Statin therapy in myopathic patients with hyperlipidemia

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Abstract

Statin-related myopathy is a clinically important cause of statin intolerance and discontinuation. It is not understood whether statin therapy is safe from patients with autoimmune inflammatory muscular disease. We examined the effect of atorvastatin (10 mg/day) on the muscle in patients with immune-mediated neuromuscular disease and hyperlipidemia. Serum LDL levels (pre-therapy, 164±14.3 mg/dl; post 1M, 92±26.6 mg/dl; post 2M, 93±15.9 mg/dl; 113±36.1 mg/dl) and TG levels (pre-therapy, 173±75.1 mg/dl; post 1M, 106±60.9 mg/dl; post 2M, 111±41.4 mg/dl; 130±28.2 mg/dl) were significantly decreased after atorvastatin therapy but serum CK levels were not significantly changed during the therapy (pre-therapy, 105±52 IU/L [mean±SD]; post 1M, 131±76.6 IU/L; post 2M, 133±97.7 IU/L; 147±33.9 IU/L). The results of the present small study indicate that acquired inflammatory neuromuscular disorders may net become a risk factor in statin myopathy.

Key Words: Statin, Myopathy, Hyperlipidemia, CK, LDL

Introduction

Statins are the most effective and practical class of drugs for reducing LDL-C levels, with a proven ability to reduce LDL-C to established and lower target levels [1,2]. They reduce the risk of essentially every clinical manifestation of the atherosclerotic process, are easy to administer, and have good patient acceptance. In general, statins have an excellent safety record [1]. Safety concerns have focused primarily on the effects on the liver and skeletal muscle. The connection between statin therapy and adverse reactions of the skeletal muscle is well established [1, 3, 4]. Between 2% and 7% of patients report myalgia, defined as proximal or diffuse muscle pain, tenderness, and/or weakness [4]. Myopathy—muscle pain, tenderness, and weakness accompanied by elevations of creatine kinase (CK) of more than 10 times the upper limit of normal (ULN)—is much rarer, affecting only 0.01% to 0.5% of patients treated with statin monotherapy [4]. Myopathy has been reported with all currently marketed statins, particularly at higher doses.

The immune-mediated inflammatory myopathies are a heterogeneous group of diseases with diverse clinicopathological features and etiologies including dermatomyositis (DM), polymyositis (PM) and inclusion body myositis (IBM). In DM a complement-dependent humoral process thought to be initiated by antibodies to endothelial cells results in a microangiopathy with secondary ischemic changes in muscles. On the other hand, in PM and IBM there is a T-cell response with invasion of muscle fibers by CD8+ lymphocytes and perforin-mediated cytotoxic necrosis. Patients with DM or PM usually respond to treatment with glucocorticoids and immunosuppressive agents. On the other hand, corticosteroids are recognized as a secondary cause of dyslipidemia. Observational studies and case reports of patients who have received long-term corticosteroid administration generally demonstrate elevations in total plasma

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cholesterol, triglyceride, 1ow density lipoprotein (LDL) cholestero1 (LDL-C) and high density lipoprotein (HDL) cholesterol (HDL-C) [5-13]. In particular, care should be taken when giving statin therapy to patients suffering from hyperlipidemia with autoimmune inflammatory muscular disease who have received treatment with corticosteroids. This is because it is not understood whether statin therapy is safe from the patients with autoimmune inflammatory muscular disease. We examined the effect of atorvastatin on the muscle in patients with immune-mediated neuromuscular disease and hyperlipidemia.

Patients and Methods

Clinical assessment

The subjects of this study included 12 patients with neuromuscular disorders. The underlying diseases are shown in Table 1. All were selected from among Japanese patients who had been treated at Tokushima University Hospital or Tokushima National Hospital from April 2006 to January 2008 and who agreed to participate in the study. All patients received oral administrations of atorvastatin (10 mg/day). Other therapies including corticosteroids or FK 506 remained unchanged during the study. The patients were evaluated one, two, and three months after treatment by measurement of hand grasp power, blood sugar level, and serum concentrations of γ-GTP, AST, ALT, CK, LDL-cholesterol, triglyceride (TG), and HDL-cholesterol.

Statistical analysis

We used StatView for Windows (version 5.0) for statistical analysis. Non-paired data and paired data were analyzed by the nonparametric Mann-Whitney U test and Wilcoxon's signed rank test, respectively.

Results

During atrovastatin hand grip power and blood sugar levels were not significantly changed, as shown in Figure 1. Taken together, serum levels of γ-GTP, AST, and ALT were not significantly changed.

