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Statins and autoimmunity: State-of-the-art

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ABSTRACT

HMG-CoA reductase inhibitors, or statins, are potent plasma LDL-cholesterol (LDL-c) lowering agents. Since the introduction of the first statin, lovastatin, in 1987, accumulating evidence showed that non-cholesterol lowering effects play an important role in their efficacy to reduce atherosclerotic cardiovascular disease (ASCVD). Thus, these non-LDL-c lowering properties could benefit patients with immune-mediated diseases. Statins and their associated immune-modulating roles have recently received much attention. Different statins have been administered in various experimental and clinical studies focused on autoimmunity. The results indicate that statins can modulate immune responses through mevalonate pathway-dependent and -independent mechanisms. The anti-inflammatory and immune-modulating effects include cell adhesion, migration of antigen presenting cells, and differentiation, as well as activation, of T-cells. In various autoimmune diseases (e.g. rheumatoid arthritis, lupus, and multiple sclerosis), promising results have been obtained to date.

Abbreviations: LDL-c, LDL-cholesterol; ASCVD, Atherosclerotic cardiovascular disease; HMG-CoA, 3-hydroxy-3-methyl-glutaryl-coenzyme A; FPP, Farnesyl pyrophosphate; GGPP, Geranylgeranyl pyrophosphate; ROS, Reactive oxygen species; APCs, Antigen presenting cells; MMPs, Matrix metalloproteinases; BBB, Blood brain barrier; PPARs, Peroxisome proliferator-activated receptors; COX2, Cyclooxygenase-2; CRP, C-reactive protein; DCs, Dendritic cells; Th, T-helper; Treg, Regulatory T-cell; RORs, Retinoic acid-related Orphan Receptors; CRAC, Ca2+-released activated Ca2+ channels; MS, Multiple sclerosis; CNS, Central nervous system; RRMS, Relapsing-remitting multiple sclerosis; GELs, Gadolinium-enhanced lesions; MRI, Magnetic resonance imaging; CSF, Cerebrospinal fluid; EDSS, Expanded Disability Status Scale; FAB, Frontal Assessment Battery; ARR, Annualized rate of relapse; CIS, Clinically isolated syndrome; ON, Acute optic neuritis; SLE, Systemic Lupus Erythematosus; ROCK, Rho-associated, coiled-coil-containing protein kinase; MAPK, Phosphor-p38-mitogen-activated protein kinase; sTNFR1, TNF-α receptor type 1; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; SLAM-R, Systemic Lupus Activity Measure-Revised; FMD, Flow-mediated dilation; RA, Rheumatoid Arthritis; HDL-c, High-density lipoprotein cholesterol; DMARDs, Disease-Modifying Anti-Rheumatoid Drugs; DAS28, Disease Activity Score 28; ESR, Erythrocyte Sedimentation Rate; PWV, Aortic pulse wave velocity; Aix, Augmentation index; MTX, Methotrexate; TG, Triglyceride; TJC, tender joint count; SJC, swollen joint count; VAS, Visual Analog Scale; TSH, Thyroid Stimulating Hormone; TPOAb, Thyroid peroxidase; TgAb, thyroglobulin antibodies; PASI, Psoriasis Area and Severity Index; AH, Arterial hypertension; DLQ1, Dermatology life quality index; APS, Antiphospholipid syndrome; LDA, Low-dose aspirin; LMWH, Low molecular weight heparin; PE, Preeclampsia; IUGR, Intrauterine growth restriction; SSc, Systemic Scleroderma; TAT, Thrombin-anti-thrombin complex; SHAQ-DI, Scleroderma Health Assessment Questionnaire Disability Index; MDA, Malondialdehyde; EDV, Endothelium-dependent vasodilation; BD, Behcet's Disease; KD, Kawasaki Disease; TA, Takayasu Arteritis; AchR, Acetylcholine receptors.

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Contents

1. Introduction

Over the last 40 years, statins have transformed the prevention of atherosclerotic coronary artery diseases. More than 30 years ago, lovastatin was introduced as the first pharmacological agent able to reduce Low-Density Lipoprotein (LDL)-cholesterol to unprecedented levels, without serious side effects. By inhibiting 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase, the first step of the L-mevalonate pathway is competitively inhibited (de Jong et al., 2018; Salvo & Franchini, 2019; Ulivieri & Baldari, 2014). Although debate continues as to whether the observed cardiovascular disease (CVD) benefits can be explained solely by the LDL-cholesterol-lowering properties or the combination of cholesterol reducing and non-cholesterol effects, numerous studies have pointed out that statins can influence anti-inflammatory, immunomodulatory, and anti-thrombotic properties, as well as endothelial function (Chruściel et al., 2016; Hashemi et al., 2017; Parizadeh et al., 2011; A. Serban et al., 2015; A. Sahebkar et al., 2015; Sahebkar et al., 2016). The proven immunomodulatory effects of statins include inhibition of the anti-phospholipid, antibody-induced endothelial cell activation, prevention of auto-reactive B-cell activation, and minimizing Th1-derived autoimmunity, to name but a few of the immunomodulatory effects. These properties raised interest in whether therapeutic benefits would be observed in patients with autoimmune disorders. In several clinical trials, that included patients at risk for Atherosclerotic cardiovascular disease (ASCVD), improved inflammatory biomarkers, such as high-sensitivity C-reactive protein (hs-CRP), were observed and contributed to superior outcomes (Ciurleo, Bramanti, & Marino, 2014; De Peretti et al., 2013; Khattri & Zandman-Goddard, 2013; Ntolkeras et al., 2019; Rehfield, Kopes-Kerr, & Clearfield, 2013; Tournadre, 2019).

2. Statins

The introduction of statins in the late 1980s was a turning point in cardiology, and the prevention of ASCVD suddenly became an achievable goal. After the presentation and publication of the Scandinavian Simvastatin Survival Study (4S), prominent critics of the cholesterol hypothesis reversed their stance and embraced statins as one of the most successful drugs to reduce CVD. In spite of several new classes of lipid-lowering therapies (Banach et al., 2015; A. Sahebkar & Watts, 2013), statins are still regarded as the first choice for the management of ASCVD. Statins are inhibitors of HMG-CoA enzyme and share structural similarity to HMG-CoA, which leads to L-mevalonate synthesis and, subsequently, reduces hepatocellular cholesterol production (De Peretti et al., 2013; Hashemi et al., 2017; Khattri & Zandman-Goddard, 2013; Rehfield et al., 2013; Tournadre, 2019). HMG-CoA reductase initiates the cholesterol synthesis pathway. By inhibiting this first step, the metabolites further down the cholesterol synthesis cascade, including isoprenoid compounds such as farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP), are affected. These two metabolites act as lipid attachments for intracellular signaling molecules including GTP-binding proteins (Rho, Rab, Ras). These post-translational protein modifications (isoprenylation) have been found to be crucial for activation and membrane translocation of proteins that play a key role in a variety of cellular functions such as cell shape, secretion, differentiation, motility, and proliferation (Ciurleo et al., 2014; Ntolkeras et al., 2019) (Fig. 1). The statin drug class includes the naturally-occurring compounds (lovastatin, mevastatin, pravastatin, pitavastatin, and simvastatin), which are fungal derivatives and synthetically-derived statins (atorvastatin, fluvastatin and rosuvastatin). All statins bind to the HMG-CoA reductase enzyme in nano-molar concentrations and act as competitive inhibitors of HMG-CoA-reductase, competing with HMG-CoA as the natural substrate (Ciurleo et al., 2014; Greenwood, Steinman, & Zamvil, 2006). Statins can be distinguished based on several intrinsic properties, for example, lipophilicity/hydrophilicity, half-life of elimination, and potency to lower LDL-c. They all share an excellent safety profile; however, tolerability remains an important clinical issue, affecting dosing and (long-term) compliance.

3. Immunomodulatory effects of statins

Besides the LDL-c lowering effect, statins can act as immunomodulatory and anti-inflammatory agents (Khattri & Zandman-Goddard, 2013; Ntolkeras et al., 2019). Kobashigawa and colleagues reported that cardiac transplant patients using statins had a better outcome compared to patients not dosed with statins (Kobashigawa et al., 1995). Thirteen years later, Pazik J et al., reported that in patients with biopsy-confirmed, post-transplant glomerulonephritis, statin treatment was associated with prolonged survival of the transplanted organ (Pazik et al., 2008). These observations show that statins trigger immunomodulatory effects that mitigate acute and chronic rejection of transplanted kidneys and hearts. These observations prompted studies investigating the anti-inflammatory and immunomodulatory effects of statins (de Jong et al., 2018) (Fig. 2).

3.1. Mevalonate pathway-dependent immunomodulatory features

The pleiotropic effects of statins are, to a great extent, related to the inhibition of protein isoprenylation. The inhibition of HMG-CoA reductase affects all downstream products of the mevalonate – cholesterol synthesis pathway. Mevalonate is an essential building block of non-steroid isoprenoid compounds (Shahbaz, Sadeghi, Penson, & Sahebkar, 2019). These non-steroid isoprenoid compounds include farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP), which are important lipid mediators for GTPase activation and intracellular signaling molecules such as Rho, Rac and Cdc42 (Liu et al., 2018). Members of Ras and Rho GTPase family are modified *via* post-translational prenylation. Inhibition of HMG-CoA reductase by statins, decreases the FPP and GGPP levels; key factors in post-translational isoprenylation of cellular signaling proteins. This process impacts cell differentiation and proliferation, as well as inflammation (Shahbaz et al., 2019; Ulivieri & Baldari, 2014).

