



Photodynamic therapy for skin rejuvenation: review and summary of the literature – results of a consensus conference of an expert group for aesthetic photodynamic therapy

Sigrid Karrer¹, Elisabeth Kohl¹, Konstantin Feise², Dagmar Hiepe-Wegener³, Stephan Lischner⁴, Wolfgang Philipp-Dormston⁵, Maurizio Podda⁶, Welf Prager⁷, Torsten Walker⁸, Rolf-Markus Szeimies⁹

(1) Department of Dermatology, University Clinic of Regensburg

(2) Rosenpark Clinic, Darmstadt

(3) Private office for dermatology, Hildesheim

(4) Group practice for dermatology, Kiel

(5) Dermatology Center Cologne

(6) Department of Dermatology, Darmstadt Hospital

(7) Dermatologikum Hamburg

(8) Private office for dermatology, Ludwigshafen

(9) Department of Dermatology and Allergology, Vest Clinic, Recklinghausen (all Germany)

Summary

Skin rejuvenating effects of photodynamic therapy (PDT) for photoaged skin has been well-documented in several clinical trials. Different photosensitizers (5-aminolevulinic acid, methyl aminolevulinate) and diverse light sources (light-emitting diodes, lasers, intense pulsed light) have been used with promising results. An improvement of lentiginos, skin roughness, fine lines and sallow complexion has been achieved with PDT. These clinically evident effects are at least in part due to histologically proven increase of collagen and decrease of elastotic material in the dermis. Effective improvement of photoaged skin, simultaneous treatment and possibly also prevention of actinic keratoses, the possibility of repeated treatments and, in contrast to other procedures, limited and calculable side effects make PDT a promising procedure for skin rejuvenation.

Introduction

Topical photodynamic therapy (PDT) with preparations containing 5-aminolevulinic acid (ALA) or methyl aminolevulinate (MAL, 160 mg/g cream) is a well-established and licensed procedure in Germany for the treatment of actinic keratoses (AK). MAL is also licensed for the treatment of Bowen disease and superficial and nodular basal cell carcinomas. Clinical experience has demonstrated that extensive treatment of AK on sun-damaged skin also produces as a positive side effect significant improvement of the signs of skin aging. These aesthetic effects of PDT subsequently have been examined in numerous clinical studies in a targeted

shion. The question of which mechanisms of action of PDT are responsible for the skin-rejuvenating effect has also been studied.

Based on a consensus conference of dermatologists involved in the field of aesthetic photodynamic therapy on 02 December 2011 in Düsseldorf, Germany, current data on PDT for skin rejuvenation was reviewed and summarized. The present paper illustrates the current status of studies on photodynamic skin rejuvenation and the underlying molecular mechanisms are discussed. In a second paper concrete treatment recommendations for different anatomic sites of sun-damaged skin and suitable techniques for pre- and after-treatment will be discussed.

Photodynamic therapy for skin rejuvenation

While the intrinsic aging process of the skin is unavoidable, particularly UV radiation – which is also responsible for the development of actinic keratoses – plays a causative role for premature extrinsic skin aging [1]. In studies on the treatment of extensive AK it was observed that after PDT not only did AK regress, but that the signs of skin aging also appeared markedly improved [2, 3]. Numerous clinical studies in the meantime were able to confirm these observations (Table 1, 2). As photosensitizers either 5-aminolevulinic acid (ALA, Levulan® Kerastick or other ALA preparations) or the methyl ester of ALA (MAL, Metvix® cream) are employed [4]. The published studies on skin rejuvenation usually employ diverse regimens deviating from the protocols licensed for epithelial tumors, which makes the comparison of the studies difficult. Not rarely the systems used themselves lead to an improvement of cutaneous findings, so that the observed positive effect is synergistic and the respective classification of the mechanism is difficult.

In the following the individual studies classified according to the light source employed are presented in more detail.

PDT with intense pulsed light (IPL)

Particularly in the USA high-energy flash lamps (intense pulsed light devices; IPL) are used for full-face treatment for what is termed “photodynamic photorejuvenation”. Even without a photosensitizer the flash lamp is capable of improving telangiectases, fine wrinkles and age spots [5], while improvement of deeper wrinkles can hardly be expected. The superior efficacy of the flash lamp in combination with a photosensitizer (ALA or MAL) as opposed to sole IPL treatment has been demonstrated in numerous studies in split-face comparison [6–9]. If ALA- or MAL-PDT in combination with a flash lamp is more effective than PDT with red or blue light, has, nonetheless, not been examined to date.

