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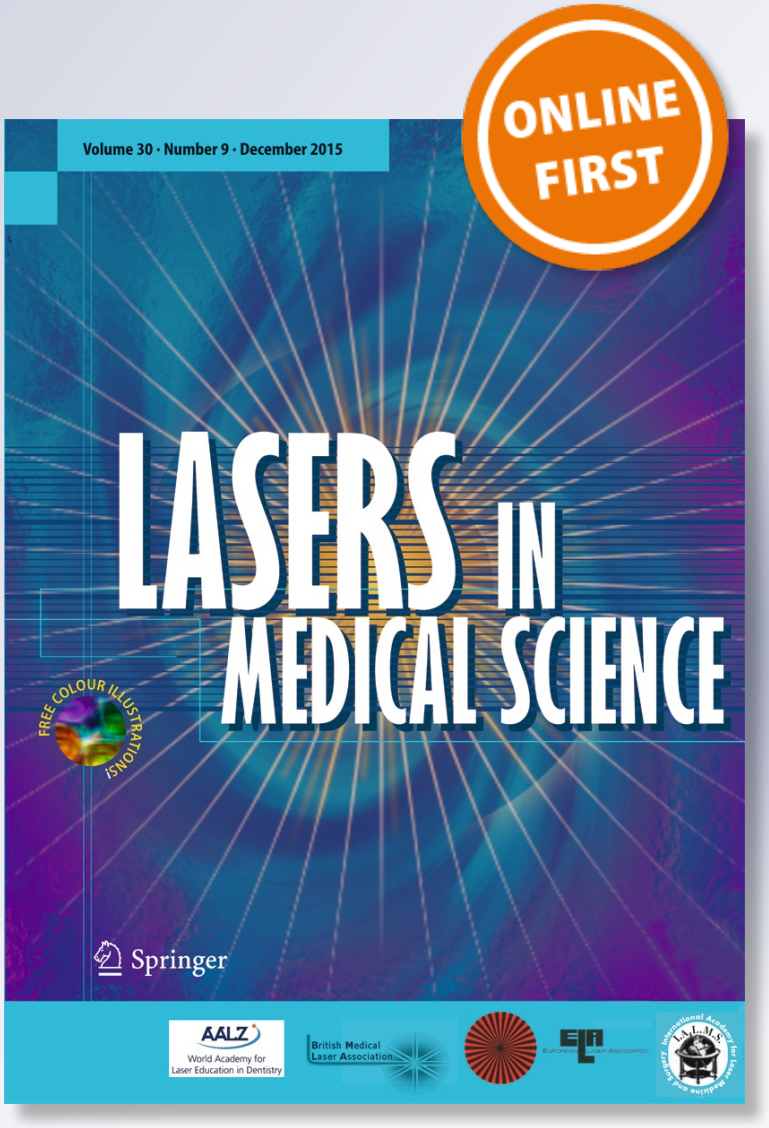

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REVIEW ARTICLE

Laser-assisted drug delivery in dermatology: from animal models to clinical practice

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Abstract Topical medicaments are the mainstay of the dermatologists' therapeutic arsenal. Laser-assisted drug delivery enhances the ability of topically applied medicaments to penetrate the skin. We discuss the mechanisms of laser-assisted drug delivery and animal models that have informed clinical practice. We review clinical studies that have employed laser-assisted drug delivery for a range of indications to date including non-melanoma skin cancer, vitiligo, scarring, vaccination, local anaesthesia, analgesia, viral warts, infantile haemangiomas and cosmetic uses. Studies thus far suggest that laser pre-treatment improves transepidermal absorption of topical agents and allows for a much deeper penetration of drugs than is possible with topical medicaments alone. This may allow more efficacious action of current treatments, such that conventional duration of treatment can be shortened or lower concentrations of active agents be used, potentially obviating side effects of treatment. The prospect of using laser technologies to facilitate transdermal vaccination and as an adjunct for inflammatory dermatoses and cosmetic indications remains in its infancy. As larger trials are published, involving greater numbers of patients and utilising various laser and topical medicament parameters, we will enhance our understanding of this nascent modality of treatment delivery.

