REVIEW ARTICLE

Hypertrophic Scars and Keloids: Advances in Treatment and Review of Established Therapies

Fabio Stefano Frech[1] · Loren Hernandez[1] · Rebecca Urbonas[2] · Ghufran Abo Zaken[1] · Isabella Dreyfuss[3] · Keyvan Nouri[1]

Abstract

Hypertrophic scars and keloids can have significant detrimental effects on patients both psychosocially and functionally. A careful identification of patient risk factors and a comprehensive management plan are necessary to optimize outcomes. Patients with a history of dystrophic scarring should avoid unnecessary procedures and enhance the wound-healing process using various preventive strategies. As there is no single, fully efficacious treatment modality, prevention remains the best approach in reducing aberrant scar formation. When prevention therapies fail, keloids have been shown to be respond to a variety of therapies including topical and injectable corticosteroids, 5-fluorouracil, radiotherapy, lasers, and surgical excision, all with varying efficacies. As such, management should be tailored to the individual patient's risk factors with the use of combination therapies to reduce recurrence rates. Still, keloid and hypertrophic scar therapies are widely diverse with novel treatment modalities providing alternatives for recurring lesions. Laser-assisted drug delivery, skin priming, and novel topical therapies may provide alternative options for the management of hypertrophic scars and keloids.

Key Points

Identification of the risk factors for the development of hypertrophic scars and keloids is essential to implement the most appropriate preventive and therapeutic strategies.

Optimization of wound healing and prevention remain the most effective methods to avoid aberrant scar formation.

Established treatment modalities generally combine the use of excision, laser, or injectables with topical products to optimize wound healing and decrease the recurrence of keloid formation.

Fabio Stefano Frech, Loren Hernandez and Rebecca Urbonas contributed equally to the article.

✉ Fabio Stefano Frech
  fsf2@miami.edu

1 Dr. Phillip Frost Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, 1150 Northwest 14th Street, Miami, FL 33136, USA

2 Charles E. Schmidt College of Medicine, Florida Atlantic University, Boca Raton, FL, USA

3 Nova Southeastern University, Dr. Kiran C. Patel College of Osteopathic Medicine, Fort Lauderdale, FL, USA

1 Introduction

Pathologic scars, classified as either hypertrophic or keloid, can have significant impacts on patient quality of life through both cosmetic and functional impairments. Surgery, trauma, burns, or inflammatory wounds are typical causes of deep cutaneous injury that can result in the formation of pathologic scars. The molecular mechanism of pathologic scar formation is still not well established but involves dysregulation of myofibroblasts and formation of a thick, highly vascularized dermis marked by an abundance of immature collagen [1, 2].

Despite the wide array of available treatment options, treatment of hypertrophic scars and keloids continues to challenge physicians as no single treatment is currently recommended for all lesions and no therapy is fully efficacious [3]. Treatment therefore often involves a combination of multiple treatment modalities with consideration needed for many features, including patient risk factors, scar properties, and anatomical location.

The goal of care is to provide patients optimal function and appearance, with a decreased risk of recurrence. In this review, we provide a comprehensive overview of the established treatments for hypertrophic scars and keloids as well as recent developments in therapeutic options, including new laser technologies, intralesional therapies, and novel prophylactic methods such as priming the skin prior to surgery.

1.1 Literature Search

A broad literature review was performed in the PubMed and Web of Science databases without a language and publishing time restriction in the areas of keloid and hypertrophic scar management. Two reviewers (FSF and RU) determined the eligibility of the studies and performed a quality assessment based on individual study content. Both reviewers agreed with the study quality and content before inclusion within this article. The following inclusion criteria were applied: (1) studies must be available in English and (2) studies must discuss keloid or hypertrophic scar management. We included retrospective studies, systematic reviews, meta-analyses, randomized controlled trials, quality-improvement studies, and guideline reviews.

2 Understanding Hypertrophic Scars and Keloids

2.1 Scar Formation

The classic model of wound healing is defined by three inter-related phases: inflammatory, proliferative, and remodeling. The initial inflammatory phase begins immediately following tissue injury and typically lasts 2–3 days with the formation of platelet plugs and the fibrin matrix to prevent further blood loss [4]. The immune system is also activated in this initial phase along with the inflammatory response to start the removal of dead tissue.