Flash lamps emit polychromatic light in a wavelength range of 500–1,300 nm. By using different cut-off filters in the handpiece, the emitted spectrum of light can be varied. For use in PDT usually handpieces with a cut-off filter allowing transmission of light above about 600 nm (used for epilation) are suitable. Pulse duration can be set at a large range in the millisecond range. Short pulse duration plays a role particularly with respect to pain. In comparison to continual irradiation with red light, PDT with a flash lamp is perceived as less painful [10]. The diverse possible parameters of IPL with respect to wavelength, pulse duration, pulse interval and energy density make a targeted use possible for the experienced dermatologist, on the one hand, but make

the comparison of different studies difficult on the other [5].

In one of the first studies on PDT with IPL in patients with sun damage and AK, the effects of a 20 % ALA solution (Levulan® Kerastick, incubation 30–60 min.) were studied [11]. After 3 treatments over 85 % of the AK healed; in addition, in over 90 % of the patients an over 75 % improvement of the signs of skin aging was seen. All patients demonstrated improvement of crow’s feet, tactile roughness, mottled hyperpigmentation and facial erythema. In a retrospective study the efficacy of ALA-PDT with IPL on sun-damaged skin was examined [12]. Improvement of mottled pigmentation was observed in 48 % of the patients and of skin texture in 25 % of patients. Fine wrinkles hardly improved.

In a study on ALA-PDT with IPL in a split-face study it was seen that multiple PDT in comparison to sole IPL treatment led to better results with respect to the global score for photoaging, improvement of fine wrinkles and mottled hyperpigmentation [7]. With respect of the improvement of sallow complexion and tactile roughness no difference was observed. Similar results were seen in a split-face study on Chinese patients with a darker skin type [9]. Combined ALA/IPL was significantly superior to sole IPL with respect to the global score for photoaging, fine lines and deep wrinkles. The efficacy and tolerability of ALA-PDT with IPL on Asian patients was also confirmed in a Japanese study [13]. In a split-face study Bjerring et al. compared two different IPL settings [14]. Here the photorejuvenation filter (530–750 nm range, double pulses of 2.5 ms, 10 ms pause, 6–7 J/cm²) was superior to the IPL filter of the wavelengths 400–720 nm (long pulse duration of 30 ms, low light dose of 3.5 J/cm²) with respect to the improvement of mottled hyperpigmentation, erythema and telangiectases. In the authors’ opinion the filter with 400–720 nm and very low doses is particularly suitable for dark-skinned or highly tanned patients, as the risk of side effects is thus reduced. Piccioni et al. employed a 0.5 % liposomal ALA spray for PDT of wrinkles in combination with IPL [15]. Three months after 3 PDT cycles a significant reduction of wrinkle depth was observed, with periorbital wrinkles responding better than nasolabial wrinkles. With this low ALA concentration no side effects of therapy were reported despite good efficacy.

Haddad et al. compared various IPL light doses for ALA-PDT of photodamaged skin and demonstrated that higher light doses of 40 or 50 J/cm² (= double pulses of 20 and 25 J/cm²) lead to better healing of AK, but not to an increase of improvement of signs of skin aging [16].

Attempts were also undertaken to improve penetration of the hydrophilic ALA solution (Levulan® Kerastick) and thus the subsequent activation of ALA [17]. For this purpose the skin was perforated 5–6 times with a microneedle roller (Roll-CIT, Environ Corp., Cape Town, South Africa). The length of the microneedles (300 µm) was sufficient to

Table 1 ALA-PDT for skin rejuvenation.

