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Editorial

Statins: A New Era in Periodontology?

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Periodontitis, whether localized or generalized, is a multifactorial chronic inflammatory disease of the supporting tissues of the teeth, caused by a group of specific microorganisms. It is highly prevalent world-wide, especially in late middle age. Periodontitis can result in bone resorption creating bony defects, which may cause tooth loss. In fact, the initiation, advancement and/or progression of periodontal tissue destruction (by oral bacterial infection) involves complex (including pro-inflammatory cytokines, anti-inflammatory cytokines, and specific cytokine receptors and tissue-degradative enzymes) interaction between oro-dental bacteria (mainly, Gram-negative anaerobic bacteria) and cells of the immune system. Hence, cytokines play an important role in the initiation, progression as well as host modulation of periodontal disease. While systemically-applied anti-microbials have been for years advocated for the treatment of severe forms of periodontitis, localized anti-microbial agent delivery into periodontal pockets, seems safer, effective and beneficial in directly targeting or tackling specific pathogenic microorganisms. However, controlling sub-gingival plaque for an enhanced periodontal tissue regeneration and repair remains more demanding and complex. Indeed, several studies have demonstrated the effects of locally-administered statins such as simvastatin (SMV) on bone formation. Incorporation into controlled-release drug delivery systems that can be placed or introduced or administered directly into the periodontal pocket and/or defect area results in an enhanced local tissue concentration of the encapsulated and released load. Yet, the use of such strategies should be considered as adjunctive or adjuvant to traditional clinical therapeutic approaches; typically including mechanical scaling, root planning and/or surgical intervention, at times.

Modern advances in biomaterials, nanotechnology and drug delivery systems, hold promise for formulating new strategies, approaches and devices to help eliminate any residual infective and/or inflammatory component still harboring within the periodontal apparatus, thereby supporting and enhancing clinical periodontal therapy for our patients.

What are the characteristics of the "best-fit" strategy and/or "ideal" drug delivery system for an optimal clinical outcome? Evidence-based studies? How about level of evidence?

Alongside mechanical instrumentation, localized drug delivery systems should also provide a simple, malleable, stable, easy-to-use, safe and cost-/time-effective modality. While a dentifrice or a gel might seem suitable, controlling the encapsulation, release kinetic profile, bio-absorption and bio-distribution (and fate), of loaded drug(s) require more sophisticated and predictable formulations. The prolonged availability of the drug(s), localized and confined within the site of interest, at the sufficient minimum inhibitory concentrations, and over a known number of days, are also expected and in high demand.

This becomes especially critical for pharmacological agents such as statins. Statins, 3-hydroxy 3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, are drugs widely used today to lower cholesterol, to effectively treat hyperlipidemia and arteriosclerosis, and are prescribed to help prevent cardiovascular and cerebrovascular diseases. Their efficacy is mainly based on their capacity to reduce serum cholesterol levels, primarily low-density lipoprotein (LDL) cholesterol. Hence, for periodontal diseases and their intra-oral application, statins should be handled with utmost caution and care, especially in light that drugs such as SMV, are also considered relatively inexpensive. Indeed, ample literature is available today demonstrating the potential of locally-applied SMV for osteogenesis, *in vitro* and *in vivo*. Yet, it has been reported that such effects are highly concentration- and dose-dependant involving signaling pathways such as the mevalonate pathway. Elucidating the underling mechanism of action of statins use is thus, a priority.

In deed, over the years, it is very common to read about the several pleiotropic effects of statins in the literature. While findings of pre-clinical as well as clinical studies involving SMV seem encouraging, especially in its effects on bone metabolism; yet its use and mechanism of action in the treatment of complex periodontal defects remains unclear. Besides the evident and to-an-extent the expected discrepancies among tested models, other properties and effects of using statins (including: anti-oxidant, anti-inflammatory and immunomodulatory), locally to enhance the healing of periodontal intra-bony defects and overall improve periodontal health, in patients, remains open, requiring long-term well-thought and executed clinical studies (an insignificant number of randomized clinical trials have, to date, reported on the use of SMV – 1.2 mg/0.1 mL: high concentration; in injectable gel format – yet limited to evaluation at sites pre-managed mechanically). Likewise, such studies ought to pay utmost attention to the local delivery system used, in terms of both, strategy as well as methodology. The administered- or locally-applied carrier should not interrupt or inhibit bony growth as it should diminish or prevent fibrous tissue engulfment of the carrier. In other words, researchers are invited to consider the localization and retention of the SMV molecules (often used in the pro-drug form: more lipophilic that the active ß-hydroxyacid form) within the site of application; in order to reduce the required concentration and dosage of SMV via providing an *in situ* matrix for mesenchymal cell infiltration and a substrate for cell growth and differentiation (passive diffusion). Important to consider as well are the following: long-term carrier stability (sterilizability and storage), biocompatibility, bio-availability and bio-distribution, encapsulation efficiency, loading capacity, pharmacokinetics of released SMV (sustained and predictable drug release over periods of time), degradation mechanism (by-products) and rate of the delivery vehicle/carrier (nanoparticle, for example), amid other parameters.

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