The proliferative phase begins with angiogenesis, the creation of new blood vessels and capillaries, to deliver oxygen and nutrients essential for the proliferation of fibroblasts and other cells [4]. Activated fibroblasts and macrophages aid in the replacement of the fibrin matrix with granulation tissue, the key marker of this phase. Proliferation may last up to 6 weeks and later involves the differentiation of fibroblasts into myofibroblasts that produce the extracellular matrix [5], mainly collagen, that will form the eventual scar [6].

The final phase, remodeling, is responsible for scar formation and is essential to understanding the formation of hypertrophic and keloid scars and their treatments. Remodeling involves interactions of proteolytic enzymes, mainly matrix metalloproteinases and their inhibitors. This phase typically lasts more than a year [6]. The goal is to degrade excess extracellular matrix and convert immature collagen type III to mature collagen type I. An imbalance between collagen production and degradation, specifically excess inflammatory mediators leading to enhanced fibroblast proliferation and differentiation into myofibroblasts, is proposed as the mechanism for pathologic scar formation [7].

Further studies are still needed to fully elucidate the molecular mechanisms of pathologic scars and represent a limitation to current treatment methods. Proteins such as decorin, a proteoglycan found in dermal connective tissue that neutralizes the stimulatory effects of transforming growth factor-β (TGF-β) on collagen and fibronectin synthesis, have been found to be decreased in keloids and hypertrophic scars and may be of therapeutic significance [8–10]. Excessive angiogenesis is another component of the pathophysiology of these scar types that furthers inflammation and is targeted in many available treatment options [11].

2.2 Diagnosis of Hypertrophic Scars and Keloids

There are several established differences between hypertrophic scars and keloids. Keloids are characterized by horizontal growth extending beyond the lateral boundaries of the initial wound and may grow for many years and spread aggressively, with a higher chance of recurrence [11, 12]. Meanwhile, hypertrophic scars tend to regress within 1 year and remain confined to the initial wound margins [1]. Keloids may appear years after the initial trauma or even spontaneously [13], whereas hypertrophic scars typically present within 4–8 weeks of wounding [14]. Histological differences have also been established. Mainly, the presence of thick, disorganized, hyalinized type I and III collagen bundles in keloids versus fine, well-organized, wavy type III collagen bundles accompanied by myofibroblast nodules in hypertrophic scars [14].

Despite the established differences, it can be difficult to distinguish between hypertrophic scars and keloids both clinically and histologically as many scars can bear overlapping features [11]. This has sparked continued debate over whether these are in fact separate entities [11, 15].

2.3 Risk Factors

Certain factors have been identified that may lead to a higher likelihood of developing pathologic scarring. Areas of cutaneous tension such as the anterior chest, shoulder, and across joints are considered high risk for the development of both hypertrophic scars and keloids. A study on the distribution of 1500 keloids in Japanese patients found 48.9% and 26.9% located on the anterior chest and scapular regions, respectively [16]. Meanwhile, none was reported on the scalp or anterior lower leg, which are areas of low stretching tension [16]. Stretching is believed to increase the likelihood of pathologic scar formation via worsening inflammation and prolonging wound healing [17]. As such, patients undergoing surgery on these areas should be monitored for 3–12 months [11]. Other anatomical locations with a higher propensity for keloid formation include the ear lobes and pelvic area. Patient-specific risk factors include age

and genetics. Ages 11–30 years are at a higher risk for the formation of pathologic scars owing to the greater inflammatory response in the skin of younger adults compared with their older counterparts [3]. The increase of hormones associated with puberty is another potential influence for the increased risk of keloids in younger individuals, which will begin to wane in the 30s and 40s [18]. Pregnant women are also shown to be at an increased risk because of the similar hormonal influence of pregnancy estrogens [19, 20]. Genetics has been established as a risk factor for keloids only, with predisposition inherited in an autosomal dominant transmission and an estimation of 5–10% being familial cases [3]. It is recommended when considering keloid treatment to first assess scar number and size, as multiple or larger scars should lead to consideration of genetic and systemic factors [11]. Darker phototypes can be considered a risk factor for the formation of hypertrophic scars, and individuals of African and Asian ancestry are known to be particularly susceptible to keloid scarring, with genetic studies having identified chromosome variants associated with keloid formation in these populations [3, 21–24]. A three to seven times increase in keloid incidence has been seen in black patients versus white patients post-surgery [25, 26]. More recently, atopic dermatitis (AD) has been indicated as an independent risk factor for keloid development, along with a rising debate over dupilumab as an emerging therapy [27–29].