Author	n	Photosensitizer Incubation time	Light source Light dose	Number of sessions (interval) Follow-up	Study design	Side effects	Result
Ruiz-Rodriguez 2002	17	20 % ALA 4 h	IPL (590–615 nm, 40 J/cm ² , double pulse, 4 ms)	2 x (1 month) 3 months	Uncontrolled	Extensive edema, erythema, crusts over 10 days	Distinct improvement of skin texture and healing of 91 % of actinic keratoses
Touma 2004	17	20 % ALA (Levulan® Kerastick) 1/2/3 h	Blue light (417 ± 5 nm, 10 J/cm ²)	1 x	Uncontrolled	Erythema, edema	Significant improvement of sallowness, wrinkles, skin quality, dyspigmentation, no improvement of deep wrinkles
Avram 2004	17	20 % ALA (Levulan® Kerastick) 1 h	IPL (560 nm, 28–32 J/cm ²)	1 x 3 months	Retrospective	Erythema, edema, scaling	55 % improvement of telangiectases, 48 % improvement of dyspigmentation, 25 % improvement of skin texture, minimal improvement of fine lines
Alster 2005	10	ALA 1 h	IPL (560 nm, 27–30 J/cm ² , double pulses of 2.4 and 4 ms)	1 x 6 months	Split-face study	Erythema, edema, dryness, crusts (more frequent after ALA-IPL)	Improvement of global score of skin aging (also greater on the ALA-IPL side)
Key 2005	14	20 % ALA (Levulan® Kerastick) 12 h	Pulsed dye laser FPD (585 nm, 2–6 J/cm ² , 40 ms, 3–4 passes)	2 x (4 weeks)	Split-face study	Erythema, edema (more intense after ALA + FPD)	Improved skin texture, improvement of pigmentation and roughness after ALA + laser, no improvement of vascular irregularities
Dover 2005	20	20 % ALA (Levulan® Kerastick) 30–60 min	IPL (IPL Quantum SR; Lumenis, Inc., Santa Clara, CA, USA) (515–1,200 nm, 23–28 J/cm ² , double pulses of 2.4 and 4 ms)	3 x split-face, 2 x only IPL (3 weeks) 1 month	Split-face study, retrospective, randomized	Erythema, scaling, purpura, little pain during irradiation (side effects more frequent after ALA-IPL)	ALA-IPL vs. IPL: 80 % vs. 45 % improvement of the signs of skin aging, 95 % vs. 60 % improvement of mottled hyperpigmentation, 60 % vs. 25 % improvement of fine lines
Gold 2006	13	20 % ALA (Levulan® Kerastick) 30–60 min	IPL (550–570 nm, 34 J/cm ²)	3 x (4 weeks) 3 months	Split-face study	Erythema, edema on both sides	ALA-IPL (better than IPL alone): 55 % improvement of crow's feet, 55 % improvement of roughness, 60 % improvement of hyperpigmentation, 84.6 % improvement of telangiectases

Table 1 Continued.

Author	n	Photosensitizer Incubation time	Light source Light dose	Number of sessions (interval) Follow-up	Study design	Side effects	Result
Bjerring 2009	37	0.5 % ALA (in liposomal spray) 1 h	IPL (Ellipse Flex, Ellipse A/S, Hørsholm, Denmark): 530–750 nm, rejuvenation filter, 6–7 J/cm ² , double pulses of 2.5 ms vs. 400–720 nm, 3.5 J/cm ² , 30 ms, 3 passes (total dose 10.5 J/cm ²)	3 x (3 weeks) 3 months	Split-face study (comparison of 2 IPL settings) prospective, randomized Fitzpatrick skin types I–III	Erythema, edema	ALA-IPL (530–750 nm) vs. ALA-IPL (400–720 nm): Significant reduction of perioral wrinkles and periorbital wrinkles on both sides, pigmentation, erythema and telangiectases better with IPL (530–750 nm)
Kosaka 2010	16	5 % ALA 2 h	IPL (StarLux, Palomar, Burlington, MA, USA) (500–670 nm and 870–1,400 nm, 23–30 J/cm ² , 20 ms, single pulses)	3 x (4 weeks) 3 months	Split-face study, retrospective Fitzpatrick skin types III–IV	Erythema, pain (more intense after ALA-IPL), hyperpigmentation in 1 patient after ALA-IPL	Significant improvement of signs of skin aging, equal on both sides (ALA-IPL and IPL alone) 75 % of patients found ALA-IPL more effective
Clementoni 2010	21	20 % ALA 1 h	LED (630 nm, 75 J/cm ²) and IPL (Lumenis, Inc., Santa Clara, CA, USA) (560 nm, 19–22 J/cm ² , double pulses)	1 x 3 + 6 months	Prospective, microneedling before ALA application	Erythema, edema, hyperpigmented crusts (up to 7 days after PDT)	Significant improvement of: global score, fine lines, hyperpigmentation, sallowness, roughness, telangiectases, no improvement of: deep wrinkles, significantly better results after 6-month vs. 3-month follow-up
Piccioni 2011	30	0.5 % ALA liposomal spray applied every 5 min. over 1 h	IPL (Ellipse Flex PPT, Hørsholm, Denmark, PL-W Applicator, 3.5 J/cm ² , 3 triple pulses, 30 ms)	3 x (3 weeks) 3 months	Multicenter, prospective	None	Significant improvement of depth of periorbital and nasolabial wrinkles 3 months after PDT

Table 1 Continued.

