Upcoming Therapeutic Modalities for the Treatment of Keloids: An Update

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Abstract

Introduction: Keloids are benign dermal tumors that generally form by local fibroblast proliferation and excessive collagen production following skin trauma. Several methods have been described for the treatment of keloid, often with suboptimal results and recurrences.

Objective: To update literature that provides information regarding upcoming therapeutic modalities for the treatment of keloids, including lasers, radiofrequency (RF), photodynamic therapy (PDT), and ultraviolet A1 (UVA1) irradiation.

Materials and Methods: A systematic review of the literature was performed for the original articles related to the treatment of keloids. The search terms ‘keloids’ and ‘lasers’ or ‘radiofrequency’ or ‘PDT’ or ‘UVA1’ was entered into a search of the National Library of Medicine’s PubMed Database.

Result: The search returned a total of 188 sources, of which, 26 articles met our inclusion criteria.

Conclusion: Combination approach is superior than solo therapy in the treatment of keloid. However, it is highly desirable that new emerging therapies undergo large-scale studies with long-term follow-up before being recommended conclusively as alternative therapies for the treatment of keloid. Moreover, lack of randomized clinical trials (RCTs) needs to be taken into consideration urgently.

Key words: Collagen; Fibroblasts; Keloid; Photochemotherapy; Ultraviolet Therapy

Introduction

Keloids are benign dermal tumors that generally form by local fibroblast proliferation and excessive collagen production following skin trauma.1 Rarely, it can occur spontaneously in the absence of antecedent trauma.2 Keloids are unique to human and occur more frequently in individuals with darker skin.3 The propensity of keloid formation in darker skin types is thought to be due in part by the larger multinucleated fibroblasts that have been described in this population.4 Keloids vary in size and shape, and do not regress spontaneously. They can be pedunculated or elevated with a flat surface, and may grow to sizes that can be disfiguring or crippling. Keloids range in consistency from soft and doughy to rubbery hard and they may be tender, painful, pruritic, or cause a burning sensation.5 Histologically, they are characterized by exuberant dermal collagen formation with random orientation and assembly of the individual collagen fibers. Uncontrolled fibroblast activity and excess collagen lead to overabundant extracellular matrix formation, and are the hallmark of these tumors.6 Although the exact pathogenesis of keloid is not elucidated, it has been known that keloid fibroblasts, when compared with normal fibroblasts, have lower rates of apoptosis.7 In addition, these cells over produce type I collagen and expresses higher levels of cytokines and growth factors, which influences

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proliferation and collagen synthesis by fibroblasts. Another factor studied in the pathogenesis of keloid formation is the role of increased skin tension. This has postulated the skin injury–wound tension theory as the corner stone theory for keloid formation.1 A wide range of treatment modalities for keloid exists, which includes cryotherapy, surgical excision, intralosomal injection with pharmacologic agents, mechanical pressure, and silicone gel dressings. None of these are 100% successful. Moreover, studies have shown lowered self-esteem and impaired quality of life in affected individuals.8 This calls for the investigation of new therapeutic interventions. Recently, attention has been drawn to the possible beneficial effects of newer therapies like lasers, radiofrequency, photodynamic therapy, and UVA1 irradiation. In the present review, we aim to update literature that provides information regarding upcoming therapeutic modalities for the treatment of keloids.

