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REVIEW

A Review of Current Keloid Management: Mainstay Monotherapies and Emerging Approaches

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ABSTRACT

Commonly affecting those with skin of color, keloids are an aberrant wound response that leads to wound tissue expanding above and beyond the original cutaneous injury. Keloids are notoriously and particularly difficult to treat because of their tendency to recur after excision. The current standard of care is intralesional steroid (triamcinolone acetonide). However, because no therapy has yet proven to be fully curative, keloid treatments have expanded to include a number of options, from injections to multimodal approaches. This review details current treatment of keloids with injections (bleomycin, verapamil, hyaluronic acid and hyaluronidase, botulinum toxin, and collagenase), cryotherapy, laser, radiofrequency ablation, radiation, extracorporeal shockwave therapy, pentoxifylline, and dupilumab.

Keywords: CO_2 laser; Cryotherapy; Intralesional injection; Keloid; Multimodal approach; Pulse dye laser; Radiation; Radiofrequency ablation; Wound healing

Key Summary Points

Keloids are a pathologic response to cutaneous injury in which wound tissue grows beyond the inciting insult.

Because keloids are prone to post-excisional recurrence, medical management plays an important role in keloid treatment.

While the standard of care for keloids is intralesional steroid (triamcinolone acetonide), new and innovative therapeutic options offer the possibility to improve and tailor management to patient preferences and qualities.

Expanding from triamcinolone acetonide alone, injection options now include bleomycin, verapamil, hyaluronic acid and hyaluronidase, botulinum toxin, and collagenase.

Additional treatment options discussed include cryotherapy, laser, radiofrequency ablation, radiation, extracorporeal shockwave therapy, pentoxifylline, and dupilumab.

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INTRODUCTION

Keloids are a pathologic response to cutaneous injury in which wound tissue grows above and beyond the inciting insult. These lesions disproportionally affect patients with skin of color, especially of African, Asian, and Hispanic backgrounds [1]. Keloids can be cosmetically disfiguring as well as symptomatically distressing, commonly causing pruritus, pain, and decreased quality of life [2].

The standard of care for keloids differs geographically; steroid-impregnated tape is the first-line treatment modality in Japan, while steroid (triamcinolone acetonide) injections are the treatment of choice in the USA [1, 3]. Other common treatments include silicone sheets, compression, intralesional administration of 5-fluorouracil, and excision. Anecdotal accounts report some improvement with topical tea tree oil and over-the-counter antihistamines. However, because no treatment has been found to be fully effective at inducing regression of keloid tissue or at preventing postoperative recurrence, much work is being done to elucidate the underlying pathology of these lesions and to devise better treatments. The use of new, innovative therapeutic options, including combinations of previously described treatments, offers the possibility of lesion regression and/or symptomatic improvement. We have gathered data assessing current therapeutic options for keloids, including new treatment options and multimodal approaches. Treatments discussed in this review include injections (bleomycin, verapamil, hyaluronic acid and hyaluronidase, botulinum toxin, and collagenase), cryotherapy, laser, radiofrequency ablation, radiation, extracorporeal shockwave therapy, pentoxifylline, and dupilumab (Table 1).

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

INJECTIONS

Bleomycin

The chemotherapeutic drug bleomycin has been used in the treatment of keloids and hypertrophic scars for decades owing to its antitumoral properties and potential reduction in collagen generation [4]. Initial studies of both bleomycin injection and topical application with penetration enhanced via multiple needle punctures showed therapeutic benefit [5, 6]. Use of a combination bleomycin and triamcinolone injection was found to be effective in a study of 35 keloids and two hypertrophic scars in 10 white patients. Four milligrams of triamcinolone plus 0.375 IU bleomycin per cm^2 led to softening of 97.3% of lesions and flattening of 64.9% of lesions after one and two sessions, respectively. Dermal atrophy was originally noted in several lesions but was only present in one lesion at 24 months. Adverse effects of this method included ulceration. While neither hyper- nor hypopigmentation was noted, these participants had Fitzpatrick skin types II–IV [7]. In another study, no statistical difference was found between outcomes of intralesionally injected bleomycin versus triamcinolone; however, this study included patients of slightly darker skin tone (Fitzpatrick III–V) and hyperpigmentation was seen in 71.4% of participants [8]. Pain is often experienced with bleomycin use [7, 8]. A study of 35 lesions treated with intralesional administration of bleomycin and electroporation showed a decrease in height and volume in all lesions [9]. In sum, while bleomycin has shown efficacy in treatment of keloids, caution should be used in patients with skin of color because of possible pigmentary changes [8].

