Treating the Infected Periodontal Foundation

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Topics included in this discussion

• Prevalence and pathogenesis of periodontal disease
  – Red complex bacteria
  – Properties of biofilms
  – Links to systemic complications
  – Limitations of mechanical treatment

• Treatment with ARESTIN® (minocycline hydrochloride) Microspheres, 1 mg
  – Microsphere technology
  – Eradication of red complex bacteria
  – Proven clinical outcomes
  – Smokers and difficult-to-treat patient groups
  – Safety and ease of use
Periodontal disease is a common, chronic, and persistent infection\(^1-6\)

• Periodontal disease is:
  – A persistent infection that can spread rapidly throughout the periodontium\(^1,2\)
  – The most common chronic bacterial infection in adults\(^1,3\)
  – A problem that affects more than 35.7 million Americans\(^4\)
  – The #1 cause of adult tooth loss in the US\(^5\)

• Three out of 4 American adults develop a periodontal infection\(^6\)

Red complex bacteria are found at the infection site

- Specific bacteria are implicated in periodontal disease and are commonly found at the site of infection\(^1,\!^2\)

<table>
<thead>
<tr>
<th>Red complex bacteria</th>
<th>Other periodontal bacteria</th>
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<tbody>
<tr>
<td><em>P. gingivalis</em></td>
<td><em>A. actinomycetemcomitans</em></td>
</tr>
<tr>
<td><em>T. denticola</em></td>
<td><em>E. corrodens</em></td>
</tr>
<tr>
<td><em>T. forsythensis</em></td>
<td><em>F. nucleatum</em></td>
</tr>
<tr>
<td></td>
<td><em>P. intermedia</em></td>
</tr>
</tbody>
</table>

- There is a direct association between red complex bacteria and 2 of the most meaningful parameters in periodontal disease diagnosis\(^1\):
  - Pocket depth
  - Bleeding on probing

Periodontal bacteria form dense biofilms

- The bacteria associated with periodontal disease reside within **biofilms** above and below the gingival margin\(^1-3\)

- Biofilms are dense **mixtures of organisms** resistant to natural antibodies and proteins that the body uses to fight infection\(^1\)

Collectively, the structure and properties of biofilms make it difficult to remove them with SRP alone\(^1,2\)

- Biofilms possess a self-protective matrix shield\(^1\)
- Each contains a microenvironment of bacteria\(^1,2\)
  - Bacteria exist in large numbers
  - Bacteria rapidly multiply, spread, and recolonize
- Biofilms cross-feed and cross-communicate\(^1,2\)
- Loosely attached and unattached bacteria found at the biofilm surface have direct contact with the epithelium of the gingival tissue\(^2\)

Biofilms shelter millions of bacteria\(^1\)

- Approximately 10 million to 1 billion bacteria have been observed in the biofilm-infected periodontal pocket\(^1\)

- The depth of biofilm-infected pockets ranges from 4 mm to 12 mm\(^1\)

Biofilms can induce bacteremia\(^1\)

- Biofilms release a variety of biologically active inflammatory products, including:
  - Bacterial endotoxins
  - Protein toxins
  - Peptides
  - Organic fatty acids

- These destructive molecules cause gingival inflammation and can enter the bloodstream, resulting in bacteremia.

Bacteremia generates an inflammatory response\textsuperscript{1,2}

- The body responds to bacteremia with inflammation and tissue destruction\textsuperscript{1}
- The body releases \textit{cytokines}, small proteins responsible for gingival inflammation\textsuperscript{1}
- Cytokines induce and enhance the production of a destructive family of \textit{enzymes}, also known as MMPs\textsuperscript{1,2}
- MMPs break down gingival tissue, leading to the formation of periodontal disease\textsuperscript{2}

C-reactive protein (CRP) levels are elevated in patients with periodontal infection

- Statistically significant increases in CRP have been observed in patients with periodontal infection vs healthy patients.\(^1\)

