

# Orthodontic Anchorage Reinforcement with Pharmacological Agents and Biomodulators: A Review

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**Abstract:** *Orthodontic anchorage is one of the most critical and challenging aspects of Orthodontics. Preventing undesired movement of teeth could result in safer and better orthodontic treatment outcome. Conventional anchorage reinforcement used in orthodontics include TPA, Nance palatal button, use of cervical or high pull headgears. Recently there has been a dramatic increase in the use of orthodontic mini-implants to preserve maximum anchorage. Orthodontic tooth movements are based on bone remodeling that occurs after the application of mechanical forces. Recent research suggests the use of certain pharmacological agents as adjuvants in preserving anchorage. Several drugs that modify osteoclasts function, such as bisphosphonates (BPs), anti-inflammatory agents, other molecules (OMs) like anti-oxidants and interferon- $\gamma$ , and biological modulators like osteoprotegrins (OPGs), and bone morphogenic proteins (BMPs) have been used to prevent anchorage loss in Orthodontics. This review aims at the potential use of pharmacological agents and biomodulators in reinforcing orthodontic anchorage.*

**Keywords:** Tooth movement. Orthodontic anchorage reinforcement. Osteoprotegerin. Bisphosphonates. Anti-inflammatory agents

## 1. Introduction

Orthodontic tooth movements can have undesirable effects on the surrounding teeth. The challenge is to design a force system that maximizes desirable tooth movement and minimize anchorage loss. Traditional methods to mitigate anchorage loss include headgears, various intraoral appliances, and elastics, all of which depend on patient compliance. Without compliance, anchorage is often lost, causing an increase in treatment time and a risk of adverse effects, such as root resorption, white spot lesions, caries, gingivitis, and compromised treatment results [1]. Orthodontic tooth movement differs markedly from physiological dental drift or tooth eruption. The former is uniquely characterized by the abrupt creation of compression and tension regions in the PDL [2]

Despite the efficacy of orthodontic techniques, there are a number of circumstances in which treatment efficiency might be improved by modulating the activity of osteoclasts, and therefore, bone turnover [3]. Several drugs that modify osteoclasts function, such as bisphosphonates (BPs), anti-inflammatory drugs and other molecules (OMs), have been used to prevent anchorage loss in Orthodontics [4], [5], [6], [7], [8], [9].

Recent studies suggest that biological modulators like osteoprotegerin (OPG), are able to inhibit osteoclasts. The local delivery of OPG adjacent to anchorage teeth may

provide a novel pharmacological approach in preventing undesired tooth movement [10].

## 2. Pharmacological Agents for Orthodontic Anchorage Reinforcement

**1) Bisphosphonates:** Bisphosphonates are potent bone resorption inhibitors frequently used to treat bone metabolism disorders, such as Paget disease, osteoporosis and bone metastases. Essentially, these drugs are internalized into osteoclasts, leading to inhibition of bone resorption and induction of osteoclasts apoptosis [11]. The clinical efficacy of bisphosphonates primarily stems from two key properties: their ability to bind strongly to bone mineral and their inhibitory effects on mature osteoclasts [12]. A single, small, locally applied dose of Zoledronate was sufficient to provide maximum anchorage in extraction space closure. Study by Ortega et al showed that, Zoledronate prevented severe periodontal bone loss at the extraction site and around the second and third molars. There were no signs of bisphosphonate-associated osteonecrosis [13]. Choi et al [14] used two different concentrations of Clodronate and assessed alveolar bone remodeling and root resorption. This study showed significantly decreased root resorption with new bone formation, especially in the lower third of the roots; they also observed dose-dependent reduction of molar movement [14].