Verapamil

The calcium channel blocker verapamil was proposed initially for keloid treatment owing to its potential to block fibrosis in in vitro studies [10]. However, this treatment has seen quite mixed results. A single-arm study using intralesional administration of verapamil intra- and

Table 1 Details of referenced studies by treatment

Treatment method	Design	No. lesions {no. patients}	Primary results	Author (year) [Reference]
Bleomycin				
Needle puncture application	Treatment comparison to baseline keloid and hypertrophic scar (HTS)	13 (7 keloid, 6 HTS) {13}	13/13 flattened, 2/13 recurrences	Espana et al. (2001) [5]
Intralesional injection	Treatment trial	40 (35 keloids, 5 HTS) {unreported}	Efficacy in 100% of lesions, 5/36 failed to achieve good results	Bodokh and Brun (1996) [6]
Intralesional injection	Combination with triamcinolone	43 (41 keloid, 2 HTS) {10}	36/38 softened with 1 treatment, 24/38 flattened with 2 treatments	Camacho-Martinez et al. (2013) [7]
Intralesional injection	Comparison to triamcinolone	26 (19 keloid, 7 HTS) {26}	No difference in outcomes	Payapvipapong et al. (2015) [8]
Intravenous injection with electroporation	Treatment trial	35 (keloid and HTS) {20}	100% response rate, average 87% volume reduction	Manca et al. (2013) [9]
Verapamil				
Intralesional injection	Comparison to triamcinolone post excision	14 {14}	Verapamil not as effective for prevention of recurrence ($p = 0.01$)	Danielsen et al. (2016) [10]
Intralesional injection	Treatment trial	19 {16}	71.4% response rate, 4/14 recurrences	El-Kamel et al. (2016) [11]
Intralesional injection	Comparison to triamcinolone, triamcinolone with hyaluronidase, intralesional RF, intralesional RF with triamcinolone	100 {100}	0% clearance rate with intralesional administration of verapamil	Aggarwal et al. (2018) [12]
Intralesional injection	Comparison to triamcinolone	100 (keloid and HTS) {50}	No clinical improvement with verapamil	Abedini et al. (2018) [13]
Intralesional injection	Comparison to triamcinolone	48 (keloid and HTS) {40}	Similar effectiveness in both groups	Ahuja and Chatterjee (2014) [14]
Intralesional injection	Comparison to triamcinolone	54 (keloid and HTS) {54}	Similar effectiveness in both groups	Margaret et al. (2008) [15]

Table 1 continued

Treatment method	Design	No. lesions {no. patients}	Primary results	Author (year) [Reference]
Intralesional injection	Comparison to control post excision	44 {44}	54% complete clearance with adjunct verapamil versus 0% control clearance	D'Andrea et al. (2002) [16]
Hyaluronic acid				
Intralesional injection	Case report using combination hyaluronic acid and triamcinolone	1 {1}	Complete keloid reabsorption	Di Stadio (2016) [18]
Intralesional injection	Comparison to triamcinolone, intralesional administration of verapamil, intralesional RF, intralesional RF with triamcinolone	100 {100}	68.75% clearance rate with intralesional administration of hyaluronic acid	Aggarwal et al. (2018) [12]
Botulinum toxin				
Intralesional injection	Treatment trial	1–3 per patient, {12}	12/12 reduced size, 12/12 flattening, 0/12 recurrence at 1-year follow-up	Zhibo and Miaobo (2009) [20]
Intralesional injection	Treatment trial	4 {4}	No clinical improvement	Gauglitz et al. (2012) [21]
	Treatment trial, 8/12 with triamcinolone adjunctive therapy	12 {12}	11 months average to flatten, 2/12 recurrences	Robinson et al. (2013) [22]
Intralesional injection	Comparison to triamcinolone	24 {24}	Similar effectiveness in both groups	Shaarawy et al. (2015) [23]
Intralesional injection	Comparison to triamcinolone, combination with triamcinolone	66 {23}	Similar effectiveness in both groups, increased symptomatic improvement	Rasaii et al. (2019) [24]
Intralesional injection	Comparison to triamcinolone	50 {25}	Superior outcome longitudinally with triamcinolone	Pruksapong et al. (2017) [25]
Intralesional injection	Systemic review and meta-analysis compared to corticosteroid, keloid and HTS	Unreported {639}	Greater efficacy with botulinum toxin	Bi et al. (2019) [26]