2.4 Epidemiology

The prevalence of hypertrophic scars is much higher than that of keloids, with estimated rates that range from 40 to 70% post-surgery and up to 91% following burn injuries [14]. Incidence rates of keloids vary across limited studies, with the highest incidence reported for patients of African descent (16% reported in Zaire) and the lowest rates seen in white individuals (0.09% in England) [30–32]. Both hypertrophic scars and keloids are more common in the second and third decades of life, hypothesized not only due to a higher risk from a stronger inflammatory response but also due to the role of cutaneous tension in younger patients [31, 33]. Equal sex distribution has been reported for hypertrophic scars but may warrant further analysis as female sex is generally considered a risk factor for hypertrophic scar formation [14, 34, 35]. Keloid prevalence is reported as slightly higher in young female individuals, possibly owing to higher rates of ear piercing as a confounding variable, but equal among both sexes in other age groups.[7].

3 Goals of Care

Hypertrophic scars and keloids can have dramatic effects on patient quality of life through pain, pruritus, and functional limitations such as contractures. Keloid scars are reported

to cause pain or pruritus in 20–40% of cases [33]. Additionally, patients are reported to experience psychological consequences owing to a perception of disfigurement [36]. The goal of care should be focused on improving both function and appearance, while minimizing recurrence rates. It is important to note that the first goal in the prevention of hypertrophic scars and keloids is proper wound care, given that it has been shown that wound healing and scar treatment should always be considered together [7, 37].

Challenges to physicians involve the lack of a "one-size-fits-all" approach and the multitude of available therapies that may be required in different combinations based on individual scar presentation and the complicated pathophysiologic mechanisms. Given the ethnic differences in scar propensity, specific healing characteristics of each patient should be accounted for through algorithms optimized to each race and achieved through international collaboration [11].

4 Non-Invasive Strategies

4.1 Preventive Measures

When addressing the sequelae of wound healing in patients, it is essential to determine the likelihood of hypertrophic scarring or keloid formation based on a patient's prior history, genetics, wound type, and anatomic location. Preventive measures are most effective when undertaken early in the wound-healing process by optimizing and encouraging epithelialization to occur as early as possible. Regardless of the wound type, repair must be prioritized, whether it be through primary closure, secondary intention healing, flaps, skin grafts, or other non-surgical methods, in order to prevent and limit greater inflammation and potential infection to ensue [38]. Additionally, after repair of the lesion is achieved, significant care must be taken in order to reduce mechanical forces on the wound type as dermal repair can take up to 3 months [39]. Excessive tensile strength that is placed on a wound has been associated with the induction of scar formation and aberrant healing through induction of myofibroblasts and fibroblasts resulting in impaired granulation tissue remodeling [40]. As such, several non-invasive preventive therapies have been developed that may decrease the chances of hypertrophic scarring or keloid formation.

4.1.1 Occlusive Dressings and Silicone Gel

Occlusive dressings have long been proposed and used as prophylactic therapy in the acute wound-healing period to prevent dystrophic scar formation. Some of the proposed mechanisms through which it promotes appropriate wound healing and prevention of abnormal scarring

include enhanced epidermal migration leading to faster healing times, increased angiogenesis, decreased infections rates, and enhanced leukocyte migration and connective tissue synthesis [41–43]. There are several types of occlusive dressings that are currently widely available for different wound types such as polymer films and foams, hydrogel dressings, hydrocolloid dressings, and alginates. Silicone dressings are currently first line and have been used in acute wound healing since 1983 to ameliorate and optimize this process [44, 45]. Some of the proposed mechanisms through which silicone dressings specifically achieve their anti-keloidal effects include the maintenance of hydration, which is lacking when no epidermal barrier exists, reduction in reactive epidermal hyperplasia, and decreasing interleukin (IL)-1 signaling [42, 46].

