ORIGINAL ARTICLE

Photodynamic therapy of persistent pockets in maintenance patients—a clinical study

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Abstract The aim of this study was to compare the shortterm performance of a session of single photodynamic therapy (PDT) and of a conventional ultrasonic debridement (UST) in persistent pockets of maintenance patients. In a prospective, randomized, controlled, single-blind clinical study, patients with chronic periodontitis with at least two persistent pockets (>4 mm) were enrolled. They were treated either with UST (n=29) or PDT (n=25). Clinical and microbiological examinations were performed at baseline and after 3 month. For UST, the mean probing depth was reduced from 5.3 to 4.5 mm (p=<0.001) and for PDT from 5.3 to 4.7 mm (p<0.001) with no difference between the two treatment modalities. Microbial counts were significantly reduced about 30% to 40% immediately after debridement but returned to baseline values at month 3 irrespective of treatment. PDT is not superior to conventional mechanical treatment of persistent pockets, but it may be a meaningful therapeutic alternative; the clinical effects were too minor to draw a definitive conclusion.

Keywords Photodynamic therapy · Maintenance · Scaling · Persistent pocket · Periodontitis

Introduction

An important goal of periodontal therapy is the removal of the bacterial biofilm from the subgingival root surface. The success of mechanical debridement decreases with increasing probing depth and with furcation involvement [13, 30, 38]. The problems inherent to subgingival scaling result from the difficult access to the root surface and from the bizarre root morphology. Therefore, complete removal of bacterial deposits in vivo is accomplished rather seldom [8, 27, 28], and bacterial reservoirs can survive in mechanically inaccessible areas. Thus, deep pockets may persist or recur after mechanical therapy.

In order to maintain stable long-term results of persistent pockets after cause-related therapy, supportive therapy has to be performed in regular intervals. During supportive therapy, recurrent or persistent pockets can be treated either with repeated mechanical root debridement or with locally delivered antimicrobial devices. Both treatment modalities have drawbacks: repeated mechanical root debridement leads to loss of root substance and dentinal hypersensitivity, and local antimicrobial devices may increase the antibiotic resistance. Thus, alternative therapies are warranted.

One possible alternative may be photodynamic therapy (PDT). Organisms absorb a dye (photosensitizer) and by irradiation with light in the visible range of the spectrum, the dye will be excited to its triplet state, whose energy is transferred to molecular oxygen. The reaction product

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formed is highly reactive singlet oxygen, which induces cell damage or cell death. Despite of its short half-life time (4µs in water), singlet oxygen exerts strong cytotoxic effects, destroying cellular constituents such as organelles, proteins, nucleic acids, cholesterol, etc. Microorganisms are killed by singlet oxygen, which include viruses, bacteria, protozoa, and fungi [24].

Even though the effects of photodynamic action have been known for a long time [16], interest in practical use only increased in the last years [9, 21, 39]. Since several studies have shown that killing of gram-positive, as well as gram-negative bacteria is possible [3, 11, 22], the Wilson group in London investigated different aspects of PDT application in dentistry in vitro and in vivo systems [42]. They studied the photosensitizing effects in lesions of endodontic, peri-implant, caries, or periodontal origin. Periodontal pathogens, e.g., Porphyromonas gingivalis, Prevotella intermedia, Fusobacterium nucleatum, and Parvimonas micra were killed by photodynamic action in vitro [19] and in vivo [41] by altering the membrane fluidity [4]. Reduction of the biological activities of the key virulence factors such as lipopolysaccharide and proteases may act as an additional benefit [19].

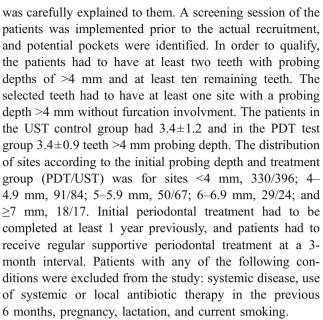
Despite the wealth of accumulated data, up to now, no established treatment protocols for the treatment of recurrent or persistent periodontal pockets exists. PDT may be a meaningful therapeutic approach since the biofilm on the root surface can be easily flushed with the dye and illuminated with light [24]. In this prospective, randomized, controlled clinical study on maintenance patients we investigated:

- whether a single PDT session can reduce probing depth in persistent periodontal pockets beyond what can be achieved with conventional mechanical debridement; and
- (2.) whether a single PDT session can change the microbial composition towards a healthier flora and decrease the total load of subgingival bacteria more than conventional periodontal therapy.