Keywords Laser · Laser-assisted drug delivery · Dermatology · Fractional thermolysis

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Introduction

Topical therapies are the mainstay of the dermatologists' therapeutic armamentarium whether used for inflammatory dermatoses, malignant and pre-malignant skin disease or aesthetic indications. For optimal therapeutic effect, delivery of the drug to the relevant compartment within the skin is required. In recent years, ablative laser devices have been employed to aid delivery of biological molecules throughout the various cutaneous compartments [1–3]. Whilst other physical mechanisms to enhance transdermal drug delivery have been investigated, including tape stripping, iontophoresis, ultrasound and microneedling [1], the focus of this article is to review the rationale underlying laser-assisted delivery of drugs, the most informative pre-clinical studies, and consider the clinical dermatological indications where laser-assisted delivery may be of utility.

Mechanisms of laser-assisted drug delivery

The stratum corneum is the outermost layer of the skin and is largely impregnable to compounds with molecular weights greater than 500 Da [4]. Once the stratum corneum is traversed, passage of molecules to the cutaneous vasculature is comparatively unimpeded.

Laser technologies deploy a particular wavelength of light to selectively destroy the chromophore of interest. Ablative lasers in common use include the carbon dioxide (CO_2; wavelength peak 10,600 nm) and erbium-doped yttrium aluminium garnet (Er:YAG; wavelength peak 2940 nm) devices, both of which have wavelengths preferentially targeting water. Laser devices have traditionally been used in continuous mode, in which the entirety of the water-containing epidermis being treated is ablated.

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More recently, ablative fractional laser technologies (AFXL) have been developed. AFXL exploits fractional photothermolysis, in which multiple vertical columns of tissue in the stratum corneum and underlying tissues are thermally destroyed to create unimpeded channels communicating with the outermost layer of the stratum corneum [1–3]. Each channel is surrounded by a cuff of dense thermally coagulated tissue, collectively referred to as microscopic treatment zones (MTZs). Only a fraction of the skin surface is treated, in which MTZs facilitate penetration of topical molecules from the surface to the layer of interest, whilst leaving most of the skin surface area untreated and intact. The untreated skin serves as a reservoir of stem cells, growth factors and inflammatory cells that are able to rapidly migrate to the traumatised skin and facilitate faster healing with less scarring [5].

Increased penetration of drug via MTZs can be understood using Fick's first law, which in its simplest form states that the degree of flux of molecule (J) across a barrier is a product of the partition coefficient (Km, a reflection of the number of molecules available for diffusion across a membrane), the diffusion constant (Dm, a reflection of the inherent diffusibility of a molecule across the membrane) and concentration difference of that molecule on either side of that barrier (ΔC), divided by the path length (L) [6]:

$$J = \frac{\mathrm{Km} \times \mathrm{Dm} \times \Delta C}{L}$$

Increased permeability of the stratum corneum via MTZs increases Km, therefore increasing overall flux of the molecule. As molecular size of the drug increases, there is greater frictional resistance to movement of the molecule and Dm decreases, hence decreasing overall flux.

Pre-clinical studies: animal models

Work on animal models has informed the clinical use of AFXL. Photodynamic therapy (PDT) comprises the photodynamic reaction between a photosensitiser, light of a select wavelength (or band) and oxygen to generate reactive oxygen species that target microbes and malignant cells. PDT is most commonly used in dermatological practice to combat non-melanoma skin cancer (NMSC) and acne vulgaris [7]. The two most commonly used photosensitisers are methyl aminolevulinate (MAL) and aminolevulinic acid (ALA). Owing to the generation of porphyrin species that can be readily identified with fluorescent microscopy, PDT is a useful experimental tool for investigating drug penetration.

Haedersdal and colleagues undertook CO_2-AFXL prior to treatment with MAL-PDT on porcine skin creating single MTZs, each 300 μm in diameter and 1850 μm in depth, surrounded by a 70 μm cuff of thermally coagulated tissue [8]. In skin treated with AFXL and MAL-PDT (AFXL-PDT), increased porphyrin fluorescence was observed in a uniform fashion up to 1.5 mm from the ablated channels. This suggested that for MAL, MTZs placed at 3-mm intervals, equating to less than 1 % surface area, could be used to treat the entirety of the lesion. This finding is substantiated by an additional study that used an Er:YAG laser to create multiple MTZs and suggested that there is no increase in lidocaine absorption if the number of pores is increased beyond a certain density. Moreover, there was no increased absorption of lidocaine if progressively higher fluences were used to extend the MTZs beyond the stratum corneum into the epidermis or dermis [9].

