Antimicrobial Photodynamic Therapy in the Treatment of Chronic Adult Periodontitis

Nicolas G. Loebel¹, Cary C. Galler² and Roger C. Andersen¹*

¹Ondine Biomedical Inc., Vancouver, BC, Canada.
²University of Toronto, Dept. of Periodontics, North York, ON, Canada.

Correspondence:
Roger Andersen, Ondine Biomedical Inc, #800 – 1100 Melville St., Vancouver, BC V6E 4A6, Canada, Fax: 425-489-1101; E-mail: randersen@ondinebio.com.

Received: 02 January 2018; Accepted: 24 January 2018

Citation: Nicolas G. Loebel, Cary C. Galler, Roger C. Andersen. Antimicrobial Photodynamic Therapy in the Treatment of Chronic Adult Periodontitis. Oral Health Dental Sci. 2018; 2(1); 1-7.

ABSTRACT

Objective: Antimicrobial photodynamic therapy (aPDT) is a new adjunctive therapy for chronic periodontitis. The study hypothesis was that aPDT applied as an adjunct to scaling and root planing (SRP) would improve 12-week clinical outcomes in the treatment of chronic adult periodontitis, compared to SRP alone.

Methods: 34 patients diagnosed with chronic periodontitis were recruited into a randomized, examiner-blinded, parallel-group study with two equal cohorts (SRP alone and SRP + aPDT). Both cohorts were treated with SRP at all probing sites ≥ 5 mm that exhibited bleeding on probing (BOP). In the intervention group a single aPDT treatment was deployed following SRP.

Results: Combination therapy (aPDT + SRP) produced significant gain in clinical attachment level (CAL) (0.53 mm, p=0.0017) and probing depth reductions (PD) (0.73 mm, p=0.0002) when averaged across all regions of the mouth, versus the SRP-only arm at 3 months. Treatment with adjunctive aPDT increased by 8-fold the number of patients experiencing >1.5 mm gain in CAL, versus the control arm (5.9% in the SRP arm, 47.1% in the aPDT arm, p=0.022) at 3 months.

Conclusions: This study demonstrated that adjunctive aPDT provided significant gain in CAL and PD reduction, compared to SRP alone in the treatment of chronic adult periodontitis.

Keywords
Periodontal diseases, aPDT, Antimicrobial photodynamic therapy, Periodontitis, Scaling, Root planning, Antibiotic resistance, Clinical trial.

Introduction

Antimicrobial photodynamic therapy (aPDT) has been demonstrated to be an effective, non-antibiotic, antimicrobial approach in vitro [1,2]. The technique involves the use of light energy to activate a photosensitive molecule which then transmits energy directly to a substrate via electron abstraction/redox interactions (type I photoreaction) and/or interacts with molecular oxygen to produce singlet oxygen and derived compounds (type II photoreaction). These photoreactions cause prokaryotic membrane damage through lipid peroxidation and other oxidative mechanisms [3-5].

aPDT has been demonstrated to exert potent antimicrobial effects against biofilms, in contrast to many antimicrobial compounds that retain efficacy primarily against planktonic cultures [6,7]. Studies have shown that biofilms of oral bacteria are much more difficult to eradicate by conventional means [8,9] than planktonic cultures because of the strong tissue adherence and physical exclusion of antimicrobial substances in biofilms [10,11]. Close proximity of one cell to another permits information exchange through quorum sensing [12], with resulting survival advantages conferred across the entire colony [7]. The fact that aPDT was found to be so effective against biofilms suggests an innate advantage over other antimicrobial periodontal therapies [13-15]. This work reports on a randomized, blinded, controlled evaluation of aPDT as an adjunct...
to scaling and root planing (SRP) in the treatment of chronic adult periodontitis.

Materials and Methods
This randomized, examiner-blinded, parallel-group study was carried out in 34 patients at a single study center in North York, ON. This site was also enrolled in a larger study (N=106) at 3 other clinical centers. The study was designed to assess the efficacy and safety of a commercial aPDT system (Periowave™, Ondine Biomedical, Inc., Vancouver, BC, Canada) in the treatment of adult subjects diagnosed with chronic periodontitis. The study included two cohorts: (1) a control group, receiving SRP Alone (“SRP Alone” arm); and (2) a test group, receiving SRP followed by aPDT treatment to the qualifying periodontal defect sites (“aPDT + SRP” arm). Gain in clinical attachment level (CAL), reduction in probing depth (PD), and reduction in bleeding on probing (BOP) were evaluated for all defect sites in all patients.