Many different lasers have been studied and utilized in the treatment of keloids including carbon dioxide (CO2) laser, 2940-nm erbium-doped: yttrium, aluminum and garnet (Er:YAG) laser, 1064-nm neodymium-doped:yttrium, aluminum and garnet (Nd:YAG) laser, and 585-595 nm pulsed-dye lasers (PDL). CO2 and Er:YAG are ablative lasers, while Nd:YAG and PDL are non ablative lasers. CO2 laser and Er:YAG laser emit beams absorbed by water in skin resulting in local tissue destruction.9,10 Since the energy of the Er:YAG laser is due to its wavelength (2,940 nm) – largely absorbed by water, there is only very minor heat dissipation into the surrounding tissue; hence the term “cold” tissue ablation.11 The CO2 laser, on the other hand, with a wavelength of 10,600 nm, generates more heat in the surrounding tissue and also coagulates small blood vessels.11 Nd: YAG laser is hypothesized to primarily treat keloids by damaging deepdermal blood vessels.12 Also, it may directly suppress fibroblast collagen expression.12 Due to its wavelength (1,064 nm), however, the depth of penetration of the Nd:YAG laser is much greater, a property shown to be useful in the treatment of Keloid scars. PDL is hypothesized to treat keloids by selective damage of blood vessels that supply the scar.13 With a wavelength of 595nm or 585nm, oxyhemoglobin is the target chromophore of pulse dye laser (PDL). The near infrared diode laser has energy and wave length characteristics that specifically target the soft tissues.14 The 980 nm diode laser is selectively absorbed by haemoglobin and selectively destroys blood vessels, minimising injury to the surrounding healthy skin. The light energy released by the diode laser transforms into heat, resulting in the vaporization of cells, a process referred to as the photothermal effect.14

Radiofrequency tissue volume reduction (RFTVR) uses very low levels of radiofrequency energy to create controlled protein denaturation or necrosis in soft-tissue structures.15 Radiofrequency ablation can be considered as minimally invasive treatment modality with no major disadvantages.16 Because of its mechanism of action, RFTVR appeared suitable for treatment of keloids.

Photodynamic therapy (PDT) is an established mode of treatment for skin conditions such as Basel Cell Carcinoma, Actinic Keratosis and Bowens Disease.

This therapy is a non-invasive therapy that utilizes light treatments along with an application of a photosensitizing agent (PA). The PA is applied to the skin, causing the skin to become more susceptible, or receptive, to light.17 Once the incubation period of PA is complete, light of a specific wave length is directed onto the area to be treated, activating the protoporphyrin 9 (PpIX) and resulting in the formation of cytotoxic reactive oxygen species. This causes cell apoptosis or necrosis, membrane and mitochondrial damage and activates many signalling molecules, e.g. TNF-α, interleukins 1 and 6.18 The potential mechanism of PDT in keloid may involve modulation of the growth factor and cytokine expression.18

Long-wave length UVA1 is different from other UV phototherapies because it offers deeper penetration as well as targeting fibrosis and other structures, i.e. fibroblasts, T-lymphocytes, Langerhans cells, mast cells, endothelial cells.19 UVA1 (340–400nm) acts deeper in the dermis and even in the subcutaneous tissue. Moreover, around 20% of the radiation reaches vascular system, which, according to some authors, provides grounds for a potential systemic action of this radiation range.19 UVA1 irradiation has been reported to be effective for the treatment of morphea and systemic sclerosis through the induction of collagenase I [matrix metallo proteinase I (MMP-1)] production by fibroblasts and decreased synthesis of procollagen. The efficacy of UVA1 for the treatment of keloid scarring may be partly the result of this action.20

Method

A systematic review of the literature was performed for the original articles related to the treatment of keloids. The search terms ‘keloids’ and ‘lasers’ or ‘radiofrequency’ or ‘PDT’ or ‘UVA1’ was entered into a search of the National Library of Medicine’s PubMed
Database. The search returned a total of 188 sources, of which, 26 articles met our inclusion criteria. Published clinical trials, case series, case reports, retrospective studies and letters reporting on keloid treatment using ablative lasers, non-ablative lasers, radiofrequency, PDT or UVA1 were included in this review. Unfortunately, randomized clinical trials on the relevant topic were not found. Only human studies and English language articles were selected. Articles about other skin conditions or scar types other than keloids, including those that collectively mentioned hypertrophic scars and keloids, were excluded. In vitro studies were excluded. Figure 1 shows schematic diagram of search strategy listing the articles that met inclusion or exclusion criteria and Table 1 summarizes the characteristics of the 26 studies included in this review.

