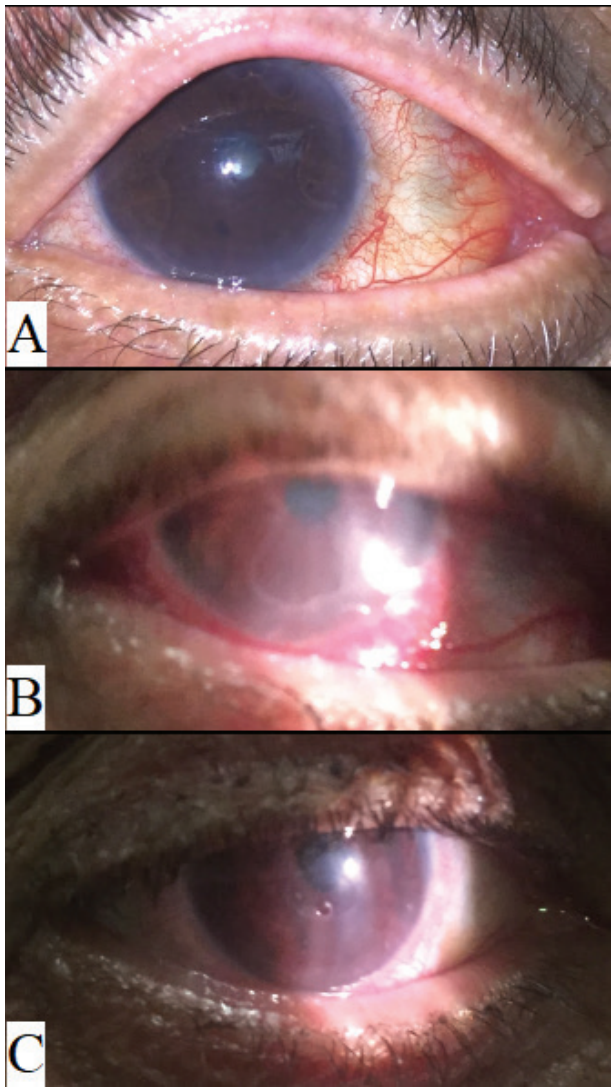

FIG 1. Photography of the right eye (A). At presentation, there was a large central corneal epithelial defect extending to the limbus with smooth rolled edges and associated ciliary injection. (B) Two days following rosuvastatin discontinuation and patching, there is marked improvement of the corneal epithelial defect. (C) One week later, there is further improvement of the corneal epithelial defect using a therapeutic contact lens. Note the small air bubble trapped under the contact lens.

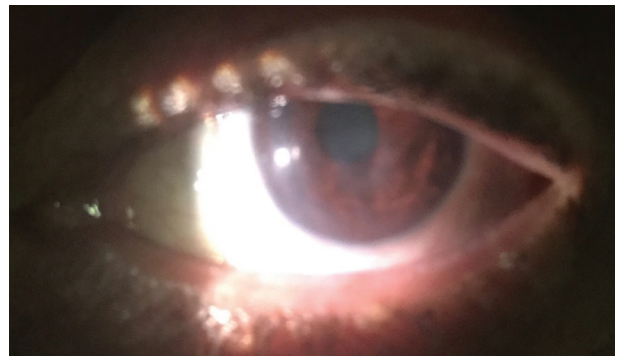

FIG 2. Photography of the left eye. One week after rosuvastatin discontinuation, there is complete healing of the corneal epithelial defect in the left eye with mild superficial central scarring.

instructed not to restart rosuvastatin therapy and 1 year later continues to do well with bilateral residual mild anterior stromal opacification and no recurrent ulceration. Table 1 illustrates the timeline of the patient's history and examination.

DISCUSSION

According to the World Health Organization criteria on drug-related adverse events, a probable association between a drug and an adverse event is made when a clinical event occurs within a reasonable time frame of drug intake and improves following drug discontinuation with the absence of other conditions or drugs that can explain the occurrence of the clinical event as in the presented case.[10]

Several drugs have been reported to be associated with the development of neurotrophic keratopathy such as neuroleptics and antipsychotics, presumably due to trigeminal nerve impairment.[8] Although statin therapy has not been previously associated with trigeminal nerve impairment, it has been associated with an increased risk of peripheral neuropathy that was thought to be due to nerve membrane alteration or mitochondrial dysfunction.[6,7] Other studies suggested a role of statins in neuropathic pain modulation, with one

TABLE 1. Timeline of the Patient's History and Examination

	Date	Event
1	3/2018	Initiation of rosuvastatin therapy for hyperlipidema
2	5/2018	Onset of visual disturbances
3	5/2018	Diagnosed as bilateral corneal ulcers and prescribed tear substitutes and topical antibiotic drops by referring ophthalmologist
4	6/2018	Patient presented to us with idiopathic bilateral stage 2 neurotrophic keratopathy: rosuvastatin therapy was discontinued and bilateral patching was done
5	6/2018	48 h later there was marked improvement of the corneal epithelial defects bilaterally and patching was substituted by therapeutic contact lenses and topical antibiotics
6	6/2018	One week later there was complete healing of the corneal epithelial defect in the left eye with further improvement of the epithelial defect in the right eye
7	6/2019	One year later she continues to do well with bilateral residual mild anterior stromal opacification and no recurrent ulceration

study showing reduction of neuropathic pain using rosuvastatin following trigeminal nerve injury in rats.[11] This may also be due to an anti-inflammatory effect of statins. A toxic effect of statins on neurons and glial cells was also found in several studies.[12,13] This data suggests that statins could potentially result in trigeminal nerve impairment leading to loss of corneal sensation and development or worsening of neurotrophic keratopathy as in the reported case.

The temporal association, bilateral involvement, and rapid improvement of symptoms after rosuvastatin discontinuation are highly suggestive of a role of rosuvastatin therapy in the development of neurotrophic keratopathy in our case. Previously reported ocular adverse events associated with statin use include diplopia, ptosis, and ophthalmoplegia. These events were associated with positive dechallenge and thought to be due to localized myositis affecting the extraocular muscles.[3] Whether a statin-induced neuropathy contributed to these events or not was not known. In a case of atorvastatin-associated ophthalmoplegia, however, ataxia and paresthesia were also present 2½ months following drug initiation and improved 2 days following drug discontinuation.[14] This, together with the presented case, indicates that cranial neuropathy may be another plausible explanation for statin-induced ocular adverse events possibly in the form of an idiosyncratic reaction.

In conclusion, we present a case of bilateral stage 2 neurotrophic keratopathy that was associated with initiation of rosuvastatin therapy and that rapidly improved following drug discontinuation. Reporting of such adverse event is important due to the wide and increasing use of statins and the difficulty in treating neurotrophic keratopathy and its vision threatening complications.

ACKNOWLEDGMENTS

None.

ETHICAL CONSIDERATION

This report was approved by Cairo University Research Ethics Committee and followed the tenets of the Declaration of Helsinki.

FUNDING

None.

CONFLICT OF INTEREST

None.

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