Author	n	Photosensitizer	Incubation time	Light source	Light dose	Number of sessions (interval)	Follow-up	Study design	Side effects	Result
Xi 2011	24	5 % ALA and 10 % ALA in particularly severely damaged areas	1 h	IPL (Lumenis, Inc., Santa Clara, CA, USA)	560 nm or 590 nm, 14–20 J/cm ² , 3.5–4 ms, double or triple pulses	3 x (4 weeks)	2 months	Split-face study, prospective, controlled, double-blind Fitzpatrick skin types III–IV	Erythema, edema, hyperpigmentation (22 % after ALA-IPL, 15 % after IPL alone)	Improvement after ALA-IPL vs. IPL: global score (50 % vs. 12.5 %), fine lines (70.8 % vs. 33.3 %), deep wrinkles (50 % vs. 12.5 %), no significant difference with respect to mottled pigmentation and roughness
Haddad 2011	24	20 % ALA (Levulan® Kerastick)	2 h	IPL (VascuLight, ESC Lumenis, 515 nm)	only IPL vs. ALA + IPL (20, 25, 40 or 50 J/cm ²)	1 x	8 weeks	Comparative, randomized	Erythema, edema, crusts, erosions	Best results after ALA + IPL with 40 and 50 J/cm ²

penetrate the epidermal-dermal barrier, but without producing point bleeding. Immediately thereafter the ALA solution was applied for one hour, followed by the IPL treatment and irradiation with red light. A significant improvement of the global photoaging score for fine lines, mottled pigmentation, sallowness, tactile roughness and telangiectases was documented 3 and 6 months after therapy.

Some advantages exist for flash lamps in PDT for aesthetic indications in comparison to other sources of light. Due to the shorter exposure times, the treatment with IPL is distinctly more rapid and less painful than irradiation with LED, while no difference was seen with respect to the remission rate of actinic keratoses between both sources of light [10].

Nonetheless, to date no clearly defined treatment parameters for PDT with IPL exist for the different manufacturers. The lack of comparability of the systems among each other despite similar power and filter characteristics could be confirmed in a study by Maisch et al. [18].

In the treatment of men with IPL in the beard region through mechanisms of action of IPL and the development of heat in the hair follicle destruction of the follicle and thus hair loss can occur. Therefore, for the beard region of men other sources of light should be favored or the power be reduced accordingly.

PDT with red light

In Germany mainly red light is used for PDT, as it has a good depth of penetration in the skin and also is licensed exclusively for PDT with ALA preparations or MAL on the market. Here both incoherent high-pressure gas discharge lamps (e.g. PDT 1200 L, Waldmann Medizintechnik, Villingen-Schwenningen, Germany) as well as light emitting diodes (LED, e.g. AktiLite® or Omnilux) are employed. In a comparative study with these two light systems, no significant differences were seen in the healing rate of actinic keratoses [19]. Some studies demonstrate the efficacy of PDT with red light in the treatment of photo-induced skin aging. Zane et al. treated patients with AK and severe photodamage with MAL-PDT and red light [20]. Significant improvement was achieved with respect to mottled hyperpigmentation, fine lines, roughness and sallowness. No improvement was seen for coarse wrinkles, telangiectases, facial erythema and sebaceous gland hyperplasia.

Issa et al. also reported improvement of wrinkles, skin texture and skin smoothness after MAL-PDT with red light (LED, 37 J/cm²). The results were even better at the second follow-up after 6 months than at the first follow-up 3 months after therapy [21].

In a split-face study MAL-PDT (incubation time 1 h vs. 3 h) with red light demonstrated moderate improvement of tactile roughness, fine wrinkles and skin smoothness

Table 2 MAL-PDT for skin rejuvenation.

