Journal of Controlled Release 215 (2015) 12–24

Contents lists available at ScienceDirect

Journal of Controlled Release

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

Review article

Potential mechanisms and applications of statins on osteogenesis: Current modalities, conflicts and future directions

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ARTICLE INFO

Article history:
Received 18 April 2015
Received in revised form 19 July 2015
Accepted 20 July 2015
Available online 28 July 2015

Keywords:
Statin
Bone healing
Routes of administration
Drug delivery systems
Anabolic mechanism

ABSTRACT

Statins are known for their beneficial effects on cardiovascular diseases. Besides the lipid-lowering properties, statins exert their anabolic effects on the bone by differentiating mesenchymal cells to osteoblasts via upregulating BMP-2 and protecting osteoblasts from apoptosis. In addition, statins have been suggested to be anti-osteoclastic by reducing the osteoclast differentiation and activity. Several in vivo and clinical studies have confirmed the beneficial effects of statins in the treatment of osteoporosis and fracture injuries. However, controversial results exist showing statins may have no benefit and in some instances, they may retard bone repair. Different factors such as type, route of administration, dose and dosage of statins, and the injury model seem to be involved for such controversies. In the present study, the most important issues regarding statins have been reviewed to find out how statins may be beneficial and statin therapy can be improved for treating osteoporosis and fracture injuries. The lipophilic statins particularly simvastatin and atorvastatin are the most investigated statins with beneficial results on bone healing and turnover. Most of the in vivo and clinical studies performed systemic route of administration for treating osteoporosis, with much higher clinical doses than the lipid lowering therapy, which increases the statin related side and out of target effects. In contrast, most of the in vivo studies that used statins for fracture repair have applied local delivery methods with much lower doses via tissue engineering approaches. However, local delivery of statins and statin therapy for fracture repair both have low application in the clinical setting and such methods are still under in vivo investigation. Future clinical trials are needed to elucidate how delivery systems and tissue engineering technologies are able to improve the outcome of statin therapy.

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http://dx.doi.org/10.1016/j.jconrel.2015.07.022
0168-3659/

1. Introduction

Osteoporosis, osteoporosis related fractures and large bone defects (LBDs) are the current problems in orthopedic research [1–7]. In a normal bone, there is a balance between new bone formation (NBF) and osteoclastic reaction (OR) which is responsible for bone health and mechanical properties [1,5,8]. In osteoporotic patients, such balance is altered; thus the biomechanical and morphological features of such bone are significantly altered which result in bone weakening and fracture injuries [1,3,4]. After the occurrence of vehicle traumas, high energy traumas, comminuted-, compound-, multiple- and complicated fractures, bone tumors, burns, osteonecrosis, osteomyelitis and osteoporosis related fractures, it is often necessary to remove the damaged bony segment/s and stabilize the remaining bone [6]. If large amounts of injured bony segment/s are removed, then this may produce LBD. If LBDs were left untreated, then delayed union, malunion, non-union and osteomyelitis may develop [5,7,9]. Prevention, management and treatment of such diseases and injuries are challenging [6]. Although many surgical and pharmaceutical options are available, because healing of the injured bone is a multifactorial process, treatment of such diseases is a state of art [5].

As a general rule, medium to large sized bone defects must be reconstructed with classic grafts (fresh and or processed auto- and allografts) or bone graft substitutes (BGSs) [5,6,10]. Classic grafts have significant limitations and tissue engineered BGSs (e.g. acellularized or demineralized bone matrices, scaffolds, hydrogels) are newer alternative options that are increasingly used for such reconstructions [11,12]. Although the BGSs have acceptable osteoconduction properties, they have no or low ability for osteoinduction and osteogenesis. In addition, they have no ability to protect the new bone from osteoclastogenesis which has occurred as a result of osteoporosis and/or remodeling phase of bone healing [6]. Thus the bone healing process in response to BGS implantation should be protected and modulated. Poly therapy by means of systemic or local application of healing promotive factors (HPFs) in combination with BGS implantation at the injured site is the most useful option [5].