Material and methods

Patients

Sixty patients with moderate to advanced chronic periodontitis (age>35 years, mean age, 48±8 years) were selected from the maintenance pool of the Unit of Periodontology, School of Dentistry, Greifswald, Germany. The protocol of the study was approved by the Ethics Committee of the Ernst-Moritz-Arndt-University of Greifswald. Patients gave their informed consent after the study



A computer-generated randomization list assigned 30 patients to the UST control group and 30 to the PDT test group. From the initially included 60 patients, six had to be excluded because five received antibiotic therapy and one developed an abscess during the observation period. Thus, we report on 25 subjects in the PDT group (eight men) and 29 subjects in the control group (seven men).

Clinical protocol

After assessment of the clinical variables during the initial examination, the patients were assigned to the test or to the control group according to the randomization list. Clinical examination was performed by a blinded investigator. During treatment, patients did not receive a detailed information on which instrument was actually used. The observation period spanned over one maintenance interval of 3 months. Clinical examination was performed at baseline and in an identical manner, 3 months later. Proper oral hygiene was reinforced in the baseline session after the clinical examination prior to instrumentation in both groups. There was no further session between baseline and the 3 months examination.

The patients of the control group (UST) were treated with Slimline® inserts (Cavitron® SPS Ultrasonic, power setting 1/4 [end of Blue zone], tips FSI-SLI and FSI-10 [Dentsply, Konstanz, Germany]; tips were chosen according to operator's preference). Subgingival instrumentation was performed on selected teeth, irrespective of bleeding on probing; the time needed was up to the operator. The patients were motivated at each appointment to perform oral hygiene regularly. Prior to subgingival instrumentation, the supragingival plaque was dyed with a disclosing agent and removed by polishing.



In the test group, treatment was performed on selected teeth with PDT (SaveDent® Dental Laser System, Asclepion-Meditec Ltd., Fife, UK; diode laser, wavelengths 635 nm; this system has been further developed by and is now sold by Cumdente, Tübingen, Germany). The pockets were rinsed with the photosensitizer (5% tolonium chloride, Asclepion-Meditec, Fife, UK) with a blunt cannula guided along the bottom of the pocket by continuous horizontal movements to achieve a complete flushing of the pocket and root surface. Flushing with the photosensitizer was restricted to 30 s on each site. A ball-shaped laser probe (SaveDent®) was used to activate the photosensitizer. The laser was guided, like an ultrasonic probe, from the pocket bottom to the gingival margin under continuous horizontal movements in order to ensure that all areas of the pocket are irradiated. Each test surface was irradiated with a light dose of 100 mW for 1 min.

Clinical parameters

Plaque index

Plaque deposits were stained with a disclosing solution and assessed as present or absent on all teeth on six sites per tooth.

Probing depth and relative attachment level

Measurements of the probing depth (PD) and the relative attachment level (RAL) were taken at the selected teeth with a computerized probe (Florida Probe Corporation, Gainsville, Florida, USA) at six sites per tooth (mesio-, mid-, and distobuccal, and mesio-, mid-, and distolingual) by an operator experienced in the use of the probe, who was blinded for the treatment modalities. PD was measured from the free gingival margin to the base of the pocket, and RAL was measured with Florida Disc Probe® (Florida Probe Corporation), taking cusps or incisal edges as reference point. PD and RAL measurements were duplicated and averaged, respectively. Deviations in the values exceeding 0.5 mm were verified by a third measurement. If three measurements had to be conducted, the one with the highest deviation was excluded.

Bleeding upon probing

Bleeding upon probing was assessed after charting the probing depth. The percentage of sites, which bled upon probing was calculated.

Microbiology

Prior to probing at baseline and at 3 months, bacterial samples were taken from the sites, which had been

identified at the screening visit. Before taking the microbiological sample, the supragingival plaque was removed with a curette, and the site was held dry using cotton rolls. Then, sterile paper tips (ISO #40, Carpgen, Münster, Germany) were inserted into the identified site of each selected tooth for 10 s and pooled for each patient. The pooled sample was analyzed for the quantitative assessment of six periodontal pathogens (Aggregatibacter actinomycetemcomitans, P. gingivalis, Tannerella forsythia, Treponema denticola, F. nucleatum, and P. intermedia), as well as for the registration of the total load of microbiota. A commercial real-time PCR test (Meridol Paro-Diagnostik, Gaba, Lörrach, Germany) was performed.