**Laser therapy**

Apfelberg DB et al reported the earliest study on laser treatment for keloids in 1984.21 Thirteen patients with well-established keloid scars of the trunk or earlobe were treated with either multiple-bore-hole argon technique alone or in combination with total excision with the CO2 laser. Only one patient with an earlobe keloid treated with argon laser alone showed total disappearance of keloid, all other patients had no improvement. In 1989, Apfelberg DB et al again treated seven patients with keloid on the trunk, nuchal region, back, and earlobe.22 Under local anesthesia, the keloids were excised sharply down to the base by CO2 laser. Only one patient with earlobe keloid showed great improvement after only nine months' follow-up, all other patients had recurrence.

Ang CC et al reported case records of 16 patients with earlobe keloids.23 The patients received different treatment modalities including CO2 laser ablation, or cold steel surgery, or combined surgery and CO2 laser ablation, or 40 mg/ml of intralesional triamcinolone acetonide. Both the CO2 laser ablation and cold steel surgery were equally useful in reducing the size of the earlobe keloids, but were not effective in preventing regrowth of the keloids, even with adjunctive intralesional steroids. In contrast to the above studies, Morosolli AR et al observed a very good esthetic and functional result in a patient with an earlobe keloid treated with CO2 laser with a 0.8-mm focus, 7 W, a power density of 2.5 W/cm2, in a continuous mode.24 Similarly, Nicoletti G et al reported effective and well-tolerated treatment of keloids by CO2 laser.25 Fifty patients with moderate to severe keloids received regional treatments (deltoid, elbow, chin, and ear) with a high-energy pulsed CO2 laser. Diminished scar bulk with a reduction in scar height and textural improvement was noted in all the patients. Scrimali L et al compared the effect of laser CO2 versus radiotherapy following surgical excision in the treatment of keloid and found that CO2 laser after surgical excision of keloids has great results with no recurrence and without the risk of carcinogenesis.26 Yang Q et al reported a study with successful use of combination approach.27 One hundred and fifty onesites of keloids in 122 patients were treated with combination methods of continuous-wave CO2 laser, ultra-pulse CO2 laser and 32P radiation. One hundred eleven of 151 evaluated sites scored "excellence" and 40 belonged to "effectiveness". These patients demonstrated local control and have remained free of local recurrence for more than two years.

**Figure 1:** Schematic diagram of search strategy listing the articles that met inclusion or exclusion criteria.
Studies on laser therapy for keloids have shown more exciting results with PDL comparing to CO2 lasers. However, multiple treatments (>six) were required to yield better results than fewer treatments: 79% versus 50%, respectively. Twelve months after final PDL treatments, keloid regression (≥50%) had occurred in 26 out of 30 patients. Another study showed better result with PDL only after three sessions of treatment. Using the Vancouver scar scale (VSS), there was an average decrease of 20.85 ±12.33% after PDL treatment. Eke et al reported on the successful use of surgical shave-excision followed by single-pass PDL therapy for the treatment of keloid. Similarly, Cannarozzo et al also reported a successful use of flash lamp pumped PDL. This study recruited 59 patients who received four to six treatment sessions with a flash lamp pumped PDL. A total of 29 patients out of 59 achieved excellent clearance, 15 patients achieved good to moderate clearance, and 12 patients obtained slight improvement. Only three subjects had little or no removal of their lesion. Martin et al combined fractional CO2 laser with PDL as well as the injection of triamcinolone acetonide into the keloids refractory to solitary treatments of triamcinolone acetonide injection and other laser modalities. Treatments were carried out once per month for seven sessions. After five sessions, dramatic improvement in the lesions was seen.

