Host modulation therapy: Periostat® as an adjunct to non-surgical periodontal therapy
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Introduction
A drug therapy marketed under the brand name Periostat® was recently introduced as an adjunctive therapy to scaling and root planing in the treatment of periodontal disease. This Clinical Update will discuss mechanisms of action and the host modulation by Periostat® as well as its potential clinical applications.

What is Periostat®?
Traditionally, doxycycline, when prescribed in 100mg tablets, functions as an antimicrobial to putative periodontal pathogens. Periostat®, which is a 20mg tablet of doxycycline, functions as a sub-antimicrobial dose of doxycycline (SDD) and essentially bypasses the microbial component of pathogenesis and focuses on the host modulation via anti-collagenase activity. Treatment with SDD did not lead to the emergence of tetracycline-resistant microbes, an outcome that has been observed after the administration of higher doses of doxycycline. From long-term sub-antimicrobial safety studies, the FDA has approved the use of Periostat® as an adjunctive therapy to scaling and root planing.

How do patients develop periodontal disease?
It is generally accepted that the tissue destruction observed in periodontitis is the result of the dynamics of pathogenic bacteria and the host immune response to bacterial virulence factors. The destruction process is the culmination of two pathways: exogenous (bacterial) and endogenous (host). The exogenous pathway includes localized tissue damage from the direct actions of anaerobic bacteria that release bacterial enzymes and toxins within the sulcus/pocket. The host initially tries to clear the site of these pathogenic bacteria by mounting a non-specific immune response. The endogenous, host-mediated response includes neutrophil chemotaxis, phagocytosis, cellular degranulation and the resulting elevated levels of proteolytic enzymes i.e. collagenase and gelatinase. Over time, repeated host responses eventually lead to the destruction of the attachment apparatus in a susceptible individual.

How does the host actually work against itself?
A key “host” inflammatory response (but not exclusionary) to the bacterial insult is the induction of destructive matrix metalloproteinas (MMPs). MMPs are comprised of a family of zinc and calcium dependent proteolytic enzymes that are secreted by neutrophils, macrophages, osteoclasts, and fibroblasts (1). MMPs are also known by more familiar terms: collagenase, gelatinase and stromelysin. When activated by pathogenic bacteria, destructive MMPs induce the excessive degradation of collagen and the extracellular matrix that can lead to the loss of attachment and supporting alveolar bone (2). Clinically, this loss of attachment occurs when there is an imbalance between these proteolytic enzymes and their endogenous inhibitors (3).

Can the body regulate the actions of proteolytic enzymes?
For most individuals, there exists a homeostatic balance of these enzymes. The body produces endogenous inhibitors of MMPs that include tissue inhibitors of MMPs (TIMPs) and α-macroglobulins. The role of inhibitors is significant because if there is a failure to inhibit the levels of activated MMPs, the host will self-induce a pathologic breakdown of the extracellular matrix (3). In several pathologic conditions, it has been demonstrated that TIMP levels rise but do not compensate for the much greater increase in the levels of destructive MMPs (3). This mechanism of destruction is seen not only in periodontitis but also in other diseases such as arthritis and tumor invasion kinetics. So, there is an inherent balance between normal collagen turnover and accelerated destruction with an imbalance posing serious health consequences.

How can the clinician modulate the host response?
Doxycycline prescribed at low doses (20mg) does not function as an antibiotic but modulates the host response. These non-antimicrobial actions include inhibition of connective tissue destruction via direct inhibition of MMPs in the gingival tissues (4), inhibition of bone resorption via regulation of osteoclast function and by blocking osteoclast MMP release (5), and finally, inhibition of MMP precursor activation (6). The therapeutic efficacy of SDD resides downstream from the bacterial insult of the destructive cascade.

How do you prescribe Periostat®?
Periostat® is prescribed in pre-packaged bottles of 100 tablets. Rx: Periostat® 20 mg Disp: 180 caps Sig: 1 cap po bid for 90 days. Take with food or a full glass of water
Prescribe for a minimum of 90 days and up to 9 months.
Cost: US Government: $0.44/cap or $79.20 per 90 day regimen.
Cost: Private sector: $0.94/cap or $179.00 per 90 day regimen.

What are the contraindications/precautions for Periostat®?
Please read all prescribing information carefully but the following should be noted when prescribing Periostat®:
Contraindications:
1. Patients with demonstrated hypersensitivity to tetracyclines.
2. Pregnant women.
3. Nursing mothers.

Precautions:
1. Patients taking multi-vitamins and calcium supplements.
2. Patients taking oral contraceptives.
3. Patients taking amoxicillin.
4. Patients receiving coumadin therapy.
5. Patients with a history of oral candidiasis.

What clinical studies support host modulation therapy?
In the phase III trial study comparing safety and efficacy of SSD, Periostat® was used as an adjunct to SRP in chronic periodontitis with the results evaluated over a 9-month period. The Periostat® group had an additional 0.48mm probing depth reduction in the >7mm sites and an additional 0.26mm probing depth reduction in the 4-6mm sites. Although these differences were statistically significant, the clinical relevance of these improved clinical outcomes is questioned in this study (7).

A similar 9-month study examining the adjunctive benefits of SDD in the management of advanced chronic periodontitis reported slightly different results. In the probing depths >7mm, the SDD group had a probing depth reduction of 3.02mm compared to 1.42mm for the SRP. The difference was less pronounced in the 4-6mm probing depths (1.20mm and 0.97mm) (8). These results demonstrate clinical significance especially in the advanced sites and may assist the clinician in justifying the additional cost of treatment with SDD in these advance type cases.

Which patients that can benefit from Periostat®?
According to available data, there are no absolute clinical indications for the use of Periostat®. The manufacturer of Periostat® recommends its use as a routine adjunct to SRP for mild to advanced chronic periodontitis. However, mixed clinical results from studies question this recommended routine application especially in the mild to moderate cases. Some potential additional applications or clinical considerations include use in the refractory or non-responsive chronic periodontitis case, periodontal maintenance cases exhibiting further attachment loss and the high-risk periodontal patient (diabetic, smoker). Each clinician must weigh both the cost of the medication and exposure to long-term medicaments with the potential clinical benefit in determining appropriate applications. Periostat® should not be a substitute for meticulous professional debridement, effective home care, and periodic maintenance appointments.

Conclusion
Using host-modulating pharmcotherapies as adjuncts to antimicrobial periodontal treatment represents an emerging concept in periodontal care. This coordinated approach toward the long-term management of periodontal disease may result in clinical outcomes that exceed those achieved by traditional approaches. An adjunctive therapy such as Periostat® that is safe, well tolerated, and improves certain clinical endpoints of periodontal therapy is a treatment clinicians should consider in their practice.

References

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