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Immune modulatory effects of statins

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Summary

Despite major advances in recent years, immunosuppressive regimens for multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus and graft-versus-host disease still have major adverse effects and immunomodulation rather than immune paralysis would be desirable. Statins inhibit the rate-limiting enzyme of the L-mevalonate pathway, the 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase. It was shown that blocking the L-mevalonate pathway reduces inflammation through effects on downstream metabolites of the pathway including farnesylpyrophosphates and geranylgeranylpyrophosphates, which are essential for the attachment of GTPases like RhoA, Rac and Ras to the cell membrane. Therefore, L-mevalonate pathway downstream products play critical roles in the different steps of an immune response including immune cell activation, migration, cytokine production, immune metabolism and survival. This review discusses the relevance of the different metabolites for the immunomodulatory effect of statins and connects preclinical results with data from clinical studies that tested statins for the treatment of different inflammatory diseases.

Keywords: inflammation; T helper type 2; tolerance; transplantation

Key Points

1 Statins regulate the immune response on several levels.
2 Recent advances in the clinical application of statins in different inflammatory diseases are being highlighted.

Introduction

Inhibition of the of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase with statins leads to depletion of L-mevalonate pathway downstream metabolites, which reduces disease severity in several preclinical models of auto-immunity and allo-immunity.[1–6] The mechanism by which statins inhibit aberrant immune responses can vary depending on the disease model and the type of statin that is investigated.[6]

Here we summarize preclinical studies and clinical trials that have evaluated the efficacy and safety of statins in inflammatory diseases including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), multiple sclerosis (MS) and graft-versus-host disease (GVHD) (Table 1).

Mechanisms of actions of statins on different immune cells

Statins inhibit the rate-limiting enzyme of the L-mevalonate pathway and thereby reduce farnesyl and geranylgeranyl residues that are required for the correct attachment of different small GTPases to the cell membrane. This modification modulates the immune response at different levels including T-cell signalling, antigen presentation, immune cell migration and cytokine production.[7] *In vitro* studies showed that lovastatin inhibited T-cell proliferation, Ca^{2+} influx and interleukin-2 (IL-2) production in T cells. Additionally recent data indicate that lovastatin blocks the Kv1.3 channel in human T cells, which presents a novel mechanism for the immunomodulatory properties of statins.[8] Besides these direct cellular effects on signalling via blockade of GTPase isoprenylation, statins impact gene expression of pro-inflammatory genes in the innate and adaptive immune systems and also in non-haematopoietic cells, including endothelial cells and fibroblasts. An important novel observation is that statins also impact the immune system through effects on immune cell metabolism. Recently a study showed that activation of the cholesterol synthesis pathway was