The aPDT system deployed in this study consisted of three components: (1) a laser base station incorporating a low power (<220 mW), continuous-wave diode laser operating at a red wavelength (670 nm) over a 60-second treatment cycle; (2) an autoclavable handpiece connected to the laser via fiberoptic cable; and (3) a treatment kit composed of a single-use light diffusing tip, a blunt-ended irrigation needle and a pre-filled syringe containing photosensitizer solution (0.01% methylene blue USP in a buffered, isotonic, viscosity-modified base).

The aPDT treatment protocol consisted of SRP using ultrasonic instrumentation, suppression of the majority of post-SRP bleeding using light direct pressure, and subsequent irrigation of the treatment site with approximately 0.2 ml of photosensitizer solution. The irrigated pocket was then immediately illuminated via the laser handpiece and light-diffusing tip for a period of 60 seconds. Residual photosensitizer was suctioned from the buccal margin after the activation cycle was completed.

CAL measurements were made from the base of the sulcus to the cementoenamel junction using a PCPUNC-15 periodontal probe. Approximately 20 gf probing force was used. Examiners were calibrated prior to study initiation via comparison of two full-mouth probing charts taken on the same patient a minimum of 20 minutes apart in time. Retraining and recalibration of the examiner was conducted if more than 5% of the PD readings differed by 1 mm or more. In the case of a crown, CAL measurements were taken from the crown margin to the base of the pocket. Gain in CAL was prospectively declared as the primary endpoint of the study. Reduction in PD was considered a secondary study endpoint. PD measurements were taken by calibrated examiners using the same PCPUNC-15 periodontal probe. Bleeding on probing (BOP) was additionally assessed and given a positive (present) or negative (absent) score. All measurements were recorded at 6 sites per tooth.

The study was reviewed and approved by a local institutional review board prior to enrollment of subjects. All patients signed a standard consent form consistent with 21 CFR 50, Protection of Human Subjects. The form was approved by the institutional review board prior to initiation of any study procedure. The study was carried out and monitored in accordance with the Helsinki Declaration of 1975, and subsequent revisions.

Statistical Methodology
The hypothesis of the study was that aPDT applied as an adjunct to SRP would improve 12-week clinical outcomes in the treatment of chronic adult periodontitis, compared to SRP alone. As defined in the protocol, the primary analysis population (by ICH-E9 definition) included all randomized subjects from whom a baseline value and at least one post-baseline measurement were generated. The primary analysis of safety included all subjects who received randomized treatment and contributed post-randomization follow-up data. Safety endpoints were based on treatment actually received. The multi-center study incorporated one primary endpoint, gain in CAL, along with the following assumptions: detection threshold for improvement = 0.4 mm; power = 90%; significance = 95%; SD of measurements = 0.63. Type I error probability was set at 5%, and type II error probability at 10%.

Descriptive statistics were used to summarize baseline information and response (SAS, Cary, NC). Fisher’s Exact test was used to evaluate the homogeneity of groups for categorical variables. Kruskal-Wallace tests were used to evaluate the homogeneity of baseline continuous measures. For inferential analyses, a p-value ≤ 0.05 was considered statistically significant.

For the CAL and PD endpoints, the methodological recommendations of Blance’s et al. publication [16] were adopted for the statistical analysis, because of the robust treatment of baseline interactions, statistical power and randomization. A repeated measures model was used to evaluate the change from baseline as a function of baseline values and selected covariates. Models were based on patient averages and included treatment, visit (6 weeks and 12 weeks), and treatment visit interactions. The second analysis approach included a region of mouth (ROM) assessment as well as treatment×region interactions. In the patient average model, the response for all treated sites was averaged for each visit. For the ROM model, the response was averaged across the anterior, pre-molars, and molars separately, and average treatment effects were obtained across the three regions via least squares (LS) means. Unstructured covariance models were used. A Kruskal-Wallace test was used in a confirmatory analysis of patient average change from baseline in CAL and PD to provide an analysis with limited distribution assumptions.