Mevalonate pathway products are essential for the production of co-enzyme Q, an important substrate of the mitochondria membrane and essential for mitochondrial energy production. TNFα- and angiotensin

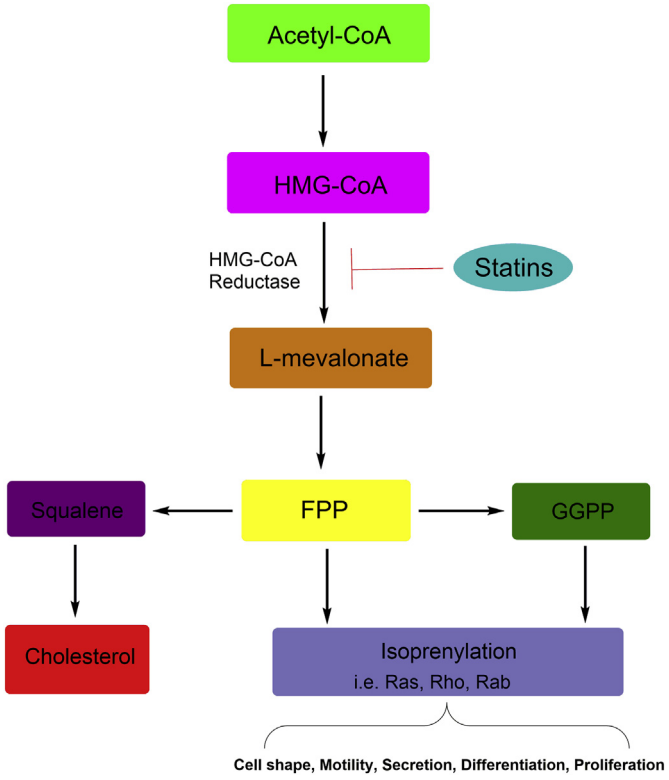

Fig. 1. Mechanism of L-mevalonate pathway inhibition by statins.

II synthesis can be hampered as well, causing changes in endothelial monocyte adhesion and the production of reactive oxygen species (ROS). This loss of prenylation can stimulate autophagy, activate the inflammasome complex, and ultimately cause cell death (L Muller & H Freed, 2017; Ntolkeras et al., 2019; Tricarico, Crovella, & Celsi, 2015).

3.2. Other immunomodulatory features

In addition to the mevalonate pathway-associated effects, statins can influence cellular trafficking, apoptosis, maturation of antigen presenting cells (APCs), and T-lymphocyte differentiation, activation, and polarization into specific subsets (Chalubinski & Broncel, 2010; Forero-Peña & Gutierrez, 2013; Ulivieri & Baldari, 2014; Xu et al., 2014; Zhang, Tao, Wang, Garcia-Mata, & Markovic-Plese, 2013).

3.2.1. Cell adhesion and migration

Statins attenuate the expression of matrix metalloproteinases (MMPs) 2 and 9 and inhibit the migration, as well as the penetration, of mononuclear cells across the blood brain barrier (BBB) (Ntolkeras et al., 2019; Reuter et al., 2015). Studies with atorvastatin and simvastatin have reported a decrease in the expression of monocyte-derived L-selectin and VLA4 adhesion molecules. Simvastatin combined with ezetimibe reduced LFA-1 gene expression. LFA-1 is an essential co-stimulator for migration and trafficking of T-cells, and various studies confirmed the inhibitory effects of statins on this molecule (Godoy et al., 2018; McInnes & Schett, 2011; Tang et al., 2011). Additionally, both atorvastatin and simvastatin interfere with Th1 cell migration by inhibiting the CD40/CD40L-associated activation of B-lymphocytes (Shimabukuro-Vornhagen et al., 2014).

3.2.2. Inflammation

Statins restrict NFκB and AP-1 activation by inhibiting NFκB-induced transcription factors and pro-inflammatory cytokines (Cheng et al., 2010). Anti-inflammatory transcription factors, peroxisome proliferator-activated receptors (PPARs), interfere with NFκB activity are activated by statins as well (Khattri & Zandman-Goddard, 2013). Statins attenuate vascular inflammation *via* a reduction in the number and activity of monocytes, as well as other inflammatory immune cells (Shahbaz et al., 2019). Simvastatin has been shown to inhibit the production of pro-inflammatory mediators by altering the gene expression of cyclooxygenase-2 (COX2) and IFN-γ (C. S. Lee et al., 2009). Numerous clinical trials have reported statin-mediated reductions in C-reactive protein (CRP), as well as inhibiting the production of MMP1 and MMP3, which are involved in connective tissue degradation (Crouse, et al., 2007; de Jong et al., 2018; Ridker et al., 2009).

3.2.3. Dendritic cells (DCs) maturation

Statins also inhibit DC maturation and the antigen presenting process in a dose-dependent manner (H. Li et al., 2015; Mira & Mañes, 2009; Tricarico et al., 2015; Yilmaz et al., 2004). This is mediated by inhibiting the production of IFN-γ and MHC transactivator class II expression on antigen presenting cells (APCs) (Khattri & Zandman-Goddard, 2013; Ntolkeras et al., 2019). Different studies have shown IFN-γ-induced MHC-II expression on endothelial cells, monocyte/macrophage, and T-lymphocytes (Arnaud, Braunersreuther, & Mach, 2005; Greenwood et al., 2006).

3.2.3.1. T-lymphocytes activation, polarization. Statins can directly and indirectly influence T-helper (Th) cells and regulate the Th1/Th2 balance. In fact, lovastatin has been shown to inhibit t-bet and STAT-4 expression and amplify GATA-3 and STAT-6, which induces polarization of Th2 and the secretion of IL-4, IL-5, IL-10, and TGF-β, while simultaneously inhibiting Th1 polarization and the secretion of IL-2, IL-12, IFN-γ, and TNF-α (de Jong et al., 2018; Kanda et al., 2007; Khattri & Zandman-Goddard, 2013; Ntolkeras et al., 2019). A different statin (simvastatin), suppress IL-6 and IL-23 cytokine production through restriction of the phosphorylation and expression of STAT-1 and STAT-3 and by induction of SOCS3 and SOCS7 expression. These effects induce regulatory T-cell (Treg) expression and inhibit Th17 subset differentiation. Zhang et al. reported that simvastatin attenuates IL-17A and its transcription factor [Retinoic acid-related Orphan Receptors (RORs)] expression in human CD4+ T-cells and directly suppresses a subtype of T-helper cell activation. This is followed by reduction in cytokine secretion, including IL-17A, IL-17F, IL-21, and IL-22 (Ntolkeras et al., 2019; Zhang et al., 2013; Zhang, Jin, Peng, Ramgolam, & Markovic-Plese, 2008). In vitro and in vivo studies by Mira and colleagues demonstrated that lovastatin influenced Treg CD4+ CD8+ cells, as well as increased migration and cell numbers in inflamed tissue, which reinforced their suppressive effects that are mediated by induction of FoxP3. Importantly, statins appear to be able to indirectly influence Treg differentiation *via* tolerogenic induction of DC's (Mira et al., 2008; Shahbaz et al., 2019).

A recently discovered immunomodulatory mechanism of action for statins is the inhibition of the Kv1.3 channel in T-lymphocytes. This is considered a potential novel target for the treatment of autoimmune disorders. Kv1.3 is a member of Shaker family, which is preferentially expressed on T-cells, which regulate the resting membrane potential along with K_{Ca} channels. This process provides a sustained driving force for Ca^{2+} influx *via* Ca^{2+}-released activated Ca^{2+} channels (CRAC) in T-cells. Ca^{2+} influx activates a Ca^{2+}-dependent signal transcription pathway and induces T-cell proliferation, activation, and IL-2 secretion in T-cell's. Zhao et al. demonstrated that lovastatin inhibits Kv1.3 channels in human T-lymphocytes in a concentration- and voltage-dependent manner. Consequently, decreased Ca^{2+} influx and Ca^{2+}-activated transcription factors can limit the activation and proliferation of T-cell's (Zeiser, 2018; Zhao et al., 2016).

These different pathways illustrate how statins can potentially mitigate immune responses by combining multiple mechanisms, including signaling, genes transcriptions, and epigenetic modifications, as well as intracellular metabolism by immune cells.