Author	n	Photosensitizer Incubation time	Light source Light dose	Number of sessions (interval) Follow-up	Study design	Side effects	Result
Ruiz-Rodriguez 2007	4	MAL (Metvix®) 3 h	LED (Aktilite®, 37 J/cm ²) and fractional laser vs. fractional laser alone	2 x (3 weeks) 12 weeks	Split-face study (only perioral)	Erythema, edema, scaling (more intense after combination therapy)	Greater improvement of fine wrinkles after combined therapy
Zane 2007	20	MAL (Metvix®) 3 h	LED (Aktilite®, 37 J/cm ²)	2 x (1 month) 2 months		Erythema, edema, pain during irradiation	Significant improvement of general signs of skin aging, hyperpigmentation, fine wrinkles, roughness, sallowness, no improvement of deep wrinkles, telangiectases, erythema and sebaceous gland hyperplasias
Ruiz-Rodriguez 2008	10	MAL (Metvix®) 1 / 3 h	LED (Aktilite®, 37 J/cm ²)	3 x (2 months) 2 months	Split-face study	Erythema, edema, crusts	Moderate improvement of: fine wrinkles, skin tightness, roughness (after MAL-PDT), no improvement of telangiectases and mottled hyperpigmentation
Sanclemente 2011	48	MAL (Metvix®) 3 h	LED (Aktilite®, 37 J/cm ²)	2 x (2–3 weeks) 1 month	Split-face study, double-blind placebo-controlled		Significant improvement (only after MAL-PDT, not after placebo-PDT) of: global signs of skin aging (roughness dyspigmentation, fine lines, sallowness, erythema), no improvement of telangiectases, Patient satisfaction 80.4 %
Palm 2011	18	MAL (Metvix®) 3 h	Blue or red light	1 x	Split-face study	Erythema	No difference between red and blue light
Szeimies 2012	26	MAL (Metvix®) 3 h (1 st PDT) 1.5 h (2 nd –3 rd PDT)	LED (Aktilite®, 37 J/cm ²)	3 x (1 month) 3 months	Prospective	Erythema, edema crusts, erosions	Significant improvement of global signs of skin aging, fine lines, sallowness, roughness, erythema, telangiectases, hyperpigmentation; no significant improvement of deep wrinkles

2 months after PDT on the side with 3 hour incubation time. No improvement was achieved with respect to pigmentary changes and telangiectases [22].

In a larger study after MAL-PDT with LED significant improvement of all parameters examined with the exception of telangiectases was seen [23]. The efficacy of MAL-PDT in dependence of the wavelength employed (blue vs. red light) was compared in a split-face study [24]. Here no difference with respect to improvement of photodamaged skin could be observed.

MAL-PDT in combination with a non-ablative fractional laser was examined in a split-face study [25]. The cosmetic results were better after the combined therapy with respect to superficial wrinkles and subjective satisfaction. Also through pre-treatment with a fractionated ablative laser (CO₂ or Er:YAG laser) additive effects can be expected for the use of low energy doses, as the formation of transcorneal and -epidermal canals improves the depth of penetration of the photosensitizer. With higher energy doses as are used alone for the improvement of cutaneous findings and for the reduction of wrinkles, the effects can even be synergistic [4]. Nonetheless, too high energy doses can result in keratinocyte necrosis, which negatively impacts the production of protoporphyrin IX [26]. The best penetration of MAL and increased porphyrin synthesis could be detected after treatment with a fractional CO₂ laser also in a pig skin model [27]. Studies that compare the skin rejuvenating effects of PDT with IPL vs. red light are still lacking.

PDT with blue light

In the USA Levulan® Kerastick in combination with blue light is licensed for PDT of AK. As ALA- or MAL-induced protoporphyrin IX has its absorption maximum at 410 nm, blue light (420–490 nm) is about 50 times more effective in the activation of protoporphyrin IV than red light (590–750 nm), which only utilizes the small absorption maximum at 635 nm. The disadvantage of blue light due to the shorter wavelength is the distinctly reduced depth of penetration in the skin (1–2 mm for blue light vs. about 4 mm for red light). For this reason, red light is usually preferred in the treatment of skin tumors. Some studies do, nonetheless, confirm the efficacy of PDT with blue light in the treatment of skin aging.