Recently, studies on other types of lasers including Nd:YAG lasers, Er:YAG lasers, and 980nm diode laser with adjunctive intralesional or topical corticosteroids have shown good results in treating keloids. The success rate in these studies varied from 50% to 75%. More recently, Chen et al reported a successful use of long-pulsed Nd:YAG laser in combination with intralesional injection of diprospan and 0.5 ml 5-fluorouracil. In terms of invasiveness, two studies provided least invasive therapy. Cavaliere M et al treated 23 patients with 70 keloids with a 2940-nm ablative fractional erbium laser and topical betamethasone cream. The median percentage of improvement was 50% and a recurrence was observed for eight lesions at 18 months follow up. Similarly, Park et al treated keloids with an ablative fractional erbium-YAG laser and an intralesional injection or topical application of corticosteroid and concluded this treatment a promising modality for the treatment of keloids.

### Radiofrequency

Some small studies have proven the clinical safety and efficacy of RF in the treatment of keloids, especially in combination with adjuvant ILCS. It was in 2011, when Kai Fruth et al for the first time applied RFTVR in 14 patients with keloids of the auricle. In six patients, RFTVR was the sole treatment modality applied, and in seven patients IL steroid injection was also performed. Good cosmetic results were achieved in 10 of 14 patients. In 2013, Klockars T et al presented the second paper on this promising novel treatment option. They applied RF ablation in 11 patients (13 auricles) with single treatment session for all except one patient who was treated three times with three and 13 months interval. The effect of RF ablation was excellent in six auricles, good in five auricles and moderate in one auricle. In 2015, Weshay AH et al presented the study on the combined effect of RF and IL steroids in the treatment of keloids. It was a pilot study on 18 patients who were subjected to three to four sessions of RF followed by IL steroid injection. A significant reduction of volume of all lesions in all patients was noted, with a mean volume reduction of 95.4%.

### Photodynamic therapy

In 2010, Nie Z et al reported the first study on PDT of keloids. It was a case report of the patient who had keloid under her chin for four years that had failed to respond to several other treatments, including surgical resection, but showed substantial improvement with PDT. After five sessions of MAL-PDT over a period of 5 months, the patient’s lesion had considerably reduced in size and become flattened and there was no recurrence at 1-year follow-up. Ud-Din S et al also, in their clinical trial of 20 patients, proved the efficacy of PDT for keloids. The patients underwent three treatments of MAL-PDT at weekly intervals. All patients showed marked improvement except one patient who experienced recurrence of KD. All other patients had no recurrence at nine-month follow-up.

### UVA1 irradiation

Asawanonda P et al reported the first study on the successful use of UVA1 irradiation for the treatment of keloids in 1999. It was a case report where patient received 2860 J/cm2 of UVA1 irradiation and responded well to the treatment. In contrary to this article reporting a successful treatment, Hannuksela-Svahn A et al found no effect of UVA1 irradiation on stable keloids. This was a study performed on three patients with a several years history of a stable keloid secondary to tuberculosis vaccine in the one patient and to acne in the other 2 patients. The patients received 1700, 1800 and 1500 J/cm2 of UVA1 irradiation given strictly to the lesion alone.
Table 1: characteristics of the studies demonstrating the efficacy of various treatment modalities for keloids.