AFXL pre-treatment of porcine skin has also been shown to increase MAL-induced fluorescence at both superficial and deep levels [10]. Additionally, no significant difference was seen between different light emitting diode (LED) energies of 37 J/cm^2 (used in clinical practice) and the much higher 200 J/cm^2 at all but one depth. Together, these findings supported the use of AFXL to enhance delivery of MAL to deeper layers of the skin, without the need to alter established clinical LED illumination parameters of PDT.

A further study by the same group on porcine skin suggested that increased surface fluorescence from MAL was observed in AFXL pre-treated skin in a shorter time frame than non-AFXL pre-treated skin [11]. In porcine skin, whilst AFXL pre-treatment increases fluorescence induced by MAL and ALA, ALA appears to induce greater fluorescence than MAL for deeper structures, putatively due to the smaller size and more hydrophilic nature of ALA [12].

5-Fluorouracil (5-FU) is a chemotherapeutic agent commonly used in dermatology for treatment of NMSCs, including actinic keratoses (AKs), Bowen's disease and superficial basal cell carcinomas (BCCs). Imiquimod (5 %) is a commercially available immunomodulatory agent that is similarly used to treat various NMSCs. Work in murine skin has suggested that 5-FU penetration was enhanced 36–133-fold following pre-treatment with Ruby, CO_2 or Er:YAG lasers [13]. Similar work has demonstrated enhanced transdermal delivery of imiquimod in porcine and murine models following a low-fluence fractional Er:YAG laser [14], with enhanced imiquimod delivery up to 65-fold after one pass and 127-fold after four passes. The authors further demonstrated that reduction in dose of imiquimod to 0.4 % delivered equivalent concentrations of imiquimod as topically applied 5 % imiquimod (commercially available) which may allow for the future use of lower concentrations of drugs leading to similar clinical efficacy.

Together, these findings in porcine skin suggest that there is a critical density of MTZs, beyond which additional MTZs confer no benefit with respect to penetration of the drug. Photosensitisers can penetrate superficial and deep levels of skin, and conventional settings for the LED illumination can be employed. Pre-treatment with AFXL permits greater

penetrance of drug, in particular larger and more hydrophilic molecules, which may act in a shorter time frame. Furthermore, AFXL pre-treatment may improve efficacy of topically applied medicaments and permit lower concentrations of active agents to be used with reduced frequency or duration of application.

Actinic keratosis

AKs are the commonest pre-malignant skin condition, included in the larger population of NMSCs [7, 15]. Treatments for AKs include physically destructive measures (cryotherapy, curettage, excision), chemically destructive means (including PDT and topical agents such as 5-FU and ingenol mebutate) and immunomodulatory agents (such as imiquimod).

In a trial looking at the effects of AFXL pre-treatment on field treatment of AKs on the face and scalp, 15 patients had conventional PDT applied to one area of skin and on the symmetrical corresponding area of skin received AFXL-PDT (10 mJ per pulse, 0.12-mm spot, 5 % density) [16]. At 3-month follow-up, AFXL-PDT was more effective than conventional PDT, with complete lesion response of 88 and 59 % respectively, with AFXL-PDT exhibiting fewer new AKs and improved photoageing. Adverse effects of PDT therapy, namely peri-procedural pain, erythema, crusting and pigmentary change were also more pronounced in AFXL-PDT-treated skin than conventional PDT alone. Clinically, these results suggest that AFXL pre-treatment prior to PDT enhances penetration and subsequent clinical efficacy of MAL, with a concomitant accentuation of side effects associated with PDT.

Owing to high doses of immunosuppressants that have to be taken, organ transplant recipients are at higher risk of NMSCs, which exhibit a lower response rate to PDT [7]. Helsing and colleagues compared a single treatment of CO_2-AFXL-PDT (30 W, 0.12-mm spot size, two passes) with CO_2-AFXL alone for treatment of AKs and warty lesions on the dorsal hands of ten organ transplant recipients with over 1000 lesions [17]. At 4 months, complete response was 73 % for AFXL-PDT versus 31 % for AFXL alone; moreover, AFXL-PDT was associated with a greater number of lesions improving to a lower grade.

