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REVIEW ARTICLE

Pulsed dye laser: what's new in non-vascular lesions?

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Abstract

Background and objective In dermatology, the pulsed dye laser (PDL) is the therapeutic instrument of choice for treating most superficial cutaneous vascular lesions. In addition, clinical experience over the last decade allowed us to treat patients with an ever increasing number of non-vascular indications. The purpose of this report is to summarize and critically appraise the scientific evidence that support the role of PDL in treating non-vascular skin lesions.

Methods A literature-based study has been conducted, including the review of publications over the period January 1995 to December 2006, using the Medline Database. We also included our own experience in managing non-vascular lesions with the PDL. Four sets of preoperative and postoperative photos are presented.

Results For viral skin lesions, PDL proved to be an alternative to other therapy options. This applies particularly to periungual warts and mollusca contagiosa. The mechanism of PDL with inflammatory dermatoses has not yet been elucidated. The effect seems to be better if there is a vascular component to the disease. With most of these indications (such as psoriasis and acne), PDL currently plays a rather minor or complementary role. Regarding collagen remodelling (hypertrophic scars, keloids, stretch marks, and skin rejuvenation), the question of whether a therapy makes sense or not has to be decided from case to case.

Conclusion With PDL, it is possible to achieve good results with numerous, partly less well-known indications (i.e. lupus erythematosu). With other diseases, PDL has so far been considered to be a complementary therapy method or to be in an experimental state.

Introduction

In dermatology, the pulsed dye laser (PDL) is considered the gold standard for many vascular indications, such as port-wine stains, initial haemangiomas, and facial telangiectasias. In addition, it is often used successfully, but not in an evidence-based way, for many other vascular-dependent and non-vascular indications. In many cases, these indications are supported only by individual reports, and the effectiveness should be evaluated in more detail and with larger numbers of patients. The mode of action of PDL is based on the principle of selective photothermolysis,[1] a targeted damaging of specific structures within the skin without damaging the surrounding tissue, and on not yet wholly explored mechanisms (e.g. immune-modulating mechanisms).

It is currently possible to vary the parameters of the laser and to adjust them (within certain limits) to the target structure. Pulse durations range from 0.35 to 40 ms. Moreover, the multi-pass technique, applied in the pulse stacking mode, proved to be an effective development of the conventional use of different pulse durations.[2] Treatment spot diameters are available up to a diameter of 12 mm. In recent years, protective cooling systems have allowed an increase in the energy fluence and improved treatment effectiveness, while at the same time reducing the rate of side-effects.[3]

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Currently, the PDL wavelengths 585 and 595 nm are most frequently used for therapeutic purposes. Unfortunately, the fields of application are limited to superficial structures due to the minor penetration depth of max. 1.5 mm at these wavelengths.[4]

Side-effects of therapy with PDL are (dependent on location, energy fluence, skin type, and pulse duration) erythema, oedema, purpura, crusting, blistering, hyperpigmentation/hypopigmentation, and rarely scarring.

The purpose of this study is to review the pertinent literature and provide updated information on the treatment of non-vascular lesions with PDL.

1. Viral infections

Verrucae vulgares

Verrucae vulgares are benign epithelial proliferations induced by several types of the human papillomavirus (HPV). It is a common problem affecting approximately 10% of the population.[5] Many different types of therapy have been used in the treatment of verrucae, such as keratolytic agents, cryotherapy, surgical excision, electrocautery, carbon dioxide laser removal, and PDL, among others.[6] As many warts disappear on their own, given time, it seems that PDL should be limited to particularly problematic or persistent warts.[7]

Although the mechanism of action of PDL in the treatment of verrucae is not fully understood, it is assumed that the laser interaction with the supporting vasculature plays a beneficial but uncertain role in the eradication of warts. Light microscopic evaluation of treated areas immediately and at 1, 6, and 13 days after treatment shows agglutinated erythrocytes in the papillary vessels, with subsequent thrombosis and endothelial and keratinocyte necrosis.[8] Such destruction may obliterate the nutrient supply to the wart or destroy the rapidly dividing epidermal cells that contain HPV. In addition, thermal injury of the heat-sensitive HPV may also contribute to the mode of action.[9]

In order to assess the effectiveness of PDL, we selected reports primarily on recalcitrant warts (for summary, see Table 1). With energy fluences of 9 to 9.5 J/cm^2, Robson *et al.* achieved complete clearance in 66% and partial clearance in 82% of cases (40 patients, 194 lesions).[10] Of note, the investigators of this study reported that the clearance rates depended on the anatomic location: The response of body warts to the treatment was better than that of verrucae plantares and periunguales. This is the only controlled prospective study, and here, Robson *et al.* treated both simple and recalcitrant warts. There was no significant difference between conventional therapy (liquid nitrogen cryotherapy and cantharidin) and PDL therapy.

To date, the best results with the largest number of patients (142 patients, 728 lesions) were achieved in a study by Kauvar *et al.*[11] They showed a clearance of 99% for body and anogenital warts, 95% for verrucae palmares, 84% for verrucae plantares, and 83% for periungual warts. Their follow-up ranged from 3 to 9 months, and fluences ranged from 7 to 9.5 J/cm^2, with a 5- and 7-mm spot size.

In a study with 134 patients, Kopera achieved an 84% overall response rate (complete remission in 63% and partial remission in 21% of cases).[12] The energy fluence was set at 8 J/cm^2. The warts in locations other than the extremities responded better than warts on hands and feet. Subsequent studies with fewer patients showed similar results.[13,14]

Schellhaas *et al.* reported on a clearance rate of 89% after a maximum of 10 sessions with palmar and plantar warts (personal communication). Of note, palmar warts responded quicker than plantar warts. In 3 of 73 patients with 366 lesions altogether, there was no remission. One patient had a relapse after 6 months. Treatment was carried out with energy fluences of 8 to 12 J/cm^2 and a spot size of 5 mm.

The only study with a longer pulse duration (1.5 ms), energy fluences of 16 to 20 J/cm^2, and a wavelength of 595 nm resulted in complete clearance in only 6.5% of cases (24 patients, 31 lesions), an improvement by more than 75% in 12.9% of cases, and an improvement by less than 50% in 29% of cases.[15] The warts were located mainly on hands and feet.

