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Keloids: Review of Pathogenesis and Evidence-Based Treatment Modalities

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Introduction

Keloids are fibroproliferative growths resulting from dysregulated healing following tissue injury with the subsequent deposition of excessive and disorganized collagen (**Figure 1**).[1] Prolonged chronic inflammation in the reticular dermis in particular during healing, is thought to precede the development of keloids. Experimental studies have demonstrated an increased release of growth factors, cytokines, and multiple immune cells.[2,3] The inflammatory cells secrete factors implicated in chronic inflammation, fibrosis and itch, among many others.[2]

Keloids demonstrate an autosomal dominant transmission with an incomplete penetrance, beginning most commonly in the 2nd and 3rd decades of life.[3] Keloids can be seen in all patients, but most frequently in those of skin of colour, particularly individuals from North Africa, South America, the Middle East, India, and China.[3] Areas of skin where keloids have the highest propensity to develop are related to other risk factors, including sites on the skin where an injury occurs due to dermatologic disease or external processes, high skin tension, and dense pilosebaceous content.[2,3] Hypertension and obesity also appear to be associated with the development of keloids at a systemic level.[2,3]

Keloids may present as a single lesion or a few lesions, or they can be widespread, developing without any known preceding trigger.[2,3]

In addition to distress from the physical appearance, keloids cause additional morbidity from pain (i.e. allodynia, burning, and stinging) and pruritus.[2] The Th2 cytokines, which are both profibrotic and pruritogenic, play a role and C-nerve fiber neuropathy ensues, producing pain and itch.[2]

Keloid Treatment Modalities

a) Preventative and Behavioural Strategies

Surgical Technique

To prevent keloid formation, especially in high tension areas of the body (eg. back, and shoulders, among others), surgeons should employ techniques that limit dermal tension, including broad undermining, placing scars along relaxed skin tension lines, dermal sutures, deep fascial plication sutures, local flaps, and Z-plasties.[5] There are no randomized controlled trials supporting this recommendation, however, the clinical