One further study looked at the effect of pre-treatment with AFXL on incubation time required prior to PDT [18]. Twenty-two patients underwent conventional PDT, with the accepted incubation time of 180 min. Twenty-four patients underwent AFXL-PDT; following AFXL pre-treatment, MAL was applied and incubated for 90 min. In both cases, MAL was used as the photosensitiser, irradiation performed using the 630-nm LED and two cycles of PDT performed with an interval of 2 weeks. Clearance rates at 10 weeks were 64.7 % in the conventional PDT group and 71.4 % in the AFXL-PDT cohort, with no significant difference between the groups. These findings suggest that AFXL pre-treatment may reduce the incubation time required before PDT but without compromising efficacy.

Ingenol mebutate is a topical medicament used to treat AKs [15]. A 68-year-old gentleman with multiple occipital AKs received topical ingenol mebutate treatment to the right side of the occiput, whilst the left side underwent Er:YAG-AFXL (spot size 350 μm, density 10 %, fluence 63 J/cm^2, one pass) prior to application of ingenol mebutate [19]. As observed in cases of PDT, AFXL pre-treatment intensified the inflammation seen after ingenol mebutate therapy, such that the inflammation persisted for 3 weeks following therapy. A second case series of three males with AKs on the hairless scalp utilised a split-scalp study [16]. On one side of the scalp, ingenol mebutate was applied in the conventional manner (once daily for 3 days); the other side of the scalp was pre-treated with CO_2-AFXL (pulse energy 10 mJ, density 5 %) prior to a single application of ingenol mebutate. At 8 weeks post-treatment, the side of the scalp pre-treated with AFXL demonstrated a greater degree of AK clearance.

These studies raise the attractive prospect of treatment of multiple NMSCs in a single episode, in which a topical agent (such as 5-FU, ingenol mebutate or imiquimod) could be applied immediately after treatment with AFXL. This may prove particularly useful for patients with reduced concordance to prescribed treatment regimens (such as older patients), lesions in areas of the body which are difficult to reach or for patients with multiple lesions.

Bowen's disease

Bowen's disease (squamous cell carcinoma in situ) represents full thickness dysplasia of the epidermis with a propensity to develop into squamous cell carcinoma if left untreated. CO_2-AFXL pre-treatment of histologically proven Bowen's disease prior to MAL-PDT facilitated a shorter incubation time of photosensitiser (only 70 min, compared to the conventional 180 min), whilst resulting in similar treatment efficacy [20].

In a randomised study involving 21 patients with 58 Bowen's disease lesions, 3-month clearance rate was much higher following a single session of Er:YAG-AFXL-PDT (93.8 %) than two sessions of MAL-PDT (73.1 %) and 12-month recurrence rate was significantly lower for Er:YAG-AFXL-PDT (6.7 %) than MAL-PDT (31.6 %) [21].

Nguyen and colleagues reported a case series of 28 patients with a total of 16 superficial BCCs and 14 squamous cell carcinomas in situ, pre-treated with a single pass of CO_2-AFXL (0.12-mm spot size, 10 mJ per pulse, single pulse, 5 % density) followed by a single application of topical 5-FU (5 %) under occlusion for 7 days [22]. After 8 weeks, histological clearance was shown in 100 % of squamous cell carcinomas in situ and 71 % of the superficial BCCs.

Basal cell carcinoma

In Europe, PDT is currently licensed for use on selected superficial and nodular BCCs. The utility of PDT for nodular BCCs is often limited by the thickness of the tumour and inability of the photosensitiser to penetrate the tumour with sufficient depth. Treatment with ALA-PDT for nodular BCCs results in 53 % complete clearance at 36-month follow-up [23], and therefore, PDT is not recommended for treatment of nodular BCCs in national guidelines [24]. The rationale behind using AFXL pre-treatment prior to PDT is to create channels through which the active photosensitising agent may penetrate the tumour.

