

Spotlight on Statins

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Summary

Statins are among the most widely prescribed drugs to prevent cardiovascular morbidity. Over recent years, statins have also been shown to exert pleiotropic immunomodulatory effects that might be of therapeutic benefit in autoimmune disorders. Interestingly, the primary mechanism by which statins alter immune function appears to be largely independent of lipid-lowering and mediated primarily through inhibition of post-translational prenylation of regulatory proteins. In

experimental autoimmune encephalomyelitis, the mouse model for multiple sclerosis (MS), statins prevent and even reverse established paralysis. Furthermore, statins were recently shown to exert synergistic benefit in combination with some agents already approved for MS therapy. Based upon these encouraging results obtained in the animal model, statins are now being evaluated in clinical trials as potential therapy for MS.

KEY WORDS:

MULTIPLE SCLEROSIS; IMMUNOMODULATORY AGENTS; STATINS; EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS; NOVEL THERAPY

Introduction

Statins are oral inhibitors of the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase which are widely prescribed to lower cholesterol. The enzyme HMG-CoA reductase catalyzes the conversion of HMG-CoA to L-mevalonate, a key intermediate for cholesterol biosynthesis¹ (see Figure 1). Since 1987, when statins were first approved for treatment of hypercholesterolemia, they have established themselves as very well-tolerated drugs with rare side-effects. Studies in animal models of autoimmune diseases have revealed statins' immunomodulatory properties which might also be of benefit in treatment of neuroinflammatory disorders, such as MS.

Statins as Immunomodulators

In 1995, 8 years after their initial approval, Kobashigawa and colleagues² reported that patients receiving a cardiac transplant had a reduced incidence of rejection episodes and decreased mortality when they were treated with pravastatin. To the authors' surprise, these effects did not correlate

with cholesterol reduction, suggesting that statin treatment had additional immunomodulatory properties which prevented transplant rejection. This landmark observation was followed by a number of studies that extensively explored the therapeutic potential of statins in treatment of autoimmune disease models such as experimental autoimmune encephalomyelitis,³⁻⁶ experimental arthritis, experimental autoimmune uveoretinitis,⁷ experimental autoimmune myocarditis^{8,9} and experimental systemic lupus erythematosus¹⁰ (see Table 1).

Recent studies investigating the molecular mechanisms underlying statin-mediated immune modulation suggest that statins primarily alter immune function through inhibition of HMG-CoA reductase but independent of their effect on cholesterol biosynthesis. Some data suggest that statins can directly bind the cellular adhesion molecule leukocyte function antigen 1 (LFA-1), resulting in reduced activation and migration of pro-inflammatory leukocytes.¹¹ However, the vast majority of statin-mediated immunomodulatory effects appear to be related to the competitive displacement