Different HPFs have been used for enhancing the behavior of the implanted BGSs and for preventing and treating osteoporosis [5,10,13]. Bisphosphonates such as alendronate and risedronate having strong anti-osteoclastogenic activity are currently used in the clinical setting. However, bisphosphonates have low ability to induce osteogenesis, they have long term and serious side effects and their local delivery through BGSs is under development and investigation [14–16]. Strontium salts, particularly the strontium ranelate (SR), have dual mode of action so that they have both osteogenic and anti-osteoclastogenic effects. Although SR has been used in the clinical patients, its application has been restricted now, due to its serious side effects [17–19].

Statins, 3-hydroxy 3-methyl glutaril coenzyme A (HMG-CoA) reductase inhibitors, were first developed to control and treat patients with hyperlipidemia and hypercholesterolemia [20]. In 1999, statins were found to have osteogenic effects which may be beneficial for osteoporotic patients [6,20,21]. To date, we know much more about statins than before. Since the discovery of statins, it has been shown that statins not only are beneficial for managing osteoporosis but also they are strong modulators of bone healing responses [4,22–25]. Based on the recent investigations, statins have the ability to modulate inflammation, enhance osteoinduction, osteogenesis and angiogenesis, and inhibit osteoblast apoptosis and osteoclastogenesis [6,20,26–39]. Therefore, statins have multi beneficial actions on bone repair by different mechanisms [6]. However, statins have many side- and out of target effects and some controversies between the studies exist showing statins may not be useful or may be harmful in bone healing [15,40–50].

Given the above explanations, in this review we summarized the most important statin related osteogenic and antiosteoclastogenic mechanisms and compared the differences between the in vivo and clinical investigations to find out a suitable answer for the controversial results. The side effects of statins have also been illustrated for the readers to have better conclusions regarding statin therapy. Finally, we discussed about the role of tissue engineering and regenerative medicine (TERM) approaches on statin delivery in bone healing and have illustrated the prospective and directions for the future of statin related researches.

2. The most important issues on statin therapy

2.1. Pleiotropic effects of statins and their action on reducing the lipid content

Statins, HMG-CoA reductase inhibitors, are principal therapeutic agents in lowering blood cholesterol [51,52]. In 1971, Akira Endo and his team began the search for a cholesterol-lowering drug and identified mevastatin, a molecule produced by the fungus *Penicillium citrinum*, as the first agent of statins [53]. In 1987, for the first time, physicians were able to obtain comparatively large reductions in plasma cholesterol level with very few adverse effects by introducing lovastatin [53]. Some of the statins have been produced by fermentation product of certain fungi; these include lovastatin (Mevacor), pravastatin (Lipostat, Pravachol) and simvastatin (Zocor). Other statins such as fluvastatin (Lescol), atorvastatin (Lipitor, Sortis) and cerivastatin (Lipobay, Baycol) are manufactured by chemical synthesis [54,55]. Hepatocytes are the major target for statin drugs where they inhibit HMG-CoA reductase enzyme. Statins not only compete with the substrate in enzyme active site, but also they induce a conformational change in the enzyme's structure [56]. In addition, a series of processes leading to increased synthesis of NO by endothelial cells, reduction of cholesterol accumulation in macrophages, regression of atherosclerotic plaque, inflammatory process, inhibition of the platelet aggregation, alteration in intracellular calcium homeostasis and inhibition of tumor cells growth is all modulated by statins [57]. Moreover, geranylgeranyl pyrophosphate (GGPP), estrogen receptor (ER), farnesyl pyrophosphate (FPP) and Ras participate in endogenous cholesterol synthesis and play important roles in bone anabolic process that may be regulated by statins [58] (Fig. 1).

2.2. Off-target effects and related adverse events of statins

As the most reported problem in patients, the musculoskeletal adverse effects of statins such as rhabdomyolysis, inflammatory myopathies,