All studies reported herein show that PDL treatment may not be as uniformly effective in treating warts. Studies by Kauvar *et al.* indicate that the multi-pass technique and a fast repetition rate (at least 1 Hz) are significant factors contributing to higher wart response rates.[11] Conceivably, the relatively poor response rates observed by Robson *et al.* might be attributable to differences in the treatment regimen. These studies used either a single- or double-pass technique, multiple passing at a lower pulse repetition rate, insufficient energy fluence, or a longer treatment interval. One has also to consider that clearance rates beyond 50% for recalcitrant warts are quite encouraging.

To sum up the present data, the best results can be achieved using energy fluences between 8 and 9 J/cm^2, a wavelength of 585 nm, and a pulse duration of 0.45 ms. The location of the warts seems to influence the efficacy of treatment. In our experience, verrucae of the hands show higher clearance rates than the one on the feet (for example, see fig. 1). Moreover, we found that treatment sessions within shorter periods of time lead to better results (every 1–2 weeks as opposed to every 3–6 weeks). Hyperkeratoses should be thoroughly removed with a scalpel prior to each laser treatment, given the limited

Table 1 Overview of published literature 'PDL in the treatment of viral warts'

Authors	Number of patients (warts)	Location of the warts	Simple(s)/ recalcitrant (r) warts	Treatment regimen	Number of treatments (average)	Fluences/pulse duration/ wavelength/spot size/passes to each site	Complete remission (%)
Huigol* *et al.*	7 (26)	Plantar, periungual	r	q 3 weeks, paring with scalpel before treatment	6	8.5–9.5 J cm^{-2}/not reported/585 nm/5 mm/not reported	No clearance
Jain* *et al.*[14]	28 (97)	Plantar	not reported	q 1–4 weeks, paring with scalpel before treatment	2.4–2.8	8.1–8.4 J cm^{-2}/0.45 ms/ 585 nm/5 mm/3–5 passes	70.1%
Kauvar* *et al.*[11]	142 (728)	Various	r/s	q 2–4 weeks, paring with scalpel before treatment	2.5	7.0–9.5 J cm^{-2}/0.45 ms/ 585 nm/5–7 mm/3–10 passes	93% (r, s)
Kenton-Smith* *et al.*[13]	28 (123)	Various	r/s	q 6–8 weeks, paring with scalpel before treatment	2.1 (r) 1.6 (s)	6.0–9.0 J cm^{-2}/0.45 ms/ 585 nm/5–7 mm/3 passes	92% (r), 75% (s)
Kopera* *et al.*[12]	126	Various	r/s	q 2–6 weeks	3.38	8.0 J cm^{-2}/0.45 ms/585 nm/7 mm/1 pass	62.69% (r, s)
Robson† *et al.*[10]	35 (194)	Various	r/s	q 4 weeks, salicylic tape and paring with scalpel before treatment	≤ 4	9–9.5 J cm^{-2}/not reported/not reported/ not reported/2 passes	76% (r), 51% (s)
Ross* *et al.*[9]	33 (96)	Various	r	q 2–4 weeks, paring with scalpel before treatment	3.4	5–10 J cm^{-2}/0.45 ms/ 585 nm/ 5–7mm/5 passes	48%
Tan* *et al.*[8]	39	Various	r	q 1–3 weeks, paring with scalpel before treatment	1.68	6.25–7.5 J cm^{-2}/0.45 ms/585 nm/ 5 mm/ not reported	72%
Wimmershoff* *et al.*[15]	24 (31)	Various	r	q 3 weeks, salicylic tape and paring with scalpel before treatment	> 4	16–20 J cm^{-2}/1.5 ms/ 595 nm/5 mm/not reported	6.5%

*Prospective, non-controlled study. †Prospective, controlled study.

penetration depth of the PDL. Side-effects were similar in all studies: during and up to 3 days after treatment, slight pain occurred and the area turned grey. The subsequent haemorrhagic crusting lasted about 10 to 14 days.

It is unclear at the present time whether or not PDL is superior to any other modality. However, in contrast to ablative techniques, the PDL does not normally produce an open wound, thus avoiding the risk of scarring. Therefore, we consider PDL the treatment of choice in cosmetically sensitive areas.

Molluscum contagiosum

Molluscum contagiosum, caused by a double-stranded DNA virus of the Poxviridae family, appears most frequently among children with atopic eczema and in immunosuppressed patients. Although benign, molluscum contagiosum causes cosmetic concern, infection, or transmission to close contacts. In most cases, they are removed by cryotherapy or superficial mechanical excision using a curette. However, conventional therapies are frequently ineffective and require multiple visits. Moreover, many of these treatments are not applicable, especially in the case of anxious children because they are often invasive, painful, time intensive, or difficult to conduct (if a stay in a hospital is necessary).

PDL provides an elegant alternative to the aforementioned treatment options, although the mechanism of action ultimately remains unclear. As discussed in *Verrucae vulgares*, both selective vascular damage and nonspecific thermal effects have been suggested to play a role. However, in contrast to plain warts, mollusca contagiosa do not have any additional blood supply.[16] Kenton *et al.* propose that a PDL-induced increase in mast cells might attract

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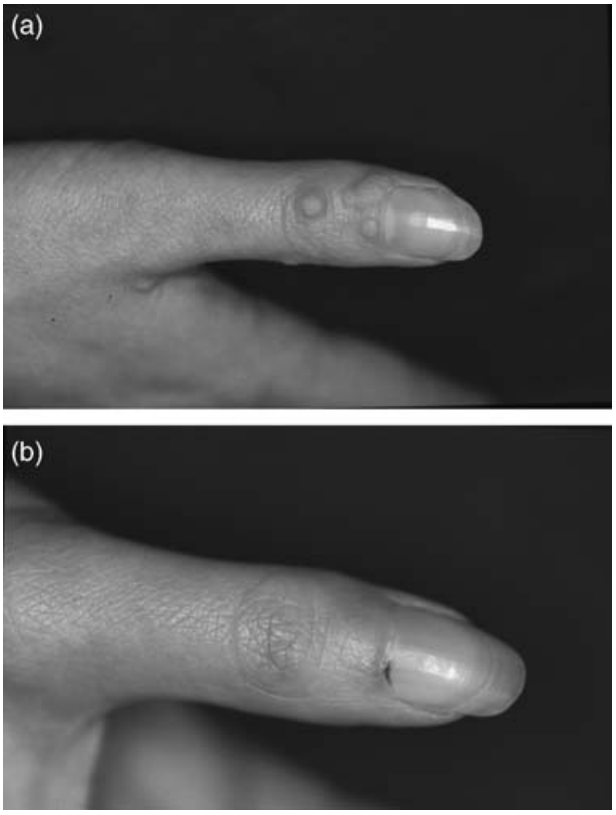

fig. 1 (a) Verrucae vulgares. (b) Verrucae vulgares after four treatments.