<table>
<thead>
<tr>
<th>Authors/Reference</th>
<th>Study type</th>
<th>No. of patients/ype</th>
<th>No. &amp; Site of keloid</th>
<th>Intervention method</th>
<th>Treatment regimen</th>
<th>Outcome</th>
<th>Follow up/Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kasab AN et al 14</td>
<td>Clinical trial, non-blinded, no control</td>
<td>12/ type 3 to type 5</td>
<td>Earlobes</td>
<td>Single repeated mode of 4 s duration, at power 5 W with an energy fluence 20 J/cm² was applied via 980-nm diode laser plus IL CS</td>
<td>2-5 sessions at 3w interval</td>
<td>Total success rate of 75% was seen</td>
<td>12m/none</td>
</tr>
<tr>
<td>Apfelberg DB et al 22</td>
<td>Clinical trial, control</td>
<td>1-/-</td>
<td>Trunk, earlobe</td>
<td>Multiple-bore-hole argon technique &amp; total excision with CO2 laser</td>
<td>3 session at 6w interval</td>
<td>One patient with an earlobe keloid responded to treatment, all other patients had no improvement.</td>
<td>6m or more/2 patients showed recurrence</td>
</tr>
<tr>
<td>Apfelberg DB et al 23</td>
<td>Case series</td>
<td>7/-</td>
<td>Earlobes</td>
<td>Excision with CO2 laser</td>
<td>The long-term benefits of keloid excision with CO2 laser is not demonstrated in this case series.</td>
<td>30-22m/6 of 9 keloids recurred</td>
<td></td>
</tr>
<tr>
<td>Ang CC et al 33</td>
<td>Retrospective</td>
<td>16/-</td>
<td>Earlobe keloids</td>
<td>CO2 laser with an 0.8-mm focus, 7 W, a power density of 2.5 W/cm², in a continuous mode</td>
<td>3 sessions at 3-4w interval</td>
<td>More than six PDL treatments provided the best results.</td>
<td>12m/none</td>
</tr>
<tr>
<td>Morosoli AR et al 24</td>
<td>Case report</td>
<td>1/-</td>
<td>Earlobe keloid</td>
<td>CO2 laser &amp; well tolerated for treatment of keloids, avoiding adverse effects &amp; lengthy recovery time.</td>
<td>-</td>
<td>Very good aesthetic and functional result was seen</td>
<td>6m/none</td>
</tr>
<tr>
<td>Nicodetti G et al 35</td>
<td>Clinical trial, non-blinded, no control</td>
<td>50/- type I-V</td>
<td>Shoulder, neck,</td>
<td>High-energy pulsed CO2 laser therapy followed by LA of HA injection at the irradiated skin. At the end of treatment cycles, a combined treatment with an adjustable silicone gel sheeting &amp; pressure massage therapy was prescribed</td>
<td>4 sessions of laser therapy</td>
<td>CO2 laser appeared effective &amp; well tolerated for treatment of keloids, avoiding adverse effects &amp; lengthy recovery time.</td>
<td>12m/-</td>
</tr>
<tr>
<td>Schmitt C et al 36</td>
<td>Clinical trial, non-blinded, no control</td>
<td>4/-</td>
<td>Earlobe &amp; retroauricular region</td>
<td>Surgical excision of scar, after 30-12 days, when the suture was removed, they were treated monthly with a CO2 laser</td>
<td>-</td>
<td>Compared to RT, CO2 laser after surgical excision of keloids has shown great results with no recurrence</td>
<td>1y/None</td>
</tr>
<tr>
<td>Yan Institute et al 37</td>
<td>Clinical trial, non-blinded, no control</td>
<td>122/-</td>
<td>132 keloids at multiple sites</td>
<td>Combination methods of lasers &amp; PDL radiation</td>
<td>3 sessions at 3-4w interval</td>
<td>More than six PDL treatments at 2-month intervals provided the best results.</td>
<td>12m/none</td>
</tr>
<tr>
<td>Kuo YR et al 38</td>
<td>Clinical trial, non-blinded, no control</td>
<td>30/-</td>
<td>Keloids at multiple sites</td>
<td>Flashlamp pumped PDL with Wavelength of 585 nm, PD 450 ms &amp; spot size 5 mm.</td>
<td>1-11 sessions at 2m interval</td>