Table 1 continued

Treatment method	Design	No. lesions {no. patients}	Primary results	Author (year) [Reference]
Collagenase				
Intralesional injection	Combination with triamcinolone	5 (3 keloid, 2 HTS) {5}	Recurrence of all lesions after initial reduction	Kang et al. (2006) [28]
Intralesional injection	Combination with compression	6 {6}	Average 50% reduction, 2/3 recurrence at 12-month follow-up	Bae-Harboe et al. (2014) [29]
Cryotherapy				
Spray treatment, intralesional treatment	Comparison spray versus intralesional methods	50 {50}	Greater improvement with intralesional therapy	Mourad et al. (2016) [30]
Spray treatment	Treatment trial, post keloidectomy	97 {66}	71% of lesions showed major flattening at 24 months follow-up	Litrowski et al. (2014) [31]
Intralesional treatment	Treatment trial	29 {27}	Average 63% reduction, 24% recurrence	van Leeuwen et al. (2015) [32]
Spray treatment	Treatment trial	10 {6}	Limited short-term and no long-term efficacy	Park et al. (2017) [33]
Intraoperative treatment	Combination with excision and platelet-rich plasma	50 {50}	Average 84% improvement, less than 30% improvement in 26% of lesions	Azzam and Omar (2018) [34]
Probe treatment	Treatment trial (before intralesional administration of triamcinolone)	35 {30}	Significantly less pain ($p < 0.1$) compared to control	Wang et al. (2017) [35]
Laser				
585 nm pulse dye laser (PDL)	Case report	1 {1}	Recurrence of previously flattened lesion	Shih et al. (2008) [37]
595 nm PDL	Case series	3 {3}	Recurrence in 0/3 lesions	Eke et al. (2013) [38]
595 nm PDL	Treatment trial	52 {26}	Significant decrease in VSS score (20.85 ± 12.33%)	Yang et al. (2012) [39]
585 nm PDL	Treatment trial	59 (HTS and keloids) {59}	44/59 patients achieved moderate to excellent clearance, 3/59 saw minimal improvement	Cannarozzo et al. (2015) [40]

Table 1 continued

Treatment method	Design	No. lesions {no. patients}	Primary results	Author (year) [Reference]
595 nm PDL	In vitro study of treated fibroblasts	20 {20}	Significantly fewer fibroblasts in proliferative phases of the cell cycle after treatment	Zhibo and Miaobo (2010) [41]
Fractional CO_2 laser	Treatment trial	19 (12 keloid, 7 HTS) {19}	Significantly decreased VSS in treatment group, low patient satisfaction	Azzam et al. (2016) [42]
Fractional CO_2 laser	Case report, combination with laser-assisted drug delivery of topical triamcinolone	1 {1}	Scar thinning and visual improvement noted	Kraeva et al. (2017) [43]
300 μs 1064 nm Nd:YAG laser	Comparison to triamcinolone and combination	44 {44}	Greater efficacy in the laser only and combination therapy group	Rossi et al. (2013) [44]
595 nm PDL, 1064 nm Nd:YAG	Comparison of laser treatments	20 (9 keloid, 11 HTS) {20}	Similar effectiveness in both groups	Al-Mohamady et al. (2016) [45]
585 nm PDL	Case report, combination with CO_2 laser and triamcinolone	Unreported {1}	Symptomatic improvement and clinical regression	Martin and Collawn (2013) [46]
Radiofrequency (RF) ablation				
6 MHz	Treatment trial	10 (6 keloid, 4 HTS) {10}	No significant improvement seen	Meshkinpour et al. (2005) [47]
12 W electrode	Treatment trial and comparison with combination triamcinolone	19 {14}	Improvement in 6/7 lesions with combination therapy, improvement in 4/7 monotherapy	Fruth et al. (2011) [48]
10 W electrode	Treatment trial	13 {11}	10/11 had significant improvement after 1 treatment	Klockars et al. (2013) [49]
4 MHz	Combination with triamcinolone	18 {18}	Average 95.4% decreased volume	Weshay et al. (2015) [50]