In a case series of three patients with nodular BCCs on the thigh, chest and lower back, pre-treatment with AFXL before MAL-PDT resulted in complete clinical and histological response in two patients and partial response in the other patient [25]. The authors mused that the partial response in the third patient may have been due to the underlying tumour being of sclerosing subtype, upon which PDT is recognised as being less efficacious. Owing to the number of cases, comparison with AFXL alone or PDT alone could not be made nor could definite recommendations be made.

Another study looked at 56 nodular BCCs each of which was ablated using a gallium arsenide 980-nm diode laser under ultrasound control [26]. Three weeks later, half of each BCC then received CO_2-AFXL, the other half curettage immediately prior to treatment with ALA-PDT. Histologically confirmed clearance rates of the half of the tumour pretreated with AFXL was 93 versus 80 % with curettage. This proof of principle study is strengthened by the inherent direct comparison of the same tumour, whilst acknowledging that there can be intralesional histological heterogeneity.

More recently, 32 patients were randomised to receive AFXL-PDT or conventional MAL-PDT for treatment of histologically confirmed nodular BCCs deemed as being high risk of recurrence. This included those with diameter greater than 15 mm, tumours on high-risk zones or on severely sun-damaged skin [27]. CO_2-AFXL-PDT (5 % density, 80 mJ, 1000-μm ablation depth) showed cure rate of 100 versus 88 % with conventional PDT at 3 months. Recurrences were reported to occur later and in lower numbers with AFXL-PDT. However, the authors could not advocate use of AFXL-PDT over PDT for treatment of nodular BCC, as the 12-month histological tumour clearance was comparable between the two modalities.

Actinic cheilitis

Thirty-three patients with actinic cheilitis were randomised to receive one session of Er:YAG-AFXL-MAL-PDT or two sessions of MAL-PDT [28]. Er:YAG-AFXL-MAL-PDT was significantly more effective (92 % complete response rate) than MAL-PDT (59 %) at 3 and 12-month follow-up, with no significant difference in cosmetic outcome or safety between the two modalities. These findings indicate the potential utility of AFXL-assisted PDT in patients with actinic cheilitis, a condition that does not respond as well to PDT as AKs but carries a similar propensity to progress to squamous cell carcinoma [29].

Vitiligo

Twenty-five patients with stable, symmetrical vitiligo, recalcitrant to other therapies, underwent a half-body comparative study, in which patches of vitiligo on one half of the body underwent CO_2-AFXL, followed by topical application of betametasone solution under occlusion followed by a course of narrowband-ultraviolet B (NB-UVB) phototherapy (treatment), whilst patches on the other side (control) received CO_2-AFXL and NB-UVB alone [30]. Treatments with CO_2-AFXL were given at half monthly intervals, whilst NB-UVB was given two to three times weekly over 6 months. Forty-four percent of patients achieved over 50 % repigmentation on the treatment arm, which was significantly better than the control arm, owing to greater penetration of corticosteroid. Whilst the results are of interest, the protracted course of treatment and associated expense may preclude this treatment in other health care systems.

Vaccination

Several current vaccinations, including the bacille Calmette–Guerin (BCG) and rabies vaccinations, are more effective when delivered via the intradermal rather than intramuscular route [31]. Owing to the abundance of cutaneous antigen-presenting cells, together with practical difficulties in using and disposing of hypodermic needles, transcutaneous delivery of vaccinations is a highly attractive prospect.

Chen and colleagues investigated the use of UltraPulse fractional CO_2 laser (5–15 % coverage) for its effect upon transcutaneous delivery of a model antigen, ovalbumin (OVA), across murine skin [32]. AFXL pre-treatment induced levels of anti-OVA serum antibody to 100-fold higher than tape stripping. This study demonstrates that AFXL pre-treatment can facilitate delivery of antigens into the skin via MTZs, which can be captured by antigen-presenting cells that can migrate via blood vessels and lymphatics to local lymph nodes where they can be translated into an immune response.

Whilst further work regarding appropriate antigen adjuvants and safety data is pending, as well as developing a portable, user-friendly laser device, the prospect of AFXL-enabled transdermal vaccination, potentially obviating the

need for needles, would be an enticing prospect to large swathes of the medical and needle-phobic populations.