<td>According to real-time PCR, the CTGF mRNA was significantly down-regulated after PDL treatment in 80.77% of patients as compared to the control group</td>
<td>-</td>
</tr>
<tr>
<td>Yang Q et al 39</td>
<td>Controlled clinical trial</td>
<td>26/- type II &amp; IV</td>
<td>Chest or scapular areas keloid</td>
<td>PDL with IR of 1.5ms, spot size 3mm, DCC duration 20 ms/delay 10 ms &amp; fluence of 10 J/cm².</td>
<td>3 sessions at 3-4w interval</td>
<td>Some hypopigmentation was noted at treated sites but this gradually improved and patient was satisfied with treatment</td>
<td>8m/none</td>
</tr>
<tr>
<td>Eke U et al 40</td>
<td>Case series</td>
<td>3/- type VI</td>
<td>Facial and posterior chest wall keloid</td>
<td>Surgical shave excision followed by 4 sessions single-pass PDL therapy</td>
<td>-</td>
<td>Based on therapeutic effectiveness criteria, 11 of 35 evaluated sites scored &quot;excellence,&quot; and 40 scored &quot;effectiveness&quot;</td>
<td>2y/none</td>
</tr>
<tr>
<td>Cannarozzo G et al 41</td>
<td>Clinical trial, non-blinded, no control</td>
<td>59/- type I-V</td>
<td>Abdomen, chest, earlobe</td>
<td>Vaporized with a CO2 ultrapulsed laser before the first FPDL or FPDL alone.</td>
<td>4-6 sessions at 1m interval</td>
<td>OVF9 patients, 29 achieved excellent clearance, 11 achieved good-moderate clearance, 12 obtained slight clearance, &amp; 3 patients had little or no improvement</td>
<td>6m/-</td>
</tr>
<tr>
<td>Martin MS et al 42</td>
<td>Case report</td>
<td>1/-</td>
<td>Upper back</td>
<td>Combination of the Affirm CO2 fractional laser combined with topical high potent CS cream</td>
<td>7 sessions at 1 month interval</td>
<td>Dramatic improvement after 5 sessions</td>
<td>-</td>
</tr>
<tr>
<td>Rossi A et al 43</td>
<td>Retrospective</td>
<td>44/- through type VI</td>
<td>Earlobe</td>
<td>Nf:YAG plus IL CS or Nf:YAG only or IL CS only</td>
<td>6 sessions at 3w interval for Nf:YAG plus IL CS group</td>
<td>Nf:YAG plus IL CS group showed best result with 100% patients showing 75% reduction in thickness &amp; erythema of keloids.</td>
<td>-</td>
</tr>
<tr>
<td>Cavalié M et al 44</td>
<td>Retrospective</td>
<td>23/-</td>
<td>Earlobe keloids at chest, shoulder, arm, face, ear, &amp; neck</td>
<td>2940-nm ablative fractional erbium laser combined with topical high potent CS cream</td>
<td>Patients had 1 laser session every other week with 4 crossed passes for a total of 30% coverage.</td>
<td>The median percentage of improvement was 30%</td>
<td>8 months/ recurrence in 8 lesions</td>
</tr>
<tr>
<td>Authors/reference</td>
<td>Study type</td>
<td>No. of patients/FSP</td>
<td>No. &amp; Site of keloid</td>
<td>Intervention method</td>
<td>Treatment regimen</td>
<td>Outcome</td>
<td>Follow up/Recurrence</td>
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<tr>
<td>Chen XE et al35</td>
<td>Randomized blinded clinical trial</td>
<td>69/-</td>
<td>One lesion (preferably on the trunk or proximal extremities) per patient</td>
<td>ILCS or ILCS+ SFU or ILCS+ SFU+1064nmNd:YAG laser with single pulse at energy density of 90100 J/cm², pulse width of 12 mec</td>
<td>3 sessions at 1m interval</td>
<td>Combination of IL CS-SFU+Nd:YAG was the most efficacious therapy</td>
<td>3m/none</td>
</tr>
<tr>
<td>Park JH et al36</td>
<td>Clinical trial, non-blinded, no control</td>
<td>10/-</td>
<td>10 keloids on the left shoulder after BCG vaccination</td>
<td>ablative fractional erbium-YAG laser+IL CS or topical CS</td>
<td>4 sessions at 6w interval</td>
<td>Both treatments showed promising result</td>
<td>12w/4 keloids appeared to be recurring</td>
</tr>
<tr>
<td>Shih PY et al45</td>
