

# Antihyperlipidemic Agents and Periodontal Therapeutics

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## ABSTRACT

Antihyperlipidemic agents have the capacity to reduce cholesterol biosynthesis, and also help in the modulation of the lipid metabolism, due to their effect of inhibition upon 3-hydroxy-3-methyl-glutaryl-coenzyme a reductase reductase. They have antiatherosclerotic effects, which decreases low density lipoprotein cholesterol level. Several studies have shown the potential of simvastatin to increase bone regeneration. The aim of periodontal therapy is to obtain true regeneration with the formation of root cementum with inserting collagen fibers, periodontal ligament, and alveolar bone. Antihyperlipidemic drugs especially simvastatin can be incorporated into various delivery vehicles, such as gelatin, polylactic acid/polyglycolic acid. Simvastatin can also be combined along with bone grafts to improve their regenerative action.

**Keywords:** Antihyperlipidemic Agents, Cholesterol, Periodontitis.

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## INTRODUCTION

Regeneration is defined as a reproduction or reconstruction of a lost or injured part in a way that both form and function of lost tissues are completely restored. The aim of periodontal therapy is to restore the tooth's supporting apparatus which has been lost following periodontitis. In periodontal regeneration, there should be formation of root cementum with inserting collagen fibers, periodontal ligament, and alveolar bone.<sup>1</sup>

Conventional surgical periodontal therapy may usually result in successful clinical details, such as probing

depth reduction and gain of clinical attachment. The gain in clinical attachment level measured with a periodontal probe was also interpreted to indicate periodontal regeneration. Repair of a periodontal defect can occur by the formation of a long junctional epithelium with increase in bone volume and density, ankylosis, and root resorption. In some cases, partial regeneration can occur involving the formation of a cementum-mediated new fibrous attachment to a pathologically exposed root surface, without new bone formation.<sup>2</sup>

For periodontal regeneration, at least four criteria must be considered in order for regeneration to have occurred.<sup>3</sup>

1. A functional epithelial seal must be reestablished at the most coronal portion of the tissues and be no more than 2 mm in length.
2. New connective tissue fibers (Sharpey's fibers) must be inserted into the previously exposed root surface to reproduce both the periodontal ligament and the dentogingival fiber complex.
3. New acellular, extrinsic fiber cementum must be reformed on the previously exposed root surface.
4. Alveolar bone height must be restored to within 2 mm of the cemento-enamel junction.

Various drugs have shown to be beneficial in enhancing bone growth. Bisphosphonates are analogs of pyrophosphate.

Bisphosphonates decrease osteoclastic bone resorption via several mechanisms:

- Inhibition of the osteoclastic proton pump necessary for dissolution of hydroxyapatite
- Reduction in osteoclastic formation
- Increase in osteoclastic apoptosis.<sup>4</sup>

Bisphosphonates, such as alendronate, zoledronate can inhibit osteoclastic bone resorption by blocking the mevalonate pathway.<sup>5</sup> Teriparatide is a recombinant preparation of first 34 amino acids of parathyroid hormone. Teriparatide is the first approved treatment for osteoporosis that stimulates bone formation. Other drugs approved for this indication inhibit bone resorption.<sup>6</sup> Statin is an inhibitor of enzyme 3-hydroxy-3-methyl-glutaryl-coenzyme a reductase reductase (HMG-CoA) of the cholesterol synthesis pathway. Statins are used orally to treat hypercholesterolemia and hyperlipidemia.<sup>7</sup>

Classification of antihyperlipidemic agents:<sup>8</sup>

- The HMG-CoA reductase inhibitors (statins): Lovastatin, simvastatin, pravastatin, atorvastatin, and rosuvastatin

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- Bile acid sequestrants: Cholestyramine, colestipol
- Activate lipoprotein lipase: Clofibrate, gemfibrozil, bezafibrate, and fenofibrate
- Inhibit lipolysis and triglyceride synthesis: Nicotinic acid.