Figure 2 shows serum levels of CK, LDL, TG and HDL. Serum CK levels were not significantly changed during the therapy (pre-therapy, 105±52 IU/L [mean±SD]; post 1M, 131±76.6 IU/L; post 2M, 133±97.7 IU/L; 147±33.9 IU/L). On the other hand, LDL levels (pre-therapy, 164±14.3 mg/dl; post 1M, 92±26.6 mg/dl; post 2M, 93±15.9 mg/dl; 113±36.1 mg/dl) and TG levels (pre-therapy, 173±75.1 mg/dl; post 1M, 106±60.9 mg/dl; post 2M, 111±41.4 mg/dl; 130±28.2 mg/dl) were significantly decreased after atorvastatin therapy. Serum HDL levels were not significantly changed (pre-therapy, 70±17.1 mg/dl; post 1M, 77±12.2 mg/dl; post 2M, 76±17.1 mg/dl; post 3M, 78±9.6 mg/dl).

Table 1. Summary of Patients

Age (y)	Underlying Disease	Duration (y)	Other Medication
58	polymyositis	7	PSL 10 mg/day
67	polymyositis	12	PSL 5 mg/day
60	polymyositis	21	–
58	polymyositis	14	–
71	polymyositis	20	FK506 3mg/day
62	dermatomyositis	5	PSL 7. 5 mg/day
51	dermatomyositis	6	PSL 2. 5 mg/day
63	dermatomyositis	11	PSL 5 mg/day
58	IBM	7	PSL 5 mg/day
65	CIDP	10	PSL 5 mg/day
64	CIDP	7	PSL 5 mg/day
59	CIDP	8	PSL 20mg/day

IBM, inclusion body myositis; CIDP, chronic inflammatory demyelinating polyneuritis; PSL, predonisolone

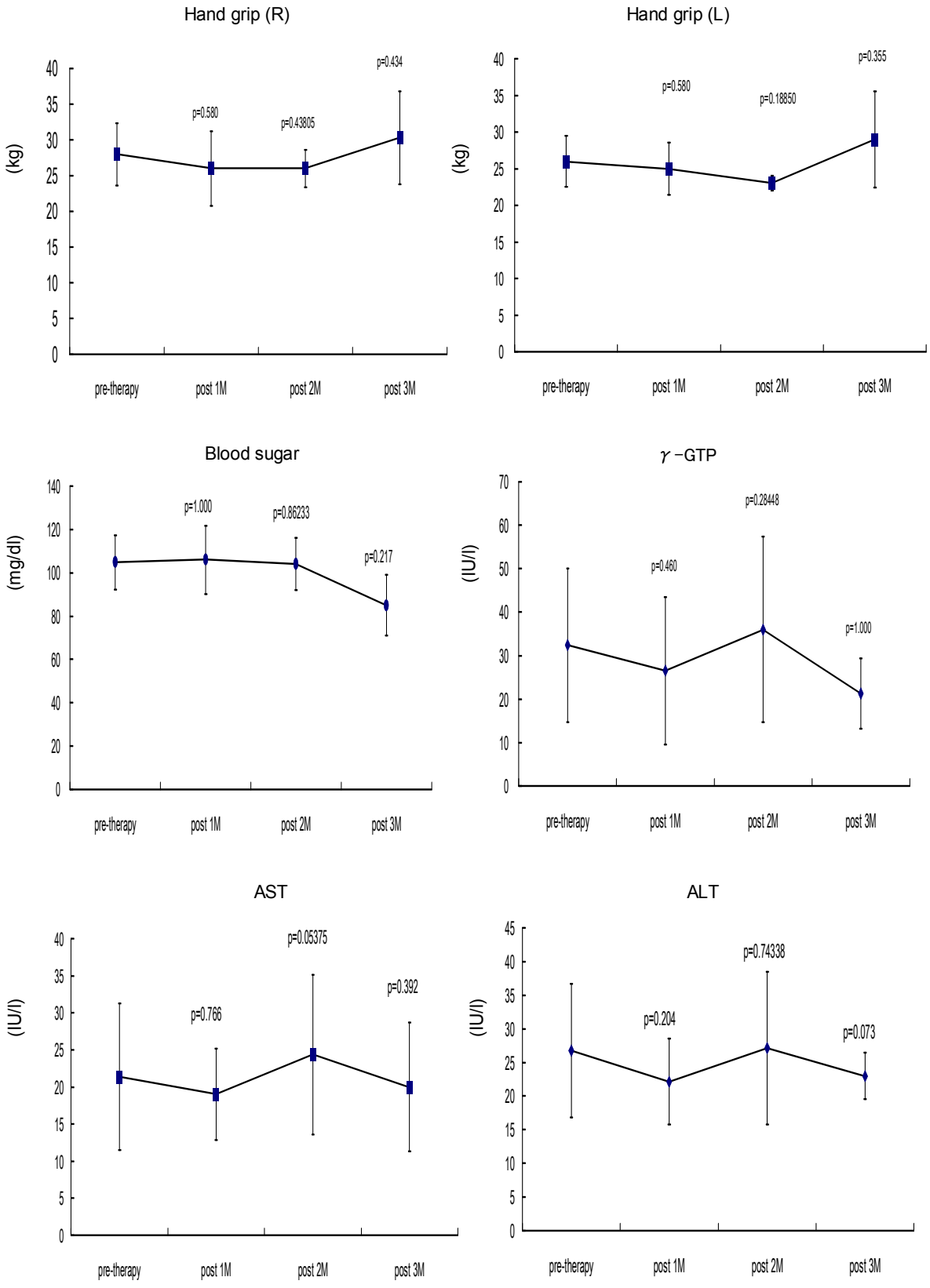

Figure 1. Hand grip power, blood sugar levels and serum levels of γ-GTP, AST and ALT during atorvastatin therapy. Significant changes were not seen after the therapy.