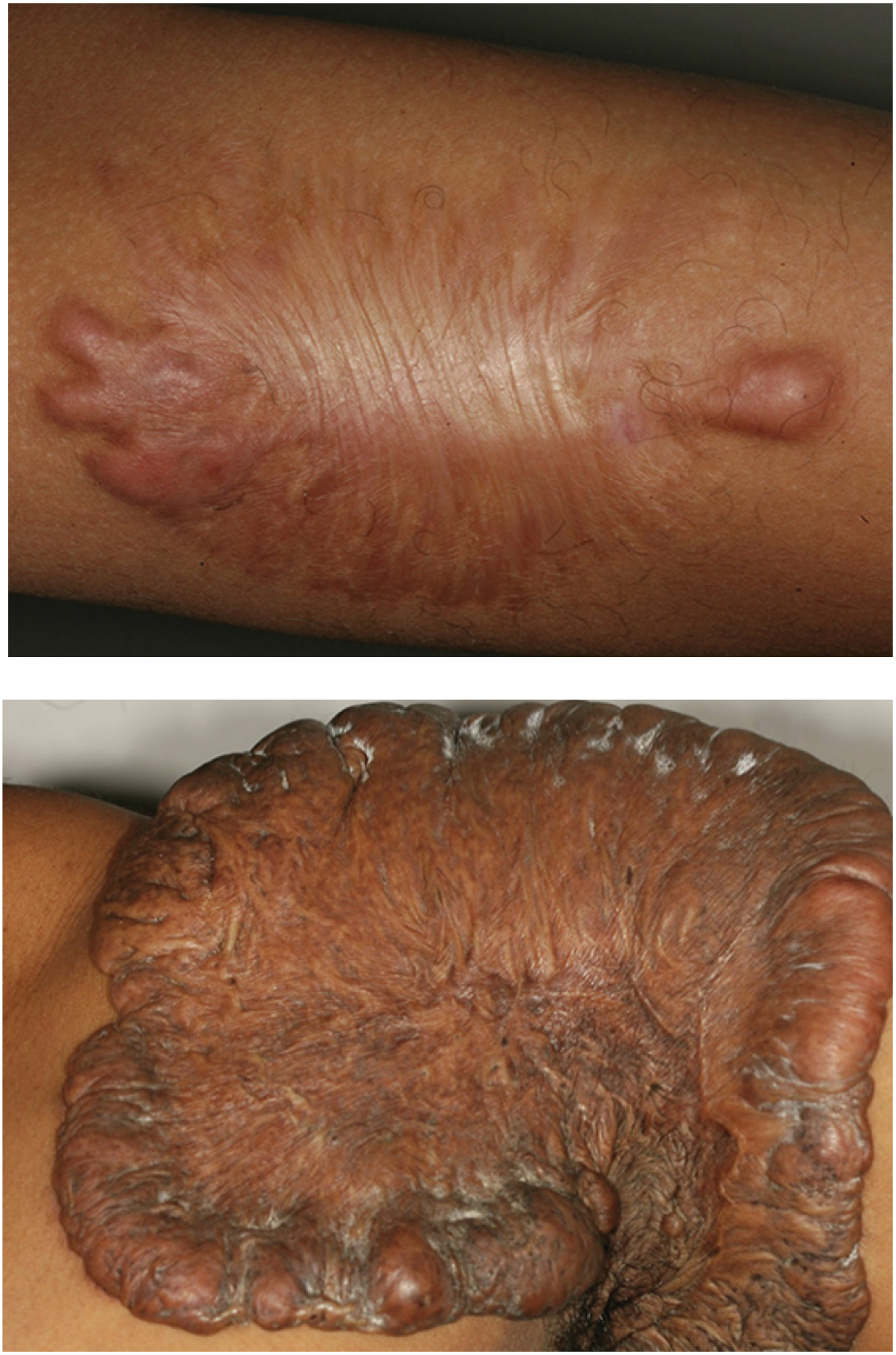

Figure 1. Keloids may appear with a sessile morphology (**top**) or a more nodular/exophytic morphology (**below**). The arrangement and anatomic location often provides a clue to the cause; *photos courtesy of* [4]*: (J. Delaleu, E. Charvet and A. Petit.Keloid Disease: Review with clinical atlas. Part 1: Definitions, history, epidemiology, clinics and diagnosis. Annales de Dermatologie et de Venereologie. 2023;150:3-15.)*

experience of most surgeons would suggest this as an expert opinion.

Silicone

Silicone based products are FDA approved for treating scarring and keloids, although they are used mostly as a preventative measure in clinical practice. The products are usually applied as either a topical gel or a sheet dressing 12–24 hours a day for 1–2 months post-operatively.

Patients commonly inquire about the use of post-procedural silicone products. The putative mechanism of action is not known, but its use may limit scar tension by decreasing skin stretching and promoting hydration through occlusion.[3,5] However, silicone has not been found to be an effective method of preventing keloids. A meta-analysis that included 10 trials comparing a silicone arm (gel or sheets) to a placebo arm did not find that silicone reduced the development of keloids in patients with a history of abnormal scarring.[6] Similarly, a Cochrane review of 20 clinical trials found that while silicone does reduce erythema and thickness, the evidence for reducing keloidal scarring is weak.[7]

b) Active Treatment Modalities

Surgical Excision

Excision alone is not recommended for keloids due to the very high risk of recurrence (up to 100%) and risk of lesions recurring at a larger size. Excision is combined effectively with other treatment modalities as outlined below.

Corticosteroids

Corticosteroids, intralesional kenalog (ILK) in particular, are the mainstay of keloid treatment by dermatologists. Corticosteroids are thought to work by reducing dermal inflammation, reducing oxygen via vasoconstriction, and inhibiting collagen synthesis.[3,5,8] Side effects include erythema, dyspigmentation, pruritus, pain, atrophy, telangiectasias, wound dehiscence and delayed healing.[8]

The literature presents a range of doses, frequencies, and injection timings for ILK treatment. A 2023 systematic review was conducted that compiled 16 studies, including 4 randomized-controlled trials and 12 prospective cohorts. They investigated the use of ILK monotherapy or in combination treatment with surgery or cryotherapy.[8] The dosage ranged from 10–40 mg/cc, administered through single injections either weekly or monthly, usually every 4–6 weeks.[8] Studies have found that ILK is most effective for treating sessile keloids (as opposed to pedunculated ones), with response rates between 50–100%, depending on the specific study, along with an overall recurrence rate of 33% and 50% at 1 year and 5 years, respectively.[8]