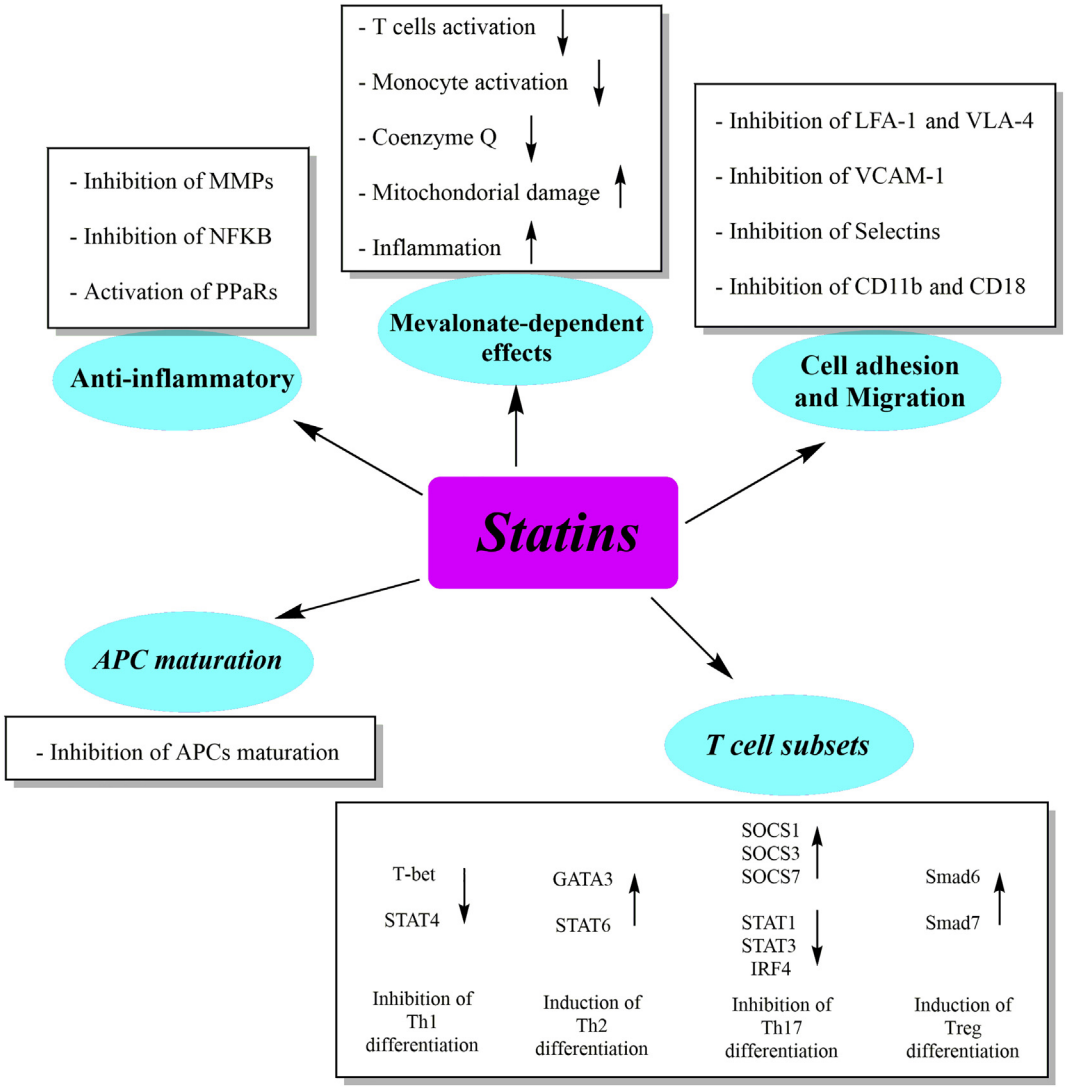

Fig. 2. Immunomodulatory effects of statins.

4. Clinical administration in autoimmune diseases (Table 1)

The following keywords and phrases, as well as the databases consulted, represent the search strategy employed for the present review. The ISI Web of Knowledge, PubMed-Medline, Scopus, and Google Scholar databases were searched using the following terms in titles and abstracts: (statin OR atorvastatin OR simvastatin OR lovastatin OR fluvastatin OR rosuvastatin OR pravastatin OR pitavastatin) AND (autoimmunity OR autoimmune disorder OR autoimmune disease OR multiple sclerosis OR MS OR systemic lupus erythematosus OR SLE OR rheumatoid arthritis OR RA OR Hashimoto's thyroiditis OR psoriasis).

4.1. Multiple Sclerosis (MS)

MS is an autoimmune disorder of the central nervous system (CNS) as well as the neuromuscular junction, characterized by demyelination, axonal destruction, and neuromuscular dysfunction (Chitnis & Weiner, 2017). Statin administration, in combination with IFN-β, has been studied for their effects on monocyte-derived dendritic cells isolated from MS patients. Despite different mechanism of action, statins and IFN-β target similar signaling pathways, but perhaps statins can effectively be used as an adjunct treatment strategy, although the precise role of statins in MS treatment remains to be determined (Bartosik-Psujek et al., 2010; Ciurleo et al., 2014; Ramgolam & Markovic-Plese, 2011).

Several clinical trials have shown the benefits of statins as add-on therapy to IFN-β in MS patients. In the first study, Sena et al., treated patients with relapsing-remitting multiple sclerosis (RRMS) with 20 mg/day lovastatin for a 12-month period and reported a decrease in the number of gadolinium-enhanced lesions (GELs), however, the clinical changes were not significant (Sena, Pedrosa, & Morais, 2003). In a second study, Vollmer and colleagues treated patients with high-dose (80 mg/day) simvastatin for 6 months, and although clinical signs and immunologic factors were not significantly different, MRI results suggested a 44% and 41% reduction in the volume and numbers of newly formed GELs, respectively (Vollmer et al., 2004). Paul et al. demonstrated that 80 mg/day of atorvastatin, with or without IFN-β in RRMS patients, not only significantly reduced the number and volume of GELs, but statin use was associated with an in increase in IL-10, as well as a reduced T-cell response (Paul et al., 2008). In the ACTIVE study by Lanzillo et al., 24 months of low-dose atorvastatin therapy in combination with IFN-β resulted in a significant reduction of GELs and also reduced the relapse rate in RRMS patients (Lanzillo et al., 2010). IN a randomized, double-blind clinical trial by Toga and colleagues, it was shown that the combination of simvastatin and IFN-β in RRMS patients was associated with an insignificant reduction in GELs based on

Table 1
Characteristics of clinical studies of statin therapy in autoimmune disorders.

Authors	Intervention			Type of study, Patients and type of disease	Findings	Ref.
	Type of Statin	Statin dose and follow-up	Other therapies			
Sena et al. (2003)	Lovastatin	20mg/day (12 months)	add-on therapy with IFN-β	7 patients with RRMS	decreased average of GEL numbers	(Sena et al., 2003)
Vollmer et al. (2004)	Simvastatin	80mg/day (6 months)	-	30 patients with RRMS	44% and 41% reduction in new GELs mean numbers and mean volume, respectively	(Vollmer et al., 2004)
Paul et al. (2008)	Atorvastatin	80mg/day (9 months)	with or without IFN-β	41 patients (16 with and 25 without) with RRMS in a phase II, open-label trial	significant amelioration of numbers and volume of GELs, increased the IL-10 production, suppressed T cell responses	(Paul et al., 2008)
Lanzillo et al. (2010) (ACTIVE study)	Atorvastatin	20mg/day (24 months)	add-on therapy with IFN-β	44 patients (21 cases and 24 control) with RRMS in a open-label, randomized, longitudinal trial	significant reduction in GEL numbers and relapse rate	(Lanzillo et al., 2010)
Togha et al. (2010)	Simvastatin	40mg/day (NM)	add-on therapy with IFN-β	85 patients (42 cases and 38 control) with RRMS in a double-blind, randomized control	insignificantly reduced GELs and T2 lesion in MRI results	(Togha et al., 2010)
Chataway et al. (2014)	Simvastatin	80mg/day (24 months)	-	140 patients (70 cases and 70 control) with SPMS in a double-blind, controlled trial	attenuated brain atrophy and disability	(Chataway et al., 2014)
Li et al. (2014)	Atorvastatin	40mg/day (6 months)	methylprednisolone	38 patients with RRMS	Significant increase in IL-10, IL-13, IL-35 and decrease in IFN-γ levels in CSF, positive correlation between IL-10 and IL-13 with EDSS scores	(X.-l. Li et al., 2014)
Chan et al. (2017)	Simvastatin	80mg/day (24 months)	-	140 patients (70 cases and 70 control) with SPMS in a double-blind, controlled trial	Improvement in the frontal lobe function and physical quality of life	(Chan et al., 2017)
Sorensen et al. (2011) (SIMCOMBIN study)	Simvastatin	80mg/day (12 months)	add-on therapy with IFN-β	307 treatment-naïve RRMS patients (151 cases and 156 control) in a multicenter, placebo-controlled, double-blind, randomized, parallel group clinical trial	No significant improvement in ARR index and new lesion formation	(Sorensen et al., 2011)
Kamm et al. (2012) (SWABIM study)	Atorvastatin	40mg/day (15 months)	add-on therapy with IFN-β1	77 patients (39 cases and 38 control) with RRMS in a multicenter, randomized, parallel group, ratet-blinded trial	No significant changes in T2 new lesions formation	(Kamm et al., 2012)
Rudick et al. (2009) (SENTINEL study)	Atorvastatin Simvastatin	NM (24 months)	With or without IFN-β1a	582 patients (40 with and 542 without IFN-β1a) with RRM	Insignificant changes in ARR, disability progression, number of GELs, number of new or enhancing T2-hyperintense lesions	(Rudick et al., 2009)
Birnbaum et al. (2008)	Atorvastatin	40mg/day and 80mg/day (6 months)	add-on therapy with IFN-β1a	26 patients (17 cases and 9 control) with RRMS in a double-blind, placebo-controlled randomized trial	Increases in the clinical disease activity and MRI findings	(Birnbaum et al., 2008)
Feng et al. (2012)	Atorvastatin	40mg/day and 80mg/day (4 weeks)	add-on therapy with IFN-β	14 patients with RRMS	significantly reduces in IFN-β responses and exacerbate disease	(Feng et al., 2012)
Abud-Menduza et al. (2003)	Simvastatin	80mg/day (8 days)	-	3 patients with SLE	Significantly reduced proteinuria and decreased spontaneous apoptosis of PBMCs and expression of CD69 and HLA-DR	(Abud-Mendoza et al., 2003)
Willis et al. (2014)	NM	NM (6 months)	-	21 patients with SLE	Decrease in SLE-related disease activity and changes in pro-inflammatory biomarkers	(Willis et al., 2014)
Yu et al. (2015)	Atorvastatin 20mg/day Simvastatin 30mg/day Lovastatin 45mg/day Pravastatin 30mg/day Fluvastatin 60mg/day Rosuvastatin 10mg/day		-	4095 patients with SLE and hyperlipidemia	Reduced mortality and cardiovascular disease	(Yu et al., 2015)
Ruiz-limon et al. (2015)	Fluvastatin	20mg/day (1 months)	-	27 patients with SLE	Decreased disease activity index, lipid levels, oxidative status, and vascular inflammation	(Ruiz-Limon et al., 2015)
Ferreira et al. (2007)	Atorvastatin	20mg/day (8 weeks)	-	88 patients (64 cases and 24 control) with SLE	Improved endothelial function with a significant increase in FMD	(Ferreira et al., 2007)
Norby et al. (2009)	Fluvastatin	40-80mg/day (24 months)	-	23 SLE patients with renal transplantation	Reduced risk of major cardiac events	(Norby et al., 2009)
McCarey et al. (2004) (TARA study)	Atorvastatin	40mg/day (6 months)	In combination with DMARD therapy	116 patients with RA	Significantly improved DAS28, faster decline in CRP levels and ESR index and reduction in SJC	(McCarey et al., 2004)
Maki-Petaja et al. (2007)	Simvastatin	40mg/day (6 weeks)	In comparison to 10mg/day ezetimibe	20 patients with RA	Significantly improved FMD and aortic PWV	(Mäki-Petäjä et al., 2007)