Already in 2002 Gold reported, that ALA-PDT with blue light was not only effective in the treatment of AK, but also led to an improvement of skin elasticity and skin texture [28]. Goldman and Atkin were able to achieve an improvement of skin texture by 72 % and pigmentations by 59 % after ALA-PDT with blue light [29]. Touma et al. were also able to demonstrate in addition to 90 % healing of AK a significant improvement of skin quality, fine lines and skin complexion after ALA-PDT with blue light [3]. Deep wrinkles and mottled hyperpigmentation did not improve.

In a three-arm study topical 5-fluorouracil and two forms of ALA-PDT, once with blue light and once with a pulsed dye laser (PDL, 595 nm), were compared. The healing rate of AK was better after irradiation with blue light than after PDL (80 % vs. 60 %). In both ALA-PDT groups, global photodamage, hyperpigmentation and tactile roughness improved. PDL-PDT was more effective with respect to hyperpigmentation and global photodamage [30].

PDT with pulsed dye lasers

After PDT with pulsed dye lasers proved its efficacy in the treatment of AK with the advantage of distinctly reduced painfulness due to the shorter exposure times, these lasers are also employed for photodynamic skin rejuvenation [31]. The pulsed dye lasers possibly have synergistic effects in combination with a photosensitizer, as they are well suited for the treatment of telangiectases that respond less well to treatment with PDT and red light.

Patients with actinic damage on the forearms were treated with ALA and a dye laser in attempt to elucidate the molecular effects of PDT [32]. Through PDT epidermal proliferation and neosynthesis of collagen resulted, but clinical effects on photodamaged skin were not reported in this study.

In a split-face study with ALA-PDT and a dye laser (585 nm, 5–6 J/cm², 40 ms, 3–4 passes) improved skin texture, disappearance of solar lentigines and improvement of skin roughness was seen after ALA-PDT [33]. Vascular alterations are the target structures of the pulsed dye laser. On the control sides no improvement of the parameters mentioned was observed.

Mechanism of action

The understanding of the possible mechanisms of action of PDT for skin rejuvenation is increasing continually in recent years due to numerous published studies. Zane et al. demonstrated with sonography that there is a significant increase in skin thickness after MAL-PDT [20]. Marmur et al. performed a split-face study to detect changes in collagen production with ultrastructural studies [34]. Skin biopsies were performed before and 3 months after ALA-PDT with IPL and revealed an increase in type I collagen in the dermis. Histological changes were studied by performing skin biopsies before and one month after ALA-PDT with red light [35]. A significant reduction of the epidermis thickness, elastotic material and the dermal inflammatory infiltrate as well as an increase of collagen and procollagen type I and III in the upper dermis were observed. TGF-β, which stimulates fibroblast proliferation and thus increases collagen synthesis, was significantly increased after PDT, as well as the TGF-β type II receptor. The expression of collagen- and elastin-degrading

matrix metalloproteinases (MMP-1, -3 and MMP-12) declined in contrast. Similar results were also observed by Issa et al., who demonstrated a reduction of elastic fibers and an increase of collagen fibers 6 months after MAL-PDT [21].

Orringer et al. were able to demonstrate after ALA-PDT with a dye laser epidermal proliferation with an increase of the proliferation marker Ki67 and a temporarily up to 1.42-fold thickening of the epidermis (2, 7 and 30 days after PDT significantly thickened, after 60 days again as before PDT) [32]. The expression of cytokeratin 16, a marker for epidermal irritation or injury, increased 2 days after PDT shortly 70-fold. P53, a marker for epidermal photodamage, did not change significantly after PDT. In the dermis within one day a strong induction of the gene expression of MMP-1 by 20-fold, that, nonetheless, returned to baseline after 24 hours. Prolyl-4-hydroxylase α , which is expressed in collagen-producing cells and is involved in collagen synthesis, was increased about three-fold one month after PDT. Through PDT a significant increase of various markers of collagen neosynthesis (procollagen type I- and III-mRNA) that achieved its maximum (2.54-fold or 3.32-fold induction) 30 days after PDT and declined again on day 60. The fact that the alterations such as e.g. increased collagen production again declined some months after PDT indicates that repeated treatments are required to maintain the good clinical effects in the sense of skin rejuvenation.