Studies using ILK as an adjuvant treatment to surgical excision are lacking control groups for the most part. For example, a recent meta-analysis that included 254 patients, pooled from 4 separate studies, did not demonstrate a reduction in the keloid recurrence rate.[9] The timing of ILK administration in the studies was inconsistent and no consensus recommendation was made.[9] However, the site of the keloid excision might have had an impact on the effectiveness of adjuvant ILK. A meta-analysis focusing on ear keloids reported a recurrence rate of 15.4% following excision. This was found to be of similar efficacy to the post-operative radiation group, which had a recurrence rate of 14%.[10]

Cryosurgery

Cryosurgery is another commonly employed keloid treatment modality, largely because dermatologists are comfortable with its use in many areas of practice. Cryosurgery causes tissue necrosis, however, it has also been shown to convert keloidal fibroblasts to a normal phenotype.[3] Side effects of cryosurgery include pain, bleeding, blistering, ulceration, dyspigmentation, and infection. While most dermatologists use spray cryosurgery, cryotherapy can also be administered by direct contact or intralesional needle methods. Intralesional cryosurgery, which involves applying the treatment to the core of the keloid, is considered to be the most efficacious cryotherapy modality.[11] A meta-analysis of 8 studies reported that intralesional cryotherapy was able to decrease the scar volume by 51–61%, with a recurrence range between 0–24%.[11] Intralesional cryosurgery is also more precise, as it allows one to limit the treatment area and minimize the amount of healthy skin that is frozen.[11]

Multiple published prospective cohorts and randomized-controlled trials have studied the combination of cryosurgery with other treatment modalities, including ILK, excision, or shave removal, and reported these techniques to be effective for the treatment of keloids (summarized here).[8]

Other Intralesional Treatments

5-fluorouracil (5-FU) has been used in various dermatologic indications. It is an anti-neoplastic drug that targets thymidylate synthase, thus inhibiting mitotically active keloidal fibroblasts.[8] Patients must be counselled on side effects including pain, bleeding, infection, ulceration, wound dehiscence, and poor healing. Meta-analyses and randomized-controlled trials (RCTs) have demonstrated its efficacy as a

monotherapy, in combination with ILK, and in reducing post-operative recurrences of keloids following excision.[3] An RCT that included 43 patients (with 50 keloids in total) compared the monthly administration of IL-5FU (50 mg/cc) to ILK (40 mg/cc), and reported that both treatment modalities were equally as effective at the 1 year follow up.[12] The former group however, had higher reports of telangiectasia and skin atrophy.[12]

By combining ILK with IL-5FU, the risk of steroid side effects can be reduced, potentially with greater efficacy. In two RCTs, one with 100 patients and one with 60 patients, ILK (40 mg/cc) monotherapy was compared to a combined treatment of IL-5FU (50 mg/cc) and ILK. The groups receiving combination treatment demonstrated a greater reduction in the Vancouver Scar Scale (VSS),[13] and a reduction in keloid volume.[14]

Just like 5-FU, bleomycin is another drug that has been used to treat other dermatologic diseases and is familiar among many dermatologists. It is an anti-neoplastic agent derived from *Streptomyces verticillus* that induces apoptosis in fibroblasts and inhibits collagen synthesis by targeting lysyl oxidase.[8] Similar to ILK, there are a wide range of reported recurrence rates following treatment of keloids with IL bleomycin monotherapy. In the largest available prospective study, 120 patients were treated with 15 units of bleomycin at 4-week intervals for an average of 4 months.[15] At the 18 month follow up, the reported recurrence rate was 14%.[15]

Bleomycin may be more effective than IL-5FU or ILK. In an RCT that included 164 patients, the authors found that IL bleomycin (1.5 IU/mL) was more effective in reducing the scores on the Patient and Observer Scar Assessment Scale (POSAS) compared to the ILK group.[16] In an RCT involving 60 patients, the authors compared treatment with either a combination of ILK (40 mg/cc) and 5-FU (1:9 mixture) or a combination of ILK (40 mg/cc) and bleomycin (1.5 IU/mL) in a 1:2.5 mixture.[17] The group receiving bleomycin and ILK showed a greater improvement in the VSS, and reported no recurrences.[17] The unique side effect of bleomycin that one must counsel patients about is hyperpigmentation, especially for patients with melanized skin. No systemic side effects were observed in these studies.