A General Estimation Equations (GEE) model was used to fit a logistic model evaluating the probability of resolving bleeding on probing. This binary model was based on evaluation of the number of sites with resolved BOP divided by the total number of treated sites.

Enrollment Criteria and Patient Demographics
Subjects diagnosed with chronic adult periodontitis with otherwise unremarkable medical histories, with at least 18 or more fully erupted teeth and with at least 4 measurement sites exhibiting
probing depth of 6-9 mm in at least two quadrants of the mouth were eligible to participate in the study. Subgingival instrumentation over the past 4 months disqualified the patient from enrollment, as did antibiotic use in the preceding 1-month period. Other exclusion criteria included known allergy to methylene blue, glucose-6-phosphate dehydrogenase enzymopathy by subject report, active periapical or periodontal abscess, history of acute necrotizing ulcerative gingivitis, pregnancy within the preceding 12 months or planned within 6 months following enrollment, or concomitant use of any photosensitizing medications.

The investigator allocated treatment according to a computer generated pseudo-random code using the method of random permuted blocks. Blinding was accomplished by utilizing a treatment-blinded dental examiner qualified to take clinical measurements who was separate from the treating clinician. The study site was trained on use of the equipment, study protocol, data collection, and CRF completion procedures prior to the enrollment of study patients. Study monitoring was conducted on a regular schedule by a trained and certified monitor, and study conduct review and close-out was conducted by a third-party clinical monitor with experience in dental clinical studies. An independent contract research organization performed data entry.

Results

39 subjects were assessed for eligibility and all were enrolled and randomized into this study. 19 patients were allocated to the aPDT + SRP treatment arm and 20 patients were allocated to the SRP Alone control arm. Two patients in the treatment arm did not present for either the 6- or 12-week follow-up visits due to unrelated issues and were lost to follow-up and analysis. One patient in the control arm received antibiotic treatment for an unrelated condition and was withdrawn from the study. A total of 34 subjects in total were therefore enrolled and randomized 1:1 to either aPDT + SRP or SRP Alone arms and subjected to analysis.

Subjects enrolled in the SRP Alone arm were screened for up to 16 days, and received two SRP procedures (one for each half of the mouth sequentially) as well as follow-up examinations at 6- and 12 weeks (a standard periodontal recall period). Subjects enrolled in the aPDT + SRP arm were screened for up to 16 days, and received one SRP treatment (for the first half of the mouth), one SRP plus the aPDT treatment (SRP for the second half of the mouth and aPDT for all selected treatment sites) and then follow-up examinations at 6- and 12 weeks. Demographics for the subjects are given in Table 1.

<table>
<thead>
<tr>
<th>Alcohol Use</th>
<th>Never</th>
<th>1 (5.9%)</th>
<th>1 (5.9%)</th>
<th>0.7937</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Past</td>
<td>1 (5.9%)</td>
<td>3 (17.6%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Current</td>
<td>15 (88.2%)</td>
<td>13 (76.5%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treated Sites per Subject [H]</th>
<th>N</th>
<th>17</th>
<th>17</th>
<th>0.0700</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (Std)</td>
<td>27.4 (15.40)</td>
<td>19.1 (9.34)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>21.0</td>
<td>17.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Min, Max</td>
<td>7, 68</td>
<td>8, 40</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient Average Baseline CAL [H]</th>
<th>N</th>
<th>17</th>
<th>17</th>
<th>0.0982</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (Std)</td>
<td>4.92 (1.00)</td>
<td>4.66 (0.76)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Min, Max</td>
<td>2.48, 5.96</td>
<td>3.25, 5.75</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient Average Baseline PD [I]</th>
<th>N</th>
<th>17</th>
<th>17</th>
<th>0.4589</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (Std)</td>
<td>5.86 (0.56)</td>
<td>5.80 (0.26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Min, Max</td>
<td>5.36, 7.51</td>
<td>5.40, 6.40</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1: Patient demographics.
[1] Sites with baseline PD ≥ 5 and bleeding on probing.
[2] P-values from Fisher’s Exact test or the Kruskal-Wallis test.

