INVITED REVIEW

ABSTRACT: Alone or as part of a multidrug immunosuppressive regimen, cyclosporine A (CsA) has been reported in isolated case studies as a cause of muscle disorders. We reviewed the current knowledge on muscle toxicity of CsA and discussed the possible role of mitochondrial dysfunction in the genesis of CsA-associated myopathy. A systematic review using Medline® and Current Contents® databases combined with a manual literature search allowed us to select 56 references. We identified 34 patients with muscle disorders possibly related to CsA, usually manifesting by myalgia or muscle weakness and plasma creatine kinase elevation. Only 2 of 34 patients were treated with CsA alone. Experimental studies have shown that administration of CsA to rats reduces capillary density in extensor digitorum longus, skeletal muscle mitochondrial respiration, and endurance exercise capacity. Cyclosporine has been shown to inhibit the mitochondrial permeability transition pore. Whether identified interactions between CsA and mitochondria can explain CsA-associated myopathy is still unclear.
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MUSCLE DISORDERS ASSOCIATED WITH CYCLOSPORINE TREATMENT

MYRIAM BREIL, PharmD,[1] and PATRICK CHARIOT, MD[1,2,3]

[1] Department of Toxicology, Hôpital Henri-Mondor, 94010 Créteil, France
[2] Department of Pathology, Hôpital Henri-Mondor, 94010 Créteil, France
[3] Groupe d'Etudes et de Recherches sur le Muscle et le Nerf (EA 2347, Université Paris XII), 94010 Créteil, France

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The immunosuppressive oligopeptide cyclosporine A (CsA) is extensively used in organ transplantation and autoimmune disorders.[9] Its therapeutic use is, however, limited by major side effects, including nephrotoxicity and hepatic disorders.[5] Cyclosporine can adversely affect other organs such as the pancreas, central nervous system, bone, and skeletal muscle.[48] Alone or as part of a multidrug immunosuppressive regime, CsA has been reported as a cause of myopathy manifesting by myalgia, muscle weakness, and plasma creatine kinase (CK) elevation.[17,20,21,44] The frequency of muscular complications may be increased when use of CsA is associated with other drugs such as hydroxymethylglutaryl coenzyme A reductase inhibitors (statins), colchicine, or pyrazinamide.[1,8,15,16,18,28,36,45,46,52,59] The mechanism of CsA myotoxicity is unknown.[17,35,48] Some clinical and experimental findings suggest that it might be related to a mitochondrial disorder, because: (1) some patients with CsA-associated myopathy have mitochondrial abnormalities and lipid droplet accumulation in skeletal muscle[17,35]; and (2) CsA decreases mitochondrial respiration in rat skeletal muscle.[7,26,40] We have reviewed the current knowledge on muscle toxicity of CsA and discuss the possible role of mitochondrial dysfunction in the genesis of CsA-associated muscle disorders.

We undertook a systematic literature review using the Medline® (National Library of Medicine, Bethesda, Maryland) and Current Contents® (Institute for Scientific Information, Philadelphia, Pennsylvania) databases. Periods screened were from 1966 to February 1999 (Medline®) and from September 1997 to September 1998 (Current Contents®). We used the following key words and strategy: for Medline® and Current Contents® search, "cyclosporine" and "mitochondria or skeletal muscle or muscular diseases or rhabdomyolysis or myositis or muscle cramps or muscle weakness or muscular atrophy or neuromuscular diseases or fibromyalgia or mitochondrial myopathy or dermatomyositis or polymyositis." We also screened relevant articles from the reference list of all articles selected by Med-

Abbreviations: CK, creatine kinase; CsA, cyclosporine A
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Correspondence to: P. Chariot, département de pathologie, hôpital Henri-Mondor, 94010 Créteil, France; e-mail: pchariot@cybercable.fr

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line® and Current Contents®. We limited our research to articles in English and French. The Medline® search provided 92 articles and Current Contents® search provided 28 articles. Two articles were found in both databases. A total number of 118 articles were thus identified. Eighty of the 118 articles were not related to CsA toxicity. Our final selection included the remaining 38 articles and 18 articles selected manually from the reference lists of these 38 articles, making a total number of 56 references.