<td>Case report</td>
<td>1/-</td>
<td>Large keloids over region of chest</td>
<td>Single course of PDL was used 3w after last IL steroid injection</td>
<td>IL CS weekly for 6w, biweekly for 4w, biweekly for 8w, &amp; monthly for 4w followed by 1 session of PDL</td>
<td>Rapid recurrence of keloid (previously flattened with IL CS) within 1 week of PDL treatment for telangiectasia.</td>
<td>At 3w follow up previously flattened keloid enlarged substantially</td>
</tr>
<tr>
<td>Fruth K et al15</td>
<td>Clinical trial, non-blinded, no control</td>
<td>14/-</td>
<td>keloids of auricle</td>
<td>RF ablation, electrode tip was inserted into keloid, &amp; preset energy of 10W was applied into keloid tissue until automatic cut-off.</td>
<td>1-3 session at 3-13 m interval</td>
<td>Effect was excellent in 6 auricles, good in 5 auricles and moderate in 1 auricle.</td>
<td>2-92m/none</td>
</tr>
<tr>
<td>Weshay AH et al38</td>
<td>Pilot study</td>
<td>19/-</td>
<td>19 keloids on head and neck</td>
<td>RF followed by IL steroid injection</td>
<td>3 to 5 sessions of RF followed by IL steroid injection.</td>
<td>Significant reduction of volume of all lesions in all patients with a mean volume reduction of 95.4%.</td>
<td>5 years/ small scar recurred in 30% cases</td>
</tr>
<tr>
<td>Nie Z et al39</td>
<td>Case report</td>
<td>1/-</td>
<td>Keloid under the chin</td>
<td>3 hours after MAL application, the area was irradiated with red light from an LED source at wavelength 633 nm, at a dose of 37 J/cm²</td>
<td>5 sessions of MAL-PDT were given over a 5-month period.</td>
<td>Keloid had considerably reduced in size and become flattened</td>
<td>3y/no recurrence</td>
</tr>
<tr>
<td>Ud-Din S et al39</td>
<td>Clinical trial, non-blinded, no control</td>
<td>20/-</td>
<td>multiple site keloids</td>
<td>MAL applied 3h prior to PDT, irradiation was conducted using a red light with a wavelength of 630 nm &amp; light dosage was administered at 371 J/cm²</td>
<td>3 sessions at 1w interval</td>
<td>PDT reduces scar formation in keloid evidenced by decreased blood flow, increased pliability, decreased collagen &amp; haemoglobin levels.</td>
<td>9m/ Only 1 patient with a keloid in a stress prone anatomical location had recurrence</td>
</tr>
<tr>
<td>Asawanonda Pet42</td>
<td>Case report</td>
<td>1/ type IV</td>
<td>Single keloid on chest</td>
<td>UV-A1 generated by a light box fitted with a UV-A1 filter allowing only wavelengths between 340 and 450 nm</td>
<td>4 times weekly for 6 weeks</td>
<td>Improvement as early as 3rd week of treatment, and after 6 weeks, marked softening and flattening were noted.</td>
<td>-</td>
</tr>
<tr>
<td>Hannikko-Lehmuslahti et al41</td>
<td>Case series</td>
<td>3/-</td>
<td>Shoulder &amp; chest keloid</td>
<td>MAL-A1 irradiation with a final CD of 3700, 1800 &amp; 1500 J/cm²</td>
<td>3 times a week for 5-6w</td>
<td>Treatment was tolerated well, &amp; of the patients experienced subjectively softening of keloid but none had any macroscopic reduction of the scar.</td>
<td>-</td>
</tr>
<tr>
<td>Polat M/42</td>
<td>Case series</td>
<td>2/ type II &amp; type III</td>
<td>Keloid on chest and heel</td>
<td>High-dose MAL-A1 355 nm laser. 160 J/cm² 3 times a week for the first 2 weeks, &amp; then 280 J/cm² for 2 weeks, 230 J/cm² for 3 weeks, &amp; 250 J/cm² for 6 weeks</td>
<td>3 sessions a week for up to 12 weeks</td>
<td>An improved VSS score was observed. However, applying highdose MAL-A1 therapy is time consuming.</td>
<td>-</td>
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</tbody>
</table>