Data and statistical analysis

The power calculation was based on patient means and revealed that when the sample size is 60, there is 80% power to detect a difference in means of 0.40 mm. Additional analyses were performed in order to assess upper limits for sample size varying in standard deviation between 0.50 and 1.00 and variance of means between 0.15 (e.g., means of 1.50, 1.75, 2.20, and 2.50) and 0.40.

As a main variable, we selected probing depth; explorative analyses were performed on bleeding, probing, attachment level, and microbiology. A paired or unpaired t test was used for the analysis of probing depth, attachment level, plaque and bleeding indices. Based on initial probing depth, categories were generated for each patient: shallow sites with a PD value of 3-3.9 mm, moderate sites with 4-5 mm and 5-5.9 mm, deep sites with 6-6.9 mm, and advanced sites with ≥7 mm. All periodontal variables were averaged per patient. For the microbiological analyses, we used the Friedman test within a study group. And if this test showed a high significance, the paired comparisons were made by means of a Wilcoxon test. The analysis between the treatment modalities was performed with the Mann-Whitney U test. A significance level of p < 0.05 was assumed for all analyses (SPSS, version 11, USA).

Results

In the UST group, no adverse events or side effects (e.g., redness, swelling, or abscesses) were observed; in the PDT group, one abscess developed.

Plaque index and bleeding upon probing

The plaque index decreased from 30.5% to 24.0% in the UST group and from 33.0% to 23.8% in the PDT group (Table 1). In both groups, bleeding upon probing (BOP) did not change significantly from baseline to the re-



examination (UST, baseline 4.7 to 5.7% and PDT, from 5.7 to 3.3%).

Probing depth and relative attachment level

The mean probing depth was significantly reduced from 3.3 to 3.1 mm by the ultrasonic treatment and from 3.5 to 3.3 mm by the photodynamic therapy (Table 1). The percentage of pockets >4 mm decreased from 30 to 23% in the UST group and from 33 to 29% in the PDT group; there was no significant difference between PDT and UST. In both groups, the mean probing depth of sites >4 mm was significantly reduced (UST, from 5.3 to 4.5 mm and PDT, from 5.3 to 4.7 mm). No significant difference was found between the two therapy groups both at baseline and in the final recording.

According to the baseline categories of the initial probing depths, Fig. 1 displays the mean probing depth and change of the attachment level after 3 months for the two therapy methods. In the probing depth category of 4–4.9 mm, a reduction was achieved from 4.5 to 4.0 mm (UST) and from 4.4 to 4.1 mm (PDT); in the probing depth category of 5–5.9 mm from 5.3 to 4.6 mm (UST) and from 5.3 to 4.7 mm (PDT); in the probing depth category of 6–6.9 mm from 6.4 to 5.2 mm (UST) and from 6.3 to 5.5 mm (PDT); and in the category ≥7 mm from 7.9 to 6.3 mm (UST) and from 8.0 to 6.8 mm (PDT).

The UST sites tended to lose attachment and to have more recession than the PDT sites. Ultrasonic scaling caused an attachment loss of 0.2 mm in the pocket category 5–5.9 mm and of 0.6 mm in the pocket category 6–6.9 mm. With PDT therapy, pockets of category 5–5.9 mm gained 0.4 mm attachment.

Microbiology

The total bacterial load was reduced in the UST group from 7.5×10^7 to 6.8×10^7 directly after the treatment (p < 0.001);

3 months later, the initial microbial load was reached again $(7.5 \times 10^7, p < 0.001)$. In the PDT group, the total bacterial count decreased from 7.6×10^7 to 7.3×10^7 directly after the treatment (p < 0.001) and reached the baseline value of 7.6× 10^7 (p<0.004) after 3 months. The differences between the UST group and the PDT group did not vary significantly (Fig. 2). Three members of the red complex (*P. gingivalis*, T. forsythia, and T. denticola), according to Socransky et al. [34], was reduced more slightly with the ultrasound therapy than with the photodynamic therapy. Two members of orange complex (F. nucleatum and P. intermedia) showed a significant difference (p < 0.011) between PDT and UST at baseline, but not after treatment and after 3 months. In the UST group, the microbiota of the orange complex was reduced more slightly than in the PDT group. A. actinomycetemcomitans was only detectable in very low counts and did not show any change no matter which therapy was applied.