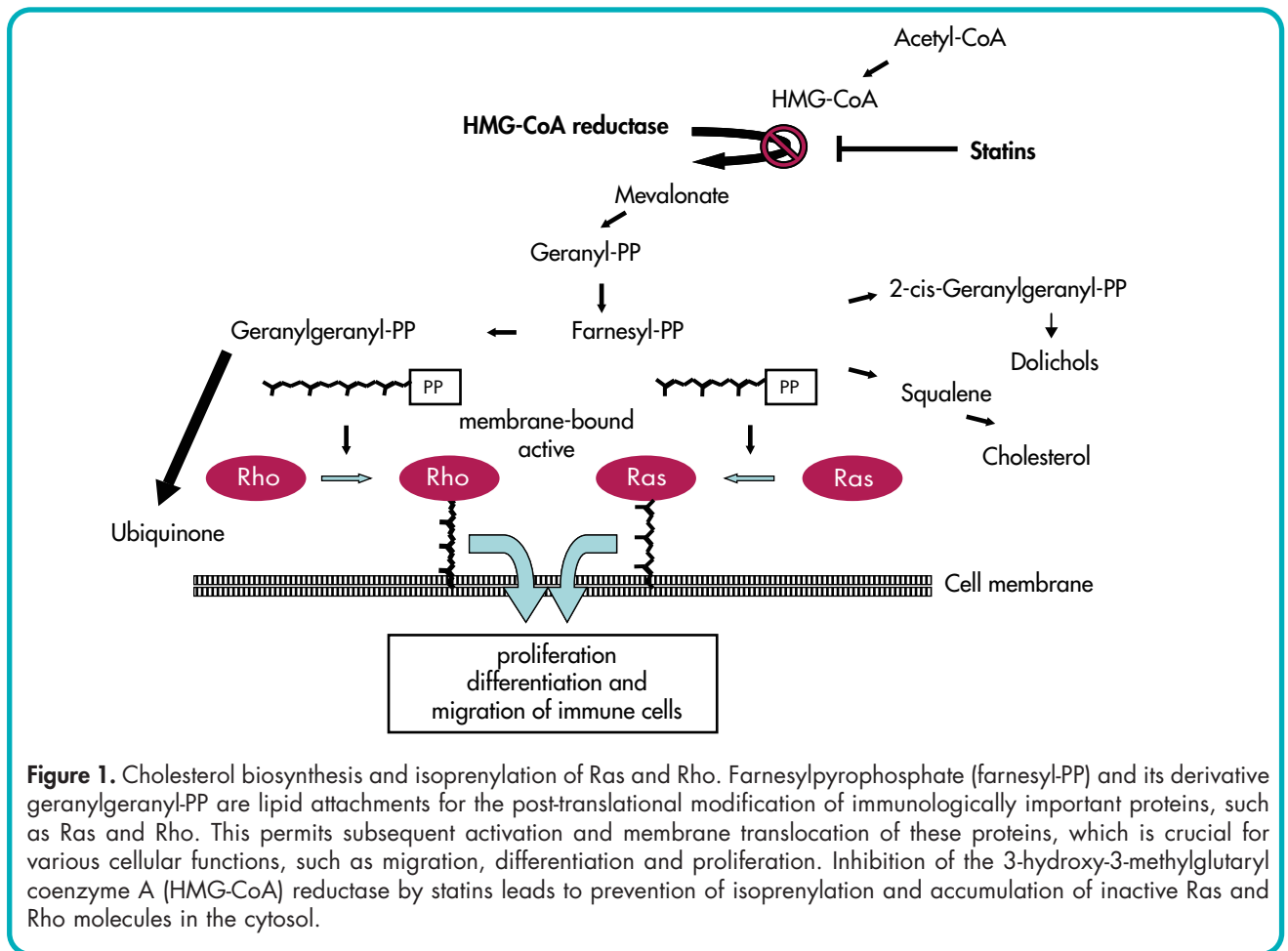


Figure 1. Cholesterol biosynthesis and isoprenylation of Ras and Rho. Farnesylpyrophosphate (farnesyl-PP) and its derivative geranylgeranyl-PP are lipid attachments for the post-translational modification of immunologically important proteins, such as Ras and Rho. This permits subsequent activation and membrane translocation of these proteins, which is crucial for various cellular functions, such as migration, differentiation and proliferation. Inhibition of the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase by statins leads to prevention of isoprenylation and accumulation of inactive Ras and Rho molecules in the cytosol.

Table 1: Inflammatory conditions in which statins have been tested

Disease/disease model	Study phase	Statin tested	Results	Reference
Experimental autoimmune encephalomyelitis	Preclinical	Atorvastatin Lovastatin	Prevention or reversal of paralysis, reduced inflammatory infiltration	3,4 6
Experimental autoimmune uveitis	Preclinical	Atorvastatin	No significant immunomodulatory effect	7
Experimental autoimmune myocarditis	Preclinical	Atorvastatin Fluvastatin	Improved cardiac function, reduced inflammatory infiltration	8 9
Autoimmune diabetes (non-obese spontaneous diabetic mouse model)	Preclinical	Atorvastatin	No effect on diabetes onset or pancreatic islet infiltration	12
Systemic lupus erythematosus	Preclinical	Atorvastatin	Decreased proteinuria, reduced glomerular Ig deposition	10
Rheumatoid arthritis	Randomized, placebo-controlled trial	Atorvastatin	Decreased disease activity score/inflammatory parameters	13
Multiple sclerosis	Open-label studies	Lovastatin Simvastatin	Decrease in number and volume of new enhancing MRI lesions	14 15

