Atorvastatin induced necrotising autoimmune myopathy

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Introduction

Between 2020 and 2021, atorvastatin and rosuvastatin were the most commonly prescribed medications available on the Pharmaceutical Benefits Scheme in Australia.[1] Statins are commonly associated with myotoxicity which can range from asymptomatic rises in creatinine kinase to rhabdomyolysis.[2] Statin-induced necrotising autoimmune myopathy (SINAM) is a rare form of myotoxicity associated with statin therapy occurring in two to three of every 100,000 patients.[3] It has been reported in patients months to years after the use of statins.[4]

One of the hallmark features of SINAM is the progressive symmetric muscle weakness despite cessation of the statin.[5] It is also characterised by evidence of necrosis on muscle biopsy, elevated serum creatinine kinase (CK)[4] and autoantibodies to 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR).[5] The pathophysiology of SINAM is not well understood. It is proposed that in genetically susceptible patients, statins can cause an overexpression of HMGCR and develop autoantibodies which damage muscle cells.[5]

Objective: To describe a case of SINAM and to highlight the need to promptly recognise this adverse drug reaction (ADR) to avoid costly treatment and poor patient outcomes.

Clinical Features

85-year-old gentleman first presented to hospital in July 2019. Initially he was experiencing difficulty with lifting his feet, tripping and was complaining of pain in his hips. At the time he was diagnosed with idiopathic polymyositis, treated with steroids and discharged from hospital. He had been taking atorvastatin since 2017 but this was not stopped until September 2019. In May 2020, he presented to hospital again but the muscle weakness had progressed. He was bed bound, experiencing upper limb weakness and swallowing difficulties. He was referred to a neurologist at a tertiary centre for investigation and diagnosed with SINAM. Please refer to Table 1 for relevant pathology and investigations.

His past medical history included

- Ischaemic heart disease
- Paroxysmal atrial fibrillation
- Benign prostatic hypertrophy
- Congestive cardiac failure
- Hypertension
- Pituitary tumour

His relative medications were atorvastatin 80mg daily up until April 2019. The dose was reduced to 40mg daily from April 2019 up until it was ceased in September 2019. The remainder of the medications were reviewed by the clinical pharmacist and no interacting medications identified.

Table 1: Relevant pathology and investigations

Investigation	Result	Reference Range
CK	6025 IU/L	44-272 IU/L
HMG-CoA reductase antibodies	>200 CU	0-20 CU
Electromyography (EMG)	Diffuse abnormality of end motor unit. More severe in proximal vs distal. Consistent with inflammatory or necrotic myopathic process	Not applicable
Muscle Biopsy	Supportive of inflammatory myopathy	Not applicable

Intervention, Case Progress and Outcomes

The patient received two 5-day courses of intravenous immunoglobulin (IVIG), intravenous (IV) and oral steroids and two doses of rituximab. A percutaneous endoscopic gastrostomy was inserted due to moderate to severe oropharyngeal dysphagia. The muscle weakness had not improved at time of discharge. However, CK had decreased to 277IU/L.

Table 2: Pharmacological interventions

Commencement date	Cessation date	Medication	Dose
15/05/2020	19/05/2020	IVIG (Kiovig)	0.4 g/kg daily
28/05/2020	01/06/2020	IV methylprednisolone	1 gram daily
02/06/2020	24/08/2020	Oral prednisolone	60 mg daily (weaned)
1st dose 10/06/2020	2nd dose 24/06/2020	IV rituximab infusion	1 gram daily
18/06/2020	22/06/2020	IVIG (Kiovig)	0.4 g/kg daily

During admission, the ward pharmacist ensured the appropriate premedication was prescribed prior to rituximab infusions to prevent infusion reactions. The pharmacist recommended monitoring blood sugar levels and initiating bone protection to prevent ADRs associated with long term steroids. The pharmacist also recommended commencing *Pneumocystis jiroveci* pneumonia prophylaxis whilst on high dose corticosteroids. Finally, the pharmacist reported the ADR to the local hospital reporting system and the national reporting system.

Follow-up: 3 months post discharge his muscle function had not improved. The patient had been admitted to a nursing home as his elderly wife was unable to care for him.

Figure 1: Timeline of events

Discussion

There are currently no randomised controlled trials comparing treatment efficacy in patients with SINAM. Treatment is currently guided by published case reports and immunosuppressive therapy is commonly used.[6] Treatment is complicated by the fact that there is continued antibody production long after discontinuation of the statin.[7] Given the cost of treatments such as IVIG, a cost effectiveness analysis is needed. A systematic review on published SINAM case reports highlighted that 83.82% required two or more immunosuppressants.[6] Only 2 out of the 57 cases that tested positive for anti-HMGCR antibody were treated with rituximab. However, there has been further case studies published on its use since then.[8] The review also emphasised that additional immunosuppressive treatment was administered as symptoms persisted after statin cessation in all cases except for two [6]

One of the most accepted algorithm's for assessing the probability of a medication causing an ADR is the Naranjo algorithm.[9] Atorvastatin scored 6 meaning it was a probable cause of the necrotising autoimmune myopathy.[9]

Early identification of SINAM and prompt initiation of immunosuppressive treatment are associated with improved outcomes.[5] The diagnosis of SINAM is difficult as it opposes the traditional belief that an ADR is more likely if the patient improves after the offending medication has been discontinued. Furthermore, the HMG-CoA reductase antibody test is not readily available. In the case described, it was sent to a neighbouring county.

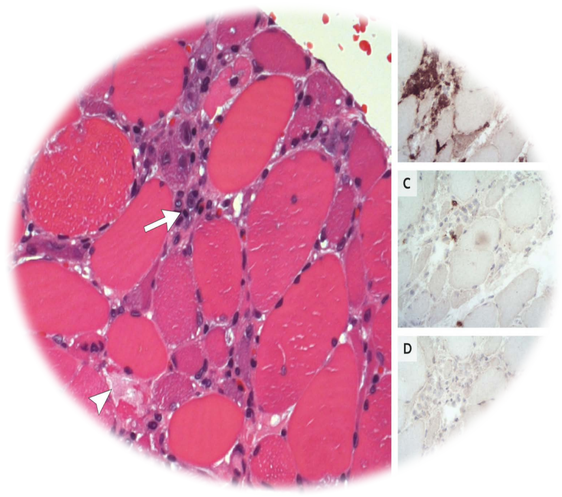

Figure 2: Muscle cell necrosis and macrophage infiltration in SINAM.[10]

It is imperative medical practitioners and pharmacists regularly review the appropriateness of medications in older adults. Clinicians should consider SINAM in those with progressive muscle weakness despite statin withdrawal. The 10-month delay between onset of symptoms and diagnosis for this patient is believed to have contributed to poorer outcomes. Prospective randomised controlled trials are needed to assess the optimal treatment of SINAM.

Conclusion

Given pharmacists expertise and exposure, they have an important role in detecting, reporting, and preventing ADRs. Although SINAM is a rare ADR of statins, case studies have highlighted the need to promptly recognise this ADR so that immunosuppressive therapy can be promptly initiated.

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