Silicone gels were developed after the rise of silicone dressings for the treatment of areas where fixation of silicone sheets was more difficult or undesirable, such as on the face, scalp, or joints. Similar to silicone dressings, many studies have proved the effectiveness of silicone gels in the treatment of hypertrophic scars and keloids [47–52]. More recently, there has been a rise in the number of silicone gel products available. A modified silicone gel combined with hypochlorous acid (Celacyn; Sonoma Pharmaceuticals, Woodstock, GA, USA) has been utilized post-procedure on recent scars and found to be effective, well tolerated, and safe [53, 54]. Hypochlorous acid is reported to act on all phases of wound healing as a potent antimicrobial, antipruritic, and anti-inflammatory agent [53]. Other formulations of silicone gels have incorporated herbal or onion extracts. A silicone gel formulation containing onion extract and aloe vera was found to be as effective as silicone gel sheeting in preventing postoperative pathologic scars [55]. Another study of 10% onion extract in a silicon derivative gel observed a significantly decreased incidence of hypertrophic scars following median sternotomy in pediatric patients [56]. Further large-scale studies are needed on the efficacy of silicone gel formulations as recent systematic reviews have identified the low quality of the current trials and their high susceptibility to bias [57, 58].

Tan et al. and Shi et al. summarize the different types of occlusion dressings with their specific characteristics and their appropriateness for various wound types [41, 59]. Interestingly, a randomized controlled trial showed that both silicone gel and non-silicone gel dressings are equally effective in treating hypertrophic scars and keloids, suggesting that the type of occlusive therapy may not significantly affect outcomes [60]. The choice of occlusive dressing for appropriate wound healing should be guided by the specific characteristics of the lesions in order to encourage the most optimal environment for that specific lesion.

4.1.2 Pressure Therapy

Pressure therapy has been widely used in combination with other more invasive treatment modalities in the acute wound-healing period since the 1960s [61]. Specifically, pressure garments have been used prophylactically in lesions showing delayed wound healing and those requiring grafts, as well as a therapeutic modality in certain hypertrophic scars [62–64]. There are many proposed mechanisms through which pressure therapy achieves the desired wound-healing outcomes including the stimulation of mechanoreceptors to induce apoptosis of extracellular matrix components, pressure-induced ischemia resulting in collagen degradation and alteration of fibroblast activity, and induction of metalloproteinase-9 and prostaglandin E2 release [65–68]. Nonetheless, the full mechanism is not completely understood. There are different types of pressure garments available for use in different locations. Some of these include elastic wraps, common wraps, elastane bandages, magnets, pressure ear molds, and earrings. Several studies suggest that pressure garments should be maintained at a pressure of 15–30 mm Hg and worn continuously (at least 23 h daily) until the scar is mature, which normally takes at least 6 months [69–72]. As such, patient compliance is highly variable because of the extensive amount of time needed for a clinically significant benefit. Additionally, this can be complicated by the location of lesions in areas of excessive movement such as joints and extremities. Although pressure garment therapy is widely used, its efficacy in preventing or treating hypertrophic scars and keloids has been questioned. A meta-analysis of six trials involving 316 patients with burns showed minor benefits in scar height only, with all studies included in the analysis deemed as high quality [73]. A recent meta-analysis of 12 randomized controlled trials involving 710 patients with hypertrophic scars due to burn injuries showed that there was improvement in thickness, brightness, pigmentation, and hardness with 15–25 mm Hg [74]. It was noted however that the analysis was limited in the inclusion of lower quality studies owing to a lack of specifications on blinding methods [74].

4.1.3 Onion Extracts

Onion extract has been commonly found in over-the-counter products for its potential in scar prevention and treatment. Flavonoids are the active compounds that are attributed to be responsible for the amelioration of excess scarring. It is hypothesized that these compounds act by the induction of matrix metalloproteinase-1 and a decrease in fibroblast proliferation [75, 76]. Nonetheless, the exact mechanism has yet to be fully elucidated. The effectiveness of onion extracts as prophylaxis and the treatment of dystrophic scarring have been reported in the literature [77, 78]; however, other studies question its

effectiveness in achieving a clinically significant effect when compared to other topical therapies [79, 80]. A recent systematic review and meta-analysis on 13 randomized controlled trials found that only five studies showed onion extract to be superior to no treatment, with the remaining studies suggesting mixed results in the benefit of onion extracts over other topical therapies [81]. As such, the current evidence in the ability of onion extracts in preventing or treating hypertrophic scars and keloids is inconclusive. Other therapies should be considered for their use in combination with onion extract to potentially optimize wound healing in the perioperative period.