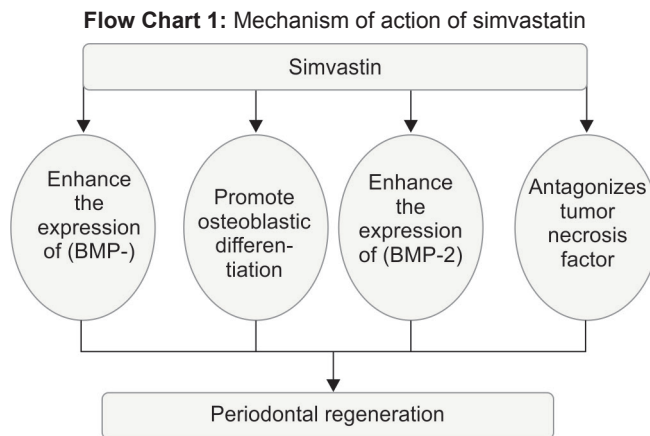
### HISTORY OF STATINS

In 1976, the first statin, called “compactin” (mevastatin), was synthesized in Japan. Merck developed lovastatin in 1984, US Food and Drug Administration approval was given in 1987 to become the first commercial statin. Lovastatin was followed by development of simvastatin with an extra methyl group. Sankyo developed compactin with an extra hydroxyl group and launched it in 1989.

Other synthetic statins subsequently developed include fluvastatin, cerivastatin, atorvastatin, rosuvastatin, and pitavastatin. Cerivastatin was discontinued due to reports of it causing myopathy (Fig. 1).<sup>9</sup>

### MECHANISM OF ACTION FOR BONE REGENERATION

The reduction in mevalonate pathway intermediates with a subsequent inhibition of prenylation by statins is responsible for a large proportion of the pleiotropic effects of these drugs. The ability of statins to enhance the expression of bone morphogenetic protein-2 (BMP-2) was first reported by Mundy et al.<sup>10</sup> Simvastatin, mevastatin, and atorvastatin were found to stimulate BMP-2 transcription and also increased endogenous BMP-2 mRNA and protein expression in human MG63 osteoblastic cells.<sup>11</sup> Simvastatin has been found to promote osteoblastic differentiation in rat bone marrow stromal cells. Simvastatin stimulates the alkaline phosphatase activity, and promotes the mineralization of the matrix by osteoblasts.<sup>12</sup> Simvastatin antagonizes tumor necrosis factor- $\alpha$  inhibition of bone morphogenetic proteins-2-induced osteoblast differentiation by regulating Smad signaling and Ras/Rho-mitogen-activated protein kinase pathway (Flow Chart 1).<sup>13</sup>



### PHARMACOKINETICS

Simvastatin is a lipophilic drug with a bioavailability of 5% and protein binding capacity of 95%. The half-life is 2 hours, it is excreted 13% by renal and 60% by faecal.<sup>14</sup>

### DOSAGE

Simvastatin has been shown to cause considerable soft tissue inflammation at high doses. Stein et al<sup>15</sup> found out that reducing single dose of simvastatin from 2.2 mg to 0.5 mg reduced inflammation to a more clinically-acceptable level without sacrificing bone-growth potential.

Özec et al<sup>16</sup> evaluated three different delivery time of a single dose of local simvastatin injection to rat mandibular defects and determined that a single injection of 0.5 mg simvastatin showed limited bone formation at the defect side for the 1st, 7th, and the 14th day delivery times. Chen et al<sup>17</sup> suggested that the best dose of simvastatin gel to stimulate bone regeneration is 0.5 mg. The successful use of simvastatin to promote bone formation *in vivo* depends on the local concentration and an appropriate delivery system. Local injection of a simvastatin loaded poly(ethylene glycol)-poly(lactic acid-co-glycolic acid)-poly(ethylene glycol) (PEG-PLGA-PEG) compound was found to promote autogenous chondrogenic disk repair and retarded disk degeneration. Devices for sustained or intermittent release of simvastatin using a blend of cellulose acetate phthalate and a poly (ethylene oxide) and poly (propylene oxide) block copolymer, implanted directly over the calvarium of young male rats resulted in enhanced bone formation.<sup>18</sup> Locally applied simvastatin in methylcellulose gel membrane can stimulate significant bone growth at an optimal dose of 0.5 mg where clinical inflammation is reduced.<sup>19</sup>

