SHORT COMMUNICATION

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Amyotrophic Lateral Sclerosis-Like Conditions in Possible Association with Cholesterol-Lowering Drugs

An Analysis of Patient Reports to the University of California, San Diego (UCSD) Statin Effects Study

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Supplementary Material

This supplementary material contains the supplement referred to in the full version of this article, which can be found at http://drugsafety.adisonline.com. Note the reference citations and reference list are independent from the published article and reference numbering will differ.

Supplement I. Description of Cases

Case	Case History	Summary
1	Case 1 (female) received a diagnosis of ALS at age 68. Lovastatin treatment for hyperlipidemia commenced at approximately age 54, during which she experienced insidious emergence of muscle aches and spasms. She suspected a statin association and requested to discontinue treatment; her physician advised that she stay on statin therapy due to normal CK and liver tests. After 14 years of statin use, she identified numbness in her left arm and muscle weakness in her left hand that were attributed to carpal tunnel syndrome; a cortisone shot was given without effect. Severe muscle spasms in her hips commenced, for which she again received cortisone shots without benefit. Four months later, she began dragging her right leg during regular walks. Over the next 6 months she experienced progressive muscle weakness until she had difficulty making it home from her walks and almost fell down her stairs twice. Her CK and aldolase levels were tested and found high. Her physician directed her to discontinue lovastatin and prescribed prednisone for a month for presumed polymyositis. Over the ensuing month after statin discontinuation, the muscle aches and spasms completely resolved but her muscle weakness progressed dramatically, leading to use of a walker. She underwent 2 EMG studies and was diagnosed with ALS. She began Q10 supplementation (300 mg/day) following ALS diagnosis and reported experiencing increased stamina. Factors meriting note include a SOD1* gene test, which was negative. She has no history of smoking†, and reports a lifelong history of healthy living habits. She has no family history of muscle problems or ALS; and cites no known environmental exposures‡.	• F • Age 68 • Lovastatin, start age 54 • Statin AE: Muscle ache, spasms that fully resolved off statin • ALS-germane sx: Muscle weakness – continued to progress off statins • Q10: Initial improvement in stamina • Tests: CK, 2 EMG studies • Dx: ALS
2	Case 2 (male) received a diagnosis of ALS at age 55. Medical problems included obesity, hypertension, and mild hyperglycemia as well as CAD for which he received a PTCA. He was treated with simvastatin 10 mg/day, then increased to 20 mg/day for 6 years, during which he experienced regular episodes of diarrhea[1] and possible mild muscle symptoms. His total cholesterol after 6 years of treatment was 150 mg/dL with LDL 86 mg/dL. His physician increased his dose to 40 mg/day to achieve a target LDL of <70 mg/dL. Prior to the dose increase he skied and regularly walked 5 miles with ease. Within 1 week of the dose increase, he developed severe muscle weakness in his legs and suffered a fall, so he discontinued statin treatment. Immediately, muscle weakness improved though incompletely, and diarrhea gradually subsided. Following an initial period of improvement, he began to experience coordination problems, hyper-reflexia in his knees and ankles, buckling of his legs resulting in falls, abnormal Babinski reflex, right footdrop, and a spastic gait. Over the next 6 months, neurological problems emerged while muscle weakness diminished. MRI of brain, neck, and spine failed to yield abnormalities to explain his neurological symptoms. Three months later, EMG was performed and revealed abnormalities suggestive of mild motor neuropathy or neuronopathy without evidence of demyelinating features or sensory nerve conduction abnormalities. His doctor noted upper hand weakness and that his gait had worsened. Concern for motor neuron disease was raised; shortly after, his neurologist diagnosed him with ALS. His diagnosis was affirmed by a second neurologist. Factors meriting note include a family history of statin sensitivity (3 of 7 siblings). He smoked 2 cigars/day for the past 10 years†. He has no family history of ALS; and cites no known environmental exposures‡.	• M • Age 55 • Simvastatin 10 mg/day; increased to 20 mg/day (6 years) • Statin AE: Diarrhea, resolved off statin • ALS-germane sx: Muscle weakness – initially subsided off then ultimately reemerged after development of neurological features; coordination problems, hyperreflexia, buckling of legs, abnormal Babinski reflex, right footdrop, spastic gait • Tests: MRI, EMG • Dx: ALS (affirmed by 2nd neurologist)

