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A review of the effects of statins in systemic sclerosis

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ABSTRACT

Objectives: We performed a literature review assessing possible benefits of statins in systemic sclerosis (SSc).
Methods: PubMed, Embase, Cochrane Databases, and Medline were searched. Full-text English publications were identified in which the effects of statins in SSc were examined. Letters, review articles, and studies on morphea were excluded.
Results: In all, 18 of 404 studies were relevant. In vitro, statins decreased transcription and translation of IL-6 and collagen, with reversal via mevalonate. Animal studies demonstrated reduced production of Ras (a protein superfamily of GTPases), Rho (part of the Ras superfamily), and extracellular signal-regulated kinases (ERK), less fibrosis and myofibroblast transdifferentiation, and improved macrovasculature. In human studies, IL-6, an inflammatory cytokine, was reduced. Usually endothelial progenitor cell concentrations increased, and flow-mediated dilatation improved. Raynaud's phenomenon, digital ulcers, and physician global assessments improved in the majority of studies of statin treatment in SSc. None of the 256 patients receiving statins experienced transaminitis or myopathy.
Conclusions: Not all findings were consistent. However, in general, in vitro, animal, and human studies demonstrated benefit in SSc pathophysiology, likely mediated through inhibition of lipid intermediate synthesis. Clinical improvement in SSc circulatory complications was observed. Statins seemed safe and well tolerated in SSc. Larger longer-term multi-site randomized trials are needed to further determine the role of statins as adjunctive treatment of this complex, heterogeneous connective tissue disease.

Introduction

Systemic sclerosis (SSc) is a rare, systemic autoimmune disorder characterized by vasculopathy, immune dysfunction, and fibrosis of the skin and other organs [1].

The vasculopathy is characterized by inflammation, abnormal vasoreactivity, fibrotic intimal hyperplasia, in situ thrombosis, and insufficient neoangiogenesis, with a gradual obliteration of vessels and decline in capillary density [2,3]. Combined with inadequate angiogenesis and vasculogenesis, these factors contribute substantially to SSc morbidity and mortality, including scleroderma renal crisis, pulmonary hypertension, Raynaud's phenomenon, digital ulceration, and microangiopathy of several other organs [2,3].

Biochemically, the humoral milieu demonstrates increased pro-inflammatory cytokines and decreased circulating nitric oxide (NO). Furthermore, circulating endothelial progenitor cells (EPCs) are significantly reduced, which is implicated in scleroderma's inadequate vasculogenesis. Endothelial dysfunction manifests with an increased prevalence of coronary, peripheral vascular, and cerebral atherosclerosis, and reduced endothelium-dependent flow-mediated dilatation (FMD)—a likely independent predictor of adverse cardiac events [4,5].

Statins, which are competitive inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, are used to treat dyslipidemia and macrovascular disease, improving survival in patients with coronary artery disease, and they are in general well tolerated and safe [6]. However, statins are also immunomodulatory agents working through several pleiotropic mechanisms, including T-cell and antigen-presenting cell (APC) modulation [7–10], suppression of major histocompatibility complex II (MHC II) expression [11], direct suppression of IL-17 production [12], and transcriptional inhibition of nuclear factor-κB (NF-κB). Importantly, they also activate peroxisome proliferator-activated receptors (PPARs), which are intracellular nuclear translocation of NF-κB [13], as well as inhibit the production of lipid intermediates (Fig. 1) [14]. Mevalonate is one such intermediate which serves as a

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substrate for pro-inflammatory GTPases such as Rho (Ras homolog gene family) and Ras (rat sarcoma protein) [1,14].

Given the above mechanisms and positive results seen from trials in other autoimmune diseases such as rheumatoid arthritis, several studies have been performed, including both uncontrolled and randomized controlled trials, to investigate potential benefits of statins in SSc [14].

While there is increased cardiovascular burden including acute coronary syndrome in SSc, and the outcomes of vascular manifestations of the disease have improved, cardiovascular mortality in SSc remains unchanged over the past four decades [5,15,16]. The purpose of this literature review was to investigate the non-cardiac effects of statins on SSc, specifically the biochemical, cellular, vascular, and clinical effects.

Methods

Pubmed, EMBASE, Cochrane library, Web of Science, and BIOSIS databases were searched from inception until December 2014, for English-language articles. The keywords searched were "scleroderma OR systemic sclerosis" AND "statin OR hydroxymethylglutaryl-CoA reductase inhibitors OR lovastatin OR pravastatin OR simvastatin OR atorvastatin OR rosuvastatin OR fluvastatin OR Pitavastatin OR Cerivastatin." Key references were also searched to ensure that articles of interest were not missing that did not result from the main search. A study was included if it investigated the effects of statin therapy in SSc. Data were extracted from in vitro, in vivo, human, or animal studies. Both positive and negative studies were reviewed. Articles were excluded if they were irrelevant (did not contain SSc-like models or SSc patients AND/OR did not study statins), review articles, duplicates, or letters to the editor.