Overall follow-up information accounting for each data unit is presented in Table 2.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Subjects</th>
<th>Regions</th>
<th>Teeth</th>
<th>Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>aPDT + SRP</td>
<td>17</td>
<td>42</td>
<td>184</td>
<td>463</td>
</tr>
<tr>
<td>SRP Alone</td>
<td>17</td>
<td>39</td>
<td>163</td>
<td>325</td>
</tr>
</tbody>
</table>

Table 2: Data unit accountability information.

Differences between the number of experimental units averaged per subject in the aPDT and control arms were not significant (p=0.07). Furcation sites represented 17% of qualifying defects in this study.

In these repeated model analyses, patient assessments were treated as repeated measurements, and baseline value for each measurement site was regarded as a covariate. Initial tested model effects included baseline CAL, gender, alcohol intake, smoking status, visit number, treatment, and treatment by visit interaction. With the exception of aPDT treatment, none of these parameters were found to be significant in the model for gain in CAL (Table 3), and therefore the models could be further reduced.

<table>
<thead>
<tr>
<th>Factors</th>
<th>ANCOVA P-values</th>
<th>Patient Average Model</th>
<th>ROM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model</td>
<td>0.3031</td>
<td>0.1250</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>0.8251</td>
<td>0.5458</td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>0.3874</td>
<td>0.2154</td>
<td></td>
</tr>
<tr>
<td>Smoking Status</td>
<td>0.1409</td>
<td>0.1448</td>
<td></td>
</tr>
<tr>
<td>Visit</td>
<td>0.9865</td>
<td>0.7797</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>0.0056</td>
<td>0.0017</td>
<td></td>
</tr>
<tr>
<td>Treatment X Visit Interaction</td>
<td>0.5259</td>
<td>0.2746</td>
<td></td>
</tr>
<tr>
<td>Region</td>
<td>NA</td>
<td>0.1712</td>
<td></td>
</tr>
<tr>
<td>Treatment X Region Interaction</td>
<td>NA</td>
<td>0.5330</td>
<td></td>
</tr>
</tbody>
</table>

Table 3: ANCOVA Model effects and associated Type III p-values.

Similarly, with the exception of baseline PD and treatment effect, none of the modeled parameters were found to be significant for
PD reduction (Table 4).

<table>
<thead>
<tr>
<th>Factors</th>
<th>ANCOVA P-value</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patient Average Model</td>
<td>ROM</td>
<td></td>
</tr>
<tr>
<td>Model</td>
<td>0.0036</td>
<td>0.3098</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>0.2660</td>
<td>0.3976</td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>0.2945</td>
<td>0.2831</td>
<td></td>
</tr>
<tr>
<td>Smoking Status</td>
<td>0.5171</td>
<td>0.2412</td>
<td></td>
</tr>
<tr>
<td>Visit</td>
<td>0.7851</td>
<td>0.8315</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>0.0025</td>
<td>0.0002</td>
<td></td>
</tr>
<tr>
<td>Treatment X Visit Interaction</td>
<td>0.8564</td>
<td>0.8413</td>
<td></td>
</tr>
<tr>
<td>Region</td>
<td>NA</td>
<td>0.2692</td>
<td></td>
</tr>
<tr>
<td>Treatment X Region Interaction</td>
<td>NA</td>
<td>0.2636</td>
<td></td>
</tr>
</tbody>
</table>

Table 4: ANCOVA Model effects and associated Type III p-value.

The correlation between treatment outcome and baseline PD is a widely recognized effect [10]. Results were further analyzed by frequency distribution analysis [17], in order to separately evaluate treatment effect on a range of different baseline pocket categories versus SRP Alone.

Clinical Attachment Level Gain

Table 5.1 demonstrates that the average CAL gain for those pockets with an initial PD ≥ 5 mm and exhibiting BOP was significantly greater in the aPDT + SRP group than in the SRP Alone group. This outcome is similarly demonstrated in Table 5.2 after adjusting for region of mouth.

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Difference (SE)</th>
<th>P-value [2]</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Diff</td>
<td>-0.53 (0.152)</td>
<td>0.0017</td>
<td>(-0.838, -0.217)</td>
</tr>
<tr>
<td>Week 6 Diff</td>
<td>-0.57 (0.152)</td>
<td>0.0009</td>
<td>(-0.882, -0.257)</td>
</tr>
<tr>
<td>Week 12 Diff</td>
<td>-0.49 (0.160)</td>
<td>0.0052</td>
<td>(-0.814, -0.158)</td>
</tr>
</tbody>
</table>

Table 5.1: CAL gain, LS means, change from baseline.