Table 1 continued

Treatment method	Design	No. lesions {no. patients}	Primary results	Author (year) [Reference]
Intralesional RF	Comparison of intralesional RF and intralesional RF with triamcinolone versus triamcinolone, triamcinolone with hyaluronidase, and intralesional administration of verapamil	100 {100}	11.76% clearance with intralesional RF alone, 75% clearance combination RF and triamcinolone	Aggarwal et al. (2018) [12]
Radiation				
Post-excision electron beam	Comparison to previous literature on kilovoltage X-ray	50 {36}	16% recurrence rate, 83% satisfaction, greater results with electron beam	Maarouf et al. (2002) [51]
Electron beam, ^{60}Co, kV X-ray, ^{90}Sr	Meta-analysis	2515 {2515}	^{60}Co and electron beam were significantly more effective ($p = 0.0014$)	Flickinger (2011) [52]
Post-excision electron beam	Treatment trial	834 {568}	9.59% recurrence rate, most effective results with treatment < 24 h after excision	Shen et al. (2015) [53]
Superficial kV X-ray	Treatment trial of parallel pair method for auricular keloids	18 {16}	Treatment satisfaction 4.7/5	Eaton et al. (2012) [54]
High-dose-rate brachytherapy	Treatment trial	32 {24}	6% recurrence, 100% symptomatic reduction	Jiang et al. (2016) [55]
Superficial photon	Combination with excision and platelet-rich plasma	21 {20}	0% recurrence rate, 2/21 with poor results (Kyoto Scale)	Jones et al. (2016) [56]
Photon	Treatment trial, comparison to previous literature regarding electron beam radiation	15 {14}	0% recurrence at 22.5-month follow-up, comparable results with both methods	Yang et al. (2019) [57]
Electron beam	Combination with excision, comparison to excision with 5-fluorouracil and triamcinolone intralesional injection	60 {60}	Electron beam inferior to injections at reducing recurrence (42.33% versus 73.33%, respectively)	Khalid et al. (2018) [58]

Table 1 continued

Treatment method	Design	No. lesions {no. patients}	Primary results	Author (year) [Reference]
Extracorporeal shockwave therapy				
Handheld probe device	Comparison to intralesional administration of triamcinolone	39 {39}	Similar effectiveness in both groups	Wang et al. (2018) [60]
Pentoxifylline				
400 mg, BID or TID	Case series	Unreported {3}	Symptomatic relief (pain, pruritus) in all patients	Wong et al. (1999) [62]
400 mg, TID, 6 months	Perioperative treatment trial in combination with intralesional administration of triamcinolone	67 {45}	Recurrence significantly reduced in high risk patients (10.5% versus 66.6%)	Tan et al. (2019) [63]
Dupilumab				
300 mg every 2 weeks	Case report	2 {1}	Substantial keloid regression without complete clearance	Diaz et al. (2019) [64]
Combination therapies				
CO_2 laser, compression, silicone sheets, and cyanoacrylate glue	Combination treatment trial	7 {7}	Good outcomes, 100% patient satisfaction	Tenna et al. (2012) [65]
Fractional erbium-glass laser, CO_2 laser, cryotherapy, and intralesional administration of triamcinolone	Combination treatment trial	Unreported {12}	5% recurrence rate, highly efficacious compared to previous literature detailing the monotherapies	Lee et al. (2019) [66]
RF ablation and electron beam radiation	Combination treatment trial	Unreported {22}	Good or fair outcomes (72.7% and 27.3%, respectively), 73.3% patient satisfaction	Zhang et al. (2019) [67]
Comparisons				
CO_2 laser versus cryotherapy	Randomized controlled trial, both interventions followed by intralesional administration of triamcinolone	101 {60}	Similar effectiveness in both groups	Behera et al. (2016) [68]

Table 1 continued

Treatment method	Design	No. lesions {no. patients}	Primary results	Author (year) [Reference]
CO_2 laser with topical verapamil or topical 5-fluorouracil versus CO_2 monotherapy	Randomized trial	Unreported (keloid and HTS) {30}	Greater efficacy with combined therapy than CO_2 laser alone	Sabry et al. (2019) [69]
Intralesional cryotherapy versus excision and triamcinolone versus excision and brachytherapy	Randomized trial	25 {25}	Intralesional cryotherapy significantly less efficacious than brachytherapy to treat previously unresponsive keloids	Bijlard et al. (2018) [70]

postoperatively (every 2 weeks for 1 month, subsequently once per month for three additional months) concluded that verapamil was an acceptable treatment, with a recurrence rate of 28.6% [11]. However, compared to the standard of care (triamcinolone), another study found that postoperative sites injected monthly with 2.5 mg/ml verapamil showed higher recurrence rates than those injected with 10 mg/ml triamcinolone (hazard ratio = 8.44, $p = 0.01$). The results of this trial are particularly significant because of its study design that featured intra-patient control; half of the scar was injected with verapamil and half with triamcinolone [10]. In a third study, intralesional injection of verapamil was again found to be inferior to triamcinolone with verapamil having a complete clearance rate of 0% (0/15) versus 75% for triamcinolone (12/16) [12]. An additional study similarly found no evidence of efficacy for intralesional administration of verapamil; it did not reduce height nor pigmentation, and showed a minimal reduction in pliability [13]. These newer results contrast with previous literature which found verapamil effective for both keloids and hypertrophic scars [14–16]. These conflicting results make future use of intralesional verapamil therapy in keloids quite unclear.

