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Simvastatin, dosage and delivery system for supporting bone regeneration, an update review

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ABSTRACT

Objective: The purpose of this review is to discuss the dosage, duration and carrier for simvastatin, and to summarize effects of topical application directly or indirectly for stimulating bone regeneration.
Methods: We have searched in Pubmed using keywords, simvastatin, dose response, bone regeneration, controlled-release delivery system. This search was complemented with a manual search of the relevant articles cited among the selected papers. The search was among the articles written in English and published in the last 10 years. The articles were revised in depth, and summarized.
Results: High dose of simvastatin increases bone formation and resorption, while low dose of simvastatin decreases bone formation and increases bone resorption, furthermore it is reported that high dose of systemic administration of simvastatin will raise the risk of liver failure, kidney disease, and other side effects. Local administration can bypass hepatic degradation of statins to achieve therapeutic concentrations in bone and avoid the systemic side effects. The choice of appropriate carrier will depend on the release kinetics determined to be the best for osteogenesis.
Conclusion: Local delivery of simvastatin from carriers appears to be an attractive solution to the problem of maintaining therapeutic doses to treat severe bone defects and to minimize the undesired side effects. Locally delivered simvastatin can increase the bone formation and accelerate healing process of bony defect. Another advantage of local delivery system is that it can stimulate new bone formation in a dose-dependent manner. Further evidence-based studies will be required to determine local delivery concentrations to promote bone regeneration.

Contents

☆ Asian AOMS: Asian Association of Oral and Maxillofacial Surgeons; ASOMP: Asian Society of Oral and Maxillofacial Pathology; JSOP: Japanese Society of Oral Pathology; JSOMS: Japanese Society of Oral and Maxillofacial Surgeons; JSOM: Japanese Society of Oral Medicine; JAMI: Japanese Academy of Maxillofacial Implants.

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1. Introduction

3-Hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors are synthetic statins [1]. Simvastatin is lipophilic statin derived from fungal metabolites and have elimination half-live of 1–3 h. Lipophilic statins are more susceptible to metabolism by the cytochrome *P* (450) system. Pravastatin and rosuvastatin are relatively hydrophilic and not significantly metabolized by cytochrome *P* (450) enzymes. The chemical structure of simvastatin governs its water solubility, which in turn influence its absorption, distribution, metabolism, and excretion. It is not well absorbed, and less than 5% of an oral dose reaches the systemic circulation [2].

Acquired bone defects from simple tooth extractions to tumor resections appear daily in our practices and present difficult reconstructive treatment plans. The gold standard in treatment of bone defect is autogenous bone graft, but it is associated with limited availability. Osteoinduction is the stimulation of osteoprogenitor cells to differentiate into osteoblasts that then begin new bone formation. A bone graft material that is osteoconductive and osteoinductive will not only serve as a scaffold for currently existing osteoblasts but will also trigger the formation of new osteoblasts, theoretically promoting faster integration of the graft. However, many alloplastic reconstructive materials are present but associated with limited osteoinductive and osteoconductive properties. Osteoconduction occurs when the bone graft material serves as a scaffold for new bone growth that is perpetuated by the native bone to guide the tissue regeneration. The material will also partially be replaced by newly formed cells. Alloplastic bone substitutes have been combined with several compounds to support osteoconductive and osteoinductive properties. In light of this, different molecules are used for the efficient induction of bone formation. Simvastatin is a compound widely prescribed for treatment of hypercholesterolemia because it prevents the synthesis of cholesterol, it can also elicit some pleiotropic effects, leading to the modulation of the process of bone regeneration at the molecular and cellular levels [3]. Simvastatin seems to play an important role in bone regeneration by participating directly in osteoblast activation (increasing BMP-2 expression) and in osteoclast inhibition [4], also indirectly, by stimulating neovascularization (increasing the secretion of vascular endothelial growth factor) [5]. Concentrations of statins in bone marrow have not been well established yet, but osteoblasts and osteoclasts may be exposed to very low concentrations of simvastatin [6]. The aim of this review is to discuss the dosage and carrier for simvastatin, and to summarize effects of topical application directly or indirectly for stimulating bone regeneration.