Probing Depth Reduction

Table 6.1 demonstrates that average PD reduction for those pockets with an initial PD ≥ 5 mm and exhibiting BOP was significantly greater in the aPDT + SRP group than in the SRP Alone group. This outcome is similarly demonstrated in Table 6.2 after adjusting for region of mouth.

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Difference (SE)</th>
<th>P-value [2]</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Diff</td>
<td>-0.73 (0.167)</td>
<td>0.0002</td>
<td>(-1.071, -0.385)</td>
</tr>
<tr>
<td>Week 6 Diff</td>
<td>-0.74 (0.163)</td>
<td>0.0178</td>
<td>(-0.918, -0.094)</td>
</tr>
<tr>
<td>Week 12 Diff</td>
<td>-0.72 (0.179)</td>
<td>0.0004</td>
<td>(-1.088, -0.352)</td>
</tr>
</tbody>
</table>

Table 6.1: PD reduction, LS means, change from baseline.

The ratio between CAL gain and PD reduction was 0.73 averaged across all teeth and time points, implying that gain in attachment dominated the response to aPDT treatment.

Bleeding On Probing Reduction

Analysis of BOP reduction demonstrated no difference in BOP rates between study cohorts at either week 6 or at week 12.

Adverse Events

No device-related serious adverse events were reported during or after the course of the study.

Frequency Distribution Analysis

The methodological recommendations of a recent publication17 underscoring the importance of presenting probing measurements as frequency distributions, rather than only means, were adopted in order to further analyze the results presented above. Table 7 provides gain in CAL (averaged across all patients), stratified in 0.5 mm increments, for the adjunctive aPDT treatment vs. SRP Alone.

<table>
<thead>
<tr>
<th>Visit</th>
<th>≤ 0.5</th>
<th>&gt;0.5 - ≤1.0</th>
<th>&gt;1.0 - ≤1.5</th>
<th>&gt;1.5</th>
<th>P-value [1]</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 Weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.022</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>4 (23.5%)</td>
<td>6 (35.3%)</td>
<td>7 (41.2%)</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>4 (23.5%)</td>
<td>7 (41.2%)</td>
<td>5 (29.4%)</td>
<td>1 (5.9%)</td>
<td></td>
</tr>
<tr>
<td>12 Weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.020</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>6 (35.3%)</td>
<td>3 (17.7%)</td>
<td>8 (47.1%)</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>3 (17.7%)</td>
<td>7 (41.2%)</td>
<td>6 (35.3%)</td>
<td>1 (5.9%)</td>
<td></td>
</tr>
</tbody>
</table>

Table 7: Distribution of patient average response.
As a confirmatory analysis, non-parametric/Wilcoxon Rank-sum tests were also used to compare the patient average changes across all sites for each subject, and these were found to be significant at both week 6 and week 12, with all p-values ≤ 0.01.

The improvement in CAL for patients receiving aPDT + SRP versus SRP Alone is plotted graphically in Figure 1, where 6-week outcomes are compared to 12-week outcomes. It may be observed that apart from a single outlier, patients in the SRP arm experienced roughly half the improvement in CAL of patients in the aPDT arm by the end of the study.

Figure 1: CAL response in treated versus control patients.

Summary Outcomes
Results of this study demonstrated that patients receiving adjunctive aPDT experienced significantly better outcomes than those receiving SRP Alone at 3 months (gain in CAL over SRP Alone 0.53 mm, p=0.0017; reduction in PD over SRP Alone 0.73 mm, p=0.0002 averaged across all regions of the mouth). Frequency distribution analysis demonstrated that adjunctive aPDT increased by 8-fold the number of patients experiencing > 1.5 mm gain in CAL, versus the control arm (5.9% in the SRP arm, 47.1% in the aPDT arm, p=0.022) at 3 months. Comparison of 6 and 12-week data between the two study arms showed that patients in the SRP arm experienced roughly half the improvement in CAL of patients in the aPDT arm by the end of the study. Gain in CAL dominated the average response to treatment (versus recession), comprising 73% of the overall pocket depth reduction.