- CRP has been linked to a number of important systemic events.\(^2,3\)

References:
According to the AAP¹:

- Periodontal bacteria can enter the blood stream, travel to major organs, and begin new infections
- Current research suggests that periodontal bacteremia may lead to:
  - Heart disease, stroke, and/or diabetes
  - Increased risk of delivering a preterm, low birth-weight baby
  - Increased health risk for people with diabetes, respiratory disease, or osteoporosis


*A causal relationship has not been fully established.
Routine, effective treatment for periodontal infection is needed

- Despite the prevalence of periodontal infection and the persistent nature of bacteria and biofilms, more than **70%** of dental practices **do not** perform regular full-mouth probing and charting.  

- Although 3 out of 4 American adults are affected by periodontal disease:
  - Prophylaxis procedures outnumber SRP procedures by a ratio of **20:1** \(^3,4\)
  - **Less than 1/2** of periodontal pockets are treated with adjunctive therapy \(^5\*\)

\(^*\)According to a utilization tracking survey evaluating 14,945 patient records from 647 offices. The average number of pockets per patient was 9.

Left untreated, serious consequences can occur

Without proper diagnosis and treatment, periodontal disease can lead to…

- The spread of infection\(^1\)
- Loss of teeth\(^2\)
- Surgery\(^2\)

**References:**
Scaling and root planing (SRP) has mechanical limitations

- Even after SRP, the bacteria in biofilms can remain, multiply, and return to baseline levels within days\(^1\)

- SRP instrumentation is limited in areas of restricted access\(^2,3\)

- In a clinical study, 58% of sites had residual calculus after SRP\(^4\)

Adding an LAA to SRP can benefit patients

- Adding a locally administered antibiotic (LAA) to SRP is proven to significantly improve periodontal treatment\(^1\)

- The American Academy of Periodontology (AAP) supports the use of LAAs as an adjunct to SRP\(^2\)

- The LAA **ARESTIN\(^\text{®} \) (minocycline hydrochloride) Microspheres, 1 mg** can help eliminate the bacteria that SRP can leave behind including\(^3,4\):
  - *P. gingivalis*
  - *T. denticola*
  - *T. forsythensis*

ARESTIN® Microspheres technology provides a sustained release of minocycline in the periodontal pocket

- ARESTIN® Microspheres deliver minocycline directly to the periodontal pocket and help maintain therapeutic drug concentrations for up to 21 days, managing the infection long after treatment with SRP

- ARESTIN® Microspheres are bioadhesive and completely bioresorbed

- ARESTIN® Microspheres kill the bacteria SRP leaves behind, including *P gingivalis*, *T denticola*, and *T forsyntphinsis*

Minocycline effectively treats the common periodontal pathogens

Concentrations of minocycline in gingival crevicular fluid (GCF) at site of administration

### Periodontal pathogens | MIC (µg/mL)
--- | ---
*A. actinomycetemcomitans* | 2.0
*E. corrodens* | 0.5
*F. nucleatum* | 0.25
*P. intermedia* | 0.25
*P. gingivalis* | 0.06

References:
ARESTIN® treats the bacterial cause of periodontal infection more effectively than SRP alone¹*

In a recent microbiological study of patients with moderate-to-severe periodontitis, ARESTIN® + SRP:

- Significantly reduced the quantity of red complex bacteria vs SRP alone \( (P=0.002) \)

*Phase IV, single-blind, randomized, parallel-group study of 127 patients with moderate-to-severe periodontitis and at least 5 teeth with ≥5 mm pocket depths.