Hyaluronic Acid and Hyaluronidase

From prevention of tumor growth to improvement of osteoarthritis to use in contact lenses, hyaluronic acid is a versatile mucopolysaccharide that is used in medical practice. In the field of dermatology, it has been used to improve skin contour and volume via injection fillers [17]. A recent case report using a combination of cortisone and hyaluronic acid over two sessions led to full clearance of the keloid with no recurrence seen at 12 months in a lesion previously refractory to cortisone injections alone [18]. Counterintuitively, an intralesional combination of triamcinolone 40 mg/ml mixed 1:1 with hyaluronidase 1500 IU/ml was also found to reduce keloid height to at most 1 mm in 11/16 lesions (68.75%, similar to 12/16 lesions (75%) with 40 mg/ml intralesional administration of triamcinolone alone). The authors state that this could be due to a synergistic effect of triamcinolone with hyaluronidase, as this mixture with a final triamcinolone concentration of 20 mg/ml was as efficacious as 40 mg/ml alone [12]. While the case report cites potential anti-

inflammatory properties of hyaluronic acid shown previously in animal studies of tendons, this does not fully explain why an implied reduction in hyaluronic acid with hyaluronidase would lead to similar results [19]. As both of these studies used combination therapy rather than hyaluronic acid or hyaluronidase alone, it may be that hyaluronidase or hyaluronic acid potentiated cortisone or triamcinolone, respectively, and did not lead to clearance of keloidal lesions of their own accord. Nevertheless, further study is warranted to illuminate the pathophysiological basis behind these conflicting results.

Botulinum Toxin

The initial trial of botulinum toxin for the treatment of keloids involved 12 patients and saw reduced size and increased flattening in all patients, with no recurrence at 1-year follow-up. Proposed mechanisms of action included both a reduction in scar tension as well as shifting cells to a more quiescent state [20]. While a subsequent study ($n = 4$) saw no clinical improvement in keloids with botulinum toxin therapy, further research has been largely supportive of this therapeutic response [21, 22]. Data has been mixed, however, as to how botulinum toxin compares to steroid injections. While studies such as those by Shaarawy et al. and Rasaii et al. found no difference between the two treatments, Pruksapong et al. found steroids to be superior, while a metanalysis performed by Bi et al. showed botulinum toxin as superior [23–26]. Factors such as decreased adverse effects and greater improvement in symptoms offer additional benefits of botulinum toxin in comparison to triamcinolone [23, 24]. Recent work using botulinum toxin in a mouse keloid model showed decreased Ki-67 (denoting decreased cell proliferation) as well as fewer and less haphazardly arranged collagen bundles, findings which were comparable to treatment of their mouse keloid model with steroid injections [27].

Collagenase

Collagenase injection currently has limited evidence. The initial evaluation yielded unsatisfactory results, as an initial reduction in keloid size in three patients (60%) was followed by recurrence in all lesions. Common side effects included pain and ulceration; pyrexia was observed in one patient [28]. A more recent study of auricular keloids ($n = 6$) found collagenase injections in combination with compression earrings to result in an average 50% size reduction in lesions; however, recurrence was a problem at 10-month and 1-year follow-up in two out of three lesions. The other three participants elected subsequent surgical treatment of their lesions, so this treatment may have use in shrinking lesions preoperatively. Compression and collagenase therapy may be especially helpful in combination, as both help to break down aberrant collagen known to be pathogenic in keloids [29]. Despite mixed results, the proposed mechanism of action of collagenase in the setting of keloids and their known connection with collagen production encourages additional research involving this therapy.