Discussion
Nonsurgical treatment of chronic adult periodontitis relies upon SRP as the gold standard for subgingival debridement [18,19]. SRP has been demonstrated to leave both calculus [20] and bacteria [21] behind in the treated area, and to open dentinal tubules, permitting invasion by the residual periopathogens with biofilm recolonization shortly thereafter [22,23]. A sub-population of patients continues to demonstrate chronic periodontal tissue breakdown after SRP. These patients often present with concomitant predisposing risk factors [24,25] such as smoking, diabetes, hereditary factors, and systemic disease [26]; chronically persistent superinfection with one or more pathogenic species may also be involved [27]. A continued inflammatory response occurs in these cases, paralleled by a sustained increase in gingival crevicular fluid flow rate (GCF) [28]. Locally-administered chemotherapeutic agents may be partially or wholly neutralized by GCF and constituents (e.g. chlorhexidine binding to anionic acid groups on glycoproteins [29] or by physical displacement through the rapid GCF exchange [30]). In addition, bacteria within the bulk layers of the plaque biofilm are metabolically less active, thereby muting drug uptake and response. Superficial layers of the biofilm may also degenerate under the bacteriostatic influence of the antibiotic, inhibiting further diffusion into the bulk layers [31]. Methylene blue-based aPDT is a rapidly cidal approach that tends to overcome these issues, demonstrating 4-6 log10 (10,000 – 1,000,000-fold) reduction in viability of microorganisms in laboratory biofilms over 60 seconds [32]. Methylene blue (3,7-bis[Dimethylamino]-phenazathionium chloride) is a cationic heterocyclic aromatic dye commonly used for histological visualization, treatment of methemoglobinemia [33], visualization of polyps during endoscopic polypectomy, tracing lymphatic drainage during sentinel lymph node dissection [34], and visualization of GI dysplasia [35]. aPDT using methylene blue is widely used in European countries for the disinfection of fresh frozen donor plasma and red cell suspensions [36]. aPDT using methylene blue has also been demonstrated to inactivate the virulence-associated protease of P. gingivalis, and to inactivate destructive host cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-1β [37], providing a potent dual pathway to suppression of the microorganisms as well as the various pro-inflammatory factors involved.

Another advantage of aPDT as a microbicidal modality is that it is not subject to the issues of resistance that plague the use of antibiotics [2]. Microbial resistance to antibiotics is upregulated by the systematic, worldwide, improper use of antibiotics for treatment of non-susceptible human infections (e.g. viral infections), by inadequate administration regimens, and through use in animal feed stocks for growth promotion [38]. Gene patterns found in resistant bacterial strains are identical in animals and humans, indicating transfer of those resistance genes between the species [39]. Low-dose (sub-antimicrobial) administration of antibiotics such as doxycycline for reduction of matrix metalloproteinase is a practice also implicated in up regulation of antibiotic resistance [40].

Finally, another advantage of aPDT lies in the fact that the low-level laser light source does not cause thermal damage to tissues. By contrast, use of higher-power lasers to physically debride tissues such as those of the gingival sulcus may be problematic, due to the side-effects of thermal injury and damage to surrounding tissues [41]. A retrospective analysis of available literature demonstrated little to no additional benefit of high power lasers used adjunctively...
bleeding suppression was accomplished by application of direct
from the sulcus. Where such cases were encountered, adequate
procedure tended to physically eject the photosensitizer solution
It was also observed that excessive bleeding after the SRP
defects into a separate appointment would probably be required.
the clinic, rescheduling patients presenting with large numbers of
scaling and root planning. From a practical utility standpoint in
the mouth could rise to an appreciable fraction of the time spent
with more than 1 defect site, the total procedural time throughout
for 60 seconds per defect site. Because a single tooth often presented
technique required light activation of the applied sensitizer solution
in a 34-patient study.
parallel-group study provides clear evidence of safety and efficacy
involved. By contrast, the present randomized, examiner-blinded,
repeated in another comprehensive review of the literature [44],
ilimited power of the meta-analysis, precluding any conclusions
of significant benefit in the adjunctive treatment of chronic adult
periodontitis over a standard recall period of 3 months.

Conflict of Interest
This study was funded by Ondine Biomedical Inc., Vancouver B.C.
Dr. Galler is in private practice and has received compensation from
Ondine Biomedical Inc. Drs. Loebel and Andersen is employed by
Ondine Biomedical Inc.

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