## 2) Biological Modulators: OPGs and BMPs

- a) **Osteoprotegrins:** It is a soluble protein that inhibits the binding of receptor-activator of nuclear factor- $\kappa$ B ligand (RANKL) to its cognate receptor, and prevents osteoclasts differentiation and activation. Dunn et al [15], used two different doses of recombinant fusion protein (OPG-Fc) on rat models, tooth movements and changes in bone quality was measured. The study concluded that local delivery of OPG-Fc, inhibits osteoclastogenesis and tooth movements at targeted dental sites. Keles et al [16] observed that OPG was more potent than pamidronate inhibition of tooth movement.
- b) **Bonemorphogenic proteins:** BMPs are multi-functional growth factors that belong to the transforming growth factor  $\beta$  (TGF $\beta$ ) superfamily. Preclinical and clinical studies have shown that BMP-2 can be utilized in various therapeutic interventions such as bone defects, non-union fractures, spinal fusion, osteoporosis. The use of bone morphogenetic protein-2 and dentin matrix protein-1 were tested like coating surface by Hassan et al. Bone morphogenetic protein-2 has an osteoinductive effect and it promotes the differentiation of mesenchymal stem cell to osteoblast and that proteins are involved in bone remodeling. It was seen that the bony activity of rabbit calvaria was significantly higher in experimental groups than original hydroxyapatite coating [17].
- c) **ANTI-INFLAMMATORY AGENTS:** Anti-inflammatory drugs are frequently used to avoid pain and discomfort caused by orthodontic treatment, but these drugs could also produce decreased or slow-down tooth movement. De Carlos et al [5] compared the effects of Diclofenac and Rofecoxib, a conventional non-steroidal anti-inflammatory and a COX-2 inhibitor respectively. It was found that Rofecoxib had more potent effects on blocking tooth movement.
- d) De Carlos et al [6] also analyzed the effect of Celecoxib, Parecoxib and Rofecoxib on tooth movement in rats, it was found that Celecoxib and Parecoxib did not affect tooth movement, while Rofecoxib completely inhibited tooth movement in rats after 50-g force application. Inherent characteristics of these drugs, such as bioavailability, half life, etc., may account for discrepant effects of these compounds.

## 3) Other molecules: anti-oxidants and interferon- $\gamma$

- a) **Anti-oxidants:** The recruitment and differentiation of osteoclasts in the compression side of PDL tissues is essential for bone resorption and tooth movement. Numerous studies have shown that pro-inflammatory cytokines, such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-1 (IL-1), IL-6 and IL-8, play an important role in orthodontic tooth movement through the regulation of osteoclast differentiation and matrix metalloproteinase expression [18]. In addition to the pro-inflammatory cytokines, vascular endothelial growth factor (VEGF) is also involved in orthodontic tooth movement. VEGF is detected within the periodontal tissues during orthodontic tooth movement, and local administration of recombinant VEGF enhances the extent of tooth movement [19]. Previous studies have demonstrated that N-acetylcysteine (NAC), an

antioxidant, decreases lipopolysaccharide-induced production of pro-inflammatory cytokines in gingival fibroblasts, and NAC decreases alveolar bone loss in experimental periodontitis [20]. NAC is a precursor of glutathione and functions as a reactive oxygen species (ROS) scavenger. These reports suggest that antioxidants may exert a regulatory effect on the rate of orthodontic tooth movement by regulating the production of pro-inflammatory cytokines. NAC and Resveratrol suppressed the expression of pro-inflammatory cytokines and VEGF, which were induced by combined treatment with mechanical compression and hypoxia in human PDLFs. Furthermore, in vivo experiments demonstrated that NAC delayed orthodontic tooth movement in rats [21].

- b) **Interferon- $\gamma$  (IFN $\gamma$ ):** Interferons were originally described in 1957 as an activity found in the supernatant of virally infected cells that directly "interfered" with viral replication. These proteins have been classified into two types based on structural and functional criteria and the stimuli that elicits their expression. Type I interferons are primarily induced in response to viral infection and have been categorized into two subgroups: IFN-alpha and IFN-beta. Type II interferons, known as IFN-gamma, are synthesized primarily by defined subsets of T lymphocytes and natural killer cells after activation with immune and inflammatory stimulus. IFN- $\gamma$  inhibits bone resorption and has an inhibitory effect on osteoclasts at the level of differentiation [22]. According to a study conducted by Mermut et al, IFN- $\gamma$  is involved in bone remodeling during orthodontic tooth movement, which strongly suppresses osteoclastogenesis. IFN- $\gamma$  administration may be clinically useful for anchorage control [23].

## 3. Conclusion

One of the most challenging problems in orthodontics is anchorage. The traditional mechanical methods of reinforcing anchorage are limited by multiple factors, but a pharmacological approach aimed at utilizing the known biological mechanisms underlying tooth movement may provide an ideal way of reinforcing orthodontic anchorage. Topical administration of BPs reduces tooth movement, which may be beneficial for anchorage procedures; also, osteonecrosis of the jaws was not found in any of the articles reviewed. Topical application of OPG reduces undesired tooth movements. OPG appears to be the most effective substance in blocking osteoclast function, being able to provide maximal anchorage after the application of orthodontic force. Topical application of anti-inflammatory drugs alters osteoclast function and, as a consequence, reduces tooth movement.

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