(continued on next page)

Table 1 (*continued*)

Authors	Intervention			Type of study, Patients and type of disease	Findings	Ref.
	Type of Statin	Statin dose and follow-up	Other therapies			
El-barbary et al. (2011)	Atorvastatin	40mg/day (6 months)	MTX and prednisone	30 patients with RA	Significant decrease in serum total cholesterol, LDLc, TG and HDLc levels. Also, significantly improved serum MDA, TNF-α, resistin, adiponectin, and FMD	(El-Barbary et al., 2011)
Tang et al. (2011)	Atorvastatin	20mg/day	-	55 patients with RA	Improved number and inhibitory function of Tregs and a significant reduction in CRP levels, ESR and disease activity scores	(Tang et al., 2011)
Mowla et al. (2016)	Atorvastatin	40mg/day (3 months)	In combination with DMARD therapy	80 patients with RA in a randomized, double-blind, placebo-controlled clinical trial	Significantly reduce DAS-28, CRP, and ESR	(Mowla et al., 2016)
Karimifar et al. (2019)	Atorvastatin or Simvastatin	40mg/day (6 months)	-	16 patients with RA in a randomized double-blind controlled clinical trial	Reduced DAS-28 score and LDL-c levels	(Karimifar et al., 2019)
Kitas et al. (2019)	Atorvastatin	40mg/day (NM)	-	3002 patients with RA in a multicenter, randomized, placebo-controlled clinical trial	Significantly decreased serum LDLc and CRP levels	(Kitas et al., 2019)
An et al. (2016)	NM	NM (12 months)	DMARDs	1522 RA patients with hyperlipidemia in a controlled cohort study	Significant association between LDL-c decline and cardiovascular events	(An et al., 2016)
Schoenfelid et al. (2016)	NM	NM (12 months)	DMARDs	2943 RA patients in a cohort study	Reduction in mortality rate	(Schoenfeld et al., 2016)
Gullu et al. (2005)	Simvastatin	20mg/day (8 weeks)	-	21 (11 cases and 10 control) patients with Hashimoto's thyroiditis	Elevation in the serum levels of free tri-iodothyronine and free thyroxine and a decrease in TSH levels, also significantly decrease in T CD8+ and NK cells along with significant increase in T CD4+ and B cells	(Gullu et al., 2005)
Krysiak et al. (2016)	Atorvastatin and Rosuvastatin	40mg/day and 10mg/day (6 months)	In combination with 10mg/day ezetimibe	38 Women with Hashimoto's thyroiditis	Increased anti-thyroid peroxidase anti-thyroglobulin antibodies titers	(Krysiak et al., 2016)
Krysiak et al. (2019)	Atorvastatin	40mg/day (6 months)	In combination with 200μg of seleno-methionine	42 Women (20 cases and 22 control) with Hashimoto's thyroiditis	Significantly decrease in the TPOAb and TgAb serum titers	(Krysiak et al., 2019)
Furukawa et al. (2006)	Pravastatin	10mg/day (8 weeks)	-	18 SSc patients	Activation of plasma vWF and inhibition of TAT factors	(Furukawa et al., 2006)
Abou-Raya et al. (2008)	Atorvastatin	40mg/day (4 months)	-	84 patients with SSc and secondary Raynaud's phenomenon	Significantly improved SHAQ-DI index and significantly decreased IL-6, TNF-α, ESR, hs-CRP, ICAM-1, sE-selectin, ET-1, MCP and oxidative markers such as LP, MDA, vWF and fibrinogen	(Abou-Raya et al., 2008)
Abou-Raya et al. (2007)	Atorvastatin	40mg/day (6 months)	-	40 patients (20 cases and 20 control) with SSc in a randomized, placebo-controlled trial	Decreased levels of endothelial activation markers including ET-1, ICAM-1, sE-selectin, vWF, fibrinogen, ESR, hs-CRP, and MDA, EDV, decreased ROS production and increased NO levels	(abou-raya et al., 2007)
Inanc et al. (2010)	Atorvastatin	20mg/day (3 months)	In comparison to the lisinopril	92 patients (31 statin, 31 lisinopril and 30 in placebo group) with Behcet's Disease	Improved endothelial function, although insignificant differences in the CRP, ESR and fibrinogen	(Inanc et al., 2010)
Duan et al. (2014)	Pravastatin	5-10mg/day (6 months)	-	13 Children with Kawasaki disease	Significantly improved endothelial function and CRP levels	(Duan et al., 2014)
Kwon et al. (2019)	NM	NM	Prednisolone	74 patients (40 cases and 34 control) with Takayasu arteritis	Significant decrease in relapse frequency	(Kwon et al., 2019)
Naseri et al. (2010)	Simvastatin	40mg/day (8 weeks)	Topical betamethasone	30 patients with psoriasis in a double-blind, randomized, placebo-controlled study	Significantly improved PASI score	(Naseri et al., 2010)
Vasiuk et al. (2010)	Atorvastatin	20 mg/day (6 months)	-	63 patients with psoriasis and arterial hypertension	significantly improved PASI scores, quality of life index, and also TNF and hs-CRP as inflammatory markers	(Vasiuk Iu et al., 2010)
Trong et al. (2019)	Simvastatin	40 mg/day (8 weeks)	topical calcipotriol/betamethasone dipropionate	128 patients with psoriasis	significantly decreased PASI scores	(Trong et al., 2019)
Faghihi et al. (2011)	Atorvastatin	40 mg/day (12 weeks)	topical therapy (emollients, keratolytics, and/or class V corticosteroids)	40 patients (20 cases and 20 control) with psoriasis	significant improvement in lesions and PASI scores	(Faghihi et al., 2011)
Chua et al. (2017)	Atorvastatin	40 mg/day (6 months)	betamethasone valerate	28 patients with plaque-type psoriasis in a randomized, double-blind, placebo-controlled trial	improvement in PASI and DLQ1 scores and hs-CRP	(Chua et al., 2017)

Table 1 (*continued*)

Authors	Intervention			Type of study, Patients and type of disease	Findings	Ref.
	Type of Statin	Statin dose and follow-up	Other therapies			
Jajoria et al. (2009)	Fluvastatin	40 mg/day (1 months)	-	9 patients with APS	significantly reduction in thrombotic and inflammatory markers such as VEGF, serum tissue factor (sTF) and TNF-α	(Jajoria et al., 2009)
Lopez-Pedrera et al. (2011)	Fluvastatin	20 mg/day (1 months	-	42 patients with APS and thrombosis	significantly inhibition of TF, protein activator receptors, VEGF and Flt expression	(Lopez-Pedrera et al., 2011)
Lefkou et al. (2016)	Pravastatin	20 mg/day (during pregnancy)	-	21 LDA+LMWH-refractory APS patients during pregnancy	Increased placental blood flow and improvement in PE features and live births that occurred close to the full term	(Lefkou et al., 2016)