3	Case 3 (female) was diagnosed with "atypical" ALS at age 71. She had been treated with atorvastatin 10 mg for hyperlipidemia (total cholesterol 257 mg/dL; LDL 172 mg/dL), and developed short-term memory loss over the first 6 months of treatment. Two years later, speech problems emerged, coupled with difficulty sleeping, altered temperature regulation (alternately sweating and freezing), joint pain, difficulty spelling correctly, and continued subjective memory loss. She suspected a statin association because atorvastatin was her sole medication, but her physician encouraged her to continue treatment. Three months later, she noted swallowing problems, leading her physician to reduce her statin dose to 10 mg every other day. She was referred to a neurologist who found no abnormalities on EMG. Symptoms worsened for the following 3 months, until she discontinued statin treatment on her own. Following statin discontinuation, improvement initially occurred in all of her symptoms, including speech. However, over the subsequent 30 months speech and swallowing problems worsened, and she developed "garbled" speech and rapid weight loss (25 pounds in 4 months). Shortly after, she was diagnosed with "atypical" ALS. She has since died of complications related to ALS. Factors meriting note include no history of smoking†, no family history of muscle problems or ALS, and no known environmental exposures‡.	• F • Age 71 • Atorvastatin 10 mg/day • Statin AE: Short-term memory loss and cognitive deficits, speech problems, difficulty sleeping, altered temperature regulation, joint pain all improved with statin discontinuation • ALS-germane sx: Problems swallowing and speech, initially improved off statin • Tests: EMG • Dx: atypical ALS
4	Case 4 (male) was diagnosed with ALS with frontotemporal degeneration at age 50. His wife describes him as a formerly healthy, vibrant, extroverted, and popular person, who experienced significant personality changes (a described statin adverse effect[2]) while being treated with atorvastatin for hyperlipidemia. His symptoms on atorvastatin developed gradually, and were first clearly recognized 9 months into treatment when his wife noticed that he became reserved around people, lost interest in sex, and developed a temper, which was very uncharacteristic. A few months later, he developed a feeling that something was stuck in his throat. Six months later, he developed memory symptoms (a described statin adverse effect[3, 4]) including problems with word recall and recognition of names, people, and places. This led his wife to "[take] him off" atorvastatin 3 months later, with no subsequent improvement. Skeptical of a statin association, his physician urged him to resume treatment with atorvastatin 3 months after statin discontinuation. Within a month of resuming statin therapy, he was unable to understand the complexity of social situations and was given a working diagnosis of semantic dementia. Cognitive symptoms worsened significantly for 2 months, which led him to discontinue atorvastatin. A month later, he began slurring words, and his speech deteriorated quickly over the ensuing 3 months. 18 months later, he began to limp on his right leg and was forced to use a cane within 5 months. Within the next 2 months, he transitioned to using a walker, then a wheelchair, lost his speech completely, and could only consume fluids. He received an MRI, lumbar puncture, extensive bloodwork, EMGs, and swallowing tests, leading to the diagnosis of ALS with frontotemporal degeneration. He has since died of ALS complications. Factors meriting note include no history of smoking† and no family history of muscle problems or ALS. He received radiation treatments to his face for acne as a teenager, and played American football in high school. (Football has been linked to increased risk of ALS in NFL players.[5]) He had no other known environmental exposures‡.	• M • Age 50 • Atorvastatin • Statin AE: Personality changes, memory sx • ALS-germane sx: Feeling of "something stuck in his throat," slurring words, limping with right leg • Tests: MRI, lumbar puncture, extensive bloodwork, EMGs, swallowing tests • Dx: ALS with frontotemporal degeneration