of the natural substrate HMG-CoA from HMG-CoA reductase as they can be reversed by addition of its downstream product mevalonate. In this regard, most notably, mevalonate is the key metabolite not only for

the synthesis of cholesterol but also for isoprenoid intermediates, such as farnesylpyrophosphate (FPP) and geranylgeranylpyrophosphate (GGPP) (see Figure 1). These molecules have key functions for the post-

translational prenylation of GTP-binding proteins,¹⁶ e.g. Ras and Rho, which have important roles in multiple signalling pathways regulating cellular differentiation and proliferation.¹⁷ Isoprenylation of these proteins is necessary for their intracellular trafficking and localization at the cytoplasmic surface of the plasma membrane where they function. Thus, by inhibition of isoprenylation of GTPases, statins modulate cellular functions required for the activation of various cell types including immune cells.

Statins in the Treatment of Experimental Central Nervous System Autoimmunity

Our current knowledge regarding the immunomodulatory potential of statins in the treatment of central nervous system (CNS) autoimmune diseases has evolved primarily from studying their treatment effect in EAE, the murine animal model for MS. EAE is characterized by relapsing or chronic paralysis mediated by myelin-specific CD4+ T-cells that cause CNS inflammation¹⁸ associated with both demyelination and axonal damage.¹⁹ Oral statin treatment at disease onset prevented the development of EAE³⁻⁶ and clinical symptoms were reversed when statin treatment was initiated after paralysis was established.^{3,4} These animal studies also revealed that statins have beneficial effects at several steps in the pathogenesis of EAE including inhibition of myelin antigen presentation which is required for T-cell activation, differentiation of T-cells into pro-inflammatory encephalitogenic T-cells and recruitment of leukocytes into the CNS.

Testing Statins in the Treatment of MS

The immunomodulatory effects of statins that have been observed in mice might translate to human autoimmune disease. Two small studies were recently published on the treatment effects of statins in patients with relapsing-remitting MS (RRMS). An open-label study tested 20 mg lovastatin in seven MS patients with an active disease course with at least two relapses during the previous 2 years.²⁰ Magnetic resonance imaging (MRI) results indicated decreased inflammation with lovastatin treatment, although no clinical changes were observed in this small cohort.

In another small open-label trial, patients were treated with 80 mg simvastatin, the highest FDA-approved dose, over 6 months. All patients enrolled had at least one gadolinium (Gd)-enhancing lesion in the 3-month pre-treatment period.¹⁴ MRI results indicated a decrease in the mean number and volume of Gd-enhancing lesions of approximately 45% in these statin-treated patients.

Notwithstanding these encouraging reports, decreased inflammatory activity under statin treatment could reflect the regression to the mean due to the small number of patients with a comparably active disease course at the time of enrolment. A placebo-controlled trial is currently being conducted in order to address this issue. Fourteen centres in North America are recruiting 152 patients who have experienced their first demyelinating attack – or ‘clinically isolated syndrome’ – who will be treated with study drug for 12 months.¹⁵ The study’s primary endpoint is a composite, either met by a further clinical exacerbation (resulting in clinically definite RRMS) or more than three new T2 or Gd-enhancing lesions in the 3-monthly brain MRIs.

Statins as Candidates for Combination Therapy

If current trials show that statins are only partially effective as monotherapy in the treatment of MS, they might be useful in combination with existing disease-modifying medications. Theoretically, medications chosen for combination therapy should have a different mode of action providing an additive or synergistic effect without overlapping toxicities.