Abbreviations: NM, not mentioned; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; GEL, gadolinium-enhancing lesion; MRI, magnetic resonance imaging; EDSS, expanded disability status scale; ARR, annualized rate of relapse; PBMC, peripheral blood mononuclear cell; SLE, system lupus erythematosus; RA, rheumatoid arthritis; FMD, flow-mediated dilation; DMARD, disease-modifying anti-rheumatoid drugs; DAS28, disease activity score 28; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; SJC, swollen joint count; PWV, pulse wave velocity; MTX, methotrexate; LDLc, low density lipoprotein cholesterol; HDLc, high density lipoprotein cholesterol; TG, triglyceride; MDA, malondialdehyde; TSH, thyroid stimulating hormone; TPOAb, anti-thyroid peroxidase antibody; TgAb, anti-thyroglobulin antibody; SSc, systemic sclerodermia; vWF, von willebrand factor; TAT, thrombin-anti thrombin complex; SHAQ-DI, sclerodermia health assessment questionnaire disability index; EDV, endothelium-dependent vasodilation; PASI, Psoriasis Area and Severity Index; DLQ1, dermatology life quality index; APS, antiphospholipid syndrome; LDA, low dose aspirin; LMWH, low molecular weight heparin.

magnetic resonance imaging (MRI) (Togha et al., 2010). Chataway et al. showed that simvastatin monotherapy in progressive multiple sclerosis (SPMS) patients attenuated brain atrophy and disability, but no effects on IL-17 levels were noted (Chataway et al., 2014). Li et al. reported that the combination of atorvastatin and methylprednisolone in patients with relapsing MS significantly increased IL-10, IL-13, IL-35, and reduced IFN-γ concentrations in the cerebrospinal fluid (CSF). The IL-10 and IL-13 CSF levels were positively correlated with scores associated with the Expanded Disability Status Scale (EDSS) (X.-l. Li et al., 2014). In another investigation, Chan et al. conducted a double-blind, controlled study of SPMS patients treated with simvastatin, or placebo, for two years. The Frontal Assessment Battery (FAB) scores were 1.2 times greater in the treatment group compared to the placebo group and the mean physical component score increased 2.5-fold. Evidences that simvastatin had a positive effect on frontal lobe function and physical quality of life were reported as well (Chan et al., 2017). In fact, positive outcomes were confirmed in a meta-analysis study conducted by Bhardwaj and colleagues. They showed that a combination of statins with IFN-β was associated with a significantly reduced relapse risk, as well as decelerated disease progression and improved EDSS scores in patients with RRMS (Bhardwaj, Coleman, & Sobieraj, 2012).

In contrast, several studies have shown no benefits of statins for the treatment of MS patients. The multi-center, randomized, double-blind placebo-controlled clinical trial by Sorensen et al. (the SIMCOMBIN study), a 12-month study comparing combination therapy of simvastatin and IFN-β to placebo in treatment-naïve RRMS patients, did not show any significant difference in clinical outcomes. The annualized rate of relapse (ARR) and new lesion formation in the treatment group was comparable to what was observed in the placebo group (Sorensen et al., 2011), which was similar to the results in the SWABIMS multi-center trial by Kamm et al. After 15 months of combination therapy with atorvastatin and IFN-β-1b, the development of new T2 lesions were equal in the treatment and placebo groups (Kamm et al., 2012). Rudick et al., reported comparable results in the SENTINEL trial. Two years of treatment with atorvastatin or simvastatin resulted in insignificant changes of ARR, disability progression, number of GELs, and number of new T2-hyperintense lesions, when compared to placebo (Rudick et al., 2009). The systematic review of Pihl-Jensen G. et al. confirmed these negative findings. Specifically, they were unable to show distinct benefits of statins for the following endpoints; RRMS, SPMS, clinically isolated syndrome (CIS), and acute optic neuritis (ON) when used as either monotherapy, or as an add-on therapy, with IFN-β (Pihl-Jensen, Tsakiri, & Frederiksen, 2015).

Evidence suggesting a harmful effect of statin use on disease severity, as well as exacerbation frequency, have been reported as well. Birnbaum et al., in a randomized, placebo-controlled, clinical trial showed that atorvastatin in combination with IFN-β-1a was associated with an increase in clinical disease activity and worsening of MRI findings in RRMS patients. A possible explanation for these findings, as suggested by the authors, was that statins may have exerted an antagonistic effect on IFN activity (Birnbaum, Cree, Altafullah, Zinser, & Reder, 2008). Also, Feng et al., reported that high-dose (80 mg) statin, when compared to low-dose statin (40 mg), significantly reduced IFN-β responses when used as add-on therapy to IFN-β. The explanation provided by the authors was that statins block STAT-1 transcription factor phosphorylation and counteract the positive effects of IFN-β, which results in an exacerbation of the disease (Feng et al., 2012).

4.2. Systemic Lupus Erythematosus (SLE)

SLE is an autoimmune disorder that remains poorly understood in terms of its pathogenesis. Characteristics are the accumulation antinuclear auto-antibodies, hyper-activation of immune cells, and ultimately multi-organ damage and failure caused by the overwhelming buildup of immune-complexes (Amirhossein Sahebkar, Rathouska, Derosa, Maffioli, & Nachtigal, 2016). Within the broad spectrum of serious complications, triggered by an immune mediated hyper-response, cardiovascular complications, especially atherosclerosis, are recognized as the leading cause of morbidity and mortality in SLE patients. Chronic inflammation is the hallmark of SLE, and statins prevent cardiovascular complications not only by drastically reducing plasma LDL-c, but also by triggering pleiotropic metabolic changes such as improved endothelial function, antioxidant properties, and anti-inflammatory effects along with decreased expression of cell adhesion molecules, pro-inflammatory cytokines and lower plasma levels of CRP (Mihos, Pineda, & Santana, 2014; Zhou & Liao, 2010).

The anti-inflammatory effects of statins have been shown to reduce the production of pro-inflammatory cytokines, especially IL-17 and IL-21, in SLE patients. This is most likely mediated through the inhibition of the Rho-associated, coiled-coil-containing protein kinase (ROCK) pathway. Chemokines and cytokines, including IL-6 and IL-8, were lower in statin-treated SLE patients, although there was a simultaneous increase in mitochondrial biogenesis and the levels of ROS. Monocyte gene expression for specific genes that regulate inflammation and oxidative stress responded to statins as well, which affirmed non-LDL-c related anti-inflammatory effects of statins. Patients with SLE that used

statins had noticeably lower plasma concentrations of inflammatory cytokines such as IFN-γ and TNF-α. Elucidation of mechanisms that may be involved included blocking downstream HMG-CoA metabolites in the cholesterol synthesis pathway, as well as CpG-induced inhibition of phosphor-p38-mitogen-activated protein kinase (MAPK) expression. A possible alternative pathway/explanation could also be the effect of statins on soluble TNF-α receptor type 1 (sTNFR1) and a reduction of plasma CRP levels, which have been documented in SLE patients (Albert, Danielson, Rifai, Ridker, & Investigators, 2001; Amuro et al., 2010; Ferreira, Teixeira, Calderaro, & Sato, 2016; Kotyla, 2008; Rozo et al., 2017; Tan, Heng, & Mak, 2019). Additionally, Abud-Mendoza et al. reported a decrease in the spontaneous apoptosis of peripheral blood lymphocytes along with a reduction in the expression of CD69 and HLA-DR after 8 days of simvastatin treatment (80 mg/day). The 8 days of simvastatin treatment also resulted in a significant reduction in proteinuria.

The Sahebkar et al. meta-analysis showed that statin therapy did not have a significant effect on the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score. No safety issues were observed, and plasma CRP levels did show a favorable response. However, the decrease observed in plasma CRP depends on the type of statin used; that is, a significant decrease in plasma CRP was observed in patients using a lipophilic statin (atorvastatin) compared to hydrophilic statins (pravastatin and rosuvastatin) (Sahebkar, Rathouska, et al., 2016).

A decrease in SLE-related disease activity, as assessed by the use of the Systemic Lupus Activity Measure-Revised (SLAM-R), was demonstrated by Willis et al. for patients during statin treatment. However, a rise in pro-inflammatory biomarkers such as IL-1β, IL-6, and IL-8, as well as pro-thrombotic antiphospholipid antibodies, were noted (Willis et al., 2014). In a large observational Taiwanese nationwide population study by Yu et al., both mortality and comorbidities (including cardiovascular disease), were reduced in SLE patients using statins. The authors proposed that the results of this large observational, retrospective study strongly suggest that a large properly-designed, placebo-controlled, randomized study is needed to confirm these results (Yu et al., 2015). The metabolic benefits for statin-treated SLE patients were studied by Ruiz-limon et al. One month of fluvastatin treatment (20 mg/day) in SLE patients improved disease activity parameters, lipid levels, oxidative status, and vascular inflammation; all, of which, contribute to slowing the progression of atherosclerosis (Ruiz-Limon et al., 2015). Ferreira et al., showed that atorvastatin use at a dose of 20 mg/day was able to improve flow-mediated dilation (FMD) in SLE patients (Ferreira, Navarro, Telles, Andrade, & Sato, 2007). In a different study by Norby et al., it was reported that post-renal transplant SLE patients that received fluvastatin demonstrated improved cardiovascular outcomes when compared to similar patients that did not receive fluvastatin (Norby et al., 2009).