immune cells, such as macrophages, that finally eliminate the virus-containing cells.[13]

Rodenbach *et al.* were the first who reported on the successful treatment of molluscum contagiosum in AIDS patients using PDL.[17] Individual case reports followed from Hindson *et al.*[18] and Nehal *et al.*[19] who also described good results with immunosuppressed patients. In 1998, Hughes was the first to apply the therapeutic procedure in a pilot study on five patients and achieved a complete removal of all lesions within one session.[20] Following that study, Hammes *et al.* evaluated the efficacy of PDL in a prospective study involving 20 patients.[21] Study end points included effectiveness, side-effects, relapse, and its applicability to children; 95.9% of the 172 lesions resolved after the first treatment, whereas the remaining 4.1% resolved after the second one (585 nm, 5–9 J/cm^2, 0.45 ms, 7 mm). In three cases, an *in loco* relapse occurred within the first two months; however, these were eliminated by further laser application.

To date, there are no reports of side-effects, especially with regard to scarring and pigmentation disorders.[21] However, one has to keep in mind that skin infections are among the recognized side-effects of treatment with the PDL, probably as a consequence of diminished skin barrier function following epidermal damage. Gopinathan *et al.* showed an increased permeabilization of the stratum corneum following exposure to laser light, even without changes on conventional microscopy.[22] This could be indicative of a decreased barrier function, resulting in vulnerability to infections including molluscum contagiosum as reported by Strauss and Sheehan-Dare.[23] As molluscum contagiosum infection is a self-limiting disease, we feel that even in the presence of molluscum contagiosum lesions, treatment with PDL could go ahead, but patients or their parents should be warned that molluscum contagiosum, if present, could spread to laser-treated areas. Last but not least, one has also to keep in mind to take care for any predisposing factors such as eczema.

In our experience, PDL is an effective and elegant therapeutic alternative for mollusca contagiosa, with a low rate of side-effects. In one to two sessions, a rapid, blood-free, and almost pain-free healing can be achieved. In some children, superficial anaesthesia might become necessary (e.g. lidocaine-prilocaine mixture). Due to the high cost as compared with the conventional therapeutic modalities, we rather apply the PDL for exposed sites, difficult cases, or if other treatment options have failed. The parameters we use are 7 to 8 J/cm^2 energy fluence, 0.45-ms pulse duration, and 7-mm spot size.

A removal using the pulsed CO_2 or Erbium-YAG laser is also possible and represents a therapeutic option particularly for very large molluscum lesions.[24] However, this approach exposes both patient and operator to an increased risk of aerogenic contamination by viral fragments that are not inactivated by the laser energy and that can be detected within the laser generated smoke plume.[25] In addition, keloid scars have been reported after applying a CO_2 laser in the continuous mode.[26]

2. Inflammatory dermatoses

Acne vulgaris

The treatment of inflammatory acne by laser and other light-based sources is still controversial.[27] Because we have excellent strategies for treating acne with various topical and oral medications, many dermatologists and general practitioners suggest that treatment of acne by these expensive technologies is without merit. Yet many current medical therapies have drawbacks, including patient compliance, systemic toxicity, teratogenicity, and bacterial resistance. On the other hand, laser complications are rare and treatments are relatively brief.

PDL has been found to affect *Propionibacterium acnes* which is a major cause in the pathogenesis of inflammatory

acne. As part of its normal metabolic process, *P. acnes* produces and accumulates endogenous porphyrins.[28] Exposure to lasers and light sources emitting wavelengths in the visible light spectrum (400–700 nm) takes therapeutic advantage of the absorption peaks of porphyrins by inducing this photosensitizer to generate cytotoxic, highly reactive free radical specimens, which subsequently cause bacterial destruction.[29] In addition, the PDL causes selective photothermolysis of dilated vasculature associated with acne's inflammatory process. Bjerring *et al.* also reported that low (subpurpuric) energy fluences stimulate cutaneous procollagen production, and improve the clinical appearance of atrophic acne scars.[30]

To date, the PDL has produced variable acne clearance rates. The results of a half-face pilot study using a 595-nm PDL were encouraging (52% reduction in inflammatory lesion count 2 months after laser treatment and topicals vs. 27% with topicals alone).[31] Two recently published randomized controlled trials (in which significant acne therapies were withheld from patients for a period prior to and during the course of the trials) have been controversial. Seaton *et al.* studied 41 patients with mild-to-moderate inflammatory facial acne.[32] Twelve weeks after a single treatment using a 585-nm PDL (1.5 J/cm^2 to half of the face and 3 J/cm^2 to the opposite site, 0.35 ms, 5 mm), they reported statistically and clinically significant reduction in acne lesions on both sides of the face.

Orringer *et al.* measured the lesion counts in 26 patients for a randomized, blinded, placebo-controlled trial (585 nm, 3 J/cm^2, 0.35 ms, 7 mm).[33] This study showed a trend towards improvement in inflammatory acne, however, without being statistically significant. At 12 weeks, changes in lesion count were not significantly different for treated vs. untreated sides. Yet, in this trial, the average number of laser pulses used to treat each patient was 385 compared with at least 500 pulses used by Seaton *et al.*, which may explain the variability of the results.