Table 1. Statins in selected clinical trials for inflammatory diseases

Disease	Type of the clinical trial	Main conclusion	Publication time (year)	References
RA	Post hoc analysis on the effect of statins in patients treated for RA with tocilizumab	Concomitant statin use reduced tocilizumab-mediated lipid increases	2017	[22]
RA	Cohort study that included RA patients with a diagnosis of hyperlipidaemia who started statin intake	The connection between lowering LDL-C and cardiovascular events in RA was comparable to the association found in matched general controls	2016	[24]
RA	Randomized, double-blind placebo-controlled trial on patients with RA treated with atorvastatin versus placebo given in addition to current disease-modifying anti-rheumatic drugs treatment	Disease activity score 28, CRP and ESR decreased in the statin group	2016	[26]
RA	Randomized, placebo controlled, multi-centre phase II study, on a combination of tofacitinib and atorvastatin	Tofacitinib-associated elevated LDL-C in RA patients were reduced by atorvastatin	2014	[25]
RA	Randomized, double-blind placebo-controlled trial on patients with RA treated with atorvastatin versus placebo	Clinical improvement, reduced CRP levels and lower ESRs were seen in the atorvastatin group compared with the placebo group	2004	[27]
SLE	Controlled phase II trial	Atorvastatin therapy improved endothelium-dependent vasodilatation in SLE patients	2007	[15]
SLE	Case studies on three systemic SLE patients	Reduction in proteinuria levels upon statin treatment	2003	[18]
MS	Double-blind, controlled clinical trial of patients with secondary progressive multiple sclerosis	At 2 years, the FAB score and the physical component score were higher in the group that was simvastatin-treated compared with the placebo group[39]	2017	[39]
MS	Phase II open-label baseline-to-treatment trial	Atorvastatin given to MS patient was safe and reduced the number and volume of CEL	2008	[41]
MS	Phase I/II trial on the safety and efficacy of simvastatin for MS	Significant reduction of CEL in magnetic resonance imaging of the brain in remitting–relapsing MS patients	2004	[40]
GVHD	Retrospective analysis	Statin intake of the recipient correlates with lower GVHD incidence	2008	[60]
GVHD	Retrospective analysis	Donor statin treatment is connected to reduced GVHD incidence in patients	2010	[55]
GVHD	Retrospective analysis.	Recipient statin treatment is connected to reduced GVHD incidence in patients	2010	[56]
GVHD	Prospective phase II trial of atorvastatin for aGVHD prophylaxis	Donor and recipient treatment with atorvastatin is effective as prophylaxis for GVHD	2013	[57]
GVHD	Phase II study of atorvastatin for aGVHD prophylaxis	Atorvastatin did not provide any benefit to standard GVHD prophylaxis alone	2016	[59]
GVHD	Phase II study to evaluate the safety and efficacy of atorvastatin-based aGVHD prophylaxis	Preliminary efficacy of atorvastatin for aGVHD prevention was seen	2017	[58]

Abbreviations: aGVHD, acute graft-versus-host disease; CEL, contrast-enhancing lesions; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GVHD, graft-versus-host disease; LDL-C, low-density lipoprotein cholesterol; MS, multiple sclerosis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

essential for immunological training of myeloid immune cells.[9] The study also reported that the metabolite mevalonate is the mediator of training through activation of insulin-like growth factor 1 receptor and mammalian target of rapamycin and subsequent histone modifications in inflammatory pathways.[9] Consistent with a role of statins in immune metabolism, another study reported that lovastatin caused potent protection against inflammation-induced loss and dysfunction of mitochondria and peroxisomes in a mouse model of MS.[10]

These different approaches show that statins affect the immune response on multiple layers including signalling, gene transcription, epigenetic modifications and immune metabolism.

Statins in SLE

Statins haven been tested for their efficacy in preclinical models of SLE[3,11–14] and in clinical trials.[15,16] Oral atorvastatin treatment of NZB/NZW mice reduced T-cell

proliferation and cytokine production when the T cells were isolated from the treated mice and tested *in vitro*. Conversely, the disease severity of SLE in this mouse model was not reduced by atorvastatin.[11]

A preclinical study analysed female LDLr$^{-/-}$ mice that underwent lethal irradiation and bone marrow transplantation from C57BL/6 mice (LDLr.B6) or SLE-susceptible B6.Sle1.2.3 mice (LDLr.Sle).[12] Sixteen weeks after bone marrow transplantation, mice were treated with atorvastatin versus mycophenolate mofetil with one end-point being the presence of SLE signs.[12] The authors reported that atorvastatin caused a decrease in cholesterol levels and atherogenesis in LDLr.B6 mice but did not diminish atherosclerotic lesion size or SLE signs in LDLr.Sle mice.[12] A study performed in the mouse model analysed the effects of the apolipoprotein A-1 mimetic peptide L-4F, alone or in combination with pravastatin in apoE$^{-/-}$ Fas$^{-/-}$ C57BL/6 mice that spontaneously develop glomerulonephritis, IgG autoantibodies, atherosclerotic lesions and osteopenia.[13] Mice treated with L-4F alone or combined with pravastatin had significantly reduced IgG anti-dsDNA levels, proteinuria, glomerulonephritis and osteopenia.[13] In mice treated with L-4F plus pravastatin the authors found less macrophage infiltration and lower levels of pro-atherogenic chemokines.[13] A preclinical study performed in an SLE model reported reduced HLA class II expression upon statin treatment and reduced T helper type 1 (Th1) -driven autoimmunity.[3]

