Acute interstitial nephritis due to statin and its class effect

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ABSTRACT

Recent reports indicate that statins can cause nephrotoxicity. However, the mechanisms of nephrotoxicity remain unclear. We report a case of acute kidney injury (AKI) in a 54-year-old man following the administration of atorvastatin Renal biopsy showed acute interstitial nephritis. Atorvastatin was withdrawn and he was treated with corticosteroid following which renal function recovered. When he was rechallenged with rosuvastatin 6 months later following an episode of acute myocardial infarction, he developed AKI again indicating class effect of statin for nephrotoxicity.

Key words: Acute interstitial nephritis, acute kidney injury, statins

Introduction

Statins are 3-hydroxy-3-methylglutaryl coenzyme-A reductase inhibitors and are very effective in reducing atherosclerotic cardiovascular related morbidity and mortality.[1] In recent years, higher doses of statins are increasingly used since they have a better cardioprotective effect compared with lower doses.[2] Despite a widespread clinical use of statins for more than two decades, no significant renal adverse effects were reported, except for a very rare occurrence of rhabdomyolysis induced acute kidney injury (AKI) and hence were considered safe. Rhabdomyolysis due to statins is very rare, with a reported incidence of 3.4/100,000 patient-years.[3] On the contrary, there is some evidence to suggest that statins exert renoprotective effect, when used prior to cardiac surgery and contrast use.[4,5] The National Lipid Association Kidney Expert Panel reviewed the published and unpublished evidence in 2006 and found no evidence to suggest that statins cause renal injury.[6] However, since then there has been a growing concern about statin induced renal toxicity.

We report a case of AKI due to acute interstitial nephritis caused by atorvastatin and AKI recurred after a challenge with another statin, rosuvastatin.

Case Report

A 54-year-old man was detected to have hyperlipidemia and was prescribed atorvastatin 20 mg and a multivitamin capsule 1 month prior to initial consultation and and received no other drug. He was detected to have diabetes mellitus 6 months ago, but received no medication. He felt unwell after taking atorvastatin and on evaluation had normal renal function (blood urea: 38 mg/dl, serum creatinine [SCr]: 1.1 mg/dl). Since he continued to feel tired, he had a review 3 weeks later and was detected to have azotemia (blood urea: 54 mg/dl, SCr: 1.9 mg/dl) and was referred to our unit. He complained of tiredness, but did not have fever, skin rash, muscle weakness or tenderness. Blood pressure was 105/80 mm Hg and pulse rate was 75/min. Clinical examination was unremarkable. Urine examination showed no albuminuria and no sediment on microscopy. Serum creatine kinase (CK) was normal (70 U/L). He denied taking any other drug, including indigenous or over the counter medications, other than atorvastatin and multivitamin capsule. He was thought to have AKI due to atorvastatin and it was discontinued. After 1 week SCr rose to 2.4 mg/dl and he underwent renal biopsy, which showed nine glomeruli, of which one showed periglomerular fibrosis. Moderate interstitial round cell infiltrates [Figure 1] were seen along with few eosinophils. Mild hyaline arteriosclerosis

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was seen. Immunoflurescence study showed minimal mesangial deposits of immunoglobulin M and was negative for other immunoglobulins and C3. The renal biopsy was consistent with acute interstitial nephritis.

He was started on oral prednisolone 1 mg/kg/day for 2 weeks and then slowly tapered the dose over 2 months and stopped. The response to corticosteroid was good and SCr improved to 1.3 mg/dl at the end of 2 months [Figure 2]. He was advised not to take statins in the future.

He was admitted 6 months after the initial presentation with acute myocardial infarction (AMI) and underwent primary percutaneous transluminal coronary angioplasty (PTCA) and stenting. He was given atorvastatin 40 mg post PTCA, but was replaced with rosuvastatin 10 mg after 2 days in view of previous allergic interstitial nephritis attributed to atorvastatin. He was explained about the possible cross reactivity with atorvastatin and SCr was monitored on weekly basis. SCr was 1.4 mg/dl at the initiation of rosuvastatin therapy and gradually increased to a peak of 1.8 mg/dl at 4 weeks [Figure 2]. Serum CK was normal (55 U/L) and there was no evidence of any other etiologic factor to account for AKI during this period. After much deliberation, rosuvastatin was stopped and he was followed closely. The renal biopsy was not repeated since antiplatelet drugs could not be stopped so early after PTCA and steroid were not given in view of possible worsening of dyslipidemia and hyperglycemia. SCr returned to baseline value spontaneously over next 2 months and remained stable over next 12 months.

Discussion

We present a case of AKI in a 54-year-old man, which occurred about 4 weeks after initiation of atorvastatin (20 mg) and no other cause could be identified to explain AKI. Renal biopsy showed features of acute interstitial nephritis with interstitial infiltration with mononuclear cells and occasional eosinophils. He had a marked recovery of renal function following withdrawal of the drug and steroid therapy. Six months later, he was initiated on rosuvastatin (10 mg) following AMI after which there was a gradual increase in SCr by 0.5 mg/dl over the baseline to a peak value of 1.8 mg/dl. SCr spontaneously returned to baseline gradually over the next 2 months after withdrawal of rosuvastatin. Renal toxicity in him was thought to be a class effect of statins.