To date, no other clinical trials on PDL therapy of acne have been published. The fact that Orringer *et al.* could not substantiate the positive results reported by Seaton *et al.* is not an indictment of laser therapy for acne in general and does not necessarily rule out the possible role of PDL. Rather, it suggests that additional well-designed studies are needed before the use of PDL becomes part of acne therapy.

Very recently, Glaich *et al.* combined the 595-nm PDL with the 1450-nm diode laser and studied 15 patients with inflammatory facial acne.[34] Patients were first treated with the 595-nm PDL (6.5–7.5 J/cm^2, 6–10 ms, 10 mm) followed by a single pass with the 1450-nm diode (10–14 J/cm^2, 30–40 ms, 6 mm). The authors evaluated acne lesions 4 to 6 weeks after each treatment and reported a mean acne lesion count reduction of 52% after one treatment, 63% after two treatments, and 84% after three treatments. They suggest that combining two lasers may have a synergistic effect by targeting both *P. acnes* and the sebaceous glands as is the case with the 1450-nm diode laser.

Lupus erythematosus

Lupus erythematosus is an autoimmune disorder that is associated with the development of chronic and disfiguring skin lesions. With cutaneous forms, failure of local therapy is not uncommon. The only alternatives are the systemic application of glucocorticoids, chloroquine, or azathioprine, although a disparity often exists in the risk–benefit analysis with small and occasional lesions.

In case studies, therapeutic success has been reported since 1986 for cutaneous lupus erythematosus foci when using the continuous wave-CO_2 and argon laser.[35,36] Against this, Wolfe *et al.* reported on the induction of lupus erythematosus after an argon laser treatment of facial telangiectasias.[37]

Nunez *et al.* (1995 and 1996) were the first who reported in a 'letter' on the treatment of lupus erythematosus, but they did not continue their investigations.[38,39] A pilot study by Maushagen-Schnaas and Raulin was able to show not just clinically but also histologically complete regression of the treated lupus erythematosus foci.[40] A biopsy taken upon completion of therapy (4 weeks) revealed only post-inflammatory hyperpigmentation. Immunohistologically, only discrete IgG and C3 deposits could be described along the junction zone.

In a retrospective study, Raulin *et al.* treated 12 patients with cutaneous lupus erythematosus, of whom two also showed systemic involvement (3–7 J/cm^2, 585 nm, 0.3–0.45 ms, 5–7 mm).[4] Six subjects had been taking chloroquine or corticosteroids for already some time at the beginning of the laser therapy without any effect, and this practice was continued by five of the patients during the laser therapy. After an average of 5.1 sessions, a clearance rate of 70% could be achieved in nine cases (for example, see fig. 2), whereas in two patients, only a reduction in hyperaesthesia and itching could be shown. One patient had no improvement following treatment. The side-effect rate was low. Over a follow-up period of 3 to 32 months (median 7 months), only one patient showed a minor relapse.

In 2003, Baniandres *et al.* reported their experience using both a 585-nm PDL (5–7.5 J/cm^2, 0.45 ms, 5 mm) and a 595-nm PDL (6–13 J/cm^2, 1.5–10 ms, 7 mm) in a series of 14 patients, including eight cases with discoid lupus and six cases with systemic lupus erythematosus.[42] After one to nine treatment sessions, clearance rates

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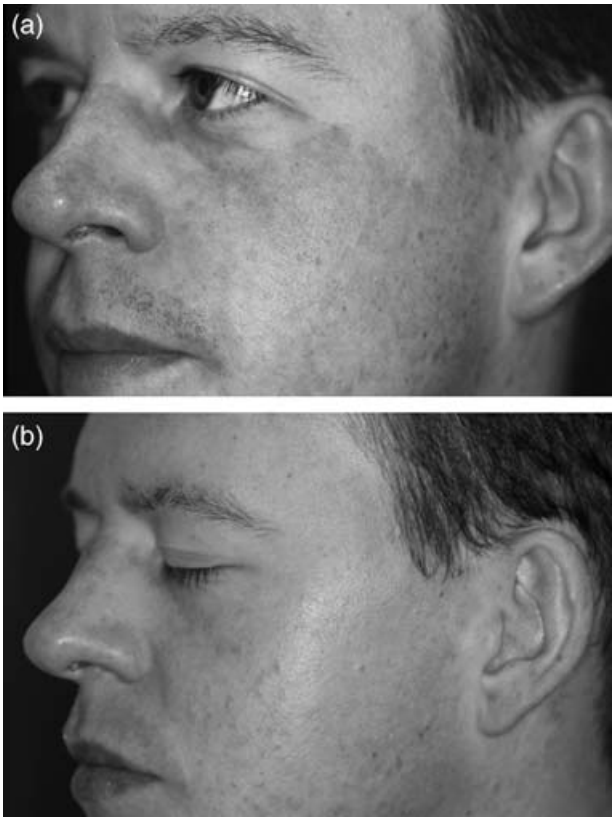

fig. 2 (a) Lupus erythematosus. (b) Lupus erythematosus after three treatments.

ranged from 30% to 90% and averaged 65%. Telangiectasia and erythema improved the most in response to laser treatment, whereas there was little change in the atrophic or hyperkeratotic components of the lesions. During follow-up (median 10 months), lesions in 3 of 14 cases showed evidence of partial relapse.

The selective destruction of vessels is thought to be the main mechanism of action. Other processes at the cellular level are also presumed, such as the stimulation of immunomodulatory processes. Biopsies obtained early after the laser treatment showed reduction in vessel size but no evidence of improvement based on direct immunofluorescent studies. In fact, in one patient, the presence of IgG, IgA, IgM, and C3 at the dermo-epidermal junction was more intense in the laser-treated vs. non-treated lesions.[42]

From the presented studies, we can not reach conclusions about the effect of PDL on disease pathology. To clarify the mechanism of action, further studies need to be carried out. The response rates are variable, but the patients are generally satisfied. Initially, we are performing spot testing to investigate the potential for disease reactivation because UV light is well known for its ability to precipitate or aggravate lupus.