In clinical studies including SLE patients, atorvastatin therapy improved endothelial function,[15] which was also reported for simvastatin.[16] The authors reported reduced TNF serum levels in SLE patients treated with simvastatin.[16] A study on the dose effectiveness and tolerability of pravastatin in SLE patients reported no major impact on disease severity.[17] Case studies on three patients with SLE reported a reduction in proteinuria levels upon statin treatment.[18] A major clinical problem in patients with SLE is that the atherosclerotic process is accelerated. Therefore, in addition to the immunomodulatory functions of statins, their lipid-lowering effects may be beneficial in SLE.[19] In agreement with this concept, simvastatin improved disease signs of SLE associated with accelerated atherosclerosis in a murine model.[14] The controversial results between different trials on statins in SLE could be connected to the type of statin applied. A recent meta-analysis of five controlled trials that had studied the effect of statin intake on SLE disease activity showed no significant effect of statin treatment on the Systemic Lupus Erythematosus Disease Activity Index.[20] However, analysis of seven controlled trials showed a reduction of plasma C-reactive protein concentrations in patients with SLE by statin treatment.[20] This observation was dependent on the type of statin applied, as the plasma C-reactive protein concentration declined significantly with lipophilic (atorvastatin) but not hydrophilic (pravastatin and rosuvastatin) statins.[20]

Statins in RA

Multiple preclinical and clinical studies have analysed the impact of different statins on RA.[21–23] Statins are given to patients with RA because of their increased risk for cardiovascular complications.[24] A cohort study that included patients with a diagnosis of hyperlipidaemia who started statin intake showed that the connection between lowering low-density lipoprotein cholesterol and cardiovascular events in RA was comparable to the association found in matched general controls.[24] Another study analysed the effect of statins in patients treated for RA with tocilizumab.[22] The rationale was that treatment with tocilizumab increases lipid levels. The authors reported that concomitant statin use reduced tocilizumab-mediated lipid increases.[22] A randomized, placebo-controlled, multi-centre phase II study, on a combination of tofacitinib and atorvastatin showed that tofacitinib-associated elevated low-density lipoprotein cholesterol was reduced by atorvastatin.[25] The RA responses were numerically greater in the group that received tofacitinib and atorvastatin compared with tofacitinib and placebo; however, this did not reach statistical significance.[25]

A randomized, double-blind placebo-controlled trial that included 80 patients with RA aged between 19 and 75 years analysed the effects of atorvastatin versus placebo given in addition to current disease-modifying antirheumatic drugs.[26] Disease Activity Score-28, C-reactive protein and erythrocyte sedimentation rate decreased in the statin group.[26] These response rates are consistent with those reported in a previous randomized, double-blind placebo-controlled trial,[27] which also reported clinical improvement, reduced C-reactive protein levels and lower erythrocyte sedimentation rates in the atorvastatin group compared with the placebo group.[27]

Besides these trials on atorvastatin, smaller trials compared simvastatin with chloroquine and found superiority of the statin group.[18] Clinical studies on the anti-inflammatory and immunomodulatory effects of low-dosage simvastatin on RA demonstrated that the Th1/Th2 and CD4/CD8 ratios in peripheral blood were significantly reduced by simvastatin.[28] Simvastatin was shown to reduce cytokine production and nuclear factor-κB activation in IL-1β-stimulated synoviocytes from patients with RA.[29]

The type of statin applied in RA may influence the clinical response. A preclinical study showed that atorvastatin and rosuvastatin had no *in vivo* efficacy against RA with respect to synovial hyperplasia, exudate and cartilage damage.[30] However, the authors could reproduce the previously described beneficial effects of simvastatin on RA.[30]

Overall novel targeted therapies of RA such as IL-6R blockade with tocilizumab or Janus-activated kinase (JAK) inhibition with tofacitinib are most likely more potent than statins but they induce hyperlipidaemia and hypercholesteraemia. The treatment of this side effect with a drug that itself has anti-inflammatory activity is promising and needs to be evaluated in future prospective trials in the RA field.