5	Case 5 (male) was diagnosed with ALS at age 71. Following an MI, he had been placed on simvastatin 10 mg every other day (for a total cholesterol of 366 mg/dL), which he remained on for 2 years. This was followed by atorvastatin 10 mg every other day for 27 months without noticeable side effects. Following an atorvastatin dose increase to 10 mg every day, he immediately experienced muscle pain, fatigue, and weakness. Symptoms worsened over the ensuing 6 months to the point that he was sometimes unable to stand up. He suspected a statin association; his physician concurred and directed him to revert to his lower dose of 10 mg every other day, but he chose to discontinue treatment. Muscle weakness and fatigue worsened slowly over the following 9 months, then accelerated significantly when he commenced treatment with simvastatin/ezetimibe 40/10 mg/day, following carotid artery surgery. He discontinued treatment within 2½ months but symptoms continued to gradually progress. He went from using a cane, to a walker, to a wheelchair in the course of 1 year. He has visited 5 hospitals since symptom worsening on simvastatin/ezetimibe; and has received 3 EMGs from different neurologists, leading to multiple affirmed diagnoses of ALS. Factors meriting note include a history of smoking for 10 years (he quit 45 years prior to ALS symptom onset)†. He has no family history of muscle problems or ALS, and no known environmental exposures‡.	• M • Age 71 • Simvastatin 10 mg every other day (2 yrs), atorvastatin 10 mg every other day (27 mo), atorvastatin 10 mg/day, simvastatin/ezetimibe 40/10 mg/day (2.5 mo) • Statin AE: Muscle pain, abdominal pain, shoulder pain • ALS-germane sx: Progressive weakness • Tests: 3 EMGs • Dx: ALS (affirmed by 3 physicians)
6	Case 6 (male) was diagnosed with ALS at age 59. He had been treated for hyperlipidemia with atorvastatin 10 mg/day, which he tolerated for 4 years before experiencing intense cramping in his legs, and muscle aches affecting his entire body. He expressed concern regarding muscle toxicity on statins to his primary care physician, who checked CK levels (380 mg/dL) and allowed him to discontinue treatment although skeptical of a statin association. His muscle symptoms improved; by 1 month CK had declined modestly to 258 mg/dL. Two months after discontinuing atorvastatin, he commenced ezetimibe. A month later, his CK was 214 mg/dL, muscle symptoms were significantly improved, and he "felt the best that [he] had ever felt in 3 years." Symptoms continued to improve for 4 more months until his muscle aches almost completely resolved. Subsequently, he noticed loss of strength and energy in his legs while walking up a hill he normally climbed without problems. Weakness progressed over several months and he began to experience "foot slap" when walking. His neurologist noted weakness and denervation changes on EMG/NCV in a right peroneal distribution. Four months later, his neurologist observed bilateral weakness and hyperactive reflexes coupled with EMG/NCV evidence of lower motor neuron involvement in the absence of significant sensory neuropathy in all 4 extremities, leading motor neuron disease to be inferred. Two months later, a diagnosis of ALS was affirmed by another neurologist. Factors meriting note include no history of smoking†, no family history of muscle problems or ALS, and no known environmental exposures‡.	• M • Age 59 • Atorvastatin 10 mg/day, ezetimibe • Statin AE: Muscle aches whole body, improved/ resolved off statin • ALS-germane sx: Muscle weakness • Tests: CK level, EMG/NCV • Dx: ALS (affirmed by 2nd neurologist)