Cyclosporine A and Myopathy. Data originating from the manufacturer indicated that 0.17% of patients developed muscle disorders related to CsA administration.[2] One brief report mentioned the existence of musculoskeletal pain in 26 of 193 patients (13.5%) treated by CsA.[38] In most cases, pain involved joints. Tendons and muscles were reported to be affected in some cases. Clinical description was scarce, and the prior existence of a skeletal muscle disease was unclear.[38]

We identified 23 papers reporting muscle disorders affecting a total of 34 patients treated with CsA.[1,2,8,10–13,15–18,20,21,28,33,35,36,44–47,52,59] Muscle symptoms included myalgia, cramps, and muscle weakness, sometimes associated with CK elevation. Myalgia occurred in 23 and muscle weakness in 19 of 34 patients. Weakness was proximal in 4 patients, generalized in 6 patients, and not characterized in 9 patients. It predominated in the legs in 2 patients. The age of 3 patients was not reported; the median age of the remaining 31 patients was 53 years (range, 26–70 years).

In 2 patients, CsA was not taken in association with other drugs known to be myotoxic.[18,45] Patients were receiving CsA at conventional doses when symptoms developed 3 weeks and 5 months after the start of the therapy. The muscle disorders were reversible and resolved after the dose of CsA was reduced[17] or discontinued.[46] In 1 patient, readministration of CsA was followed by recurrence of muscle pain.[44]

In 32 patients, CsA treatment was associated with steroids (29 of 32 patients),[1,2,8,10–13,15,16,18,20,21,28 33,35,45–47,52,59] statins such as simvastatin or lovastatin (11 patients),[1,8,12,16,33,45,52] colchicine (14 patients),[13,15,21,28,36,46,47,59] or pyrazinamide (1 patient).[19] Patients were receiving CsA at conventional doses for between 5 days and 9 years (median, 3 years) when symptoms developed. Median durations of concomitant drug treatment were as follows: steroids, 24 months (range, 3 days to 8.5 years); colchicine, 3 weeks (range, 3 days to 8 years); statins, 9 months (range, 2 weeks to 3 years); and pyrazinamide, 3 days. The median daily dose of steroids was 10 mg. Muscle symptoms were reversible and resolved after the dose of CsA was reduced (9 cases) or discontinued (12 cases). Cyclosporine treatment was not modified in 11 cases, where myopathy was thought to be due to colchicine,[15,28,36] lovastatin,[33] pyrazinamide,[18] or an interaction between itraconazole and simvastatin,[52] or in a case in which the patient died during the course of diagnostic investigations.[35] In one case, rhabdomyolysis was observed in a renal transplant recipient treated with CsA and steroids. Well-recognized nontoxic causes of rhabdomyolysis were absent, and muscle damage resolved spontaneously without tapering CsA and steroid dosages.[11] In all cases, steroid treatment was not modified, but other myotoxic drugs associated with CsA were stopped. The medications taken concurrently with CsA—e.g., statins—were not associated with particular muscle symptoms. Creatine kinase level was high in 27 patients (range, 6–100 times the normal value), normal in 5 patients, and not reported in 2 patients.

Muscle biopsy (Fig. 1) performed in 15 of the 34 patients showed moderate atrophy (5 of 15 patients)[13,17,18,20,44] predominating in type 2 fibers in most cases (3 of 5),[17,18,20] necrotic fibers (4 of 15),[13,35,44,45] excessive number of central nuclei (1 of 15),[36] and mitochondrial abnormalities such as accumulation of mitochondria, ragged-red fibers, or lipid vacuoles (2 of 15).[17,35] In only one case, typical ragged-red fibers affecting 2% of fibers were found in a 65-year-old man.[35] Histology was normal in one patient[8] and showed nonspecific abnormalities in 2 patients.[2,16] Vacuolar myopathy was found in 6 patients who were also treated by colchicine.[13,15,46,47]