Psoriasis

Psoriasis is a chronic inflammatory skin disease, in which epidermal proliferation is closely associated with excessive microvascular and T-cell expansion within the papillary dermis.[43,44] Psoriatic lesions improve with PDL treatment by the destruction of their supporting vasculature. However, the remission in PDL-treated lesions is usually transient. Studies have shown that the persistent secretion of cytokines in treated psoriatic lesions were responsible for endothelial re-proliferation causing a rebound in vasculature and return of psoriatic plaque.[45] In the study by Hern *et al.*, the effect of the PDL was limited to the superficial capillary bed, with no changes in the microvessels of the upper reticular dermis.[45] Although there was significant clinical improvement in plaques after treatment, complete clearance of lesions was not achieved. Selective photothermolysis of psoriatic capillaries caused a significant reduction in both endothelial surface area and endothelial cell proliferation in the superficial dermis. Interestingly, endothelial expression of surface adhesion molecules important in angiogenesis was not altered by treatment. The $CD4^+$ and $CD8^+$ T-cell infiltrate was reduced in the superficial papillary dermis but not in the epidermis or upper reticular dermis. PDL treatment significantly reduced epidermal thickness but did not alter epidermal keratinocyte proliferation. These results show that dermal capillary changes alone are unlikely to be causal in psoriasis. They rather indicate that the expanded psoriatic capillaries may be important in facilitating the access of activated T cells to the skin and in maintaining psoriatic plaques.

Whatever the aetiology of psoriasis, it is clear that the superficial dermal vasculature is a major contributor to the pathogenesis of this disease. Because the psoriatic blood vessels seem to play such an important role, even if only as a conduit for lymphocytes, it is obvious that selectively removing the abnormal psoriatic vasculature may be of benefit for potential treatment.

Hacker and Rasmussen treated 20 patients using 5, 7, and 9 J/cm^2 (0.45 ms, 5 mm).[46] In 11 of 19 patients, there was clinical improvement after one session in the area that had been treated with 9 J/cm^2, but there was no case of complete remission. The areas that had been treated with lower energy fluences showed no improvement.

In the study involving the largest number of patients (36 patients), Zelickson *et al.* achieved significant clearance in two to five sessions.[47] They compared the pulse durations 0.45 and 1.5 ms with energy fluences of 7.5 to 8.5 J/cm^2 at a spot size of 5 mm; no difference was observed.

Hern *et al.* used similar parameters (7.5–8.5 J/cm^2, 0.45 ms, 5 mm) in eight patients and observed a significant decrease of the thickness of the epidermis but not a complete regression (biopsy before and after treatment). Several studies followed showing similar results.[48,49]

Taibjee *et al.* conducted a controlled, prospective trial to evaluate both excimer laser and PDL for the treatment of psoriasis.[50] Twenty-two patients were selected for the study; 15 patients completed full treatment, and 13 were followed for 1 year. All 22 patients received four different treatment options, one each to four plaques: (i) excimer laser twice weekly until lesions cleared or for 12 weeks total; (ii) salicylic acid pretreatment and one PDL treatment monthly for 4 months; (iii) salicylic acid alone for 4 months; and (iv) no treatment (serving as control). Nine patients cleared with the excimer laser, with an average of 10 weeks of treatment. Six patients cleared with PDL, with a median of four treatments. Four patients in each group remained disease-free at 1 year of follow-up. Psoriasis activity and severity index and clinical response (CR) rate was greater in the excimer group when compared with the PDL group. CR in the PDL group was greater than salicylic acid alone or untreated controls. The authors concluded that excimer laser therapy was efficacious for the treatment of psoriasis, and although less efficacious, PDL therapy was effective in a small subset of patients.

More recently, de Leeuw *et al.* evaluated the safety and efficacy of PDL therapy for the treatment of psoriasis of the hands and feet.[51] The study included 41 patients treated with PDL (585 nm, 0.45 ms) once every 4 to 6 weeks, in addition to calcipotriol ointment and salicylic acid between laser treatments. Altogether, 76% of the patients treated achieved more than 71% clearance after an average of 4.2 treatment sessions. In order to assess remission, follow-up was conducted through 36 months of post-lesion clearance. The average duration of remission was 10.7 months for patients who achieved more than 71% improvement. Although promising, the study was limited by small sample size and concomitant use of keratolytic agents between treatments.

In conclusion, the body of evidence addressing the use of laser therapy for psoriasis is limited. Most studies lacked the statistical rigor needed to determine the effectiveness of laser therapy in the general clinical setting: they had small sample sizes, lacked randomization and adequate controls, and involved short follow-up times. Moreover, none of the studies provided a rigorous comparison of laser therapy with standard therapies for psoriasis, and few provided a direct comparison of the different laser types. Larger well-designed clinical trials are needed to prove the short- and long-term effectiveness and safety profile in the general clinical setting; to establish optimal, laser-specific treatment protocols; to resolve the technical limitations; and to define appropriate patient selection criteria.

3. Connective tissue diseases

Hypertrophic scars

A hypertrophic scar is a scar that has become raised, red, and nodular but that remains within the confines of the original skin damage. When treating hypertrophic scars, further scar formation must always be avoided; thus, conservative treatment strategies should be favoured.

In 1993, Alster *et al.* showed that PDL not only reduced the erythema of scars secondary to treatment of vascular lesions but it also reduced the size of the scar.[52] The precise mechanism responsible for this is unknown but it has been suggested that a therapy-induced reduction in the lesional vessel volume results in a decrease in the total tissue volume. Laser-induced destruction of the microvasculature presumably leads to ischaemia, which may induce collagen turnover so that the end result is a non-erythematous scar with a more uniform skin surface texture. However, this only partially explains its effectiveness because non-vascular malformation-associated scars have also been noted to respond to PDL treatment. In a histologic study, Alster and Williams observed a proliferation of local mast cells.[53] Conceivably, these cells could indirectly influence the growth of normal and keloid-producing fibroblasts via the release of histamine.[54] One could also hypothesize that sufficient heat is conducted from the blood vessels to the surrounding dermis directly to alter the collagen composition of the scar.

In 1994, Alster *et al.* reported an average improvement of 57% after the first treatment and 83% after the second treatment for surgical and traumatic scars.[55] In addition to a reduction in erythema, a flattening, a clear reduction in itching and pain, and an optimization of the skin structure have been observed. The entire scar in each patient was exposed to PDL at a wavelength of 585 nm, a pulse duration of 0.45 ms, and a fluence of between 6.5 and 7.25 J/cm^2. The laser treatments were separated by 6 weeks.