7	Case 7 (male) was diagnosed with ALS at age 70. He was treated for CAD (MI at age 60, received bypass surgery at age 68), hyperlipidemia, and hypertension. Lipid medications sequentially included simvastatin, atorvastatin, pravastatin, fluvastatin, cerivastatin, and rosuvastatin. Each was discontinued after short times, up to several weeks, due to severe myalgias that improved with discontinuation. After 6 statins were tried unsuccessfully, he was placed on ezetimibe. Within 3 months he developed muscle pain, fasciculations in his hands and legs, and a skin rash leading him to discontinue the drug with his physician's approval. However, some symptoms continued to progress – he experienced hand "lock-up" in a gripping position, which required him to force his hand open from this position; and additional pain and weakness in his hands and arms. Four months after discontinuing ezetimibe, he was examined by a neurologist who noted diffuse fasciculations in all 4 extremities, particularly his bilateral upper extremities, with no obvious atrophy. Five months later, symptoms worsened in association with a course of antibiotics, followed by partial improvement with discontinuation. Two months later, his strength was improved, although he was still very weak, and he experienced increasing speech problems and fasciculations. Shortly after, he received an EMG, and a diagnosis of ALS. Less than a year later, he died of complications of his condition. Although a diagnosis of ALS was officially made, his physician reportedly noted that he never fully met formal criteria for ALS. Factors meriting note include a history of smoking for 45 years, quitting 10 years prior to ALS symptom onset†. He has no family history of muscle problems or ALS. He did have occupational exposure to lead solder for over 45 years. Otherwise, he had no other known environmental exposures‡.	• M • Age 70 • Simvastatin, atorvastatin, pravastatin, fluvastatin, cerivastatin, rosuvastatin, ezetimibe • Statin AE: Severe muscle pain that repeatedly resolved with statin discontinuation and recurred with rechallenge; skin rash • ALS-germane sx: Weakness (initially improved off statins, then reprogressed), speech problems, fasciculations • Dx: ALS
8	Case 8 (female) was diagnosed with motor neuron disease and possible ALS at age 62. She was treated for hyperlipidemia with rosuvastatin 20 mg/day, which she tolerated for 2 years, followed by emergence of symptoms of chest pain, arm ache, general muscle ache, muscle weakness, personality change (a described statin adverse effect[2]), and memory loss (a described statin adverse effect[3, 4]). Her symptoms worsened over the subsequent 24 months; she could not recognize some friends and family members, began slurring her speech, experienced significant weight loss (60 lbs), and developed severe muscle weakness precluding lifting even light objects or standing without assistance. Her daughter advised her to discontinue rosuvastatin. She experienced significant recovery of muscle symptoms over the ensuing 6 months, including restoration of ability to walk and complete housework. Progression of her cognitive symptoms arrested, but no improvement was apparent. She received a CT scan of her brain (no evidence of stroke); EMG/NCV tests, CK tests, and blood work from 5 neurologists to date, leading to a diagnosis of motor neuron disease and possible ALS. Her doctors describe her condition as atypical because of her cognitive impairment and her unaffected breathing. Factors meriting note include no history of smoking†, no family history of muscle symptoms or ALS, and no known environmental exposures‡.	• F • Age 62 • Statin AE: Personality change, memory loss, muscle ache. Symptoms improved and/or progression arrested with statin discontinuation • ALS-germane sx: Severe muscle weakness: initially improved markedly after statin discontinuation • Dx: Motor neuron disease and possible ALS (atypical)