Electrophysiological findings included myopathic changes (15 of 21 patients),[2,8,13,15,20,21,35,36,46,47] sensorimotor neuropathy (6 patients),[13,15,17,46,47] and in one instance, myotonic discharges.[13] Electrophysiological studies were normal in 4 patients.[12,18,44]

Skeletal Muscle Abnormalities in Patients Treated with CsA without Muscular Symptoms. Skeletal muscle studies have been reported in patients treated with CsA who had no muscular symptoms.[20,34,57] Atrophic fibers, accumulation of mitochondria, and lipid vacuoles were reported in a case study of 2 patients.[20] Impaired skeletal muscle energy metabolism in heart transplant recipients treated with CsA was detected by ^{31}P magnetic resonance spectroscopy.[57] In another study, the ultrastructure of skeletal muscle tissue did not differ from healthy controls in 16 heart transplant recipients

treated with CsA.[36] Mitochondrial volume density was normal. Capillary density was significantly lower than in healthy control subjects, but there was no control for CsA.[36]

Cyclosporine Administration to Patients with Duchenne Muscular Dystrophy. Cyclosporine has been used in human experiments with myoblast transfer therapy in patients with Duchenne muscular dystrophy.[39,41,53] In two studies, muscle force generation improved, but there was no control for CsA.[41,53] A controlled study did not show any effect of CsA on muscle strength.[39] If it does occur, any increased muscle strength due to CsA may relate to an increase of available calcium from intracellular stores or to interference by CsA with the production of cytokines preventing damaged muscle fibers from regenerating.[39] In these three studies, 31 patients received CsA for 8 weeks (15 patients),[53] 6 months (6 patients),[39] or 7 months (10 patients),[41] and none of them reported cramps or myalgia.

Experimental Findings. *Experimental toxicity in skeletal muscle.* Early toxicological evaluations of CsA did not mention any change in skeletal muscle of treated animals,[49] but there is no evidence that muscle examination was performed extensively. Administration of CsA to rats for 4 weeks reduced capillary density in extensor digitorum longus but not in soleus and diaphragm.[7] Muscle oxidative capacity measured by succinate dehydrogenase activity was also reduced. Fiber-type proportion and cross-sectional areas were unchanged.[7] In another study, administration of CsA to rats for 2 weeks decreased skeletal muscle mitochondrial respiration and endurance exercise capacity.[40]

An experimental study performed in rats showed that CsA associated with statins, but not CsA alone, induced a myopathy characterized by the presence of necrotic fibers, inflammatory cell infiltration, and interstitial edema.[55] Plasma concentrations of statins were higher when statins were administered with CsA.[55] Another article published by the same group seems to have been a duplicate publication.[56]

Cyclosporine and mitochondria. Inhibition of respiration induced by CsA has been reported in isolated mitochondria obtained from rat skeletal muscle.[26,40] Cyclosporine decreases peripheral ability to use oxygen and inhibits coupled and uncoupled muscle mitochondrial respiration in vitro.[26]

Mitochondrial dysfunction induced by CsA has been studied mainly in kidney in both in vivo[38,59] and in vitro[27,29,30,54,58] studies. Histochemistry for succinate dehydrogenase, a part of respiratory chain complex II, performed in rat kidney after CsA administration showed focal areas with decreased enzyme activity, suggesting a decreased number of functional organelles.[51] Cyclosporine inhibited succinate- and glutamate-malate supported respiration of mitochondria isolated from rat[27,29,54] or human[30] kidney. Cyclosporine also inhibited mitochondrial swelling and adenosine triphosphate uptake of rat kidney mitochondria and the prooxidant-induced calcium release from rat kidney mitochondria.[13,21,50,54] Combined administration of CsA, prednisolone, and azathioprine had an increased inhibitory effect on respiration as compared with CsA administration alone.[54] In vivo studies yielded similar results on measurement of mitochondrial swelling but significantly different results on oxidative phosphorylation. Cyclosporine given orally to rats for 7 days inhibited mitochondrial swelling.[58] Cyclosporine given orally to rats for 30 days increased glutamate-malate–supported respiration, indicating enhancement of complex I activity.[37] Increase of complex I activity was thought to be related to the reduction of renal blood flow observed in CsA-treated rats.[37]