Statins are, in general, well tolerated, and most patients do not experience serious side effects (including SLE patients that participated in clinical studies aimed at evaluating the benefits and/or harmful effects of statins). However, it should be noted that there were case reports of patients that experienced lupus-like syndrome, autoimmune hepatitis, autoimmune-mediated necrotizing myositis, subcutaneous lupus-like skin lesions, and dermatomyositis (Graziadei, Obermoser, Sepp, Erhart, & Vogel, 2003; Hamann, Cooper, McHugh, & Chinoy, 2013; Noël, Cerottini, & Panizzon, 2001).

4.3. Rheumatoid Arthritis (RA)

Rheumatoid arthritis is a systemic autoimmune disease with a significant inflammatory burden. There are several pathophysiological mechanisms that can accelerate atherosclerosis and increase cardiovascular risk, especially the risk of coronary artery disease (Aletaha et al., 2010; Robertson, Peters, McInnes, & Sattar, 2013; Smolen et al., 2014). In RA patients, especially in those with active progression of disease, lipid parameters deteriorate. High-density lipoprotein cholesterol (HDL-c) levels are reduced and the atherogenic, apoB carrying lipoproteins are elevated together with virtually non-existent protective antioxidants, which creates an extremely pro-oxidative and pro-atherogenic vascular environment. The increase in pro-inflammatory mediators results in accelerated atherosclerosis, as well as endothelial cell damage and degradation (González-Gay & Gonzalez-Juanatey, 2016; González-Gay & González-Juanatey, 2014; Steiner & Urowitz, 2009). There is increasing interest for the use of statins to mitigate the inflammatory conditions/environment and attenuate the rheumatoid disease process. Their role as an adjuvant therapy for the control of inflammation in RA has prompted numerous experimental and clinical studies. Statins, combined with Disease-Modifying Anti-Rheumatoid Drugs (DMARDs), are now considered part of the routine pharmacological treatment for RA patients and has been recommended in rheumatology guidelines (Agca et al., 2017; Arts, Fransen, den Broeder, Popa, & van Riel, 2015; Avina-Zubieta, Thomas, Sadatsafavi, Lehman, & Lacaille, 2012; Castañeda et al., 2015; Demoruelle, Deane, & Holers, 2014; Hippisley-Cox, Coupland, & Brindle, 2017; Joint British Societies' consensus recommendations for the prevention of cardiovascular disease (JBS3), 2014; Lindhardsen et al., 2011; Ogdie et al., 2015; Sattar, McCarey, Capell, & McInnes, 2003). Statins are beneficial for reducing the risk for ASCVD complications, improving the lipid profile, and controlling RA disease activity. It is noteworthy that the lipid-lowering effect of statins remains intact even in the presence of drugs known to have a deteriorating effect on lipid metabolism, e.g. corticosteroids (Okamoto et al., 2007; Soulaidopoulos, Nikiphorou, Dimitroulas, & Kitas, 2018). Since TNF-α, IFN-γ, and many other cytokines are key factors in the chronic arthritic process, the ability of statins to reduce these mediators could produce anti-inflammatory effects in RA. Numerous clinical trials that have determined hsCRP as part of the treatment protocol have demonstrated that statins exert potent anti-inflammatory effects, but are also able to decrease inflammatory mediators such as IL-6 (Burska, Boissinot, & Ponchel, 2014; Matsuno et al., 2002; Pereira et al., 2014; Tikiz et al., 2005). The TARA (Trial of Atorvastatin in Rheumatoid Arthritis), by McCarey et al. in 2004, was the first trial to show promising anti-inflammatory effects of statins in RA. Atorvastatin (40 mg/day), combined with DMARD therapy during a six-month period, showed significant benefits for RA patients in the active treatment arm of the clinical trial. Results showed a significantly improved Disease Activity Score 28 (DAS28) and faster decline in CRP levels and the value of the Erythrocyte Sedimentation Rate (ESR), as well as a reduction in the Swollen Joint Count (SJC) (McCarey et al., 2004). In a study by Maki-Petaja et al., non-invasive evaluations of vascular function and morphology were evaluated in RA patients, which included flow-mediated dilatation (FMD), aortic pulse wave velocity (PWV), and augmentation index (Aix). These investigators found that simvastatin (40 mg/day) significantly decreased both FMD and aortic PWV (Mäki-Petäjä et al., 2007). El-barbary et al. studied the effect of 6 months of atorvastatin (40 mg/day) combined with methotrexate (MTX) and prednisone. They reported a significant decrease in serum total cholesterol, LDLc, triglyceride (TG), and HDL-c levels. This regimen also significantly improved serum MDA, TNF-α, resistin, adiponectin, and FMD (El-Barbary et al., 2011). In a different study by Tang et al., a daily dose of atorvastatin (20 mg) showed improved numbers and inhibitory activity of Tregs, as well as a significant reduction in CRP levels, ESR, and disease activity scores in RA patients (Tang et al., 2011). A meta-analysis by Lv et al. evaluating the effect of statins on RA disease activity, as well as inflammatory factors, confirmed that statins potentially attenuate disease activity, significantly reduce ESR and CRP levels, and downregulate inflammatory factors including TNF-α, IL-1, and IL-6. These same investigators also found that tender joint count (TJC) and swollen joint count (SJC) improved as well (Lv et al., 2015). Their data would strongly suggest that statins improve biochemical and clinical parameters associated with vascular and articular inflammation. A randomized, double-blind, placebo-controlled clinical trial by Mowla et al. tested atorvastatin (40 mg/day) *versus* placebo when combined with

DMARDs over a three-month period in 80 RA patients. They demonstrated that DAS-28, CRP, and ESR were significantly lower in the statin group compared with patients assigned to the placebo group (Mowla et al., 2016). In a clinical trial conducted by Karimifar et al., RA patients received atorvastatin or simvastatin (40 mg/day) for six months. DAS28 and a Visual Analog Scale (VAS) were used to assess the severity of pain in the RA patients. The ESR and lipid profile of patients were measured before, and at the end of month three and month six. Both statins effectively improved disease activity, reflected by a reduced DAS-28 score and also improved LDL-c levels (Karimifar et al., 2019). Kitas et al. evaluated the efficacy of atorvastatin for preventing cardiovascular complications in RA patients. A significant decrease in both serum LDL-c and CRP levels was associated with the use of atorvastatin at a dose of 40 mg/day in these RA patients (Kitas et al., 2019). In a different observational cohort study, which included hyperlipidemic RA patients using statins, it was found that a reduction in LDL-c was associated with a significant decrease in the risk of cardiovascular events in statin users when compared to controls (non-statin users) (An et al., 2016). To further our understanding on the potential benefits of statins in RA patients, Munoz et al. conducted a meta-analysis in which all randomized and non-randomized clinical trials were analyzed to evaluate the effect of statins on mortality, cardiovascular complications, lipid fractions, and disease activity in RA patients. Results of Munoz et al. showed that statin therapy significantly reduced total cholesterol, LDLc, and TG levels, without significantly altering HDL-c. Disease activity also improved mildly over a three-month period as reflected by the values of the DAS28 index (Muñoz, Carrasco, Castelblanco, García, & Fernández-Avila, 2019). Another general population-based cohort study by Schoenfeld et al., confirmed that statin use was associated with a lower overall mortality risk in RA patients (Schoenfeld et al., 2016). In contrast, a systematic review and meta-analysis by Li et al. investigated the anti-inflammatory effects of statins in RA patients and found no significant differences in serum total cholesterol levels between conventionally-treated and atorvastatin-treated patients. In a pooled analysis, atorvastatin use was associated with an increase in plasma HDL-c, as well as a decrease in plasma LDL-c and TGs. Additionally, plasma CRP, values of the ESR, and RA disease activity (as scored based on the DAS28 index), also improved following the use of atorvastatin. Interestingly, when comparing simvastatin with atorvastatin, the anti-inflammatory effects were superior in patients that used atorvastatin (G.-m. Li et al., 2018).

4.4. Hashimoto's thyroiditis

Hashimoto's thyroiditis, a cell and antibody-dependent autoimmune disease of the follicular thyroid cells, is the most common cause for hypothyroidism (Caturegli, Kimura, Rocchi, & Rose, 2007; Hiromatsu, Satoh, & Amino, 2013).

Gullu et al. reported that in patients using simvastatin, serum levels of free triiodothyronine and free thyroxine increase and Thyroid Stimulating Hormone (TSH) levels decrease. Statins can have an effect on circulating immune cells resulting in significantly decreased T CD8+ and NK cell populations, as well as increased T CD4+ and B-lymphocytes (Gullu, Emral, Bastemir, Parkes, & Lazarus, 2005). Women with Hashimoto's disease were included in a study by Krysiak et al., which compared the effects of high-dose statin *vs.* low-dose statin + ezetimibe. The combination therapy was associated with an increase in anti-thyroid peroxidase and titers of anti-thyroglobulin antibodies. However, high-dose statin therapy showed a greater effect on the reduction of thyroid autoimmunity markers when compared to regimen involving combination therapy (low-dose statin + ezetimibe) (Krysiak, Kowalcze, & Okopień, 2016). In a different case-controlled study by Krysiak et al., the effects of a statin combined with selenium were evaluated in women with Hashimoto's thyroiditis. Patients were treated with either 200 μg seleno-methionine + atorvastatin (40 mg/day), or placebo, for six months. Serum titers of thyroid peroxidase (TPOAb) and thyroglobulin (TgAb) antibodies were significantly decreased in the seleno-methionine + atorvastatin-treated group compared to the control (placebo) group (Krysiak, Szkróbka, & Okopień, 2019).