Discussion

The aim of this randomized, controlled single-blind pilot study was to compare the clinical and microbiological effects of PDT treatment with conventional subgingival instrumentation (UST) in persistent pockets of chronic periodontitis patients. Our hypothesis that PDT is superior to mechanical periodontal therapy was rejected. We hypothesized that flushing and insertion of the fiber-optic applicator should allow an easier access into deep pockets and thus, would lead to a significant decrease of microbial load with a concomitant improved clinical healing. We had on our mind that new devices or treatment options should be superior to conventional treatment options as long as they are more expensive. Our results correspond, however, to those of de Oliveira et al. [10] who showed in patients with aggressive periodontitis that nonsurgical treatment with PDT alone resulted in a similar pocket depth reduction

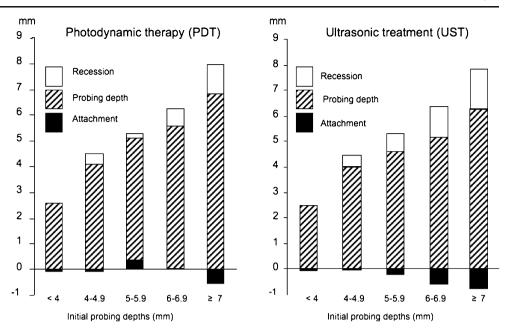
Table 1 Photodynamic (PDT) and ultrasonic treatment (UST)

		Baseline	3months	pvalue
Plaque index (%)	UST	30.5±16.5	24.0±9.5	NS
	PDT	33.0 ± 11.7	23.8 ± 9.0	NS
Bleeding on probing (%)	UST	4.7 ± 4.8	5.7 ± 8.7	NS
	PDT	5.4±4.6	3.3 ± 4.3	NS
Mean probing depth (mm)	UST	3.3 ± 0.5	3.1 ± 0.4	p<0.001
	PDT	3.5 ± 0.4	3.3 ± 0.5	p = 0.018
Probing depth, >4 mm (%)	UST	29.8 ± 11.6	23.3 ± 12.8	NS
	PDT	32.7 ± 12.7	28.7 ± 13.6	NS
Mean relative attachment level (mm)	UST	10.6 ± 1.3	10.7 ± 1.2	NS
	PDT	11.4 ± 1.70	11.4±1.6	NS
Probing depth, >4 mm (mm)	UST	5.3 ± 0.5	4.5 ± 0.6	p<0.001
	PDT	5.3 ± 0.6	$4.7\!\pm\!0.7$	<i>p</i> <0.001

Mean and standard deviation, plaque index in percentage, bleeding on probing in percentage, mean probing depth in millimeter, percentage of sites with probing depth >4 mm, and mean relative attachment level in millimeter *NS* not significant



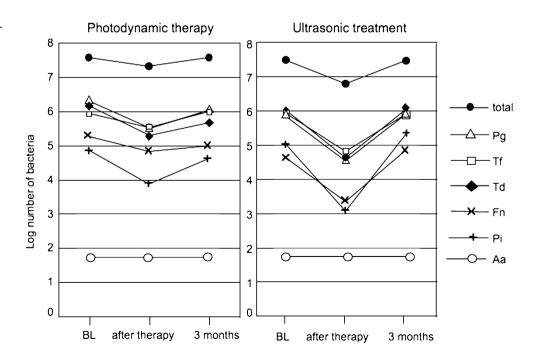
Fig. 1 Change of probing depth during the 3-month observation period split according to initial probing depth category and treatment group (PDT/UST). The distribution of sites according to the initial probing depth category and treatment group (PDT/UST) was for sites <4 mm, 396/330; ≥4–4.9 mm, 91/84; ≥5–6 mm, 50/67; ≥6–7 mm, 29/24; and ≥7 mm, 18/17



as conventional scaling in cause-related phase. Considering the clinical results, both treatment groups presented a small reduction in the percentage of sites >4 mm (5–7%) and a mean PD reduction of about 0.7 mm after 3 months in sites >4 mm. If we just regard the mean change of probing depth >4 mm in nonmolars (data not shown), an improvement of about 1 mm occurred in both treatment groups. These results correspond to those found by Kocher et al. [18] where a Vector® ultrasonic device was compared with a conventional ultrasonic for the treatment of persistent pockets during the maintenance therapy. Both units achieved a 1 mm reduction of the probing depths from