Cyclosporine has been shown to inhibit the mitochondrial permeability transition pore with high affinity.[14,19,60] Permeability transition is a calcium-dependent increase of inner membrane permeability to solutes with molecular mass less than 1500 Da.[43] Pore opening, or permanence in the open state, is favored by Ca^{2+} binding to two sites on the matrix side of the membrane.[60] Pore opening also depends on the transmembrane potential difference and matrix pH.[6] The various effects of CsA on mitochondrial function might be explained by considering that CsA does not act on a specific respiratory chain complex but inhibits the whole electron transport chain via a decrease of transmembrane potential and adenosine triphosphate synthesis and a perturbation of mitochondrial permeability transition. Whether CsA toxicity is related to its ability to inhibit the mitochondrial permeability transition pore is uncertain.

DISCUSSION

The occurrence of skeletal muscle disorders in a number of patients treated by CsA is now established. Their frequency seems to be low, but the only data available on this point originate from the manufacturer.[2] Published observations have shown nonspecific manifestation that include myalgia, cramps, and muscle weakness, sometimes associated with CK elevation. Histological findings have been heterogeneous, and mitochondrial abnormalities have been

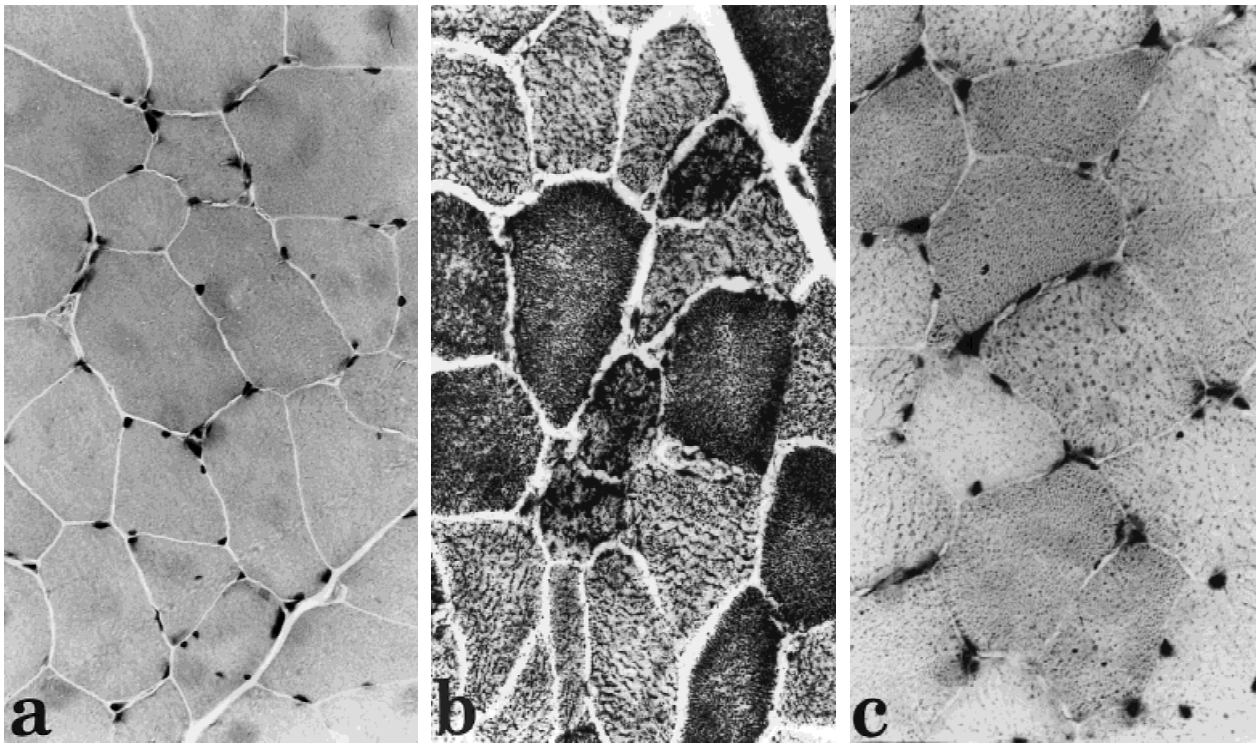

FIGURE 1. Cyclosporine-associated myopathy. A 65-year-old woman with a history of renal transplantation and a sensory peripheral neuropathy was receiving CsA, amitriptyline, and clonazepam when moderate weakness developed in the lower limbs. Pathologic findings were similar to those reported by others.[18,36] **(a)** Moderate abnormalities consisting of scattered atrophic fibers (cryostat section, hematoxylin & eosin, magnification ×400). **(b)** Some atrophic fibers have an increased number of mitochondria and focal aggregation of oxidative activity (cryostat section, NADH-TR, magnification ×400). **(c)** Mild to moderate lipid excess in some fibers (cryostat section, Sudan red, magnification ×400).

found in a minority of patients. Because most patients received CsA as well as other medications known to be myotoxic, such as prednisone, statins, or colchicine, it is difficult to ascribe the clinical and histological findings solely to CsA. The main argument supporting the existence of CsA myotoxicity is the reversibility of clinical symptoms and biologic alterations after CsA discontinuation or reduction, without other treatment modification. Reversibility, reported after CsA dose discontinuation or reduction was observed in 21 of 34 patients. However, in 13 of these 21 patients, the direct role of CsA in myotoxicity remains unproven, because other myotoxic drugs taken in association with CsA (i.e., colchicine, statins, or pyrazinamide) were stopped as well as CsA. Cyclosporine, which is known to have a cholestatic effect,[32] could interfere with the biliary excretion of statins, resulting in higher systemic statin levels.