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The use of simvastatin in bone regeneration

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Abstract

Simvastatin is a chemical modification of lovastatin, a rate-limiting enzyme of the cholesterol synthesis pathway. Simvastatin has been reported to promote osteoblastic activity and inhibit osteoclastic activity. It is also reported to have an anti-inflammatory effect that works by decreasing the production of interleukin-6 and interleukin-8. The successful use of simvastatin to promote bone formation in vivo depends on the local concentration, and there have been continuous efforts to find an appropriate delivery system. Different doses produce different effects and doses should be prescribed with caution considering benefits and risks. There have been many studies demonstrating the bone-promoting effect of local application with different carriers in various animal models. Simvastatin is shown to increase cancellous bone volume, bone formation rate, and cancellous bone compressive strength.
In this review, the summary was made of the various in vitro and in vivo studies. The effects of simvastatins based on different methods of administration, dosage and carriers were also described.

Key words: *Bone regeneration, simvastatin, carrier, dosage.*

Introduction

Statin is a specific inhibitor of 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase, rate-limiting enzyme of the cholesterol synthesis pathway (1). Simvastatin is a chemical modification of lovastatin, which is obtained by the replacement of 2-methyl-butyryl side chain of lovastatin with a 2,2-dimethyl-butyryl group. Simvastatin is an inactive lactone drug that, after oral administration, is converted to its active dihydroxy open acid form by the intracellular enzyme cytochorome P450 (3A4 isozyme) in the liver (1).
Simvastatin is not well absorbed, and less than 5% of an oral dose reaches the systemic circulation. Concentrations of statins in bone marrow have not been well established yet, but osteoblasts and osteoclasts may be exposed to very low concentrations of statin with existing oral regimens. Attempts have been made to escape the accumulation in the liver and to deliver the statins to the peripheral tissue by subcutaneous injection or transdermal patch (2).
There have been many studies demonstrating the bone promoting effect of local application with different carriers in various animal models. The aim of this review is to describe the mechanism, dosage and carrier for the drug and to summarize in vivo effects on the bone regeneration.

Concept

-(1) Mechanism

Simvastatin has been reported to promote osteoblastic activity and inhibit osteoclastic activity. There have been some suggestions for the mechanism of the action.

Simvastatin is suggested to support bone morphogenetic protein (BMP)-induced osteoblast differentiation through antagonizing TNF-α-to-Ras/Rho/mitogen activated protein kinase and augmenting BMP-Smad signaling (3). Simvastatin has demonstrated to reverse the suppressive effects of tumor necrosis factor and prevents the inhibition of BMP-2 mediated by Smad 1, 5 and 8 phosporylation. The decrease in osteoclast number was seen by histological study after oral administration of simvastatin and lower activity of serum tartrate-resistant acid phosphatase 5b was reported indicating the decreased osteoclast activity (4). Osteoblasts and marrow adipocytes are originated from a common mesenchymal progenitor and adipogenic agents is reported to suppress osteoblast differentiation (5).

Simvastatin enhances alkaline phosphatase activity and mineralization, as well as increases the expression of bone sialoprotein, osteocalcin and type I collagen, and it is shown to have anti-inflamatory effect by decrea-sing the production of interleukin-6 and interleukin-8 (6). Simvastatin is reported to stimulate vascular endothelial growth factor (VEGF) release in dose-dependent manner and the authors suggested that statins may promote osteoblast differentiation and bone nodule formation by stimulating VEGF expression in bone tissue (7).

-(2) Carriers

The successful use of simvastatin to promote bone formation in vivo depends on the local concentration and there have been continuous efforts to find an appropriate delivery system (8). There are a number of advantages to an appropriate carrier, including localization and retention of the molecule to the site of application thus reducing the loading dose and providing a matrix for mesenchymal cell infiltration and a substrate for cell growth and differentiation. The carrier may also help to define the shape of resulting new bone and the optimal carrier has a degradation rate that does not inhibit bone growth and prevent fibrous tissue formation or fibrous encapsulation of the carrier. There have been many studies demonstrating the osteopromotive effect achieved by the local application of the drug with different carriers in various animal models (Table1).

Gelatin sponge is biocompatible, bioresorbable, and adapts easily to the shape of defects because of its sponge-like form (9). 3 mm diameter defect in the angulus mandibular region of Wista albino rats were grafted with simvastatin gelatin sponge graft and the grafts produced 240% more new bone than the control group (9). Polylactic acid/polyglycolic acid copolymer carries with 1 mg of simvastatin were implanted into extraction sockets of mandibular incisors and local application of simvastatin is reported to preserve the residual alveolar bone effectively by promoting bone formation in the extraction socket (8). Critical-sized bone defects in rat calvaria were treated with calcium sulfate or with combination of 1 mg simvastatin and calcium sulfate. It was reported that the combination of simvastatin and calcium sulfate stimulated bone regeneration (10).