Statins in MS

Multiple sclerosis was one of the first autoimmune models in which the anti-inflammatory effects of statins were reported. Meanwhile multiple preclinical studies and clinical trials have investigated the impact of statins on MS. The results vary depending on the type of statin used, the disease model and the clinical setting, respectively.

Statin treatment in mice developing experimental autoimmune encephalomyelitis (EAE), which is a standard animal model of MS, showed potent clinical response rates.[1,31,32] After these initial pivotal reports, others have shown that statin treatment in EAE reduced central nervous system lesion formation and delayed disease onset.[1,31,33–35] Statin effects in EAE were mediated via tolerogenic modification of antigen-presenting cells, the Th-1/Th1 cytokine profile, IL-6 and IL-23 transcription.[36] A more recent study in which mice were immunized with myelin oligodendrocyte glycoprotein,[35–55] showed that the treatment with simvastatin improved clinical disease scores.[37] Additionally, anti-inflammatory transforming growth factor-β mRNA expression was increased while IL-6, IL-12p40, IL-12p70, RANTES and macrophage inflammatory protein-1β were decreased.[37] In agreement with these findings the authors also reported lower central nervous system inflammatory mononuclear cell levels and less Th1 and Th17 cell infiltration in the central nervous system.[37] Furthermore, simvastatin diminished the proliferation of T cells co-cultured with primary microglial cells. Although the initial studies had suggested that statin treatment causes a Th2 induction, follow-up reports showed that atorvastatin treatment did not induce IL-4-producing Th2 cells *in vivo*. Conversely T cells from atorvastatin-treated IL-4 reporter mice preferentially differentiated into Th2 cells when reactivated *in vitro*.[38] The studies confirmed that atorvastatin reduced antigen-specific T-cell proliferation and secretion of interferon-γ, tumour necrosis factor, IL-17 and IL-12. Signal transducer and activator of transcription 6 (STAT6) is required for Th2 induction but the studies showed that also in STAT6-deficient mice atorvastatin treatment prevented EAE, although these animals cannot generate IL-4-producing Th2 cells.[38] The studies also showed that Foxp3$^+$ regulatory T cells were not required for the statin effects.[38]

In a recent double-blind, controlled clinical trial of patients with secondary progressive MS, patients were randomly assigned to either simvastatin (n = 70) or placebo (n = 70).[39] At 2 years, the frontal assessment battery score was 1·2 points higher in the group that was simvastatin-treated compared with the placebo group.[39] Furthermore, the authors reported that the simvastatin group also had a 2·5-point improved mean physical component score of the SF-36.[39] This study provides solid evidence of a positive effect of simvastatin on frontal lobe function and a physical quality-of-life measure in patients with secondary progressive MS.

Earlier clinical trials on the safety and efficacy of simvastatin for MS had shown a significant reduction of contrast-enhancing lesions in magnetic resonance imaging of the brain in patients with remitting–relapsing MS.[40] A phase II open-label baseline-to-treatment trial reported that atorvastatin given to patients with MS was safe and reduced the number and volume of contrast-enhancing lesions.[41] Mechanistically increased levels of anti-inflammatory IL-10 were reported in patients treated with atorvastatin.[41] A meta-analysis on data available in EMBASE, PubMed and CINAHL databases, clinical trials registries, and unpublished conference meeting abstracts showed that in secondary progressive MS, statin monotherapy showed significant reduction in brain atrophy and disability progression but no effect on relapse rate.[42] There was no clear evidence that certain statins were more effective than others for MS treatment.[42] The reported effects of statins in neuroinflammation warrant confirmation but underline the potential of this class of drugs in MS.

