Pharmacological Research 87 (2014) 133–143

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Review

Role of statins in the treatment of multiple sclerosis

Rosella Ciurleo[a,*], Placido Bramanti[a], Silvia Marino[a,b]

[a] IRCCS Centro Neurolesi "Bonino-Pulejo", Messina, Italy
[b] Department of Biomedical Sciences and Morphological and Functional Imaging, University of Messina, Messina, Italy

ARTICLE INFO

Article history:
Received 20 January 2014
Received in revised form 10 March 2014
Accepted 11 March 2014
Available online 20 March 2014

Chemical compounds studied in this article:
Atorvastatin (PubChem CID: 60823)
Lovastatin (PubChem CID: 53232)
Simvastatin (PubChem CID: 54454)

Keywords:
Combination therapy
Immunomodulatory effect
Multiple sclerosis
Neuroprotection
Randomized clinical trial
Statins

ABSTRACT

Statins as inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase are widely prescribed for hypercholesterolemia treatment. In the last years, statins have also been shown to exert immunomodulatory and anti-inflammatory effects which appear to be related to inhibition of isoprenylation of small GTP-binding proteins and, at least in part, independent of their cholesterol-lowering effects. These "pleiotropic" effects make statins an attractive treatment option for immune-mediated disorders such as multiple sclerosis. Studies in vitro and in experimental autoimmune encephalomyelitis animal model seem to support not only the efficacy of statins as immunomodulatory agents but also their potential neuroprotective properties, although the exact mechanism with which statins exert these effects has not yet been fully understood. The immunomodulatory, anti-inflammatory and neuroprotective properties of statins provided the incentive for several clinical trials in multiple sclerosis, in which they were tested not only as mono-therapy but also in combination with interferon-β. However, the attempt to translate the results of animal model studies in humans produced conflicting results. Further large, prospective, randomized, double-blind, placebo-controlled trials, designed to evaluate the long-term effects of statins alone or in add-on to other disease-modifying therapies, are needed to support their routine clinical use in multiple sclerosis.

Contents

Abbreviations: APC, antigen-presenting cell; ARR, annualized rate of relapse; BBB, blood–brain barrier; CNS, central nervous system; DC, dendritic cell; DMT, disease-modifying therapy; EAE, experimental autoimmune encephalomyelitis; FPP, farsenyl pyrophosphate; GA, glatiramer acetate; GEL, gadolinium-enhancing lesions; GGPP, geranyl–geranyl pyrophosphate; GTP, guanosine triphosphate; HLA-II, human leucocyte antigen class II; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; ICAM-1, intracellular adhesion molecule 1; IFN-β, interferon-β; IFN-γ, interferon-γ; IL, interleukin; LFA-1, lymphocyte function-associated antigen 1; MHC, major histocompatibility complex; MMP, matrix metalloproteinase; MS, multiple sclerosis; NF-kB, nuclear factor-kB; NO, nitric oxide; ODC, oligodendrocyte; PPAR, peroxisome proliferator-activated receptor; ROS, reactive oxygen species; RR, relapsing–remitting; SOCS, suppressor of cytokine signalling; STAT, signal transducer and activator of transcription; T-bet, T-box expressed; TGF-β, transforming growth factor; Th, helper T; TLR, toll-like receptor; TNF-α, tumour necrosis factor α; Treg, regulatory T; VCAM-1, vascular cell adhesion molecule 1; VLA-4, very late activation antigen-4.

* Corresponding author at: IRCCS Centro Neurolesi "Bonino-Pulejo", Via Palermo S.S. 113, C.da Casazza, 98124 Messina, Italy. Tel.: +39 090 60128960; fax: +39 090 60128850.
E-mail address: rciurleo@libero.it (R. Ciurleo).

http://dx.doi.org/10.1016/j.phrs.2014.03.004
1043-6618/

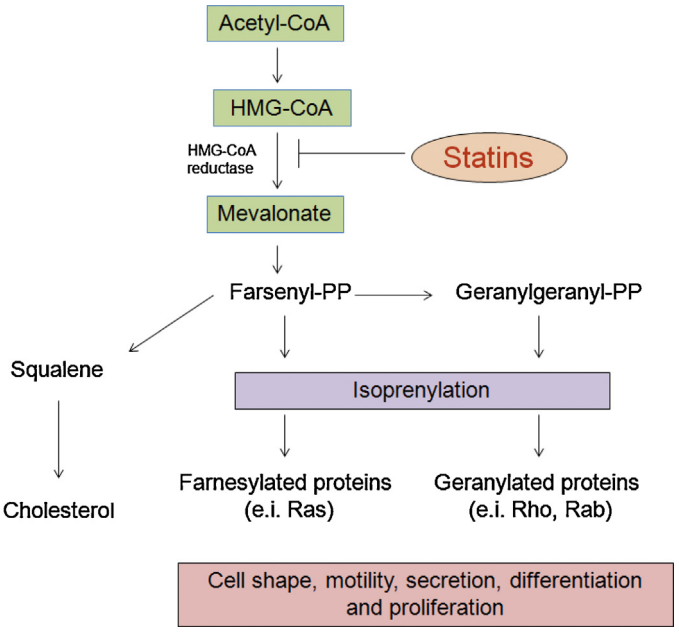

Fig. 1. Cholesterol biosynthesis and protein isoprenylation. Farsenyl pyrophosphate and geranylgeranyl pyrophosphate serve as lipid attachments for a number of intracellular signalling molecules including the GTP-binding proteins, such as Ras, Rho and Rab. This isoprenylation permits activation and membrane translocation of these proteins, which are decisive for a variety of cellular functions, such as cell shape, secretion, differentiation, motility and proliferation. The inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase by statins leads to decreased production not only of cholesterol but also of isoprenoid metabolites and then prevents the activation of regulatory proteins. Abbreviations: HMG, 3-hydroxy-3-methylglutaryl; PP, pyrophosphate.