CRYOTHERAPY

Cryotherapy has quickly become a popular modality for discussion in keloid literature; when used to treat keloids, cryotherapy leads to both decreased inflammation and increased collagen organization [30]. In a retrospective study of 97 auricular lesions treated with immediate cryotherapy post keloidectomy, 71% of keloids showed 80–100% flattening at 24 months follow-up. Although there was a 36% recurrence rate after one treatment, 68% of these recurrent lesions achieved flattening after a second treatment. Hypopigmentation was seen more in patients with darker skin; however, this did not reach significance, possibly as a result of a largely European population [31]. This is supported by results from a different study that found that both hypopigmentation and recurrence after intralesional cryotherapy were significantly more likely in patients with

Fitzpatrick type V–VI than I–II [32]. Comparing intralesional to spray cryotherapy, the former seemed to be more effective, although good results were seen with both. Spray also required a larger number of sessions (2 weeks apart) to achieve similar results [30]. Results of a smaller study done by Park et al. using spray cryotherapy supported the need for sessions at 2-week intervals to maintain results. Additionally, they saw substandard results for several cases, particularly for thicker keloids, and thus concluded that spray treatment should not be performed as monotherapy [33]. Combination therapy of excision, handheld cryotherapy, and platelet-rich plasma found an average Vancouver Scar Scale (VSS) improvement of 84%, although 26% of lesions failed to flatten by more than 30%. One hundred percent of patients experienced hyperpigmentation [34]. In sum, while cryotherapy is known to be painful, intralesional cryotherapy is efficacious, especially with newer lesions [30]. Table 2 lists the treatment specifications of the aforementioned cryosurgery studies. Cryotherapy also has a clear application in keloid treatment as anesthesia; a study using a cryotherapy probe before steroid injections showed a statistically significant reduction in reported pain [35].

LASER

Laser therapy continues to be of interest in the field of dermatology in general, and interest in its use with respect to keloids is no different.

Pulse Dye Laser (PDL)

PDL was one of the earliest laser interventions used to treat keloids. This type of laser destroys hemoglobin, making it useful in vascular keloids [36]. While an early case report actually found PDL (585 nm) to result in keloid recurrence after previous flattening, subsequent studies have shown efficacy in keloid treatment [37]. A case series (n = 3) found post-shave-excision PDL treatment (595 nm) of keloids to result in no recurrence of lesions (0/3), and hypopigmentation was only seen in one patient [38]. A study of 26 patients with keloids who were treated with 595 nm PDL resulted in a significant decrease in VSS score, including improved pain and itch, pliability, and erythema [39]. Improvements were similarly seen in a study of 59 patients with keloids and hypertrophic scars (Fitzpatrick I–IV) treated with 585 nm PDL. Of 59 patients, 44 showed moderate to excellent results, with only 3/59 patients resulting in minimal improvement. Of 59 patients, 55 were satisfied or very satisfied

Table 2 Cryotherapy specifications

	Specifications	Freeze–thaw cycles	Additional information
Mourad et al. [30]	Spray or intralesional	1	Pretreated with topical lidocaine, repeated every 2 weeks
Litrowski et al. [31]	Post-excisional spray	1	Stopped freezing when impedance meter reached 1000 kΩ
van Leeuwen et al. [32]	Intralesional	1	Pretreated with 0.5% bupivacaine local anesthesia
Park et al. [33]	Spray	2	Repeated every 2 weeks
Azzam and Omar [34]	Intraoperative treatment	1	Stopped freezing when impedance meter reached 1000 kΩ, combination therapy with excision and platelet-rich plasma

with these results, although 7/59 exhibited some degree of hyperpigmentation [40]. Additional work to detail the mechanism of action of this efficacious treatment found that keloid fibroblasts treated with PDL had a statistically different cell cycle phase distribution than control fibroblasts, with the majority of treated fibroblasts being in G0 and G1 versus control fibroblasts being in proliferative phases [41]. With both a sound scientific basis and evidence of efficacy in trials, this treatment method could become a more common option for keloid treatment.

Carbon Dioxide (CO_2) Laser

More recent work has focused on the use of fractional carbon dioxide laser. An early study CO_2 laser monotherapy (four sessions, 6 weeks apart) was shown to have mixed results in a study of both keloids and hypertrophic scars. While statistically significant reduction of VSS scores was seen (largely because of increased pliability), many patients were not satisfied with this therapy [42]. A case report found that treatment with fractionated CO_2 laser and laser-assisted drug delivery of topical triamcinolone caused scar thinning and visual improvement [43]. Such limited data makes these results difficult to generalize.