Radiation

The mechanism of action for radiation treatment of keloids includes inhibition of fibroblasts, inhibition of angiogenesis, along with downregulation of TGFβ and histamine from inflammatory cells.[3,8] Radiation is not often provided as a monotherapy, unless it is used for symptom control, in the aged population, or for very large keloids where surgery or intralesional treatment is not possible.[3] Instead, radiation is most useful as an adjunct therapy. A meta-analysis that included 72 studies totalling 9048 keloids revealed a 22% recurrence rate following surgery and post-operative radiation treament.[18] This meta-analysis revealed that monotherapy had a 37% recurrence rate, although pain and pruritus improved significantly in most patients.[18] The timing of radiation post-procedure appears to be important, with most studies documenting administration of radiation within 24 hours of the procedure yielding the best response (reviewed here).[8] There are however no clear recommendations on radiation dosing and scheduling.

The three main radiation modalities are: brachytherapy, electron beam therapy, and photon beam therapy.[19] While it is not clear which one is most effective, a systematic review that included 33 studies reported that adjuvant radiation with brachytherapy had a 15% recurrence rate while photon beam therapy and electron beam therapy both had a recurrence rate of 23% in their subgroup analyses.[18] Radiation can cause both acute (i.e. erythema, edema, pain, ulceration, and blistering) and chronic (i.e. telangiectasias and dyspigmentation) side effects. While radiation in general has been associated with the development of secondary malignancies, there is no definitive link between skin cancers and the short treatment protocols used in the adjuvant treatment of keloids.[18]

Lasers

While there is actually limited published data on lasers for the treatment of keloids, both ablative (CO_2, Erbium-doped yttrium aluminum garnet [Erb:YAG] and non-ablative lasers (pulsed dye laser [PDL], Neodymium-doped yttrium aluminum garnet [Nd:YAG], diode) have been described. Case series and small prospective cohorts have described laser treatment in combination with various intralesional therapies (ILK, 5-FU, interferon) or surgical excision. While there is very limited data, an interesting application of ablative lasers is as a method to improve the penetration of corticosteroids.

In one study, of 41 patients were treated with CO_2 followed by triamcinolone ointment under occlusion every 4 weeks for a total of 8 sessions and at 24-month follow up, there was a 10.5% recurrence rate.[20] In a split side-controlled prospective study, 30 patients were treated with ILK (10 mg/cc) compared to Erb:YAG (2940 nm) followed by application of betamethasone diproprionate ointment under occlusion 4 total times at 4 week intervals.[21] VSS reduction was statistically significant, but may not really be clinically significant (reduction from 6.90 to 2.63 vs. 2.07) at 12-week follow up after completing the last session.[21]