In this regard, glatiramer acetate (GA) is a well-tolerated, polypeptide-based therapy approved for RRMS. GA treatment appears to preferentially cause a Th2 deviation of T-cells that are specific for CNS autoantigens.^{21,22} Recent data indicate that GA treatment also mediates immunomodulatory activity on antigen-presenting cells (APC), promoting the secretion of anti-inflammatory cytokines and inhibiting the secretion of pro-inflammatory cytokines.^{23,24} One can envisage that an agent that augments GA’s effect on myelin-reactive lymphocytes or APC may enhance the efficacy of GA in the treatment of MS. A recent study reported that the combination of GA and atorvastatin indeed synergistically ameliorated CNS autoimmunity

in the EAE mouse model.²⁵ Combination of both agents at individually suboptimal doses was found to facilitate differentiation of T-cells into anti-inflammatory Th2 cells. Further *in vitro* experiments revealed that atorvastatin and GA also altered the cytokine profile of activated monocytes in an additive manner. Based primarily on these findings, clinical trials testing atorvastatin in combination with GA are being planned.

Similarly encouraging results were obtained from testing the combination of atorvastatin and 5-aminoimidazole-4-carboxamide-1-beta-D-ribofuranoside, an immunomodulating agent that activates adenosine monophosphate-activated protein kinase. The combination of these drugs was additive in EAE prevention and was associated with decreased cellular infiltration in the CNS. In addition, this combination therapy lessened inflammation-associated neurodegeneration, which might be of particular interest for treatment of MS at later disease stages. Preliminary data suggest that the combination of atorvastatin with high-dose beta interferon-1a (IFNB-1a), another approved drug for MS treatment, may not be of clinical benefit. Patients on treatment with full dose IFNB-1a for at least 6 months were randomized in a double-blind fashion to one of three groups as add-on therapy: daily placebo, daily medium-dose atorvastatin (40 mg per day) or daily high-dose atorvastatin (80 mg per day). In nine out of 13 subjects receiving atorvastatin either at 40 or 80 mg per day, but only in one of nine subjects on placebo, new MRI lesions and/or clinical relapses were observed, suggesting that the combination of a high-dose IFNB with a statin may not benefit patients with RRMS.²⁶

Potential Neuroprotective Effects of Statins

Independent from their effect on immune cells, statins appear to have additional effects on neuronal and glial cells which might be of particular importance for recovery in relapsing phases of CNS autoimmune disease. Statins have been shown to protect neurons in culture from excitotoxic death, a form of neuronal death primarily caused by brain ischaemia.²⁷ Statin-mediated neuroprotection was significantly attenuated by co-treatment with either mevalonate or cholesterol, indicating that this effect might be directly correlated to inhibition of neuronal cholesterol biosynthesis.

Lovastatin inhibited degeneration of oligodendrocyte progenitors,²⁸ a process that is believed to be responsible for impaired remyelination after inflammatory damage of the myelin sheath. In fact, lovastatin treatment restored remyelination in the spinal cord of mice with EAE and increased expression of myelin proteins and transcription factors associated with differentiating oligodendrocytes.²⁸ These findings might be of therapeutic relevance not only for inflammatory demyelinating CNS disease but also for neurodegenerative disorders such as Alzheimer's disease.²⁹

Conclusion

Statins have shown pleiotropic immunomodulatory effects in various models of inflammatory disorders. In EAE, statins have been reported to target key elements of the immunological cascade that leads to glial and neural tissue damage in MS. Recent EAE studies indicate that statins modulate pro-inflammatory immune mechanisms through inhibition of small GTPases, regulatory proteins involved in activation and proliferation of immune cells. Two small open-label trials testing statins in treatment of RRMS reported encouraging preliminary results. Furthermore, statins might exert additive or synergistic effects in combination with other disease-modifying agents (although there may be adverse consequences when adding to high-dose, frequently administered IFNBs). Thus, placebo-controlled trials testing atorvastatin as monotherapy in early MS and in combination with other medications are anticipated with high expectations.

Conflicts of Interest

No conflicts of interest were declared in relation to this article.

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