5.4 to 4.4 mm. A very similar experiment was performed by Tomasi et al. [40] who treated maintenance patients with persistent pockets either with an Er:YAG laser or with an ultrasonic instrument. Both instrumentation modalities reduced the probing depth from about 6.0 to about 5.0 mm after 4 months. In a study of Chondros et al. [7], patients receiving supportive therapy were treated either with subgingival scaling followed by PDT or scaling and root planing alone. They found no difference between the test and control group in terms of PD reduction or attachment change at 3 and 6 months, but a higher improvement of BOP in the test group.

Fig. 2 Log number of subgingival bacteria. Samples were taken before and directly after photodynamic treatment (PDT) or ultrasonic treatment (UST) and after 3 months of observation time. Aa Aggregatibacter actinomycetemcomitans, Pg Porphyromonas gingivalis, Tf Tannerella forsythia, Td Treponema denticola, Fn Fusobacterium nucleatum, Pi Prevotella intermedia, total total load



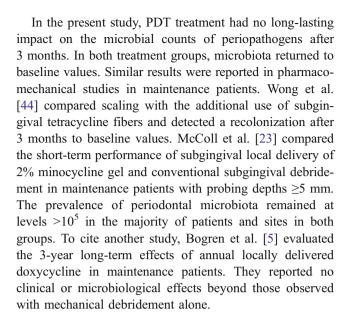


Eickholz et al. [14] investigated the effect of either scaling or exclusive subgingival application of a doxycycline gel in subjects with persistent pockets >4 mm. Six months after the treatment, both groups exhibited statistically significant reductions of probing depths (doxycycline gel, 1.4 mm and scaling, 1.1 mm). However, there were no statistically significant differences between both therapies. In a study of McColl et al. [23], sites with residual pocket probing depths ≥5 mm were repeatedly treated with minocycline gel at baseline and 3, 6, and 9 months or with scaling and root planing only at baseline as well. In both groups, a persistent reduction in the probing depths of approximately 10% to 15% was measured.

Summarizing these clinical studies with maintenance patients, we have to conclude that retreatment in sites with a residual probing depth >4 mm usually ensures only a slight clinical probing depth reduction and attachment gain [18, 23, 40]. Explanations for this observation may be that major healing effects were obtained during the cause-related phase and that such sites represent a negative selection of inaccessible sites for instruments to remove and to influence the biofilm.

The contradicting microbial results in our study and those reported in in vitro and animal studies pinpoint the problematic transfer of in vitro and animal results into clinical reality. Various in vitro studies have shown that periopathogens can effectively be killed with PDT procedures [29, 32, 35–37, 42]. These in vitro results, however, are not reflected in our clinical results. There may be different reasons for these results. Other combinations of sensitizers and light sources might be more powerful than the combination used. Sigusch et al. [33] pointed out that the success of PDT depends on the photosensitizer used. They could show in an animal study with gingivitis that chlorine e6 was more effective than BLC1010 in suppressing P. gingivalis and F. nucleatum. Another explanation is that photodestruction of plaqueresiding bacteria effects less in biofilms than in a culture broth [43]. An uptake of photosensitizers into the plaque may be impeded in the same way as the uptake of antibiotic drugs. Recently, Müller et al. [25] presented a study about the efficacy of photodynamic therapy on a multispecies biofilm in vitro. In this study, PDT had a minimal effect on the viability of microorganisms organized in a biofilm.

In contrast to findings in rat and dog models [20, 33], we could not show any bactericidal efficacy to periodontal bacteria. Chondros et al. [7], who treated maintenance patients either with scaling and root planing plus PDT or root planing alone (control group), found 3 months after therapy a statistically significant reduction of *F. nucleatum* and *Eubacterium nodatum* in the PDT test group; but at 6 months, statistically higher significant numbers of *Eikenella corrodens* and *Capnocytophaga* species were detected in the test group.