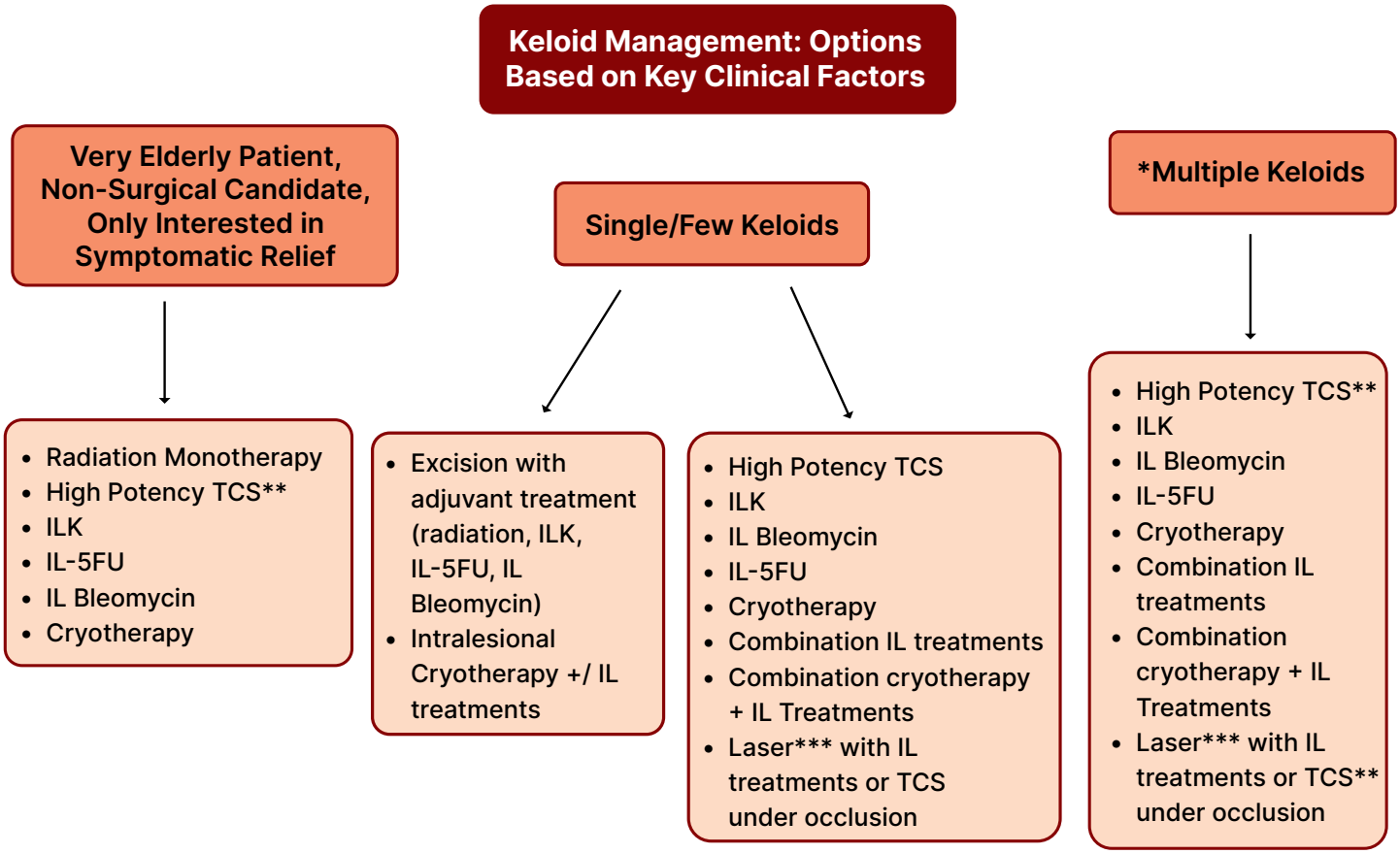

Figure 2. Algorithm for keloid management; *courtesy of Robert Bobotsis, MD, MSc SLI, FRCPC, DABD.*

***Multiple keloids (eg. involving a regional area of the body such as the chest) should be differentiated from widespread keloidal disease, the latter of which is extremely difficult to treat. Treatment options should be reviewed with patients along with honest discussion around realistic expectations.

****Corticosteroid ointments and creams can also be used to treat keloids over many months (usually under occlusion) and have the benefit of being painless.

*****The literature on laser treatment for scarring mostly focuses on hypertrophic scars.

Abbreviations: TCS: topical corticosteroids, **IL:** intralesional, **5-FU:** 5-fluorouracil

International Guidelines on Keloid Management
Gold MH, Berman B, Clementoni MT, Gauglitz GG, Nahai F, Murcia C. Updated international clinical recommendations on scar management: part 1--evaluating the evidence. Dermatol Surg. 2014;40(8):817-24,
Gold MH, McGuire M, Mustoe TA, Pusic A, Sachdev M, Waibel J, *et al*. Updated international clinical recommendations on scar management: part 2--algorithms for scar prevention and treatment. Dermatol Surg. 2014;40(8):825-31.
Ogawa R, Akita S, Akaishi S, Aramaki-Hattori N, Dohi T, Hayashi T, *et al*. Diagnosis and treatment of keloids and hypertrophic scars-Japan scar workshop consensus document 2018. Burns. Trauma. 2019;7:39.
Juckett G, Hartman-Adams H. Management of keloids and hypertrophic scars. Am Fam Physician. 2009;80(3):253–60.
Lv K and Xia Z. Chinese expert consensus on clinical prevention and treatment of scars. Burns. Trauma. 2018;6:27.