Statins in GVHD

Acute and chronic GVHD occur in patients undergoing allogeneic haematopoietic cell transplantation and cause a high morbidity and mortality.[43,44] Different groups have shown in preclinical models that statins reduce the severity of acute GVHD (aGVHD).[4,45] In murine GVHD, model statin treatment caused increased levels of intracellular IL-4 in CD4$^+$ T cells, indicating that a shift towards Th2 was protective. Another group showed that lovastatin reduced GVHD through its inhibitory effect on lymphocyte function-associated antigen 1.[45] Statins inhibited allogeneic immune responses in human cell systems *in vitro*.[46] Mechanistically, statins inhibit the rate-limiting enzyme of the L-mevalonate pathway and were shown to reduce farnesyl and geranylgeranyl residues that are required for the attachment of different small GTPases to the cell membrane.[7] Modifications of the anchoring of these GTPases can modulate the allogeneic immune response.[7] *In vitro* studies showed that interfering with protein geranylgeranylation or farnesylation reduced both pro-inflammatory cytokines, whereas IL-10 was increased when a farnesyltransferase inhibitor was used.[47] Consistent with this

finding, *in vitro* studies on human and murine T cells have demonstrated that different types of farnesyltransferase inhibitor block cytokine production of T cells in response to activating stimuli at the post-transcriptional level.[47] The reduction in the migratory capacity of antigen-presenting cells *in vitro* and *in vivo* when protein geranylgeranylation or farnesylation was blocked[7] was in agreement with reports showing that depletion of geranylgeranylpyrophosphates and farnesylpyrophosphates reduced monocytes and T-cell migration (Fig. 1).[48,49] More recently, a study analysed the effects of simvastatin on angiopoietin-1 (Ang-1) and Ang-2 expression in a mouse model of aGVHD.[50] The authors found that simvastatin increased Ang-1 production and simultaneously inhibited Ang-2 release from EA.hy926 endothelial cells.[50] Furthermore, treatment with simvastatin reduced aGVHD-related death and histopathological aGVHD grades. Simvastatin also increased the plasma levels and aortic endothelial levels of Ang-1.[50] Given the role of neovascularization in GVHD[51,52] these studies connect endothelial protective function of statins with aGVHD severity. Statins are also interesting for combination therapies with recently evolving GVHD treatments such as JAK inhibitors,[53,54] which may affect the cholesterol levels.

In patients undergoing allogeneic haematopoietic cell transplantation, some studies showed that statin intake by the donor[55] or host[56] was connected to a reduced GVHD incidence.[55–58] In contrast, one trial showed that the