4.5. Psoriasis

Psoriasis is regarded as not only a chronic inflammatory skin disorder, but also an immunometabolic systemic disease in which dyslipidemia is a frequent comorbidity. Naseri and colleagues used topical betamethasone with/without oral simvastatin for psoriatic patients in a randomized, double-blind, and placebo-controlled clinical trial. They reported that betamethasone plus 40 mg/day of simvastatin for 8 weeks significantly improved the Psoriasis Area and Severity Index (PASI) scores in comparison with betamethasone alone. They also showed that simvastatin increased the therapeutic effects of topical steroids in the treatment of psoriasis without any side effects (Naseri, Hadipour, Sepaskhah, & Namazi, 2010). In a different study, Vasiuk et al. evaluated the efficacy and safety of atorvastatin (20 mg/day) when compared to standard therapy in psoriatic patients with arterial hypertension (AH), and demonstrated that statin therapy for a 6-month period significantly improved PASI scores and quality-of-life indices. Also, TNF-α and hsCRP (as inflammatory biomarkers) were significantly reduced at the end of the third week and persisted for 6 months (Vasiuk Iu, Perlamutrov Iu, Shkol'nik, & Shkolnik, 2010). Additionally, Trong et al. reported that treatment with oral simvastatin (40 mg/day) in combination with topical calcipotriol/betamethasone dipropionate for 8 weeks decreased PASI scores and suggested that it may represent an effective treatment for both the control of dyslipidemia and improvement in the disease conditions (Trong et al., 2019).

On the other hand, Faghihi and colleagues reported no significant difference between topical therapy (emollients, keratolytics, and/or class V corticosteroids) with/without oral atorvastatin (40 mg/day) for 12 weeks in patients with acute or chronic plaque-type psoriasis; that is, oral atorvastatin was not associated with therapeutic benefit when given to patients with baseline PASI scores less than 12 who were also treated with standard topical therapies (Faghihi, Radfar, Mehrabian, Ehsani, & Rezaei Hemami, 2011). A similar finding was also shown by Chua et al. in a study in which atorvastatin (40 mg/day) was used as an adjuvant therapy with betamethasone valerate in plaque-type psoriatic patients. Despite greater numerical improvements in PASI and dermatology life quality index (DLQ1) scores, as well as serum hs-CRP levels, the differences did not reach statistical significance when compared with betamethasone monotherapy (Chua et al., 2017).

Socha et al. conducted a meta-analysis of clinical trials with a minimum treatment period of 8 weeks in psoriasis patients >16 years of age. It was concluded that the improvement in PASI scores was greater in the patients who received statins, with subgroup analyses suggesting significant and non-significant results for simvastatin and atorvastatin, respectively, when each was compared to the control group (Socha et al., 2020).

Despite the positive effects of statin therapy in psoriatic patients, Salna and colleagues reported a case with bilateral erythematosus plaques on the extensor surfaces of arms as a result of long-term pravastatin therapy. These lesions were diagnosed as statin-induced eczematous dermatitis and discontinuation of the statin led to the gradual resolution of the symptoms (Salna, Singer, & Dana, 2017).

4.6. Antiphospholipid syndrome (APS)

Statins also have a key role in APS due to their anti-thrombotic and anti-inflammatory effects. Jajoria and colleagues reported that fluvastatin therapy (40 mg/day for a 1-month period) significantly reduced thrombotic and inflammatory markers such as VEGF, serum tissue factor (sTF), and TNF-α (Jajoria et al., 2009). Additionally, Lopez-Pedrera et al. demonstrated that 20 mg/day of fluvastatin for 1 month

in APS patients with thrombosis significantly inhibited TF, protein activator receptors 1 and 2, VEGF, and Flt1 expression that was related to the inhibition of p38 MAPK and NFκB/Rel DNA-binding activity (Lopez-Pedrera et al., 2011). The results from this study suggest that fluvastatin has multiple profound effects on monocyte activity and may potentially represent a new therapeutic strategy to prevent thrombosis in APS patients.

Statins are contraindicated in pregnancy due to the results of various animal studies in the late 1980s and the early 1990s. A case report was published on a VACTERAL (vertebral anomalies, anorectal malformations, cardiovascular malformations, tracheoesophageal fistula, esophageal atresia, renal anomalies, and limb deformities)-associated born child in 1992 that had in utero-exposure to lovastatin (Dostal, Schardein, & Anderson, 1994; Ghidini, Sicherer, & Willner, 1992; Maierean et al., 2018; Minsker, MacDonald, Robertson, & Bokelman, 1983). The systematic review of Karalis et al. showed no obvious association between statin exposure and congenital anomalies in pregnancy. The dose of statins used in the mentioned animal studies were significantly higher when compared to statin dosages used in humans (Karalis, Hill, Clifton, & Wild, 2016). The benefits of statin use in pregnant women have been reported as well. In pregnant women with a high risk of developing preeclampsia, statins can protect pregnant women and fetuses from serious and life-threatening complications. Of note, in studies where pregnant women with, or at-risk for, preeclampsia were treated, statins were started after the 1st trimester with the aim of avoiding teratogenic effects during the early, most vulnerable phase of fetal development (Costantine & Cleary, 2013; Marrs & Costantine, 2017). Ming-Sum et al. investigated the association between statin exposure during first trimester of pregnancy and fetal ventricular septal defect in a cohort study of 379,238 pregnancies. They showed that congenital cardiac anomalies were reported in 5% of statin-exposed pregnancies and 1.4% of non-exposed cases and confirmed that statin exposure during the first trimester of pregnancy is associated with teratogenic events (M. S. Lee, Hekimian, Doctorian, & Duan, 2018).

Lefkou et al. investigated the efficacy of pravastatin (20 mg/day) in combination with low-dose aspirin (LDA) plus low molecular weight heparin (LMWH) in refractory APS patients with a strong medical history of multiple pregnancies with preeclampsia (PE) and/or intrauterine growth restriction (IUGR) during treatment with LDA+LMWH and were at risk of adverse pregnancy outcomes. Increased placental blood flow and improvement in PE features were reported in the first 10 days after pravastatin therapy, which was associated with live births that occurred at near-term in all the women that received pravastatin. This was in sharp contrast with the control group. Only six of the 11 neonates survived, and of those six, three showed abnormal development. These results suggested that pravastatin could improve the outcome of pregnancy in women with refractory obstetric APS (Lefkou et al., 2016).

4.7. Other rheumatic and vasculitis disorders

4.7.1. Systemic Scleroderma (SSc)

In SSc, the microvasculature is targeted and severely affected. Clinical features of SSc are intimal proliferation, medial thinning, and adventitial fibrosis of the microvascular system, which ultimately leads to vascular obliteration. Pivotal in the aggressive disease progression is the activation of the immune system, which triggers the autoimmune-mediated destruction of small blood vessels (Abou-Raya, Abou-Raya, & Helmii, 2007). Furukawa et al. studied the effects of 10 mg pravastatin for 8 weeks on activation/injury markers of endothelial cells, as well as its effect on coagulation biomarkers. This treatment resulted in a reduced activity of plasma Von Willebrand factor (vWF) and inhibition of the thrombin-anti-thrombin complex (TAT) (Furukawa et al., 2006). In a second study that included SSc patients with secondary Raynaud's disease, the effects of 40 mg/day of atorvastatin over a 4-month treatment period was evaluated. Patients using atorvastatin had not only improved SSc-related biomarkers, but also indicated that they felt better overall. Moreover, their Scleroderma Health Assessment Questionnaire Disability Index (SHAQ-DI) indicated a better score. Inflammatory biomarkers such IL-6, TNF-α, ESR, hs-CRP, as well as endothelial activation markers including ICAM-1, sE-selectin, ET-1, and MCP all significantly improved. In addition to improvement in both inflammatory and endothelial activation biomarkers, there was also significant improvement in oxidative stress markers such as LP, MDA, vWF, and fibrinogen activity. Furthermore, FMD, which reflects vascular endothelial function, also significantly increased during treatment (Abou-Raya, Abou-Raya, & Helmii, 2008). . In a study by Abou-Raya et al., a similar finding was noted for SSc patients treated with 40 mg/day of atorvastatin for six months. The SSc patients in the study by Abou-Raya et al. experienced a significant improvement in their endothelial function. The atorvastatin-treated patients had decreased levels of endothelial activation markers including ET-1, ICAM-1, sE-selectin, vWF, fibrinogen, ESR, hs-CRP, and malondialdehyde (MDA), as well as a reduction in endothelium-dependent vasodilation (EDV), when these same parameters were compared to corresponding values for patients that received a placebo. Additionally, these same authors found that the SSc patients treated with atorvastatin for 6 months exhibited a decrease in ROS production and an increase in NO levels when compared to the same parameters in patients that received a placebo (Abou-Raya, et al., 2008). Recently, Goncalves et al. demonstrated that simvastatin had a dose-dependent immunosuppressive effect on PBMCs in SSc patients. In this study, patients using simvastatin showed a reduction in cytokine release in T-cell subsets (IL-2, IL-4, IL-6, IL-10, TNF-α, IFN-γ, IL-17A, and IL-17F) (Gonçalves et al., 2019).