Figure 3. International guidelines on the management of keloids.[22-26]; *courtesy of Robert Bobotsis, MD, MSc SLI, FRCPC, DABD.*

Discussion

When reviewing the available literature, it is difficult to assess efficacy because of several factors, such as the variability in the quality of studies, the scarcity of direct comparisons between combination treatments and monotherapy, lack of control groups, or poor control for numerous factors including keloid size, skin type, previous treatments, and the body site of the keloid, among many other factors. Also, most studies did not use validated outcome measures such as the VSS or POSAS. Importantly, many studies did not reliably differentiate between hypertrophic scarring and keloids, for which natural history, prognosis, and treatment are vastly different. There is minimal evidence for which treatments work best based on the anatomic site. An exception is perhaps ear keloids, which have the most data supporting the use of combination treatments. It is possible that anatomic factors play a role in ear keloids, which appear to have lower recurrence rates across multiple types of maintenance therapies (i.e. compression and intralesional treatments). While IL-5FU and IL bleomycin look promising as both monotherapy and adjuvant treatment to prevent the recurrence of keloids, unlike ILK, there is a lack of long term (i.e. 5 year) follow up data in the literature for these treatments.

While this review is limited by its non-systematic nature, it does summarize available RCTs, systematic reviews, and meta-analyses to provide practical, up-to-date, and efficacious keloid treatment options. The most effective keloid management likely necessitates a multimodal approach. However, the optimal treatment plan will need to be individualized to patient specific factors, taking into account adherence, cost, their ability to tolerate procedures, and their expectations. **Figure 2** provides an approach to treating keloids based on the data summarized in this paper. In addition, **Figure 3** lists international guidelines that the interested clinician can reference.

Conclusions

Keloid treatments can be categorized into topical, intralesional, surgical, radiation, and laser options. Unfortunately, there is no single treatment approach one can apply that guarantees consistent results and no risk of recurrence. While ILK remains the most commonly used treatment by dermatologists, there are a wide array of other options we can offer our patients who are seeking symptomatic and cosmetic treatments for this disabling condition.

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Financial Disclosures

None declared.

References

1. Lee CC, Tsai CH, Chen CH, Yeh YC, Chung WH, Chen CB. An updated review of the immunological mechanisms of keloid scars. Front Immunol. 2023;14:1117630. doi:10.3389/fimmu.2023.1117630
2. Hawash AA, Ingrasci G, Nouri K, Yosipovitch G. Pruritus in keloid scars: mechanisms and treatments. Acta Derm Venereol. 2021;101(10):adv00582. doi:10.2340/00015555-3923
3. Ogawa R. The most current algorithms for the treatment and prevention of hypertrophic scars and keloids: a 2020 update of the algorithms published 10 years ago. Plast Reconstr Surg. 2022;149(1):79e-94e. doi:10.1097/prs.0000000000008667
4. Delaleu J, Charvet E, Petit A. Keloid disease: review with clinical atlas. Part I: definitions, history, epidemiology, clinics and diagnosis. Ann Dermatol Venereol. 2023;150(1):3-15. doi:10.1016/j.annder.2022.08.010
5. Ekstein SF, Wyles SP, Moran SL, Meves A. Keloids: a review of therapeutic management. Int J Dermatol. 2021;60(6):661-671. doi:10.1111/ijd.15159
6. Hsu KC, Luan CW, Tsai YW. Review of silicone gel sheeting and silicone gel for the prevention of hypertrophic scars and keloids. Wounds. 2017;29(5):154-158.
7. O'Brien L, Jones DJ. Silicone gel sheeting for preventing and treating hypertrophic and keloid scars. Cochrane Database Syst Rev. 2013;2013(9):Cd003826. doi:10.1002/14651858.CD003826.pub3
8. Walsh LA, Wu E, Pontes D, Kwan KR, Poondru S, Miller CH, et al. Keloid treatments: an evidence-based systematic review of recent advances. Syst Rev. 2023;12(1):42. doi:10.1186/s13643-023-02192-7
9. Shin JY, Kim JS. Could 5-fluorouracil or triamcinolone be an effective treatment option for keloid after surgical excision? A meta-analysis. J Oral Maxillofac Surg. 2016;74(5):1055-1060. doi:10.1016/j.joms.2015.10.002
10. Shin JY, Lee JW, Roh SG, Lee NH, Yang KM. A comparison of the effectiveness of triamcinolone and radiation therapy for ear keloids after surgical excision: a systematic review and meta-analysis. Plast Reconstr Surg. 2016;137(6):1718-1725. doi:10.1097/prs.0000000000002165
11. van Leeuwen MC, Bulstra AE, Ket JC, Ritt MJ, van Leeuwen PA, Niessen FB. Intralesional cryotherapy for the treatment of keloid scars: evaluating effectiveness. Plast Reconstr Surg Glob Open. 2015;3(6):e437. doi:10.1097/gox.0000000000000348
12. Hietanen KE, Järvinen TA, Huhtala H, Tolonen TT, Kuokkanen HO, Kaartinen IS. Treatment of keloid scars with intralesional triamcinolone and 5-fluorouracil injections - a randomized controlled trial. J Plast Reconstr Aesthet Surg. 2019;72(1):4-11. doi:10.1016/j.bjps.2018.05.052
13. Saleem F, Rani Z, Bashir B, Altaf F, Khurshid K, Pal SS. Comparison of efficacy of intralesional 5-fluorouracil plus triamcinolone acetonide versus intralesional triamcinolone acetonide in the treatment of keloids. Journal of Pakistan Association of Dermatologists. 2018;27(2):114-119.