The treatment was tolerated well, and two of the patients experienced subjectively softening of the keloid but none had any macroscopic reduction of the scar. The lack of response in the second experiment might be due to low dose of UVA1 comparing to the first study where high dose of UVA1 (2860 J/cm²) was used. Recently in 2016, Polat M et al presented the results from two patients who underwent high dose UVA1 laser therapy. The treatment protocol applied in this study was: 160 J/cm² three times a week for the first two weeks then 180 J/cm² for two weeks, 230 J/cm² for three weeks, and 250 J/cm² for six weeks for one patient. 140 J/cm² three times a week for the first three weeks, and then at 160 J/cm² for three weeks, 180 J/cm² for two weeks, 230 J/cm² for two weeks, and 250 J/cm² for two weeks for another patient. An improved VSS score was observed following treatment and complaint of itching and tenderness decreased significantly.

Discussion

In the past, the most recommended treatment strategy for keloid has been prophylaxis using silicone gel sheeting or paper tape starting on the second week after wounding, combined with other treatments, including massage, pressure therapy and intralesional corticosteroids, depending on each patient and scar's origin and type. None of these therapeutic options has been found completely effective and satisfactory. Moreover, patients with keloid scars suffer a severe impairment of quality of life, by causing physical, psychological and social sequelae. Recently, the promising results of some big and small studies have drawn attention to the possible beneficial effects of upcoming therapeutic modalities like lasers, radiofrequency, photodynamic therapy, and UVA1 irradiation. Among lasers, CO₂ laser was seen to be effective for keloids as a solo therapy. It was also effective as an adjuvant therapy following surgical excision. Results with other lasers like PDL, 980nm diode laser, Nd:YAG lasers, and Er:YAG lasers were also good in terms of patient satisfaction and recurrence. In these studies, combination approach showed better result than solo therapy. Laser treatments were mainly combined with surgical excision or ILCS. However, not all studies with laser showed exciting results. 2 studies with CO2 laser and 1 study with PDL showed complete recurrence of keloids. These different outcome conclusions are likely due to variations in keloid size, location and duration and also variations in treatment dosimetry and protocols.

Similarly, studies with RF showed better result when adjunctive ILCS was used. Three studies on RF reviewed here, all of which showed good result with no recurrence except one study where a small scar recurred in 10% of cases at five year follow up. However, none of the other studies did this long duration follow up of five years. Both the studies on PDT reviewed here used MAL as a photosensitizing agent and irradiated the lesions using a red light with a wave length of 630 nm and light dosage at 37 J/cm². All the patients showed marked improvement and no recurrence except one patient with a keloid in a stress prone anatomical location that recurred. Unfortunately, studies on UVA1 failed to give exciting results. Three studies on UVA1 reviewed here reported the improvement in symptoms like itching and tenderness, but none reported the reduction of scar volume.

Unfortunately, most of the studies on keloids are non-controlled, non-blinded, and non-randomized. The challenge of conducting double-blind RCTs for keloid treatment is the inherent difficulty in blinding patients and treatment operators. This may be the reason why cutaneous scar management has relied mainly on the experience of practitioners rather than on the results of large-scale randomized, controlled trials and evidence-based studies.

Conclusion

In the case of keloids, combination approach is the best treatment modality. Successful therapeutic management need to address the conditions that initiate keloid formation, if not, keloid recurrence is likely and optimal management may not be achieved. In addition, it is highly desirable that many standard practices and new emerging therapies undergo large-scale studies with long-term follow-up before being recommended conclusively as alternative therapies for the treatment of keloid. Moreover, RCTs are urgently needed.

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