### LITERATURE REVIEW

Thylin et al<sup>20</sup> evaluated the effect of 2 single-dose drug delivery system of simvastatin, methylcellulose gel with

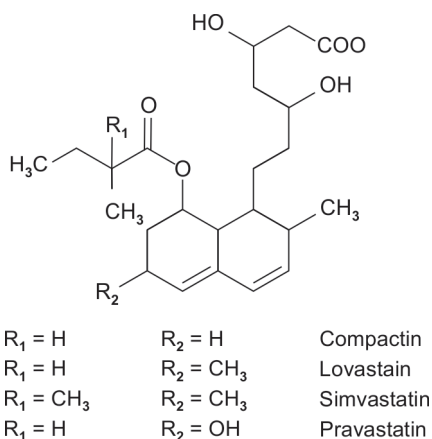


Fig. 1: Chemical structure of statins

simvastatin polylactide membrane containing gel, and simvastatin on murine calvarial bone. It was found out that a single, high dose of simvastatin gel can stimulate murine cranial bone apposition, particularly when delivered under an occlusive membrane.

Yazawa et al<sup>21</sup> determined that simvastatin promotes cell metabolism, proliferation, and osteoblastic differentiation in human periodontal ligament cells.

Sakoda et al<sup>22</sup> provided evidence for the first time that simvastatin reduces IL-1 $\alpha$ -induced production of inflammatory cytokines, such as IL-6 and IL-8 by human oral epithelial cells, and evidence suggesting that the inhibitory action of simvastatin could be mediated by the prevention of Rac prenylation.

Vaziri et al<sup>23</sup> evaluated the effects of simvastatin on ligature-induced bone resorption in the mandible of the ovariectomized rat, and concluded that simvastatin shows protective features against the impact of periodontitis on attachment apparatus, and alveolar bone.

Lindy et al<sup>24</sup> examined the association of statin use and clinical markers of chronic periodontitis. Patients on statin medication exhibit fewer signs of periodontal inflammatory injury.

Nassar et al<sup>25</sup> determined that the simvastatin therapy leads to a reversal of the cyclosporine A-induced bone loss, which may be mediated by downregulation of interleukin-1 $\beta$  and prostaglandin E2 production.

Saxlin et al<sup>26</sup> investigated the association between statin medication and periodontal infection in an adult population. Statin medication appeared to have an effect on the periodontium, i.e., dependent on the inflammatory condition of the periodontium.

Pradeep and Thorat investigated the effectiveness of simvastatin, 1.2 mg, in an indigenously prepared biodegradable controlled-release gel as an adjunct to scaling and root planing in the treatment of chronic periodontitis. There was a greater decrease in gingival index, and probing depth and more clinical attachment level gain with significant intrabony defect fill at sites treated with scaling and root planing plus locally delivered simvastatin in patients with chronic periodontitis.<sup>27</sup>

Cáceres et al<sup>28</sup> analyzed the effects of simvastatin on several cell responses involved in tissue repair, including cell adhesion, cell migration and invasion, actin cytoskeleton remodeling, and cell viability.

## APPLICATIONS IN PERIODONTAL THERAPY

Periodontitis is characterized by inflammation and breakdown of the supporting tissues of the teeth.<sup>29</sup> The aim of periodontal therapy is to obtain true regeneration with the formation of new root cementum with inserting collagen fibers, new periodontal ligament and new alveolar bone. The ability of statins to enhance the expression of

BMP-2 was first reported by Mundy et al.<sup>11</sup> Simvastatin can be incorporated into various delivery vehicles, such as gelatin, polylactic acid/polyglycolic acid. Simvastatin can also be combined along with bone grafts to improve their regenerative action.<sup>22</sup>

## CONCLUSION

Simvastatin is commonly used to treat hyperlipidemia. Several studies have shown the potential of simvastatin to increase bone regeneration. However, further studies are needed to determine the optimum dosage, mode of application, and the effectiveness for periodontal regeneration in statin dependent patients.

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