9	Case 9 (female) was diagnosed with ALS at age 48. She was treated for hyperlipidemia (total cholesterol 296 mg/dl) with lovastatin 20 mg/day for 3 years without symptoms; followed by fluvastatin 20 mg/day for 2 years, on which she experienced chronic abdominal pain (a described statin adverse effect[1]) and headaches (a described statin adverse effect[6, 7]); then simvastatin 20 mg/day for 2 years, with continued abdominal pain and headaches and onset of muscle pain and occasional muscle cramping. Simvastatin was increased to 40 mg/day for 2 years, with increased muscle pain, fatigue, and cramping; and persistent headaches and abdominal pain. She then received simvastatin 40 mg/day plus ezetimibe 10 mg/day for 23 months, on which she experienced increased muscle cramping with persistence of all other symptoms. Subsequently, her dose was decreased to simvastatin 20 mg/day plus ezetimibe 10 mg/day for one month, without improvement. She was changed to the Vytorin preparation of simvastatin/ezetimibe 20/10 mg/day, on which she developed hand weakness with muscle atrophy, right arm weakness, fasciculations and aching in her arms and legs, muscle stiffness, "pins and needles" pain in her hands (neuropathy is a described statin adverse effect[8]), and increased pain, aches, and burning in her neck and shoulders. In addition to the aforementioned symptoms, she reports that she experienced sleep problems (a described statin adverse effect[9]) and memory problems (a described statin adverse effect[3, 4]) on cholesterol-lowering drugs. Her muscle fasciculations led her neurologist to perform an EMG/NCV test, which itself precipitated exacerbated muscle fasciculations sustained over the following 2 months. Shortly after, she visited another neurologist and was diagnosed with ALS. Immediately after stopping treatment, she experienced blurred vision and an overall "fuzzy feeling", which resolved after a month. A month after stopping cholesterol treatment, she started taking a Q10 supplement, on which she noticed improvement in her muscle and peripheral neuropathy symptoms for 6 months, followed by reemergence of muscle weakness in her right arm. Three months later, left arm weakness emerged and has progressed steadily till the present for 10 months. Factors meriting note include a 5 year smoking history†. She has no family history of muscle problems or ALS, and no known environmental exposures‡.	• F • Age 48 • Lovastatin 20 mg/day (3 yrs), fluvastatin 20 mg/day (2 yrs), simvastatin 20 mg/day (2 yrs), simvastatin 40 mg/day (2 yrs), simvastatin 40 mg/day and ezetimibe 10 mg/day (23 mo), simvastatin 20 mg/day and ezetimibe 10 mg/day (1 mo), Vytorin™ 20/10 mg/day • Statin AE: Abdominal pain, headaches, muscle pain, peripheral neuropathy, memory problems, sleep problems • ALS-germane sx: Muscle weakness • Tests: EMG/NCV • Dx: ALS
10	Case 10 (male) was diagnosed with ALS at age 63. He was treated for hyperlipidemia and CAD with simvastatin 10 mg/day following coronary artery bypass surgery, developing fatigue within one month of treatment. His fatigue worsened leading him to discontinue statin treatment 5 months later, with resolution of fatigue. Six months after discontinuing simvastatin, he commenced treatment with atorvastatin 10 mg/day, which he tolerated for 9½ years until his dose was increased to atorvastatin 40 mg/day, with development of overall fatigue, muscle pain, muscle weakness, muscle fatigue, peripheral neuropathy (a described statin adverse effect[8]), and problems with coordination and balance. These symptoms persisted and 3½ years later he also developed severe muscle cramping, which intensified over the following 1½ years at which time he noted a slap-foot while walking for exercise. A month later, he began taking Q10 200 mg/day, then a month later, his doctor identified abnormalities on EMG/NCV and referred him to a neurologist who noted fasciculations in his legs, tongue, and throat and suspected ALS. A spine MRI excluded spinal problems, B12 test returned normal, and his CK was found to be high. He increased his Q10 to 400 mg/day, and experienced improvement of his fasciculations within 1 day, improvement in leg pain after 1 week, and has suffered only 1 leg cramp since. He suspected a statin association and discontinued atorvastatin, which led to improvement of all symptoms for 1 month followed by reemergence of fasciculations which progressively worsened. Four months later he was diagnosed with ALS. Factors meriting note include a smoking history of a pack/day for 30 years until he quit at age 46†. He has no family history of muscle problems or ALS, but reports a family history of Parkinson's disease (2 uncles on his	• M • Age 63 • Simvastatin 10 mg/day (5 mo), atorvastatin 10 mg/day (9½ yrs), atorvastatin 40 mg/day • Statin AE: fatigue, muscle pain, muscle fatigue, peripheral neuropathy • ALS-germane sx: Muscle weakness, coordination and balance problems • Tests: EMG/NCV, spine MRI, B12 test, CK level • Dx: ALS

	father's side). His wife notes possible pesticide exposure because he regularly mows his lawn, which is treated with pesticides by their lawn service. He had no other known environmental exposures‡.	