In contrast, Bagazgoitia et al. found that the expression of p53, an early marker of epidermal carcinogenesis that is not expressed in normal skin, was significantly reduced after PDT [36]. The authors conclude from this that PDT can reverse the process of carcinogenesis in photodamaged skin. The patients received 3 therapy cycles; biopsies were performed before therapy and three months after the last session. In all patients the global score for skin aging improved significantly, in 89.5 % the AK healed. The results after 2 PDT sessions were just as good as after 3 sessions. Histologically, a significant reduction in degree and extent of keratinocyte atypia, a significant increase in collagen content of the skin, a reduction of solar elastosis and an increase of tenascin C were observed. The increase of MMP-1 and procollagen I were not significant. This study suggests that PDT via a reduction of keratinocyte atypia and reduced expression of TP53 results in a reduction of the carcinogenic potential in photodamaged skin. The significant increase of collagen and the reduction of solar elastosis explain the clinically observed skin-rejuvenating effects of PDT.

The molecular alterations after MAL-PDT with red light were also studied in the animal model [38]. Two days after PDT in the murine skin there was strong induction of proinflammatory cytokines (IL-1 β , TNF α), TGF- β 1, MMP-1 (the most important agent for the degradation of type I collagen), MMP-2, MMP-3 and MMP-9. Histology revealed necrotic alterations in the epidermis one day after PDT, epidermal re-

generation and inflammatory infiltrates in the dermis 2 days after PDT and a completely restored epidermis after 4 days. After 8 days the epidermis was distinctly thickened and after the 12th day the collagen fibers were significantly thickened. Procollagen I- and III-mRNA was significantly elevated 12 days after PDT. In this study it could be shown that PDT induces epidermal and dermal matrix molecules that are of significance for skin rejuvenation. In summary, most studies have demonstrated that PDT results in an increase of collagen and a decrease of solar elastosis.

Discussion

PDT is a very promising approach for treatment of photo-induced skin aging and takes a place between ablative and non-ablative methods for skin rejuvenation. Pre-treatment with a fractional CO₂ laser represents a new option to improve absorption of the photosensitizer and thus possibly results in improved efficacy.

High-energy flash lamps with different cut-off filters as well as red light, blue light and pulsed dye lasers were able in various studies to prove their efficacy in skin rejuvenation together with a photosensitizer. Nonetheless, hardly any studies exist comparing the efficacy of the different light sources for PDT with each other, so that no statement can be made which light source is indeed the most effective. The selection of the light source depends on a variety of factors. When particularly lentigines and telangiectases are present, IPL or PDL appear appropriate. When AK are also present, for security reasons licensed treatment protocols should be favored. For practical reasons particularly the light source available in the practice or clinic will be employed.

The most widely studied photosensitizers are 20 % ALA (Levulan® Kerastick, not licensed in Germany); MAL (Metvix® 160 mg/g cream, approved in Germany); and various ALA preparations (concentrations from 0.5 % to 20 %). The phototoxic reactions increase in proportion to longer incubation times, higher photosensitizer concentrations and light doses, with it being unclear, if more intensive PDT regimes actually lead to better cosmetic results. The reversible side effects of PDT include pain, erythema, edema, scaling and crusting, in darker skin types also post-inflammatory hyperpigmentation. A series of 3 treatment cycles, as in most studies, appears sensible, as histological and molecular signs of actinic damage were still detected after a single PDT session. Nonetheless, the positive effects achieved are also evident to their full extent only after weeks to months, as the restructuring processes responsible (degradation of elastotic material and induction of collagen neosynthesis) require time [4, 37].

Most studies utilized a 5-point score (Table 3) to assess signs of skin aging. After PDT improvement of particularly fine wrinkles [7, 8, 20, 22] and tactile skin roughness

Table 3 5-point scale for the evaluation of the signs of skin aging [7, 20].