1. Introduction

Statins are potent inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the enzyme that catalyzes the conversion of HMG-CoA to L-mevalonate, an intermediate necessary for the biosynthesis of cholesterol (Fig. 1) [1].

Because of their ability to inhibit the cholesterol biosynthesis, statins are widely prescribed as therapy for hypercholesterolemia. In addition, statins have been shown to reduce risk of coronary artery disease and cardiovascular morbidity and mortality in patients with and without coronary heart disease [2,3]. The statin family comprises lovastatin, mevastatin, pravastatin and simvastatin, which are fungal derivatives, and fluvastatin, atorvastatin, cerivastatin, pitavastatin and rosuvastatin, which are synthetic compounds (Fig. 2). These therapeutic agents have different lipophilicity, half-life and potency, are administered orally and have good safety profile. The ability of statins to inhibit HMG-CoA reductase leads to a decrease in the production not only of cholesterol but also of isoprenoid metabolites such as farsenyl pyrophosphate (FPP) and geranyl–geranyl pyrophosphate (GGPP) (Fig. 1). GGPP and FPP serve as lipid attachments for a number of intracellular signalling molecules including the guanosine triphosphate (GTP)-binding proteins Ras, Rab and Rho. This lipid attachment, termed isoprenylation, permits activation and membrane translocation of these proteins, which have a crucial role in a variety of cellular functions, such as cell shape, secretion, differentiation, motility and proliferation [4]. The inhibition of isoprenylation leads to accumulation of inactive GTP-binding proteins in the cytosol and prevents thus the cellular functions of various cell types, including cells of immune system.

Statins have been shown to exhibit pleiotropic immunomodulatory and anti-inflammatory effects, which make them promising candidates for the future treatment of immune-mediated disorders such as multiple sclerosis (MS). MS is a multifactorial, complex, chronic, inflammatory, immune-mediated disorder of the central nervous system (CNS), which induces disability in young adults [5]. Although the exact mechanism underlying the disease has not yet been fully understood, the pathological hallmarks of MS lesions include immune-mediated inflammation, oxidative stress, excitotoxicity, demyelination, axonal degeneration and neuronal loss. The aetiology of MS remains unknown. However, environmental factors in genetically susceptible individuals are accountable for the direct involvement of the immune system in the destruction of myelin and neuronal death. Increasing knowledge about MS immunopathogenesis has given rise to a number of new potential therapeutic targets, which interact with the immunological system on several levels. Currently available disease-modifying therapies (DMTs) for MS include interferon-β (IFN-β), glatiramer acetate (GA), natalizumab, mitoxantrone and fingolimod. Moreover, a number of DMTs for MS, including oral agents, are in advanced development (in phase II and phase III clinical trials) and likely to be available soon [6]. Although the first-line therapies, IFN-β and GA, are well tolerated, they are only partially effective in preventing relapse rate and long-term disability. The second-line therapies, mitoxantrone and natalizumab, are administered by intravenous infusion and have greater efficacy, but they are not free from severe side effects. Oral fingolimod has recently been approved as the first oral DMT for MS. Although fingolimod offers patients a convenient alternative to regular self-injection, it is associated with severe side effects, such as bradycardia and atrioventricular block at treatment initiation, macular oedema, serious infections, skin cancer and asymptomatic elevations of liver enzymes. Therefore, more effective immunomodulatory and neuroprotective agents, with good bioavailability and favourable safety profile, are required. Oral statins are an attractive opportunity for MS treatment because they have immunomodulatory and anti-inflammatory effects and a favourable safety profile, and offer a high level of compliance with treatment.

Starting from immunopathogenesis of MS, we will provide a comprehensive overview of recent evidence on the possible molecular mechanisms responsible for immunomodulatory activity of statins along with the results obtained from clinical trials, in which statins were tested not only as mono-therapy for MS but also in combination with IFN-β. Furthermore, the possible neuroprotective effects of statins will be discussed.

2. Immunopathogenesis of multiple sclerosis

The complex inflammatory aetiology of MS involves resident CNS innate cells as well as invading adaptive immune cells (Fig. 3). Processes such as molecular mimicry, where T cells respond to environmental antigens which resemble self-antigens, could be a potential mechanism by which these cells get activated [7]. Studies in the experimental autoimmune encephalomyelitis (EAE) animal model have contributed to the understanding of processes that initiate altered immune response [8]. In EAE, induced by immunizing animals with myelin-derived proteins, the inflammatory demyelination is driven by myelin-specific $CD4^+$ T cells. Antigen-presenting cells (APCs), such as dendritic cells (DCs) and B cells, play a critical role in the initiation of MS. In particular, DCs can modulate innate and adaptive immune responses [9]. In the peripheral lymphoid tissue, immature DCs capture antigens for processing and presentation to naïve T cells. They acquire a mature phenotype expressing on surface the class 2 molecules of the major histocompatibility complex (MHC-II).

This process is important for efficient T cell activation. Moreover, a second signal, called co-stimulatory signal, is also required for T-cell activation. Antigen-activated T cells express CD40