Dermal application of statins was tried in hydrophilic petrolatum to make the higher percentage of statin to arrive at bone cells and the results showed that a marked increase in bone formation and cancellous bone volume was achieved in the rat models (2). Immobilization of simvastatin onto titanium implants is suggested to promote osteogenesis in the bone tissue surrounding the implants through its topical application (11).

Further studies should be performed to find an appropriate carrier scaffold that can release an optimal amount of simvastatin gradually through a slow degradation and also provide an osteconductive surface over which bone formation can take place.

Consideration-Dosage

Mundy and colleagues reported increased trabecular bone volume among ovariectomized rats given simvastatin at a daily dose of 5-10 mg/kg for 35 days (4). Animal testing indicated that high-dose simvastatin (20 mg/kg/day) increases bone formation, while low-dose simvastatin (1 mg/kg/day) decreases bone formation and increases bone resorption (12). Extreme high dose of 120 mg/kg/day was reported to be administered by preparation of a diet with simvastatin (13).

Regarding pharmacokinetics, the authors 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 are 10 times faster than in humans (13). So 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. The clinically

Table 1. Different kinds of carriers.

Type of carrier	Defect	Reference
Gelatin	Bone defect in mandible	(9)
Polylactic acid/polyglycolic acid	Extraction sockets in mandibular incisors	(8)
Calcium sulfate	Calvarial defect	(10)

effective dosage range to treat hypercholesterol in humans by oral administration is up to 1.0 mg/kg/day and authors have administered 20-40 mg/day for 12 weeks up to 12 months in clinical applications (14).

However, a topical dose is reported to affect a localized area of bone, whether in a 70 kg human or 0.3 kg rat. It was reported that even the injection of 1.5 mg/kg/week compares favorably with the 7 mg/kg/week in human oral regimens (15). The authors injected simvastatin into the subcutaneous tissue overlying the rat calvaria three times per day for 5 days in the dose of 1, 5, 10 mg/kg/day (4). The dose of simvastatin 5-10 mg/kg/day was applied locally into the fracture region (13). Subcutaneous injection of even higher doses of 50 mg/kg/day was done to measure the possible effect of simvastatin on implant osseointegration in rabbit (16).

It is reported that exceedingly high dose of systemic applied simvastatins will raise the risk of liver failure, kidney disease, rhabdomyolysis, myalgia and other side effects (1). Simvastatin possesses topical and systemic anti-inflammatory properties, but this property alters at high-dose local applications. It has been shown that local application of approximately 70 mg/kg causes inflammation and scabbing of the overlying skin (17). Stein et al. applied simvastatin at different doses and found the signs of clinical inflammation can be reduced by lowering the simvastatin dose. Injection of 1.7-2.0 mg/kg simvastatin in rat is shown to effectively reduce soft tissue swelling while preserving bone growth compared to the control.

Doses should be chosen with caution considering benefits and risks and further studies are needed to confirm the optimal dosage for the therapeutic effects (Table 2).

Results

-Application-In vivo

Simvastatin is reported to increase cancellous bone volume, bone formation rate and cancellous bone compressive strength in vivo (14). Local application of simvastatin showed to promote fracture healing compared to the control group (13).

Twice weekly injections of simvastatin appeared to reduce bone resorption in a ligature-induced periodontitis model and it was suggested that statin could inhibit the inflammatory reaction in periodontal disease. Mechanical and histologic data showed superior stability and osseous adaptation at the bone/implant interface for the simvastatin group and it was suggested that simvastatin has potential as a means of enhancing bone ingrowth (16). The administration of simvastain increased the value of both bone contact ratio to pure titanium implant and bone density around the implant installed in tibiae (18).

However, there have been some conflicting results. Anbinder et al. reported that simvastatin administration either orally or subcutaneously did not improve bone repair of experimental defects and did not alter blood cholesterol levels in rats and simvastatin also failed to stimulate bone formation, despite the verification by liquid chromatography/mass spectrometry of the active simvastatin beta-hydroxy acid metabolite in mouse serum (19).

Taken together, these suggest a number of variables may be important in modulating the effects of simvastatin including the dosage, mode of application and animal model.

Conclusion

A number of studies have demonstrated the potential for statins to increase bone regeneration. Although relatively abundant information about simvastatins indicates their possible beneficial effect on bone, available both in the preclinical and clinical field, there have been some conflicting results on the effect of simvastatin. This is due to the fact that the effects of simvastatins may be influenced by a range of factors including the method of administration, duration of exposure, experimental animal model and bioavailability.

Further research is needed to determine the optimal therapeutic threshold, mode of application and the effectiveness for humans for bone regeneration.

Table 2. The effect of different dosages.

Mode	Dosage	Effects	Reference
Oral	1 mg/kg/day	Decreased bone mineral density	(12)
Oral	20 mg/kg/day	Reduced loss of canellous bone induced by ovariectomy	(20)
Subcutaneous	50 mg/kg/day	Enhanced bone ingrowth	(16)
Intraperiotoneal	10 mg/kg/day	Increased bone density and bone contact ratio	(18)

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