Local anaesthetics

Many dermatological procedures are performed under local anaesthesia. Topical agents have a long latency before effect, and anaesthesia may be incomplete owing to poor penetration of the skin, whilst injections are associated with pain.

Pre-treatment with the conventional Er:YAG laser prior to application of topical 4 % lidocaine has been shown to reduce sensation to needle prick within 5 min compared to laser plus placebo (62 % reduction) or lidocaine alone (61 % reduction) [33]. Similarly, a blinded randomised controlled trial (RCT) of 61 patients (adults and children) attending the emergency department who required cannulation showed that pain upon cannulation was significantly lower when pre-treated with the Er:YAG laser prior to application of 4 % lidocaine [34].

There appears to be no diminution in the degree of analgesia at lower energy laser settings (2.0 J/cm^2), compared to the high energy (3.5 J/cm^2) settings used in the aforementioned studies, as inferred from an intra-individual study of 30 patients comparing both settings, with one used on each antecubital fossa [35].

Meesters and colleagues showed that pre-treatment of all ten subjects in their study with CO_2-AFXL (5 % density, 2.5 mJ/microbeam) was considered a painless procedure [36]. Pre-treatment with AFXL prior to application of commonly used local anaesthetic agents, articain hydrochloride 40 mg/ml with epinephrine 10 μg/ml solution (AHES) and lidocaine 25 mg/g with prilocaine 25 mg/g cream (EMLA cream), resulted in significantly lower subject-reported discomfort following a painful stimulus 10 min later, compared to sham laser pre-treatment. AFXL combined with AHES facilitated the most effective anaesthesia, perhaps owing to the liquid nature of the vehicle.

These proof-of-principle studies are supported by clinical applications. In a randomised, split-face clinical study of 12 patients, Yun and colleagues looked at the effect of pre-treating one side of the face with low-fluence Er:YAG prior to application of 5 % topical lidocaine and whole face resurfacing in two passes [37]. Subjective pain scores on the side of the face that had been pre-treated with ablative laser were significantly lower than the side not pre-treated with ablative laser. However, only 56 % patients were able to tolerate the second pass of the resurfacing, forcing us to question its value in future work.

Analgesia

Non-steroidal anti-inflammatory drugs (NSAIDs) have a wide array of uses, typically for analgesia in chronic inflammatory joint disorders, however are renowned for potentially serious side effects including gastritis, peptic ulceration and renal impairment, many of which could be averted with topical delivery. Bachhav and colleagues investigated the effects of AFXL on diclofenac permeation and deposition in porcine and human skin [30]. They found that the permeation of diclofenac across the skin was correlated with the frequency of pores (from 0 to 900) and laser fluence used (surrogate of depth of pores). Potential clinical applications include AFXL pre-treatment of skin to enhance local absorption of topically applied diclofenac, which may avert the systemic sequelae of NSAID ingestion, with potential indications ranging from inflammatory arthritis to AKs.

Opioids form the third stage of the World Health Organisation (WHO) analgesic ladder and are regarded as the mainstay of analgesia for chronic pain. Systemic opioid use can be associated with a range of side effects, including constipation, nausea, vomiting and hallucinations, some of which may be abrogated through use of topical agents. In an in vitro porcine model, Lee and colleagues demonstrated increased permeability to three opiates (morphine, nalbuphine and bupenorphine) following pre-treatment of skin with the Er:YAG laser with enhanced drug permeation of 10–35-fold, depending on the opiate used and fluence selected [32]. Enhanced permeation of morphine and nalbuphine compared to bupenorphine was postulated to be due to increased lipophilicity and higher molecular weight of the latter agent.

Whether the enhanced delivery of analgesics (including opioids, NSAIDs) through pre-treatment with laser devices is of academic interest or clinical utility relies in part upon comparison with current methods of opiate delivery, including ibuprofen gel and transdermal patches, and on the prospect of combination therapy.

Scarring

Improvement in the appearance of scars is often observed following AFXL treatment and likely is attributable to removal of a section of the fibrotic scar and a relative normalisation of collagen structure and composition [33].

