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Retrospective Review of Combined Sirolimus and Simvastatin Therapy in Lymphangioleiomyomatosis

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BACKGROUND: Combined simvastatin and sirolimus therapy reduces tuberous sclerosis complex 2-null lesions and alveolar destruction in a mouse model of lymphangioleiomyomatosis (LAM), suggesting that therapy with both drugs may benefit patients with LAM.

METHODS: To determine whether simvastatin changed the prevalence of adverse events or altered the therapeutic effects of sirolimus, we recorded adverse events and changes in lung function in patients with LAM treated with simvastatin plus sirolimus (n = 14), sirolimus alone (n = 44), or simvastatin alone (n = 20).

RESULTS: Sirolimus-related adverse events in the simvastatin plus sirolimus and sirolimus-only groups were 64% and 66% for stomatitis, 50% and 52% for diarrhea, 50% and 45% for peripheral edema, 36% and 61% for acne, 36% and 30% for hypertension, 29% and 27% for proteinuria, 29% and 27% for leukopenia, and 21% and 27% for hypercholesterolemia. The frequency of simvastatin-related adverse events in the simvastatin-only and simvastatin plus sirolimus groups were 60% and 50% for arthralgias and 35% and 36% for myopathy. Before simvastatin plus sirolimus therapy, FEV_1 and diffusing capacity of the lung for carbon monoxide (DLCO) yearly rates of change were, respectively, -1.4 ± 0.2 and -1.8 ± 0.2% predicted. After simvastatin plus sirolimus therapy, these rates changed to $+1.2 \pm 0.5$ ($P = .635$) and $+0.3 \pm 0.4$% predicted ($P = .412$), respectively. In 44 patients treated with sirolimus alone, FEV_1 and DLCO rates of change were -1.7 ± 0.1 and -2.2 ± 0.1% predicted before treatment and $+1.7 \pm 0.3$ and $+0.7 \pm 0.3$% predicted after treatment ($P < .001$).

CONCLUSIONS: Therapy with sirolimus and simvastatin does not increase the prevalence of drug adverse events or alter the therapeutic effects of sirolimus.

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ABBREVIATIONS: DLCO = diffusing capacity of the lung for carbon monoxide; GTP = guanosine triphosphate; GTPase = guanosine triphosphatase; LAM = lymphangioleiomyomatosis; mTOR = mechanistic target of rapamycin; Rheb = Ras homolog enriched in brain; TSC = tuberous sclerosis complex

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Lymphangioleiomyomatosis (LAM) is a multisystem disease affecting predominantly women and is characterized by cystic lung destruction, abdominal angiomyolipomas, and lymphatic tumors (eg, lymphangioleiomyomas).[1-3] The clinical and pathologic features of LAM result from proliferation of a neoplastic LAM cell that has characteristics of both smooth muscle cells and melanocytes.[3,4] LAM associated with tuberous sclerosis complex (TSC) and the sporadic form of LAM are both caused by mutations in the *TSC1* or *TSC2* suppressor genes.[5-7] *TSC1* and *TSC2* encode hamartin and tuberin, two proteins that form a cytosolic complex acting upstream of the intracellular serine/threonine kinase mechanistic target of rapamycin (mTOR), which mediates growth factor, energy, and stress signaling and regulates cell growth and proliferation.[8-10] Two complexes involving mTOR have been described[11]: mTORC1, which contains raptor (regulatory-associated protein of mTOR), and mTORC2, which contains rictor (rapamycin-insensitive companion of mTOR).[11,12] Regarding regulation of mTORC1, tuberin acts as a GAP (guanosine triphosphatase [GTPase]-activating protein) for the guanine nucleotide-binding protein Ras homolog enriched in brain (Rheb), promoting the formation of inactive Rheb-guanosine diphosphate from active Rheb-guanosine triphosphate (GTP).[9,10] Inhibition of TSC1/2 by growth factor stimulation inhibits GAP activity and promotes accumulation of active Rheb-GTP.[9,10] Rheb-GTP stimulates mTORC1, which phosphorylates ribosomal S6 kinase and eukaryotic initiation factor 4E-binding protein, leading to enhanced translation and protein synthesis.[9,10,13]

Sirolimus and everolimus, two immunosuppressant compounds, form a complex with FK506-binding protein-12, which binds and inhibits mTORC1.[14,15] In clinical studies, sirolimus and everolimus have been shown to be effective in decreasing the size of renal angiomyolipomas in patients with TSC and sporadic LAM,[16-18] improving and stabilizing lung function while reducing the size of chylous effusions and abdominal lymphangioleiomyomas in patients with LAM[19,20] and reducing the size of giant cell astrocytomas in patients with TSC.[21,22] Although mTORC1 is acutely sensitive to sirolimus, in some cases, mTORC2 is only sensitive to prolonged sirolimus exposure.[23,24] Experimental data, however, have shown that both mTORC1 and mTORC2 are necessary for TSC2-dependent cell proliferation and survival.[25] In TSC-null and human LAM-derived cells, RhoGTPase activity was required for cell proliferation and survival.[25] In the absence of TSC2, RhoA GTPase activity was increased, resulting in enhanced cell survival.[25] Downregulation of RhoA in TSC2-deficient rat-derived TSC2-null Eker leiomyoma/myosarcoma tumor-derived 3 cells increased apoptosis, suggesting that pharmacologic inhibition of RhoA in TSC2-null cells may impair their survival.[25] Because sirolimus and everolimus only suppress mTORC1, there is a rationale for new therapies targeting mTORC2 signaling.[25,26]

HMG-CoA (3-hydroxy-3-methyl-glutaryl-coenzyme-A) reductase is essential for cholesterol metabolism and geranylgeranylation of RhoA GTPase, which is necessary for its attachment to cell membranes.[27] Statins are HMG-CoA reductase inhibitors,[27] which inhibit geranylgeranylation of RhoGTPases and farnesylation of the small GTPases Ras and Rheb.[27] In agreement, atorvastatin was reported to inhibit the growth of $Tsc2^{-/-}$ Eker leiomyoma/myosarcoma tumor-derived 3 and mouse embryonic fibroblast cells while impairing Rheb-GTPase activity and function.[28] In another study, simvastatin was shown to inhibit RhoA GTPase activity and proliferation of TSC-null cells and TSC2-null tumor growth in mice and to promote apoptosis.[25] Treatment with sirolimus and simvastatin prevented recurrence of the tumors even after discontinuation of both drugs, an effect that required administration of both sirolimus and simvastatin.[25] This effect appeared to be specific for simvastatin because atorvastatin failed to reduce the size of liver and renal tumors in a mouse model of TSC.[29] In a mouse model of LAM carrying Tsc2-null lesions that showed ά smooth muscle-actin expression, mTORC1 activation, vascular endothelial growth factor D expression, increased lymphangiogenesis, and lung cystic destruction, simvastatin prevented alveolar space enlargement and, together with sirolimus, blocked matrix metalloproteinase upregulation and alveolar destruction.[30]

Preliminary clinical observations suggested no correlation between statin use and angiomyolipoma response to sirolimus in patients with TSC or sporadic LAM.[16] In a retrospective study, the rate of decline in lung diffusion capacity for patients with LAM treated with statins for hypercholesterolemia was greater than that of matched off-statin control patients.[31] However, the number of patients on simvastatin was small, and the patients were not given an mTOR inhibitor. For several years, we have followed a cohort of patients with LAM being treated with sirolimus; some of these patients also are being treated with simvastatin for hypercholesterolemia. We reviewed the clinical and physiologic characteristics,