Score	0	1	2	3	4
Global score for photoaging	No significant fine lines or unevenness of pigmentation	One area with significant roughness, dyspigmentation or fine lines	Two areas with significant roughness, dyspigmentation or fine lines	Three areas with significant roughness, dyspigmentation or fine lines	Four areas with significant roughness, dyspigmentation or fine lines
Fine wrinkles	None	Rare, widely spaced	Several discrete fine lines	Moderate, number of lines in close proximity	Many fine lines, densely packed
Mottled pigmentation	Evenly pigmented skin	Mild hypo- or hyperpigmentation involving small areas	Moderate hypo- or hyperpigmentation involving small areas or mild hypo- or hyperpigmentation involving moderate areas	Moderate hypo- or hyperpigmentation involving moderate areas or pronounced hypo- or hyperpigmentation involving small areas	Pronounced hypo- or hyperpigmentation
Sallowness	Pink skin	Pale skin	Some suggestion of yellowness, grayness of skin	Pale skin with a yellow-gray shade	Pale skin with a pronounced yellow-gray shade
Tactile roughness	Smooth skin	Smooth skin with occasional roughness	Mild roughness	Moderate roughness	Severe roughness
Telangiectases	None	Few, widely spaced	Several, discrete	Moderate, close	Numerous, densely packed
Coarse wrinkles	None	Superficial at one site	Superficial at more than one site or moderate at one site	Moderate at more than one site or deep at one site	Coarse wrinkles at more than one site
Facial erythema	None	Small areas with mild erythema	Small areas with moderate erythema or moderate areas with mild erythema	Moderate areas with erythema	Large areas with erythema
Sebaceous gland hyperplasias	None	Few in one skin area	Few in several areas or several in one area	Several in several areas or many densely packed in one area	Numerous, densely packed in more than one skin area



Figure 1 Man with sun-damaged skin and actinic keratoses on the back of the hand prior to PDT.



Figure 2 Same patient 3 months after 3 cycles of PDT using Metvix® every 4 weeks. Cure of actinic keratoses and marked improvement of mottled pigmentation, fine lines, skin roughness and sallow complexion.

[3, 8, 12, 33] an increase in skin smoothness and improvement of actinic elastosis and skin color [3, 20] and reduction of hyperpigmentation [3, 20] were reported. Less improvement was seen for coarse wrinkles and sebaceous gland hyperplasia. An improvement of telangiectases and mottled hyperpigmentation was seen particularly after PDT in combination with the flash lamp, with IPL-PDT being significantly superior to exclusive IPL treatment [7, 8, 12].

Even though a multitude of procedures are available for treatment of signs of skin aging (laser for treatment of vascular or pigmentary lesions or lasers that induce collagen neosynthesis, high-energy flash lamps, surgical procedures, topical therapies, chemical peelings, fillers, botulinum toxin, and others), these methods usually improve only one or a few components of skin aging. In addition, simultaneously present AK in the treatment area are not adequately addressed. The simultaneous improvement of numerous components of skin aging in combination with an effective therapy of possibly existing AK represents the strong point of PDT (Figure 1, 2). This does, however, necessitate the selection of a treatment protocol that guarantees effective therapy of the precancerous lesions. Despite the fact that no studies on the long-term skin-rejuvenating effects of PDT exist, it appears highly probable that regular PDT is not only sensible in order to reduce the risk of development of non-melanocytic skin cancer, but also for long-term maintenance of the skin-rejuvenating effect [39].

Conclusions

While therapy protocols for PDT of skin tumors have in the meantime been clearly defined, the treatment parameters for treatment of signs of skin aging have not yet been standardized and vary in part quite greatly between the different studies. Nonetheless, as frequently in photodamaged skin AK or even field cancerization are present, it is advisable to employ therapy protocols licensed for the treatment of AK for such patients in order to guarantee effective treatment of epithelial skin tumors.

Conflict of interest

Prof. Karrer has received honoraria for lectures for Galderma and has participated in licensing studies in the field of dermatology as trial investigator. Dr. Kohl receives honoraria for lectures for Galderma. Dr. Lischner is a member of the advisory boards of the companies Almirall, Biofrontera, Spirig and Galderma and receives honoraria from these firms for lectures. Dr. Philipp-Dormston is a member of the scientific advisory boards of Allergan, Biofrontera and Galderma, holds lectures and conducts clinical studies for these companies. Prof. Szeimies is a member of the scientific advisory boards of Biofrontera, Galderma, Leo Pharma and Spirig, receives honoraria from these firms for lectures and

has participated as trial investigator in numerous licensing studies in the field of dermatooncology.

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Correspondence to

Prof. Dr. Sigrid Karrer
Department of Dermatology

University Clinic of Regensburg
Franz-Josef-Strauss-Allee 11
93042 Regensburg, Germany

E-mail: sigrid.karrer@klinik.uni-regensburg.de

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