ALS – amyotrophic lateral sclerosis; CAD – coronary artery disease; CK – creatine kinase; CT – computed tomography; dx – diagnosis; EMG – electromyography; LDL – low density lipoprotein cholesterol; MI – myocardial infarction; MRI – magnetic resonance imaging; NCV – nerve conduction velocity; PTCA – percutaneous transluminal coronary angioplasty; Q10 – coenzyme Q10; sx – symptoms; yrs – years.

* Mutations in the SOD1 (Superoxide Dismutase) gene have been linked to familial cases of ALS.[10-13] SOD is an enzyme involved in inactivating superoxide free radicals.[14]

† Smoking, presumably via activation of alpha-7 nicotinic acetylcholine receptors, is a putative protective factor for neurodegenerative disease[15] though an association to ALS *per se* has not been shown.

‡ Environmental exposures which are conducive to oxidative stress with an apparent connection to ALS include: heavy metals, chemicals, or pesticides.[16, 17]

"Age" in column 2 refers to age at onset or diagnosis of ALS or ALS-like condition.

References

1. Scott RS, Lintott CJ, Wilson MJ. Simvastatin and side effects. New Zealand Medical Journal 1991; 104 (924): 493-5
2. Golomb BA, Kane T, Dimsdale JE. Severe irritability associated with statin cholesterol-lowering drugs. Q J Med 2004; 97 (4): 229-35
3. Evans MA, Golomb BA. Statin associated cognitive problems reported by 171 subjects. Pharmacotherapy. In press
4. Wagstaff LR, Mitton MW, Arvik BM, et al. Statin-associated memory loss: analysis of 60 case reports and review of the literature. Pharmacotherapy 2003; 23 (7): 871-80
5. Abel EL. Football increases the risk for Lou Gehrig's disease, amyotrophic lateral sclerosis. Percept Mot Skills 2007; 104 (3 Pt 2): 1251-4
6. Shuster J. Lipid-lowering drugs and headache. Nursing 1998; 28 (11): 32.
7. Rapoport D. Unrecognized adverse drug reactions. CMAJ 1993; 149 (9): 1233
8. Gaist D, Jeppesen U, Andersen M, et al. Statins and risk of polyneuropathy: a case-control study. Neurology 2002; 58 (9): 1333-7
9. Golomb BA, Kwon EK, Criqui MH, et al. Simvastatin but not pravastatin affects sleep: findings from the UCSD Statin Study. Circulation 2007; 116: II-847
10. Suzuki M, Irie T, Watanabe T, et al. Familial amyotrophic lateral sclerosis with Gly93Ser mutation in Cu/Zn superoxide dismutase: A clinical and neuropathological study. J Neurol Sci 2008; 268 (1-2): 140-4
11. Fukada K, Zhang F, Vien A, et al. Mitochondrial proteomic analysis of a cell line model of familial amyotrophic lateral sclerosis. Mol Cell Proteomics 2004; 3 (12): 1211-23
12. Radunovic A, Leigh PN. ALSODatabase: database of SOD1 (and other) gene mutations in ALS on the Internet. European FALS Group and ALSOD Consortium. Amyotroph Lateral Scler Other Motor Neuron Disord 1999; 1 (1): 45-9
13. Liu J, Lillo C, Jonsson PA, et al. Toxicity of familial ALS-linked SOD1 mutants from selective recruitment to spinal mitochondria. Neuron 2004; 43 (1): 5-17
14. Fridovich I. Superoxide radical: an endogenous toxicant. Annu Rev Pharmacol Toxicol 1983; 23: 239-57
15. O'Neill MJ, Murray TK, Lakics V, et al. The role of neuronal nicotinic acetylcholine receptors in acute and chronic neurodegeneration. Curr Drug Targets CNS Neurol Disord 2002; 1 (4): 399-411
16. Praline J, Guennoc AM, Limousin N, et al. ALS and mercury intoxication: a relationship? Clin Neurol Neurosurg 2007; 109 (10): 880-3
17. Morahan JM, Yu B, Trent RJ, et al. Genetic susceptibility to environmental toxicants in ALS. Am J Med Genet B Neuropsychiatr Genet 2007; 144 (7): 885-90