Reference: 1. Goodson, JM. Antimicrobial Efficacy of Arestin in Periodontitis Therapy. Presented at the 35th Annual Meeting of the American Association for Dental Research; March 8-11, 2006; Orlando, FL.
ARESTIN® treats the bacterial cause of periodontal infection more effectively than SRP alone\(^1\)

In a recent microbiological study of patients with moderate-to-severe periodontitis, ARESTIN® + SRP:

- Significantly reduced **proportions** of red complex bacteria vs SRP alone \((P=0.0005)\)
- Significantly reduced pocket depths and bleeding on probing, and increased clinical attachment levels\(^2\)

\(^*\)Phase IV, single-blind, randomized, parallel-group study of 127 patients with moderate-to-severe periodontitis and at least 5 teeth with \(\geq 5\) mm pocket depths.

**Reference:**
1. Goodson, JM. Antimicrobial Efficacy of Arestin in Periodontitis Therapy. Presented at the 35th Annual Meeting of the American Association for Dental Research; March 8-11, 2006; Orlando, FL.
2. Bland PS. Clinical efficacy and safety with ARESTIN® in patients with periodontitis. Presented at the 35th Annual Meeting of the American Association for Dental Research; March 8-11, 2006; Orlando, FL.
ARESTIN® + SRP is significantly more effective than SRP alone in reducing pocket depth\(^1\)

ARESTIN® + SRP demonstrated a greater therapeutic effect than SRP alone throughout 9 months (\(P<0.001\))\(^1\)

ARESTIN® + SRP is significantly more effective than SRP alone in reducing pocket depth¹

More than 60% of pockets that responded to ARESTIN® + SRP had a reduction of ≥2 mm¹

- In 65% of patients, ARESTIN® + SRP reduced pocket depth from ≥6 mm to <5 mm¹
- Compared to SRP alone, ARESTIN® + SRP is nearly 3 times more likely to reduce mean probing depth from ≥6 mm to <5 mm²

*In clinical studies, 37% of pockets treated with SRP alone did not respond to therapy vs 29% of pockets treated with ARESTIN® + SRP.¹

Smoking is a major risk factor for periodontal infection\textsuperscript{1,2}

- Smoking may be responsible for more than 1/2 of adult periodontal cases in the US\textsuperscript{3}

- Clinical studies show that smokers exhibit increased\textsuperscript{1,2}:
  - Pocket depth
  - Alveolar bone loss
  - Gingival recession
  - Tooth loss
  - Clinical attachment loss
  - Number of furcations

ARESTIN® + SRP is more effective than SRP alone in reducing pocket depth in smokers with periodontal disease

Statistically significant pocket depth reduction vs SRP alone

MONTH 1
21%

MONTH 6
33%

MONTH 9
32%

GREATER THERAPEUTIC EFFECT
p<0.05

*Subgroup analysis (n=271) of the single-blind, Phase III trial comparing ARESTIN® + SRP to SRP alone and SRP + placebo (n=748). SRP was performed for all groups at baseline. ARESTIN® or vehicle was administered to periodontal pockets ≥5 mm in the adjunctive therapy groups at baseline, 3 months, and 6 months. Efficacy was evaluated over 9 months.

• According to the AAP, smokers can be up to 6x more likely to exhibit periodontal destruction vs nonsmokers²

• Compared to SRP alone, ARESTIN® + SRP is nearly 4x more likely to reduce periodontal pockets to <5 mm in smokers¹*

*Multivariate analysis of the univariate, multicenter Phase III trials of ARESTIN® that compared the efficacy and safety of ARESTIN® + SRP to SRP + placebo and SRP alone. Odds ratios were adjusted to allow for the simultaneous effect of influential variables, such as treatment center, smoking status, age, and baseline pocket depths.

ARESTIN® + SRP has a greater therapeutic effect than SRP alone* in other difficult-to-treat patient groups1-3

Based on pocket depth reduction scores at 9 months†

Greater therapeutic effect**‡

*Adapted from Williams RC, Paquette DW, Offenbacher S, et al.4
†748 patients with moderate or advanced periodontitis with bleeding on probing. SRP was performed at baseline. Clinical assessments were conducted at baseline and 1, 3, 6, and 9 months. ARESTIN® or vehicle was administered to all sites with pocket depths >5 mm.
‡Change in pocket depth from baseline to 9 months was recorded for ARESTIN® + SRP and SRP alone. Therapeutic effect was derived by calculating the percent difference between the 9-month scores.