14. Srivastava S, Patil AN, Prakash C, Kumari H. Comparison of intralesional triamcinolone acetonide, 5-fluorouracil, and their combination for the treatment of keloids. Adv Wound Care (New Rochelle). 2017;6(11):393-400. doi:10.1089/wound.2017.0741
15. Huu ND, Huu SN, Thi XL, Van TN, Minh PPT, Minh TT, et al. Successful treatment of intralesional bleomycin in keloids of Vietnamese population. Open Access Maced J Med Sci. 2019;7(2):298-299. doi:10.3889/oamjms.2019.099
16. Khan HA, Sahibzada MN, Paracha MM. Comparison of the efficacy of intralesional bleomycin versus intralesional triamcinolone acetonide in the treatment of keloids. Dermatol Ther. 2019;32(5):e13036. doi:10.1111/dth.13036
17. Sharma S, Vinay K, Bassi R. Treatment of small keloids using intralesional 5-fluorouracil and triamcinolone acetonide versus intralesional bleomycin and triamcinolone acetonide. J Clin Aesthet Dermatol. 2021;14(3):17-21.
18. Mankowski P, Kanevsky J, Tomlinson J, Dyachenko A, Luc M. Optimizing radiotherapy for keloids: a meta-analysis systematic review comparing recurrence rates between different radiation modalities. Ann Plast Surg. 2017;78(4):403-411. doi:10.1097/sap.0000000000000989
19. Liu EK, Cohen RF, Chiu ES. Radiation therapy modalities for keloid management: a critical review. J Plast Reconstr Aesthet Surg. 2022;75(8):2455-2465. doi:10.1016/j.bjps.2022.04.099
20. Wang J, Wu J, Xu M, Gao Q, Chen B, Wang F, et al. Combination therapy of refractory keloid with ultrapulse fractional carbon dioxide (CO(2)) laser and topical triamcinolone in Asians-long-term prevention of keloid recurrence. Dermatol Ther. 2020;33(6):e14359.
21. Abd El-Dayem DH, Nada HA, Hanafy NS, Elsaie ML. Laser-assisted topical steroid application versus steroid injection for treating keloids: a split side study. J Cosmetic. Dermatol. 2020; 20(1):138–42
22. Gold MH, Berman B, Clementoni MT, Gauglitz GG, Nahai F, Murcia C. Updated international clinical recommendations on scar management: part 1--evaluating the evidence. Dermatol Surg. 2014;40(8):817-824. doi:10.1111/dsu.0000000000000049
23. Gold MH, McGuire M, Mustoe TA, Pusic A, Sachdev M, Waibel J, et al. Updated international clinical recommendations on scar management: part 2--algorithms for scar prevention and treatment. Dermatol Surg. 2014;40(8):825-831. doi:10.1111/dsu.0000000000000050
24. Ogawa R, Akita S, Akaishi S, Aramaki-Hattori N, Dohi T, Hayashi T, et al. Diagnosis and treatment of keloids and hypertrophic scars-Japan Scar Workshop Consensus Document 2018. Burns Trauma. 2019;7:39. doi:10.1186/s41038-019-0175-y
25. Juckett G, Hartman-Adams H. Management of keloids and hypertrophic scars. Am Fam Physician. 2009;80(3):253-260.
26. Lv K, Xia Z. Chinese expert consensus on clinical prevention and treatment of scar. Burns Trauma. 2018;6:27. doi:10.1186/s41038-018-0129-9