Waibel and colleagues investigated 15 patients with hypertrophic scars resulting from trauma, injury or burns. Each patient received up to five treatments with CO_2-AFXL (10–15 % density) followed by topical triamcinolone application (10 or 20 mg/ml) [38]. Blinded observers noted improvements in texture, degree of hypertrophy and dyschromia at 6 months following the final treatment session. AFXL as a method of drug delivery may have benefit over triamcinolone injections owing to uniformity of depth and distribution of triamcinolone as well as avoiding the pain associated with intralesional injections.

Cavalie and colleagues reported the treatment of a total of 70 keloid scars in 23 patients with 2940 nm AFXL (180 J/cm^2, 5 % coverage) every other week with concomitant betametasone cream twice daily under occlusion until either complete flattening of the scar was achieved or no further improvement was seen [39]. After a median of nine laser treatments, there was a median 50 % percentage improvement in scar appearance, gauged through photographic evaluation by two independent observers. Eight months after treatment, keloid recurrence was 22 %: All recurrences were noted within 2 months of cessation of laser treatment.

Atrophic scars

Poly-L-lactic acid (PLLA; Sculptra) is commonly used as a subcutaneous filler for facial volume restoration, which is purported to stimulate fibroblast proliferation and collagen formation. Nineteen patients with atrophic scars from various causes, including acne, trauma and surgical, were treated with CO_2-AFXL (spot size 120 μm, depth 375–500 μm, density 10 %) followed by topical application of PLLA [40]. The treatments appear to be tolerated with post-procedural mild pain, erythema and swelling as the most commonly cited concerns. Each patient required an average of one single treatment. Improvements in scar contour, atrophy and colour were reported by four blinded observers 3 months after treatment. Treatment of cadaveric cheek with the same protocol (CO_2-AFXL followed by PLLA topical application) and subsequent histological analysis demonstrated penetration of the PLLA into the dermis and thus providing proof of principle that molecules as large as PLLA can penetrate the epidermis following AFXL.

Haemangioma

The treatment of infantile haemangiomas (IHs) has been revolutionised by the use of systemic propranolol, avoiding the need for surgery and use of systemic corticosteroids. Severe side effects, whilst rare, have to be monitored for initially and include hypoglycaemia, hypotension and bronchospasm [41], and treatment normally is continued for several months. Topical timolol (also a beta blocker) solution has more recently been mooted as a potential treatment for superficial IH. Ma and colleagues sought to extend the use of topical timolol solution to treat deeper IH [42]. In a study of nine infants (aged 1–6 months), CO_2-AFXL was applied to the skin surface of deep IH (25–30 mJ/pulse, 5 % density, single pulse) at weekly intervals. Topical timolol maleate solution (0.5 %) was applied under occlusion five times per day for an average of 14 weeks. Four patients (44 %) showed excellent regression of lesions, four (44 %) showed good response and one (11 %) showed moderate response, as gauged by the haemangioma activity score. The treatments appeared to be well tolerated with no systemic or cutaneous side effects noted, and plasma timolol concentrations were not detected after application of the first dose. Whilst systemic propranolol treatment is unlikely to be usurped as treatment of choice for IH and further long-term efficacy and safety data are needed, AFXL treatment prior to application of topical timolol solution may be a viable possibility for those infants in whom systemic beta-blockers are contraindicated or for very localised small IH.

Viral warts

Various laser devices have previously been reported to be of utility for treatment of viral warts. One study to date has investigated the effect of AFXL pre-treatment of viral warts upon response to PDT. Twelve Korean patients with total 40 periungual warts were enrolled and lesions treated using CO_2-AFXL, immediately followed by PDT, whereby MAL was applied and the lesions illuminated with red light 180 min later. After an average of 2.2 treatments per wart, 90 % of lesions showed complete clinical clearance, with 5 % demonstrating no apparent response to therapy [43].