In another study published in 2004, Alster *et al.* carried out two treatments with the PDL (4.5–5.5 J/cm^2, 1.5 ms, 10 mm) either with or without injection of triamcinolone into hypertrophic scars resulting from breast reduction.[56] Eight weeks after therapy, the results concerning clinical appearance and scar induration were comparable (50–60% improvement), and with the subjective symptoms, the hypodermically injected side was superior.

Manuskiatti's research group compared PDL therapy with intralesional application of triamcinolone (20 mg/mL),

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5-fluoruracil (50 mg/mL), or a combination of both medications against control.[57] In each case, clear clinical improvements could be shown in comparison with the control group but without any significant differences between the treatment groups.

McCraw *et al.* also described preventive effects from using PDL.[58] Only scars after surgical interventions and primary wound closures were considered in their study. Therapy began either 2 weeks after surgery or 1 to 2 weeks after removal of the sutures. Both scar hardening and reddening normalized more rapidly, and hypertrophic scars occurred more rarely. Because this was not a comparative study, the results must be interpreted with caution. Similarly, Nouri *et al.* treated half of each scar (11 patients) directly after removal of the suture threads and twice in monthly intervals. A clear improvement in all scar parameters was found in the treated area according to the Vancouver Scar Scale.[59]

In contrast to the above cited results, a study by Chan *et al.* failed to show any clinical improvement using PDL against hypertrophic scars.[60] In 27 hypertrophic scars, one side of which was treated (585 nm, 7–8 J/cm^2, 2.5 ms, 5 mm), they found no superiority of the treated half after three to six treatments regarding thickness and elasticity, although pain and touch sensitivity were far better on the treated side. The negative study findings were most likely due to differences in treatment parameters. Several reports have shown a trend towards better clinical improvement using low to moderate fluences rather than fluences sufficient to cause purpura.[61] Furthermore, when treating a scar a larger spot size should be used. This principle was shown in an earlier study by Nouri *et al.*[59]

In our experience, 5 to 10 PDL sessions only lead to a moderate reduction in hypertrophy but a relevant decrease in irritation and pain. Apart from the unavoidable purpura and the occasional blisters and crusts (provided one chooses to treat in a purpuric manner), no other side-effects are common. PDL, therefore, represents a recommended option for the treatment of erythematous hypertrophic scars (for example, see fig. 3).

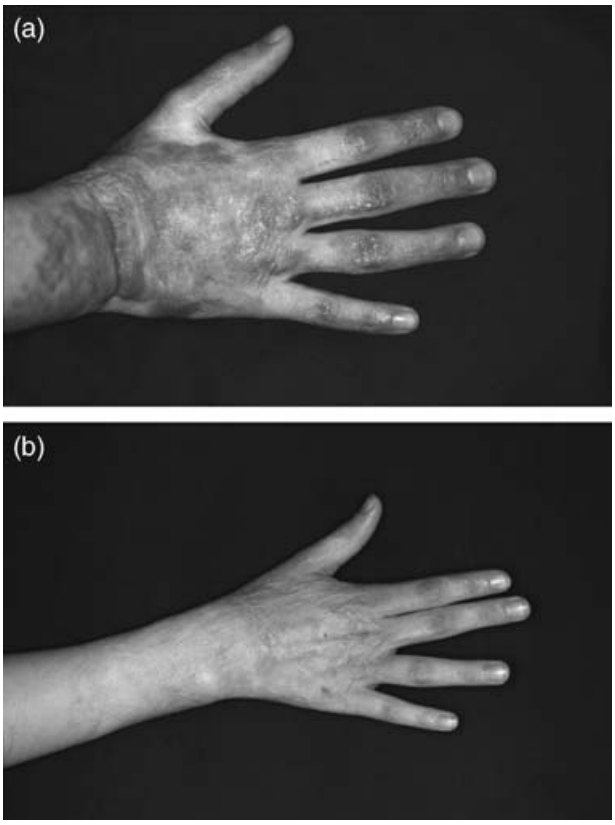

fig. 3 (a) Scars. (b) Scars after 20 treatments.

Keloids

Keloids are excessive formations of collagen that typically develop beyond the area of the initial wound.

Alster *et al.* were the first to report good results among patients with keloids after sternotomy.[53] Kuo *et al.* achieved an improvement of about 50% in 26 of 30 patients with keloids after five to six treatments using 10 to 18 J/cm^2 (585 nm, 0.45 ms, 5 mm).[62]

Because of its restricted skin penetration, PDL is certainly suitable for thin and highly vascular keloids. Just as with cryotherapy, several sessions are necessary in order to achieve an effect. The parameters should be chosen in the same way as for treatment of hypertrophic scars. In our experience, a substantial reduction in the size of the keloids is rare. However, the tortuous irritation can be reduced or even eliminated.

Stretch marks

Stretch marks are usually hormonally conditioned, striated atrophies of the skin. After an erythematous initial phase, atrophic striations with cigarette paper-like folding of the epidermis are found. Stretch marks typically occur on the thighs, hips, abdomen, and breasts. Histopathologically, initial striations show dilated dermal blood vessels, which can be viewed as potential absorber targets for laser therapy.

According to McDaniel *et al.* and Alster, a clinical improvement in early and still red striations can be achieved after several courses of PDL therapy using low energy densities (3 J/cm^2).[63,64] Jimenez *et al.*, however, were not able to find any clear effectiveness after two treatments

when compared with untreated lesions (585 nm, 3 J/cm^2, 0.45 ms, 10 mm).[65] The size of the striations reduced in both groups (70% vs. 65%), the red striations paled as a result of therapy but with pale striations, no clinically significant alterations were observed.

Non-ablative dermal remodelling

Since dermal collagen rather than epidermal structures proved to be the actual target of skin resurfacing,[66] efforts have been made to establish an effective laser treatment preserving the epidermis and avoiding the side-effects after laser resurfacing.