ARESTIN® is easy to administer

The administration of ARESTIN® does not require local anesthesia. Sterilize the handle tip between patients. ARESTIN® does not have to be removed, as it is bioresorbable. ARESTIN® does not require an adhesive or dressing.

1. Insert the ARESTIN® cartridge into the handle while exerting slight pressure.

2. Twist until you feel and hear the cartridge “lock” into place.

3. Should you need to manipulate the cartridge tip to reach difficult-to-access areas, gently bend the tip, leaving the blue cap on. Bending the tip after removal of the blue cap may cause the internal plunger to rupture the cartridge wall.
ARESTIN® is easy to administer

**Place the cartridge tip into the periodontal pocket, parallel to the long axis of the tooth. Be sure not to force the tip into the base of the pocket.**

**Gently press the thumb ring to express the ARESTIN® powder while withdrawing the cartridge tip away from the base of the pocket. If you feel any resistance during delivery, withdraw the device further.**

**Once delivery is complete, retract the thumb ring and remove the ARESTIN® cartridge with your free hand. Appropriately discard the cartridge and sterilize the handle prior to reuse.**
ARESTIN® is safe and well tolerated in clinical trials

<table>
<thead>
<tr>
<th>Treatment-emergent AEs</th>
<th>SRP alone N=250</th>
<th>SRP + Placebo N=249</th>
<th>ARESTIN® + SRP N=423</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>7.2%</td>
<td>11.6%</td>
<td>9.0%</td>
</tr>
<tr>
<td>Infection</td>
<td>8.0%</td>
<td>9.6%</td>
<td>7.6%</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>8.4%</td>
<td>6.8%</td>
<td>6.4%</td>
</tr>
<tr>
<td>Mouth ulceration</td>
<td>1.6%</td>
<td>3.2%</td>
<td>5.0%</td>
</tr>
<tr>
<td>Flu syndrome</td>
<td>3.2%</td>
<td>6.4%</td>
<td>5.0%</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>3.2%</td>
<td>1.6%</td>
<td>4.3%</td>
</tr>
<tr>
<td>Pain</td>
<td>4.0%</td>
<td>1.2%</td>
<td>4.3%</td>
</tr>
</tbody>
</table>

Summary

- Three out of 4 American adults develop periodontal disease, yet this persistent infection often goes untreated.

- The AAP reports that periodontal bacteria can enter the bloodstream, travel to major organs, begin new infections, and potentially lead to additional health problems.

- SRP instrumentation has mechanical limitations and can leave bacteria behind in the periodontium.

*A causal relationship has not been fully established.

ARESTIN® is a locally administered antibiotic that can help eliminate the bacteria that SRP leaves behind.

ARESTIN® maintains therapeutic drug concentrations in the periodontal pocket for up to 21 days, managing the infection long after treatment with SRP.

ARESTIN® + SRP has been shown to significantly reduce quantity and proportions of red complex bacteria vs SRP alone.

ARESTIN® is significantly more effective than SRP alone in reducing periodontal pocket depth, even in smokers and difficult-to-treat patients.

ARESTIN® is indicated as an adjunct to scaling and root planing (SRP) procedures for reduction of pocket depth in patients with adult periodontitis. ARESTIN® may be used as part of a periodontal maintenance program which includes good oral hygiene, and scaling and root planing.

ARESTIN® contains minocycline, a tetracycline derivative, and therefore should not be used in children and in pregnant or nursing women. The use of drugs of the tetracycline class during tooth development may cause permanent discoloration of the teeth.

The most common treatment-emergent adverse events were headache (9.0%), infection (7.6%), flu syndrome (5.0%), and pain (4.3%). These occurred at a similar rate to SRP and SRP + placebo.

Please see accompanying full Prescribing Information.