Cosmetic applications

Trelles and colleagues investigated 14 subjects with signs of photoageing in a split-face study, in which both halves of the face were treated with CO_2-AFXL, with a predetermined regimen of manufacturer-recommended topical agents before and after AFXL treatment [44]. After AFXL resurfacing, PixelTreatSR serum (Alma Lasers, Caesarea, Israel) was applied to one half of the face immediately followed by ultrasound pulses to stimulate transepidermal passage. The serum contains a variety of keratolytics, lipids, vitamins and bioactive peptides. Improvements were noted by a blinded physician who assessed before and after photographs on a numeric rating scale. Parameters assessed included pigmentation, fine lines/wrinkles, overall aging and degree of improvement. No statistical significance between the observer-graded appearance of either side was evident until after 6 months, when pigmentation, fine lines/wrinkles and overall aging were reportedly better on the side that received the additional treatment. Whether this improvement is attributable to the use of ultrasound, the additional serum used or other idiosyncrasies remains unclear. However, the results could support further trials of the use of AFXL-assisted application of topical cosmeceuticals.

Botulinum neurotoxin type A (BoNTA) is a neurotoxin secreted by *Clostridium botulinum*, an anaerobic, gram-positive bacterium and is increasingly being used by aesthetic

practitioners to reduce the appearance of wrinkles and rejuvenate the skin. BoNTA is typically injected into the subcutaneous or intramuscular compartments with potential associated pain, discomfort, erythema, bruising and risk of infection. Recent work suggests that topical application of BoNTA (in its current form) may not penetrate the stratum corneum to elicit clinically discernible endpoints compared with injected toxin [45]. A spilt face study was conducted on ten subjects involving CO_2-AFXL of the face with application of topical BoNTA on one side and normal saline on the other side as a control [45]. Compared with the control side, topical application of BoNTA resulted in significant reduction in the number of periorbital wrinkles at 1 week and 1 month following treatment. These results suggest that BoNTA delivery can be enhanced with pre-treatment with AFXL. Comparison with injectable BoNTA and newer topical formulations of Botulinum neurotoxin [46] remains to be performed and will guide development of this novel method of delivery.

Non-ablative fractional laser

More recently, work has been undertaken using non-ablative fractional lasers (NFXL), in which a controlled zone of thermal injury is generated, rather than a fully ablated MTZ. Pretreatment with the non-ablative 1550-nm erbium glass laser has been shown to enhance delivery of ALA in human subjects, as gauged by cutaneous porphyrin fluorescence [47]. Advantages of non-ablative devices are increased patient tolerability and reduced post-procedural downtime. Use of such technology is yet to be borne out in larger clinical studies.

Future considerations

Larger trials with greater numbers within treatment and control arms are required for each of the proposed therapies to corroborate efficacies and side effects of therapy. Future cohorts will need to account for differing body sites and efficacy of treatments in varying ages, genders and ethnicities. Optimal laser parameters, including fluence, density and scheduling of treatments, need to be determined to facilitate maximal drug penetration, whilst allowing rapid recuperation of the skin.

As well as selecting which drug within a category (such as corticosteroids) is likely to yield the best result, the optimal vehicle for topically applied medicaments, whether gels, patches, creams or ointments, together with duration and frequency of application and the necessity for occlusion is yet to be determined. Additional consideration needs to be afforded to potential toxicity from medicaments, as already has been demonstrated with lidocaine toxicity occurring following AFXL resurfacing [48]. Furthermore, these drugs or molecules were designed for topical application, and their current concentrations may prove too high or toxic for direct dermal introduction.

Rigorous health economic analyses comparing the efficacies and cost-effectiveness of these new modalities of treatment compared to tested, longer established treatments may ultimately determine the take-up of these new technologies.

Conclusions

Work on animal models and preliminary initial studies have supported the use of AFXL technology as a future adjunct to topical therapies. Studies thus far suggest that AFXL improves transepidermal absorption of topical agents and allows for a much deeper penetration of drugs than is possible with topical medicaments alone. This may allow more efficacious action of current treatments, such that conventional duration of treatment can be shortened or lower concentrations of active agents be used, potentially obviating side effects of treatment. The prospect of using AFXL to facilitate transdermal vaccination and as an adjunct for inflammatory dermatoses and cosmetic indications remain in its infancy. As larger trials are published, involving greater numbers of patients and utilising various laser and topical medicament parameters, we will enhance our understanding of this nascent modality of treatment delivery and better serve the patients whose lives we strive to improve.

Compliance with ethical standard

Conflicts of interest Dr. Ali and Dr. Al-Niaimi declare no conflicts of interest.

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