The theoretical model of 'non-ablative dermal remodelling' depends on the photothermal induction of pro-collagen III expression resulting in subsequent collagen deposition. Based on Anderson and Parrish's concept of selective photothermolysis, this is achieved through the heating of the subdermal microvasculature by selectively targeting oxyhaemoglobin and to a lesser extent deoxyhaemoglobin as its target chromophores. The generated supraphysiologic level of heat is able to induce a heat shock response, which can be defined as temporary changes in cellular metabolism.[67] These changes are characterized by the production of a small family of proteins termed 'heat shock proteins' (HSP). Recent experimental studies have shown that HSP70, which is overexpressed following laser irradiation, may play a role in the coordinated expression of growth factors such as transforming growth factor β (TGF-β). TGF-β is known to be a key element in the inflammatory response and the fibrogenic process.

Biochemical analyses done on the interstitial liquid of suction blisters on the forearm taken before and 72 h after laser treatment showed an increased rate of pro-collagen type III after treatment.[68] Histologic evaluation in a study by Zelickson *et al.* showed a decrease in the accumulation of degenerated elastotic fibers in the dermis, the presence of activated fibroblasts 12 weeks after the treatment, a thickening of the superficial collagen band, and an increase of the mucine quantity in the superficial dermis.[69] In the same study, the investigators reported the most encouraging results with PDL treatment of sun-induced facial wrinkles. They evaluated the effect of a single-pulse PDL treatment at 585 nm and 0.45-ms pulse on 20 patients using energy densities between 3 and 6.5 J/cm^2. Half of the patients had mild to moderate, the other half had moderate to severe sun-induced rhytids. Nine of 10 patients with mild wrinkling improved 50% or more, with 30% showing improvement of 75% or more. Maintenance of this effect was variable over the 12-month follow-up period. Of note, no statistical analysis of data was presented in this qualitative study.

Two groups of volunteers, totalling 40 patients, were involved in a study by Bjerring *et al.*[68] One group of 10 patients was selected for biochemical analysis of the laser-treated site, whereas the second group of 30 subjects was treated with identical laser parameters for facial rhytids (585 nm, 2.4 J/cm^2, 0.35 ms). Interestingly, there was an increase in pro-collagen production at the treatment site but lower pro-collagen production at sites that were multiply treated, suggesting the additional energy dosage had a negative physiologic effect. In contrast, Tanghetti *et al.* found modest improvement in wrinkles, independent of the number of passes with multiple subpurpuric treatments.[70] Following this report, Reynolds *et al.* showed that the 595-nm PDL set at 0.5-ms pulse width and 2.5 to 3 J/cm^2 energy fluence is not effective in subpurpuric, non-ablative periorbital wrinkle reduction.[71] This was the case despite single and multiple passes being done over the treatment area. Similar results were found by Hohenleutner *et al.* after treating 12 patients with 2.5 J/cm^2, 585 nm, and 0.45 ms.[72]

Altogether, the published literature is difficult to interpret because of varying laser settings between the studies. Basic and clinical research have provided the evidence to support its potential efficacy, although the clinical outcome in reducing facial rhytids is often subtle, and the objective measurement of outcomes remains challenging. Friedman *et al.* have reported on a digital system for evaluating the effect of non-ablative dermal remodelling on skin but only two patients were studied.[73] Interestingly, when valid and reliable end point measures, such as optical profilometry, have been done, they have shown improvement. Surprisingly, however, this has not always correlated with the clinical findings. Similarly, almost all of the relevant histological studies have shown fibrosis after treatment, but this again has not always been consistent with clinical improvement. At present, there seems to be no clear clinical evidence of efficacy, and the studies reviewed herein raise a plethora of questions, such as: What about long-term complications of non-ablative dermal remodelling? Although the epidermis is protected during the procedure, we are actually delivering a large amount of energy to the dermis. Could this eventually lead to dermal ageing or premature fibroblastic apoptosis? Furthermore, what are ideal treatment parameters? And how does the PDL compare in efficacy with established treatments such as the CO_2 laser? Why do some respond better than others?

4. Anecdotal reports

Hidrocystoma

Eccrine hidrocystomas are benign cystic lesions that pose a significant treatment challenge because of their facial

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location and tendency to scar following traditional surgical and other destructive modalities.

Tanzi and Alster treated a patient's multiple pale-blue hidrocystomas at 6- to 8-week intervals with 7 to 7.5 J/cm^2 (585 nm, 1.5 ms, 7 mm).[74] After four treatment sessions, there was an almost complete resolution. During the follow-up period of 18 months, the authors reported no relapse.

In our experience, the haemorrhage into hidrocystomas is the basis for response to the PDL, which in turn explains why hidrocystomas without haemorrhage do not respond as well to PDL therapy (for example, see fig. 4).

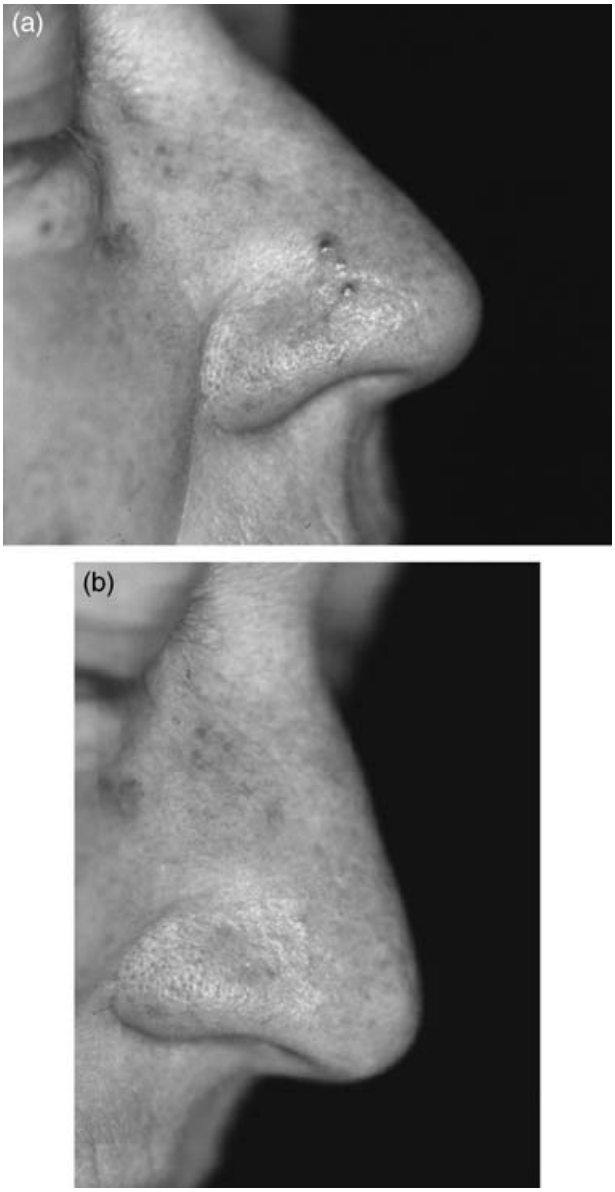

fig. 4 (a) Hidrocystoma. (b) Hidrocystoma after two treatments.