Data were extracted by one reviewer (KL) and reviewed by J.P. Consensus on what to include and exclude was reached and interpretation of results was agreed upon. Data were divided into human, animal, and in vitro studies. Results were systematically reviewed.

Results

Figure 2 summarizes the literature search. A total of 18 publications were appropriate for this review.

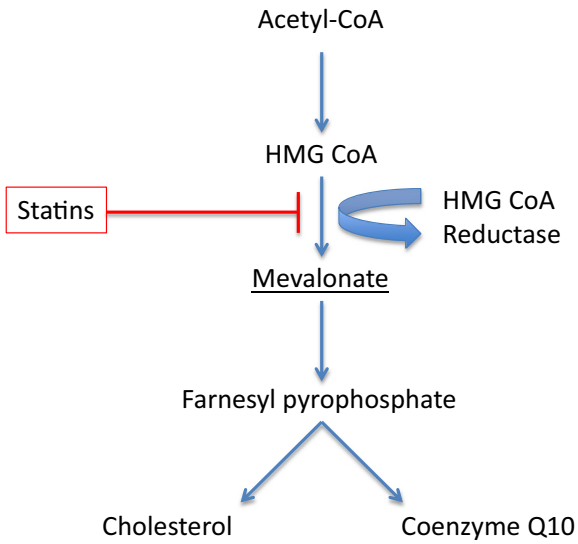

Fig. 1. Metabolism of lipids and effect of statins.

In vitro effects on SSc fibroblasts by statins

Table 1 summarizes the results. All three in vitro studies showed positive in vitro effects of statins on SSc fibroblast cultures [18–20]. Atorvastatin and simvastatin decreased fibrosis and inflammation at a transcriptional level [18,19]. Simvastatin down-regulated several promoter constructs of the Collagen-1a gene [20]. At a translational level, statins reduced production of pro-collagen c-peptide, type 1 Collagen, and IL-6, and possibly ICAM-1. The effects were dose dependent. The addition of mevalonate or geranyl pyrophosphate (GGPP), but not farnesyl pyrophosphate (FFP), completely reversed the observed effects [19,20].

Effects on SSc animal models by statins

Two studies by Bagnato et al. [21] examined the effects of statins on hypochlorous acid (HOCl) animal models of SSc [22]. Animals were divided into HOCldaily injections, HOCl + simvastatin, and sham [21]. Western blot analysis of tissue samples showed significantly reduced expression of Ras (a protein superfamily of GTPases), Rho (part of the Ras superfamily), and extracellular signal-related kinase (ERK). No difference was found in TGF-B activity between the HOCl and HOCl+simvastatin groups [21].

Simvastatin markedly attenuated lung and skin myofibroblast differentiation as determined by α-SMA (α-smooth-muscle-actin) quantification.

Assessments of both cutaneous and pulmonary random tissue segments showed significant protection against fibrosis in the HOCl + simvastatin group.

Bagnato et al. also demonstrated that aortic intimal medial thickness more than doubled in oxidative animal models, and that intima:media ratios were deranged. Simvastatin treatment

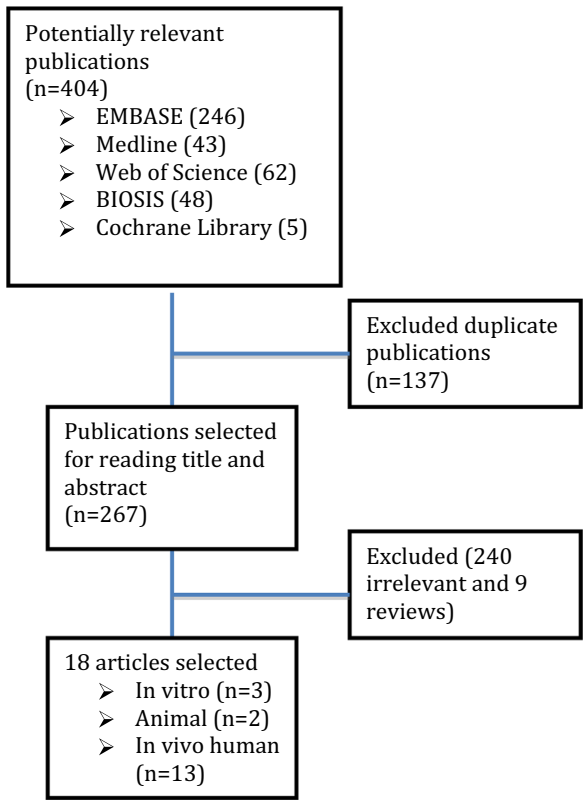

Fig. 2. Disposition of articles that were searched.