2. Mechanism of action of simvastatin on bone regeneration

Mechanism of action involves reduction in mevalonate pathway intermediates and inhibition of prenylation by statins is responsible for a large proportion of the pleiotropic effects of these drugs. Mevalonate, farnesyl pyrophosphate and geranyl pyrophosphate all inhibited statin stimulated bone formation [7]. Simvastatin, mevastatin and atorvastatin are activators of bone morphogenetic protein (BMP2) which accounts for major osteoinductive potential of bone [8]. Furthermore, because geranyl pyrophosphate inhibited statin stimulated bone formation, inhibition of prenylation due to geranyl geranylation must play a major role in the stimulation of bone formation by these drugs [9]. Also, statins influence the production of receptor activator of nuclear factor kappa-B ligand (RANKL) and osteoprotegrin by human gingival fibroblasts to favor bone catabolism under non-inflammatory conditions [10].

3. The effect of statins on osseointegration and periodontitis

Topical application of statin affects bone healing around implants [11]. According to Takeshita et al. a meshlike woven bone structure was predominantly formed around the implant 5 days after implantation, and then diminished gradually [12]. Also Ayukawa et al. showed that simvastatin promotes osteogenesis around titanium implants. Under the administration of statin, a similar meshlike structure of bone was seen around the implant even at 30 days after the implantation which resulted in an improved implant fixation and that the bone network can successfully disperse the stress applied to the implant [13]. Fajardo et al. applied (20 mg/day) of Atorvastatin for 3 months. The results of this study suggest that atorvastatin might have beneficial effects in periodontal diseases with bone alveolar loss and tooth mobility [14].

4. Dosage and duration of simvastatin for bone regeneration

The conflicting results of animal and clinical studies suggest that orally administered statins may be degraded in the liver, so little of the drug is available to accumulate in bone [15]. It is reported that high dose of systemic applied simvastatin will raise the risk of liver failure, kidney disease, rhabdomyolysis, myalgia and other side effects [16]. For that, caution should be exercised regarding the dosing of the simvastatin, since several authors have reported a dose-dependent inflammatory response [17]. Several studies have shown that the dose of simvastatin modulates the ability of the drug to increase bone volume [18–21]. Dose response of simvastatin, administered orally, for bone formation and resorption are different. Study of Ho et al. showed that simvastatin (20 mg/kg/day) enhances bone formation by increasing osteoblast numbers and osteogenic protein expression in ovariectomized rats [22]. Contradictory results about the effect of simvastatin on bone formation have also been reported in literature [23,24]. High dose of simvastatin (20 mg/kg/day) increases bone formation and resorption, while low dose (1 mg/kg/day) of simvastatin decreases bone formation and increases bone resorption [23]. Oxlund et al. reported that (20 mg/kg/day) of simvastatin orally twice daily for 3 months reduced loss of cancellous bone caused by ovariectomy [25]. Also Mousavil et al. reported that a daily dose of 10–20 mg/kg/day for 45 days of Pravastatin orally increases bone formation and accelerate healing process of bone defect [26]; as well as, Mundy et al. concluded that simvastatin increased trabecular bone volume among ovariectomized rats when given simvastatin at a daily dose of 5–10 mg/kg for 35 days [8], while Maritz et al. reported that (1 mg/kg/day) for 12 weeks decreased bone mineral density [23]. In one clinical study, simvastatin (40 mg/day) for one year significantly increased bone mineral density at the lumbar spine and femoral neck [27]. Therewith dose optimization may help in increasing the bioavailability and distribution of statins to the bone microenvironment [28]. Wang et al. considered a 10 mg/kg/day dose to rats about equivalent to 70 mg/day for humans, taking into account that metabolic process in rodents is 10 times faster than in humans [29]. So a dose of 10 mg/kg/day is higher than the routine dose in clinical applications (20–40 mg/day) and dosages tested on rats, when adjusted for humans, were sometimes much higher than the standard dose in patients. However, it was reported that even the injection of 1.5 mg/kg/week compares favorably with 7 mg/kg/week in human oral regimens [2]. Pasco et al. also in case–control study reported a 60% reduction in fracture risk in patients treated with statins [30]. Furthermore no dramatic change in bone mineral density was found in a one-year prospective