Lichenoid dermatitis

Lichenoid tissue reactions occur in a number of inflammatory skin diseases, including pityriasis lichenoides et varioliformis, lupus erythematosus, chronic graft-versus-host disease, and lichenoid drug-related exanthema.

In 2002, Greve *et al.* reported on the treatment of a drug-induced (roxatidine, H_2 receptor antagonist) lichenoid dermatitis on a female patient's back.[75] The skin lesion was resistant to a 10-month treatment course with topical corticosteroids. Within six treatment sessions using 5.5 to 6.0 J/cm^2 (585 nm, 0.45 ms, 7 mm) at 6-week intervals, complete remission was achieved. There was no relapse within the follow-up period of 54 months. Because the drug was discontinued at nearly the same time that laser treatment began, the authors conclude that PDL treatment may have accelerated the clearance of the skin lesion.

Lichen sclerosus et atrophicus

The cause of lichen sclerosus et atrophicus is still unknown. Genetic, autoimmune, and infectious factors have been discussed. Irrespective of the causative agent, there is a unifying sequence of events leading to altered fibroblast function and microvascular changes (both being a target for PDL treatment).

Rabinowitz was the first to show the successful therapy of an erosive and bleeding genital lichen sclerosus et atrophicus in a 7-year-old girl.[76] Four treatment sessions were carried out using 5.75 to 6.25 J/cm^2 (585 nm and 5 mm).

Greve, Hartschuh, and Raulin reported on a case of a 17-year-old female patient with a therapy-resistant extragenital lichen sclerosus et atrophicus around the neck, chest, umbilicus, wrists, and elbows.[77] The skin lesions had been entirely eliminated after four treatment sessions at 4- to 6-week intervals (5.3–6 J/cm^2, 0.45 ms, 7 mm). The patient experienced no recurrence within a 7-month follow-up period.

Following this report, we have been able to reproduce these results (data not published). Although it is not always possible to reach a restitutio ad integrum, the accompanying itching can be successfully eliminated, which in most cases is a more realistic goal of therapy.

Solitary reticulohistiocytoma

Reticulohistiocytoma is a non–Langerhans cell histiocytosis. On exposed skin areas, it is a cosmetic problem causing mechanical irritation due to its prominent nature.

Warncke *et al.* successfully treated a solitary reticulohistiocytoma on the back of a 60-year-old female with PDL (585 nm, 7.8 J/cm^2, 7 mm). After two treatment sessions, the authors achieved complete remission.[78] At 28-month follow-up, no recurrence was seen. This result could be reproduced in several other cases (data not published).

Sebaceous hyperplasia

Sebaceous hyperplasias are benign skin lesions and generally do not require treatment. However, lesions can be cosmetically unfavourable and cumbersome when irritated. Therapy is mostly mechanical (e.g. excision, cryotherapy, and CO_2 laser, among others), thus bearing the risk of scarring.

Schönermark *et al.* reported for the first time on the complete remission of sebaceous hyperplasia in two patients using 6.5 to 8 J/cm^2 (585 nm, 0.45 ms, 5 mm) after two to three treatments. There was no relapse reported within the follow-up period of 13 months.[79]

Likewise, Gonzales *et al.* successfully treated a patient's sebaceous hyperplasias with 7 J/cm^2 (585 nm, 5 mm).[80] Through confocal imaging, the authors were able to show selective photothermal damage confined to blood vessels. At follow-up consultations (2 weeks and 2 months), the sebaceous hyperplasias were no longer visible.

Aghassi *et al.* evaluated 29 lesions (10 patients) with three stacked pulses at 7 to 7.5 J/cm^2 (585 nm, 0.45 ms, 5 mm).[81] They achieved complete remission in 28% and flattening in 93% of cases. However, 28% recrudesced after initial involution.

Xanthelasma palpebrarum

Xanthelasma palpebrarum is the most common cutaneous xanthoma. Although a benign condition and almost never limiting functioning, its appearance is often regarded as cosmetically disturbing. Numerous options are available for removal, including surgical excision and ablative laser therapy, all bearing the risk of scarring in a delicate location near the eye.

Schönermark and Raulin reported on the successful use of PDL with xanthelasma palpebrarum in a case study.[82] After five treatments with a fluence of 7 J/cm^2 (585 nm, 0.45 ms, 7 mm), complete remission was achieved.

The efficacy of the PDL, however, is limited by its short penetration depth requiring at least four to eight treatment sessions and bearing a considerable risk of recurrence. Therefore, we recommend the use of this laser only for the therapy of initial, flat xanthelasma. In practice, we prefer the combination of PDL directly following treatment with CO_2.

Conclusion

Clinical experience enduring over years has allowed conventional parameters to be continually optimized for already known treatments and to discover new areas of therapy.

Very good results can be achieved using PDL with numerous and sometimes less well known indications (e.g. lupus erythematosus). For other indications (e.g. psoriasis), PDL at this time is only valued as an alternative, supplementary, or experimental treatment. Generally, it can be stated, however, that with a simple and safe treatment for new indications or therapy-refractory individuals (for which the dye laser might theoretically be suitable), a treatment should be attempted on an experimental basis. The many new adjustments and modalities of PDL will provide further improvement in therapeutic effectiveness as well as an expansion into new indications for treatment.

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