Discussion

The precise mechanisms underlying statin myopathy are incompletely understood. Proposed mechanisms for statin-related myopathy include decreased cholesterol content of skeletal myocyte membranes inducing instability, depletion of isoprenoids (farnesyl pyrophosphate and geranyl pyrophosphate) or coenzyme Q10, and mitochondrial dysfunction. Decreased cholesterol synthesis with membrane destabilization is unlikely to be an important mechanism because in experimental models, non-statin lipid-lowering agents, most importantly fibrates, induce myopathy through distinct non-overlapping pathways [14-16]. Furthermore, decreasing cholesterol synthesis by inhibiting squalene synthase does not result in myopathy [17] .

Although the present study is preliminary, we found that atorvastatin therapy significantly reduced serum LDL and TG levels. However, serum CK levels were not significantly changed during the therapy. These findings indicate that the onset of side effects does not occur in everyone equally. Recent results suggest that genetic factors increase the risk of statin-related muscle complaints. Some patients are susceptible to statin myopathy because of pre-existing subclinical inherited muscular disorders, or genetic variation in statin uptake proteins encoded by SLCO1B1 or the cytochrome P enzyme system [18]. The results of the present small study indicate that acquired inflammatory neuromuscular disorders may net become a risk factor of statin myopathy.

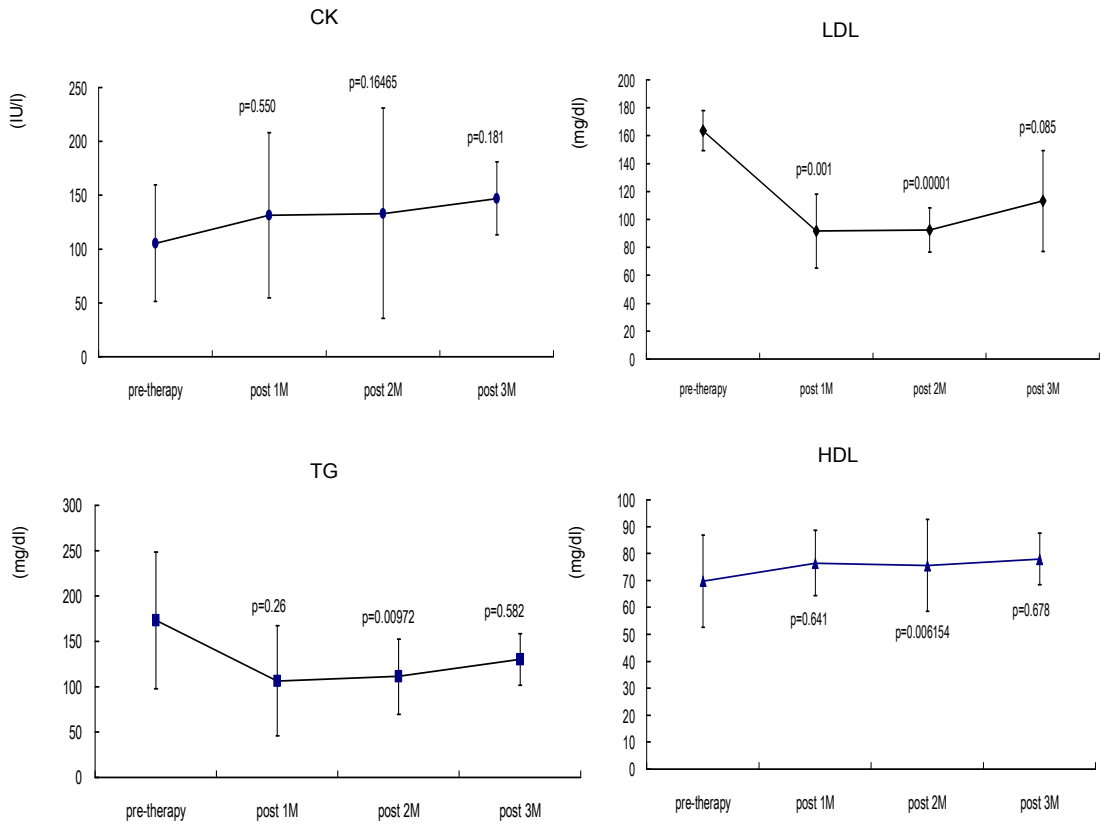

Figure 2. Scores of positive SUBI (A) and negative SUBI (B). Neither the scale of positive SUBI or negative SUBI were significantly changed in patients with PD compared with those of controls. In addition, these scales were not significantly changed during candesartan therapy.

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