4.1.4 Skin Priming

Early intervention in the wound-healing process has been posited as a possible means to prevent poor scarring outcomes. Specifically, the treatment of the skin prior to a surgical procedure can be "primed" with other topical or intralesional therapies to optimize wound healing and aberrant scar formation. An in vivo study involving the pre-treatment of diabetic mice having full-thickness incisional wounds with proangiogenic growth factors and endothelial progenitor cells showed reduced wound-healing time and improved tensile strengths compared with the control [82]. This suggests that pretreatment of tissue prior to surgery might significantly improve wound healing. Similarly, other studies have suggested that the use of prophylactic negative-pressure therapy may decrease surgical-site infection and optimize wound healing [83, 84]. Skin priming has also been reported to be successful with the use of fractional carbon dioxide (CO_2) lasers used immediately after scar revision surgeries [85]. Ozog showed in a randomized split-scar study that the intraoperative treatment of wound edges with a CO_2 laser improves the appearance and texture of scars [86].

Topical therapies such as epigallocatechin-3-gallate have been shown to be beneficial pre-operatively in optimizing future scarring. A double-blind, randomized, placebo-controlled study evaluating the pre-emptive use of epigallocatechin-3-gallate prior to surgery showed reduced mast cell components, blood flow, and increased elastin compared with the control [87]. Priming the skin prior to surgical intervention may provide a way to improve wound healing and avoid aberrant scarring, especially in high-risk patients. More studies are needed to fully elucidate the role of skin priming in wound healing and establish standardized guidelines.

4.2 Available Treatments

4.2.1 Corticosteroids and 5-Fluorouracil

Corticosteroids have been extensively utilized in the treatment of hypertrophic scars and keloids. Currently, they are considered first line in the treatment of keloid scars [88].

Although they are generally used as first-line treatment for the regression of these scars, they are also commonly used in conjunction with other more invasive modalities such as surgery and laser therapies. Their effectiveness has been attributed to their ability to inhibit fibroblast growth, through apoptosis and inhibition of TGF-β1 expression, as well as inhibition of angiogenesis through disruption of vascular-endothelial growth factor and alpha-globulin signaling [89–93]. Triamcinolone acetonide (TAC) remains the most commonly used injectable form at a concentration range of 2.5–40 mg/mL depending on the size and location of the lesion. Intralesional formulations have been associated with a response rate of 50–100% and recurrence rates of 9–50% [65, 94–96]. Additionally, intralesional TAC monotherapy has also been shown to be effective in reducing keloid recurrence rates [97, 98]. Nonetheless, injectable corticosteroids are often combined with other therapies such as intralesional 5-fluorouracil (5-FU), laser, and surgery owing to their improved efficacy compared with monotherapy [99]. In the Japanese guidelines for the treatment of hypertrophic scars and keloids, corticosteroid tapes and plasters are now considered first-line therapy with injectables used as adjuncts when lesions are unremitting [100]. Tapes and plasters have been associated with decreased coloration and flattening of the lesions [101]. Corticosteroid ointments and creams in combination with injections have also shown some efficacy in both treating and preventing keloid formation [38, 102]. If used, ointments and creams should be utilized as adjunctive treatments rather than monotherapy because of the lack of randomized controlled trials assessing their effectiveness.

5-Fluorouracil is an antineoplastic agent involved in the inhibition of thymidylate synthase [103]. In vitro studies have shown that 5-FU has the capacity to inhibit fibroblast proliferation and TFG-β expression [104]. 5-Fluorouracil emerged in the treatment of keloids and hypertrophic scars as a therapy to avoid the potential adverse effects of corticosteroid injections. Combination therapy of 5-FU and TAC has been shown to increase the effectiveness of keloid management while avoiding the side effects associated with corticosteroid therapy such as atrophy, hypopigmentation, and telangiectasia [105]. A randomized controlled trial assessing combination therapy in keloid treatment showed that the skin atrophy rate and telangiectasia formation were 44% and 50%, respectively, with TAC monotherapy compared with 8% and 21%, respectively, with combination therapy [106]. It was noted that there was no clinical or statistical difference in the remission rate after 6 months of follow-up [106]. 5-Fluorouracil alone or in combination with TAC has been shown to reduce the keloid recurrence rate. Interestingly, there is conflicting evidence with some studies finding no recurrence with the use of 5-FU for keloid treatment [107–109], while other studies report higher recurrence rates with longer follow-up times [104, 110].