Combinations and Comparisons

Combination treatment using both triamcinolone and 300 μs 1064 nm neodymium-doped yttrium aluminum garnet (Nd:YAG) laser (2000 pulses at 13–18 J/cm^2), an additional laser used for keloid treatment, reduced height and erythema to a greater degree than triamcinolone monotherapy. This study showed no adverse pigmentary changes, which is always a concern when treating these lesions on skin of color [44]. A study comparing Nd:YAG to PDL in 20 patients with keloids or hypertrophic scars found both therapies to be efficacious, with neither being statistically superior, although Nd:YAG was found to be more painful [45]. A case report using combination treatment including PDL, CO_2 laser, and triamcinolone on a keloid that was previously unresponsive to triamcinolone alone showed alleviation of symptoms after two treatments and regression by seven [46]. These results support the use of laser as an adjunct therapy.

RADIOFREQUENCY (RF) ABLATION

While early experimentation with use of RF ablation on keloids saw limited benefits, recent evidence has been rather favorable [47]. Fruth et al. treated auricular keloids with RF ablation (1–7 treatments), half in combination with intralesional administration of triamcinolone, and saw improvement in 6/7 treated with combination therapy and 4/7 with RF ablation monotherapy [48]. A subsequent study saw improvement in 12 out of 13 lesions (92.3%), with only one patient requiring multiple treatments; the authors acknowledged that there was no explanation for the divergence between their results and those of Fruth et al. [49] Further evaluation of combination therapy with RF ablation and steroid injection was found to decrease keloid volume (95.4% reduction), pain, and pruritus [50]. Support of these results was found in a comparison of triamcinolone, triamcinolone and hyaluronidase, verapamil, RF, and RF with triamcinolone. Triamcinolone with hyaluronidase and RF with triamcinolone were found to have the highest clearance rates (75%), although RF ablation carried an increased rate of adverse effects such as atrophy, ulceration, and depigmentation [12]. In summary, although complications could pose an increased risk with this treatment, optimization should be sought, as this treatment has been shown to be effective.

RADIATION

Surgical excision followed by radiation has become a mainstay of keloid treatment in an effort to prevent postoperative recurrence. Early research showed that electron beam radiation may be superior to conventional kilovoltage X-ray therapy owing to its more even tissue distribution, touting only a 16% recurrence rate

and a patient satisfaction rate of over 83% [51]. A large review (n = 2515) of post-keloidectomy radiation found the least likelihood of recurrence with electron beam or ^{60}Co radiation as compared to other radiation options [52]. Another large retrospective study of 568 patients with 834 keloids treated with electron beam radiation post excision showed a 9.59% recurrence rate, with recurrences significantly more likely in patients who were young (up to 29 years old), female, with large (greater than 5 cm) keloids, or with keloids in more tense locations. Additionally, relapses were less likely with a shorter interval from surgery to radiation, with radiation within 24 h being the least recurrent [53]. In a survey of patients with auricular keloids who were treated with conventional kilovoltage radiation, satisfaction with treatment was high (4.7/5), although the number of responses was low (n = 5) [54].

Brachytherapy is a newer radiation option that has limited but positive results; recent work found a 6% recurrence rate after perioperative high-dose brachytherapy was used in patients who had failed previous treatments. Symptoms were also completely eliminated from all previously symptomatic patients [55]. Lastly, superficial photon radiotherapy has become popular, potentially owing to the development of new in-office machines. A study of 21 keloids using in-office postoperative radiation therapy achieved a 0% recurrence rate. Although the study size was limited and there may have been a degree of confounding due to the adjunct use of platelet-rich plasma and a proprietary topical cream, the results are nonetheless promising [56]. Recent work comparing electron beam radiation to low-energy photon radiotherapy found significantly fewer recurrences in the low-energy photon radiotherapy group, which supports previously discussed work [57]. In summary, years of data largely support radiation as an integral component in prevention of postoperative keloid recurrence. However, a study comparing excision and electron beam radiation to excision and 5-fluorouracil/triamcinolone injections found that the injections were more efficacious in reducing recurrences than radiation (73.33% versus 42.33% efficacy, respectively) [58]. As radiation is not without risks, from pigmentary changes to purported malignancy potential, additional data is needed to confirm which patients could be best candidates for this treatment [56, 58].

OTHER

Extracorporeal Shockwave Therapy

Use of shockwave therapy for scar improvement is a fairly new phenomenon. A study of extracorporeal shockwave therapy on hypertrophic scars recently showed that it improved parameters such as wrinkles after 3 weeks of treatment (three sessions) [59]. A comparison of extracorporeal shockwave therapy to intralesional steroid showed no significant difference in improvement of keloids between these groups, as determined by both Patient and Observer Scar Assessment Scale (POSAS) and clinical features [60]. Such limited study prevents drawing a strong conclusion about this therapy.