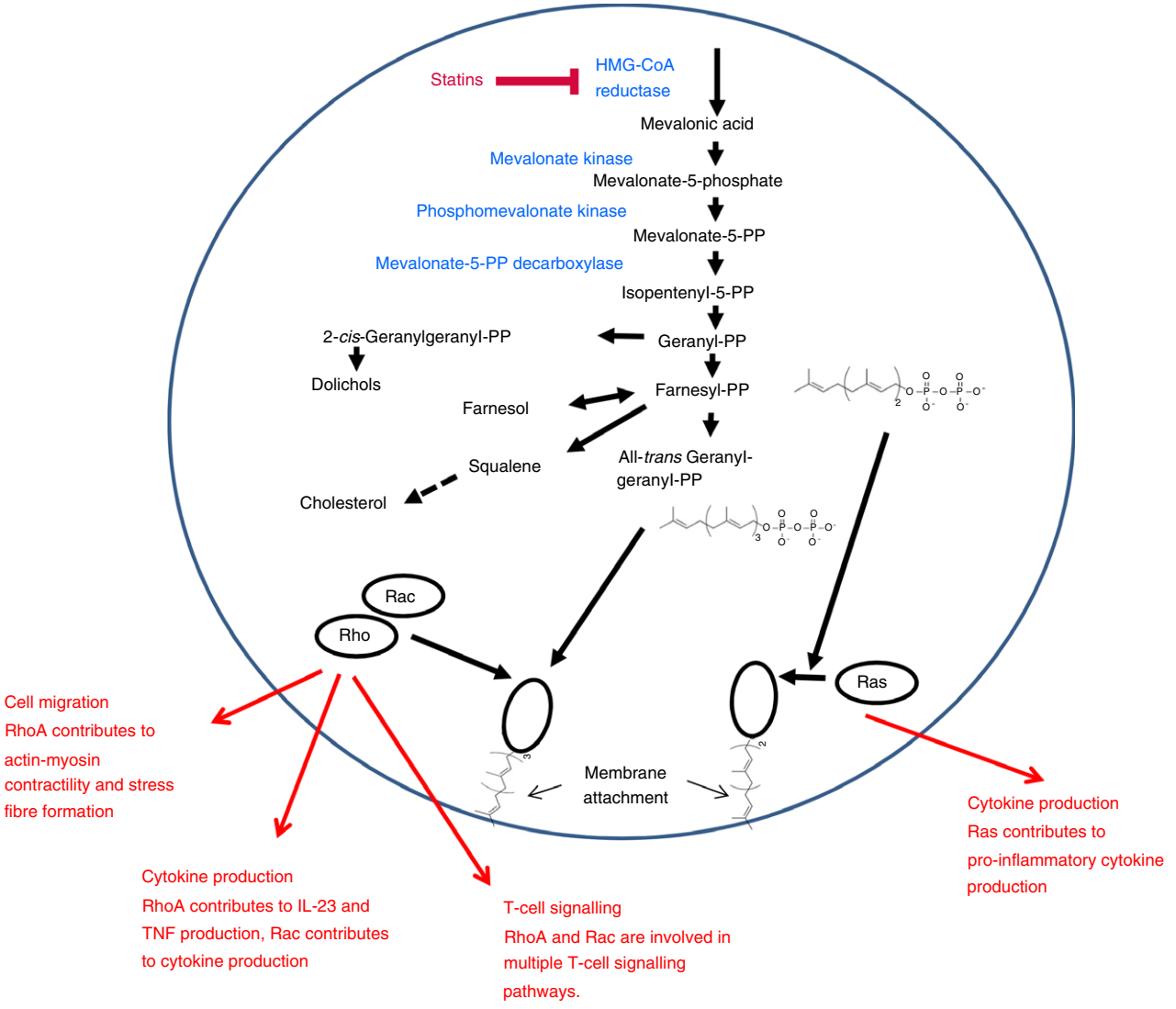

Figure 1. Simplified sketch showing the mode of action of statins as immunosuppressive strategy. Statins inhibit the rate-limiting enzyme of the mevalonate pathway leading to reduced levels of its downstream products. The pyrophosphate downstream products are critical for geranylgeranylation or farnesylation of GTPases that mediate multiple steps in the immune response such as cell migration, activation, signalling and cytokine production.

addition of atorvastatin to standard aGVHD prophylaxis did not provide a benefit with respect to GVHD rates.[59]

Summary

The immunomodulatory effects of statins in different disease models have meanwhile been supported by robust data from multiple independent groups. The potency of statins with respect to immunosuppression is lower than that of many of the established immunosuppressive drugs, which may be an advantage when immune-modulation rather than strong immunosuppression is required. Also, based on their mode of action, which is mainly via inhibition of protein geranylgeranylation and protein farnesylation, a combination strategy with inhibitors of different pathways may result in a synergism. In agreement with this, early studies on such combination therapies have been completed, combining statins with cytokine receptor inhibitors such as tocilizumab against IL-6R or JAK inhibitors. Interesting novel aspects are the increased Production of Ang-1 under certain statins, which thereby impact endothelial function, and the direct effects on T cells via calcium ion influx and IL-2 production. Overall, statins hold promise for combination therapies as they reduce cholesterol levels induced by certain immunosuppressive drugs and modulate the immune response.

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Author contribution

RZ collected literature, discussed the studies and wrote the manuscript.

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