4.7.2. Behcet's Disease (BD)

Behcet's disease is a chronic systemic vasculitis of unknown etiology that is associated with recurrent muco-cutaneous manifestations, as well as chronic uveitis. This disease may also cause vascular aneurysms throughout any segment of the arterial tree in addition to thrombophlebitis of the superficial veins (Tremoulet, 2015). A randomized, double-blind, placebo-controlled trial in Behcet's patients by Inanc et al. evaluated the effect of atorvastatin therapy for three months. In patients that were administered atorvastatin, endothelial function was improved when compared to patients in the placebo group, but no significant difference in CRP, fibrinogen plasma concentrations, or ESR were observed between the two treatment arms (Inanc et al., 2010).

4.7.3. Kawasaki Disease (KD)

KD is a self-limiting vasculitis of unknown etiology and is the most common cause of acquired heart disease in children. In a recently published case study, a 40-year-old man with a history of KD and large aneurysm of the left coronary artery was treated with pitavastatin for two years. The pitavastatin therapy was associated with reduced coronary artery inflammation (Suda et al., 2015). Another study, this time including children aged 2-10 years with median to giant coronary aneurysms detected at least one year after the onset of disease, were treated with pravastatin to determine whether there would be an improvement in endothelial function and biomarkers associated with inflammation. Six months of pravastatin therapy was associated with significantly improved endothelial function, as well as reduced plasma CRP levels (Duan, Du, Wang, & Jia, 2014).

4.7.4. Takayasu Arteritis (TA)

TA is a chronic inflammatory disease of the vasculature characterized by severe vasculitis, which primarily affects the aorta and its main branches. Statins can improve endothelial function by increasing endothelial NO production, which is considered essential for proper vascular structure and function. Thus, based on this property, it has been suggested that statins could potentially benefit patients with vasculitis (Mason, Walter, & Jacob, 2004). Evidence suggests that the anti-inflammatory role of statins is related to mitigating the endothelial inflammatory response, as well as a systemic inhibitory effect on cellular

immunity. Statins mediate a reduction in the secretion of IL-2, IL-12, and IL-17 in addition to inhibiting both Th1 and Th17 responses. In fact, these two processes appear to play a key role in triggering large-vessel vasculitis (Greenwood & Mason, 2007). Kwon et al. examined the clinical benefits of statins in TA patients, and showed a significant decrease in the relapse rates of patients suffering from TA (Kwon et al., 2019).

5. Autoimmune side effects of statin therapy

Statins are generally recognized as safe and well-tolerated drugs with acceptable side-effect profiles. The most commonly reported side-effect with statin therapy is statin-associated muscle symptoms (SAMSs). The majority of these patients recover spontaneously after discontinuation of the statin treatment (Echaniz-Laguna, Mohr, & Tranchant, 2010; Mammen, 2016; Thompson, Panza, Zaleski, & Taylor, 2016). SAMSs are non-specific and vary widely in frequency and severity from mild myalgia to potentially fatal rhabdomyolysis, frequently occurring in the first month after initiation of treatment or dose intensification. Fortunately, SAMSs typically disappear within weeks after discontinuation of the statin. The mechanism of muscle toxicity is complex and only partly understood. SAMSs may be related to an increased plasma concentration and subsequent exposure of the statin, or its active metabolites, to muscle cells. Processes related to an increase in statin plasma concentrations and subsequent muscle cell toxicity are impaired hepatic metabolism, drug-drug interactions, factors associated with genetic predisposition, and muscle fragility (Gale & Danesh-Meyer, 2014; Kearney, Carr, McConville, & McCarron, 2012; Radcliffe & Campbell, 2008; Tournadre, 2019). The risk of statin-related fatal rhabdomyolysis is extremely low, and has been estimated to be < 1-2:1,000,000. The process of rhabdomyolysis is caused by drug-mediated destruction of muscle tissue, which leads to a massive release of creatine kinase and myoglobin into the bloodstream and results in serious damage to the kidneys and, ultimately, renal failure (Gilbert, Al-Janabi, Tomkins-Netzer, & Lightman, 2017).

Autoimmune myopathy is characterized by muscle weakness, evidence of muscle cell necrosis upon biopsy, and the presence of autoantibodies against HMG-CoA reductase. Unlike most patients with side-effects during statin therapy, patients with statin-associated autoimmune myopathy may have progressive weakness that needs to be controlled by immunosuppressive drug therapy. This is a rare side-effect of statin administration that does not have a well-accepted rate of incidence, but it has been estimated to occur in 2-3/100,000 statin-treated patients (Mammen, 2016). Diagnosis is generally based on proximal symmetric weakness of the large arm and leg muscles and increased creatine kinase levels, which reach 2000 IU/L in about 90% of cases (approximately 10-15 times greater than the normal range of 0-150 IU/L) (Mammen et al., 2011). Auto-antibodies against the HMG-CoA reductase enzyme are the hallmark of necrotizing myopathy, and are less frequently observed in patients with other musculoskeletal conditions associated with statin exposure (Allenbach et al., 2014; Alshehri, Choksi, Bucelli, & Pestronk, 2015; Klein et al., 2015; Mammen et al., 2011; Watanabe et al., 2015). It is not known why patients begin developing antibodies against HMG-CoA reductase and cases have been described without statin exposure. Most patients with statin-associated autoimmune myositis do not improve after statin discontinuation and will require treatment (oftentimes for years) with immunosuppressant agents including corticosteroids (Limaye et al., 2015; Needham et al., 2007). Borges et al. reported statin-induced dermatomyositis (DM) and polymyositis (PM) in a case series and literature review. Both DM and PM are systemic autoimmune myopathies and, in the case of DM, there is also cutaneous involvement (Borges, Silva, Misse, & Shinjo, 2018). In a retrospective cohort analysis, the use of statins, in patients with stable SAM, was reported to be safe and did not lead to clinical intercurrences, while the lipid profiles improved (Borges & Shinjo, 2019).

A less common side-effect of statins is the development, or exacerbation of, myasthenia gravis, an autoimmune disease that is often caused by autoantibodies against acetylcholine receptors (AchR) in the neuromuscular junction. Myasthenia gravis patients may experience exacerbation of symptoms during statin therapy that could be related to statins (Oh et al., 2008). Gale et al. demonstrated that there was a nearly 4-week temporal relationship between the initiation of statin therapy and the onset of seropositive ocular myasthenia. Thus, it has been hypothesized that the immunomodulatory effects of statins could potentially induce new autoantibody-dependent diseases. The suggested underlying mechanism for this hypothesis is the direct effect of statins to modulate T-cell function from the Th1 to the Th2 phenotype (Gale & Danesh-Meyer, 2014). This shift in the immune response can abolish immune homeostasis, leading to insufficient self-tolerance and induction of autoimmunity (Noel, 2007; Youssef et al., 2002). In addition, statins are potential pro-apoptotic agents that may initiate or exacerbate cellular apoptosis, which leads to release of intracellular antigens that may accelerate the production of pathogenic autoantibodies (de Jong et al., 2018).

6. Conclusion

The studies discussed in this review provide evidence that statin therapy has effects beyond lipid lowering. They suggest that statins could be used as complementary therapy in immune-mediated diseases due to their anti-inflammatory and immunomodulatory features. Statin therapy has beenshown to be efficient in reducing DAS28 scores in RA patients and, in addition, they have been shown to improve endothelial function and reduce the risk of cardiovascular disease, as well as exhibit promising therapeutic benefits in other autoimmune conditions including SLE, MS, and other less-common autoimmune-related diseases. Their promise in autoimmune conditions appears to result from improvement in the inflammatory cytokine profiles and clinical parameters, such as CRP and ESR, associated with these diseases. What remains enigmatic are the underlying mechanism(s) and the precise doses required for statins to exert immunomodulatory effects, as well as those doses that trigger a statin-mediated autoimmune response as a side effect of statin therapy. These concerns represent very important clinical issues that warrant further research.

Declaration of Competing Interests

MB has served on the speaker's bureau and as an advisory board member for Amgen, Sanofi, Aventis and Lilly. NK has given talks, attended conferences and participated in trials sponsored by Amgen, Angelini, Astra Zeneca, Boehringer Ingelheim, Galenica, MSD, Novartis, Novo Nordisk, Sanofi and WinMedica. PL has received honoraria for consulting and speaker activities from Aegerion, Amgen, Astra Zeneca, Ferer Incode, Fresenius, Kaneka, Merck Sharp & Dohme, Pfizer and Sanofi-Regeneron. KAR received a research grant from Sanofi, and served on the speaker's bureau and as an advisory board member for Sanofi, Astra Zeneca and Pfizer. Other authors have no competing interests to disclose.

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