Pentoxifylline

Pentoxifylline, a methyl xanthine derivative, has shown variable uses in keloid therapy. Early work showed that pentoxifylline decreased fibrosis broadly, including fibrosis resulting from radiation, and use in keloids showed potential to decrease the recurrence rate by repressing wound contraction [52, 61]. Wong et al. showed that additional benefits of pentoxifylline include halting the progression of keloids, as well as the reduction of bothersome symptoms such as pruritus and pain [62]. This symptomatic benefit could be especially useful to provide relief in patients whose keloids are large, numerous, or otherwise suboptimal for surgical consideration. In a retrospective study evaluating the addition of 6 months of postoperative pentoxifylline (400 mg, TID) to the standard of care (intralesional triamcinolone injections), recurrence of lesions was found to be significantly decreased in high-risk patients who received the adjunct therapy versus those that did not (10.5% versus 66.6%, respectively) [63]. With postsurgical recurrence of keloids

being one of the most serious and difficult treatment complications, current data supporting this treatment is encouraging.

Dupilumab

A single case report of an African American patient with atopic dermatitis and two concomitant popliteal fossa keloids cited dupilumab (anti-IL-4, anti-IL-13) as causing substantial keloid regression (without complete clearance). In studying skin samples from three patients with keloids but without atopic dermatitis, the authors found increased *IL-4R* expression in keloids, and increased *IL-13* and *CCL18* expression in both keloids and non-lesional skin (as compared to race-matched controls with neither a history of keloids nor atopic dermatitis) [64]. However, as this result has only been shown in one patient who had a concomitant inflammatory skin condition, more data is needed to show efficacy in patients with keloids.

COMBINATION THERAPIES

Because no one treatment has proven to be wholly efficacious and because treatment of keloids is dependent on a variety of factors such as location, Fitzpatrick skin type, and history of recurrence, many studies have been performed that combine established treatments to ideally generate an additive or synergistic response. For example, excision is a mainstay of therapy that has been combined with other modalities to improve recurrence rates. A study evaluating excision with CO_2 laser additionally used compression, silicone sheets, and cyanoacrylate glue to improve results [65]. Likewise, triamcinolone injections are often added to other treatments owing to their known efficacy. Combination therapy including two types of laser (nonablative fractional erbium-glass and ablative fractional CO_2), superficial cryotherapy (using a handheld device, three freeze–thaw cycles), and triamcinolone injection was found to produce a large improvement in a relatively short amount of time as compared to previous literature of the monotherapies [66]. Another study showed that combination therapy including RF ablation and electron beam radiation reduced VSS scores (all characterized as "good" or "fair") while largely improving patient satisfaction (73.3% reported extremely satisfied). The authors proposed that this treatment combination could be especially useful in patients with large or multiple keloids that are not appropriate for surgery [67].

COMPARISONS

As a result of the breadth of keloid treatment options, some work has been done to directly compare various therapies. Behera et al. compared results of keloid destruction with cryotherapy (using a cryoprobe; two freeze–thaw cycles) vs CO_2 laser, both followed by steroid injections. While some initial differences were seen between the groups, differences in parameters such as recurrence and VSS score were not statistically significant at 12 months. While pain reduction was significantly higher in the CO_2 laser group, the authors largely found that these two treatments are equivalent [68]. Sabry et al. found that the combination of CO_2 laser with either topical verapamil or 5-fluorouracil was more efficacious than laser alone, with no adverse effects [69]. A randomized controlled trial evaluating intralesional cryotherapy as compared to excision and steroid or excision and brachytherapy performed by Bijlard et al. was stopped because of significantly inferior results in the intralesional cryotherapy group. Specifically, they note that brachytherapy is more efficacious for keloids that historically were unresponsive to intralesional corticosteroid therapy or recurrent after surgery. While an improvement was seen with cryotherapy in keloids that were not treatment-resistant, corticosteroids nevertheless seemed to give a more robust improvement [70].

CONCLUSION

There have never been more options for keloid treatment than what is available currently. However, because the majority have either seen conflicting results or have not progressed to

optimization, it is difficult to compare results across the board to suggest what may be the most advantageous treatment option. Additionally, as patient characteristics such as age, Fitzpatrick skin type, gender, keloid location or size, keloid number, history of recurrence, and personal interest in various therapies can play an important role, the increased number of efficacious options allows for an ever more dynamic interaction between patients and their healthcare providers about their disease and treatment options.

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