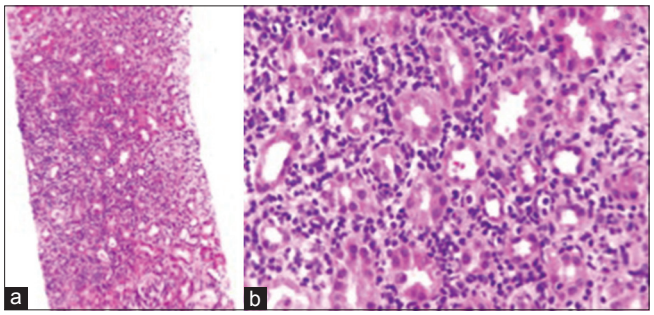

Figure 1: Microscopy of renal biopsy (a: ×10; b: ×40) showing acute interstitial nephritis

Concern about significant renal toxicity is reported from recent large epidemiological studies. Hippisley-Cox and Coupland reported in a large study from UK that statin use was associated with significantly increased risk of AKI, which was dose dependent and was seen across all statins, except rosuvastatin.[7] More recently, Dormuth *et al*., in a study of over 2 million patients who were newly treated with a statin, found a significant relative increase of 34% in the rate of hospitalization for AKI within 120 days of initiation for patients receiving high potency statins versus low potency statins.[8] The nephrotoxicity associated with statin was dose dependent and was seen in all statins. Though rosuvastatin is more potent and has a longer half-life, there is no evidence to suggest that rosuvastatin is more nephrotoxic than atorvastatin.

Acute kidney injury due to statins is probably under recognized and hence under reported due to following reasons:

1. Patients who generally receive statins are elderly, have several comorbid conditions such as diabetes, hypertension, atherosclerotic renovascular disease which are confounding factors for renal dysfunction and receive several drugs such as renin angiotensin aldosterone blocking agents and diuretics that can cause AKI
2. They often receive antiplatelet agents and hence may not undergo renal biopsy for AKI, and
3. Acute or subacute tubule-interstitial nephritis due to

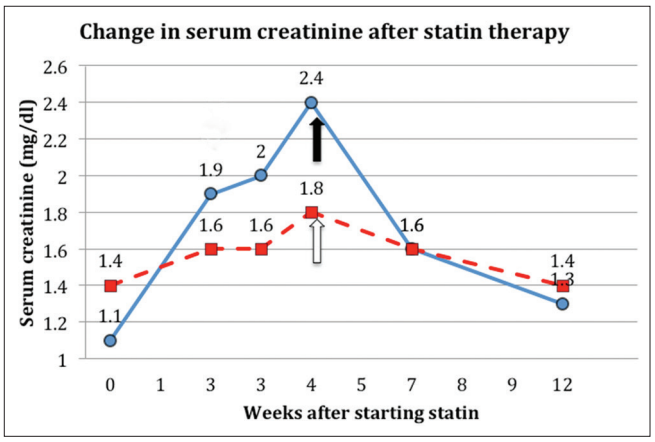

Figure 2: Serum creatinine over period after starting atorvastatin 20 mg (solid line) and after rechallenge with another statin, rosuvastatin 10 mg (interrupted line). Black arrow indicates initiation of corticosteroid; white arrow, indicates withdrawal of statin

statins may be subtle and subclinical and hence may go unrecognized when not routinely monitored for renal function.

The pathophysiological mechanisms of the increased incidence of AKI reported in recent epidemiological studies remains unclear. The prime suspect for AKI due to statins is rhabdomyolysis. However, the data from JUPITER study, which was subsequently reported to Food and Drug Administration showed that only 1 out of 8901 patients who received rosuvastatin 20 mg developed rhabdomyolysis (0.01%), whereas AKI was seen 19 (0.21%) patients and another 16 (0.18%) developed doubling of SCr, indicating that rhabdomyolysis did not account for AKI in them.[9] Another putative cause for AKI is statin induced suppression of production of coenzyme Q10 (CoQ-10), which has antioxidant properties.[10] This enzyme is involved in generation of adenosine triphosphate in the mitochondria. CoQ10 is reported to have renoprotective effect in experimental AKI in animals[11] and humans with chronic kidney disease.[12] Yet another possible mechanism is an acute or subacute tubulo-interstitial nephritis. Acute interstitial nephritis due to statin has been reported only on two previous occasions. Londrino *et al*., reported a case of rosuvastatin induced biopsy proven acute interstitial nephritis in an 83-year-old male, who showed complete recovery following withdrawal of the drug and steroid therapy.[13] Van Zyl-Smit *et al*. described a case similar to ours in which rosuvastatin caused AKI due to renal tubular toxicity, which resolved after the withdrawal of the drug.[14] A renal biopsy showed both acute as well as chronic interstitial nephritis. Later on the introduction of atorvastatin at 40 mg produced similar pattern of AKI, which resolved when the dose was reduced to 20 mg. They demonstrated dose dependency and also class effect of statins on renal tubular toxicity. These and our case report[13,14] suggest acute or subacute interstitial nephritis as another possible cause of AKI due to statins.

Despite several recent reports of increased nephrotoxicity due to statins, it is admittedly rare. The current evidence does not support the notion that our current practice to use of statins should be restricted in population who are likely to benefit from its use, for fear of potential nephrotoxicity. However, clinicians should be aware of a potential renal toxicity of statins, especially at higher doses. We feel that it would be a prudent practice for the clinicians to be vigilant and routinely monitor renal function during the first few months after initiation of statin, especially when higher doses of statin is used.

Conclusion

We report a case of AKI due acute interstitial nephritis caused by atorvastatin, which resolved after withdrawal of the drug and steroid therapy. On rechallenge with rosuvastatin after 6 months, he developed AKI again, which resolved after withdrawal of the drug. Our results suggest a possible direct or immune mediated renal interstitial injury as a possible mechanism for statin induced AKI.

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