[3,33,55] Of note is the rare occurrence of muscle disorders in patients receiving tacrolimus, another immunosuppressive agent, which is structurally very different from CsA, although it has a similar mechanism of action.[25] Only one case of rhabdomyolysis has been reported,[25] but hypertrophic cardiomyopathy has also been observed in pediatric transplant patients treated with this drug.[4]

There is limited evidence of CsA-associated myotoxicity in animals. Experimental studies have not shown significant myopathic changes in rats given CsA.[7] Activities of enzymes commonly used in the diagnosis of skeletal muscle disorders such as CK were not evaluated. A reduced capillary density was found in extensor digitorum longus.[7]

Mitochondrial abnormalities have been found at muscle biopsy in some patients with myalgia or weakness who were treated by CsA.[17,35] Such findings are reminiscent of the mitochondrial dysfunction induced by CsA in kidney.[29,30] Experimental data have established the effects of CsA on skeletal muscle mitochondrial respiration in vivo and in vitro.[26,40] The mechanisms underlying the reduced oxidative capacity of muscle fibers are unclear. Cyclosporine inhibits the calcium-dependent pore in inner mitochondrial membrane and interferes with the integrity of mitochondrial membrane. Pore opening has been identified as an important event in the pro-

cess leading to death of injured cells.[6] Closed pore maintained by CsA would decrease the efflux of mitochondrial calcium with subsequent mitochondrial dysfunction and reduced respiration.[26,43]

It is unknown whether the mechanisms resulting in a reduced capillary network and oxidative capacity depend on each other. One possibility is that long-term treatment with CsA is associated with a reduced capillary density, possibly resulting in mitochondrial dysfunction. It has been demonstrated for years that chronic ischemia can induce mitochondrial abnormalities, including impaired respiratory rate in liver and kidney mitochondria and ragged-red fibers and giant mitochondria in skeletal muscle.[22,23,42] Mitochondrial dysfunction and capillary loss related to CsA administration may take part in the reduction of exercise capacity associated with an increase of plasma lactate levels in heart transplant recipients.[31,34]

The frequent use of multiple drugs by patients receiving CsA makes it difficult to characterize CsA-associated myopathy unambiguously. A prospective study of the muscle disorders associated with CsA therapy may be helpful in characterizing their incidence and cofactors. It remains unclear whether identified physiological interactions between CsA and mitochondria can explain the occurrence of a CsA-associated myopathy.

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