Since we took the microbial samples immediately after the treatment, we can exclude that the microbiota stemmed from the recolonization of the ecological niches other than the treated periodontal pocket. That means that the operator was not able to mechanically remove the bacterial load beyond 90%. This corresponds to Petersilka et al. [28] who reported that mechanical scaling reduced the cultured bacterial load of one log step in maintenance patients. Another explanation may be that bacteria have been flushed in from "healthy" not treated neighboring sites of the same tooth. Real-time PCR assays provide a better detection tool for oral pathogens than culturing [6, 17], but it do not differentiate between living and dead microbiota and PDT. Since PDT may not physically remove but only kill bacteria, it is feasible that the microbial test may not have been completely appropriate to investigate the effect of PDT on microbiota. Probably, a life/dead staining or culturing method may have better reflected the action of PDT.

This explanation is supported by findings of Dörtbudak et al. [12] who took bacterial samples before and after PDT treatment in peri-implantitis sites and cultured *A. actino-mycetemcomitans*, *P. gingivalis*, and *P. intermedia*. PDT treatment reduced the bacterial counts by two log steps on average; complete elimination of bacteria, however, was not achieved. Rhemrev et al. [31] investigated the reduction in the number of microorganisms obtained directly after subgingival debridement by culture. Significant reductions were found for *T. forsythia*, *P. micra*, *F. nucleatum*, and spirochaetes. No reductions were observed for *A. actino-mycetemcomitans*, *P. gingivalis*, *P. intermedia*, and *C. rectus*.

Since clinical periodontal treatment protocols have not yet been established for PDT when we started our study, we took a fiber-optic, which was developed for endodontic treatment, and followed the manufacturer's recommendations for flushing, power setting, etc. for endodontic treatment. In the meantime,



systems have been introduced in the market, which are designed for periodontal use with other fiber-optic systems [10]. These new devices and adapted treatment protocols might produce better clinical outcomes. A further explanation may be that the operator did not flush the complete pocket area or did not move the laser over the complete pocket surface. It can be questioned whether pockets inaccessible to mechanical treatment devices should offer better accessibility to a laser device. Nosal et al. [26] showed that the coolant of an ultrasonic instrument does not spread lateral to the insert. Thus, if the operator was not able to rinse and stain the complete biofilm with the canule and to move the laser in regular overlapping strokes over the complete pocket area, there would still be left some microbiota without PDT treatment. Therefore, it may not be the fault of the PDT procedure itself that it did not work to our expectations; it may be the inherent problems of mechanical obstructions for devices to get access to all parts of the pocket.

As in most studies with maintenance patients [2, 18, 23, 40], in our study, no negative control subjects were included who perform only supragingival plaque control. Thus, it is not possible to estimate if the treatment effect observed had been influenced by a *Hawthorne* effect [1]. The trial situation presumably caused the operator and/or patient to take considerably greater effort in supra- and subgingival plaque control than it would have been the case in routine sessions. Furthermore, we did not include a control group with only irrigation or only irradiation. However, neither pocket irrigation alone [15] nor a soft-laser treatment with a low-power application alone [33, 45] has shown any clinical benefit.

This study reported similar results after retreatment of persistent pockets with UST and PDT during SPT. UST is likely to remove dental hard tissue, whereas, PDT is unlikely to do so. Thus, there are two competing therapies resulting in the same clinical effect. However, PDT is less harmful to teeth, particularly, if one considers the need of repeated retreatment over years. The sample size of this study was too small to show equivalence of UST and PDT because the power calculation was based on the assumption to detect a difference in means of 0.40 mm between UST and PDT. Future studies with more test power may confirm the equivalence of this two treatment approaches, and they should use as a secondary outcome questionnaire to assess quality of life with respect to pain

In conclusion: In our study in maintenance patients, we did not find any additional significant improvement with photodynamic therapy in terms of PD or RAL. Microbial counts reduced about 30% to 40% immediately after debridement but returned to baseline values at month3 irrespective of treatment. Because of the pilot nature of this study, the results are too inconsistent to detect clinically relevant differences. Satisfying treatment solutions for

persistent pockets sites still remain a problem. Until today, it seems that no new device or therapeutic regimen could overcome this problem and proved to have really superior clinical effects to conventional scaling devices. However, the concept of PDT is plausible and could foster new therapeutic concepts in the treatment of periodontal diseases. The knowledge available so far justifies the devotion of more research efforts to this method.

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Conflict of interest The authors declare that they have no conflict of interest.

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