4.2.2 Imiquimod

A toll-like receptor agonist, imiquimod, has been posited as a potential therapy for keloid treatment owing to its immune-modulating activities by the induction of tumor necrosis factor-α, interferon-α, and IL-1, IL-6, and IL-8 [111–113]. Notably, imiquimod is generally used as adjunct therapy with other treatment modalities in order to prevent keloid recurrence. In combination with surgical excision of keloids, imiquimod has been shown to have a recurrence rate of 24.7% [114]. While some studies suggest some improvement, others have shown no benefit in the postsurgical use of imiquimod for keloids [115, 116]. A recent meta-analysis of seven studies and 82 keloids showed that the recurrence rate after application of topical 5% imiquimod was 39%, with no alteration in the recurrence with surgical excision [117]. More clinical trials are needed to concretely ascertain the clinical efficacy of topical imiquimod.

4.2.3 Verapamil

Verapamil is a non-dihydropyridine calcium channel blocker that is currently approved by the US Food and Drug Administration for the management of hypertension, chronic stable and unstable angina, and supraventricular tachycardia [118]. Alterations in intracellular calcium can induce collagenase activity as well as inhibit signaling factors associated with keloid formation, such as vascular-endothelial growth factor, TGF-β1, and IL-6 [119]. A recent parallel-group study comparing intralesional verapamil, TAC, and, fractional CO_2 therapy for the treatment of keloids showed that verapamil was as effective as TAC [120]. However, another randomized controlled trial comparing TAC and verapamil found that 2.5 mg/mL of intralesional verapamil every 3 weeks showed no therapeutic benefit in treating keloids [95]. Similarly, another study showed that verapamil is not as effective as TAC for keloid management [96]. A meta-analysis of six studies and 331 patients showed that verapamil therapy was not associated with improvements in hypertrophic scars and keloids compared to other treatment modalities, suggesting that verapamil may serve as a potential alternative only when other intralesional therapies may not be available [121].

5 Invasive Therapies

5.1 Surgery

The goals of surgical excision are to reduce tensile forces affecting the area, debulk large lesions, and improve a limited range of motion as a result of aberrant scarring [7]. Surgical excision has proven to be inferior as a monotherapy because of recurrence rates that range from 45 to 100% [122]. As such, surgical excision should be carried out with other adjunct therapies including occlusive dressings, compression therapy, intralesional triamcinolone, radiotherapy, and lasers. Specific surgical techniques such as Z-plasties, W-plasties, and flaps may provide a benefit in decreasing the likelihood of keloid or hypertrophic scar recurrence in areas of high tension [94].

A case-series study of 141 patients with keloids who were treated with subcutaneous or fascial tensile reduction sutures and z-plasties in combination with postoperative radiotherapy over 3 consecutive days showed that only 10.6% of lesions recurred [123]. Similarly, a meta-analysis of surgical excision of auricular keloids in combination with 5–10 mg/mL of intralesional triamcinolone postoperatively has shown a recurrence of 15.4% after a 12-month follow-up [124]. Combination therapy with other topicals such as mitomycin-C (MMC) and imiquimod has also been reported to be successful with recurrence rates of 16.5% and 24.7%, respectively [114]. Thus, surgical excision should generally be reserved when lesions are not amenable to other less invasive modalities and combination therapy should be pursued in order to minimize the risk of recurrence.

5.2 Lasers

Argon and CO_2 laser therapy for the treatment of hypertrophic scars and keloids was first proposed in the 1980s with little success [125]. Fractional ablative lasers, namely erbium-doped yttrium aluminum garnet and CO_2 lasers, have since been evaluated for the treatment of hypertrophic scars and keloids. These lasers exert their effects by targeting water molecules within the cutaneous tissue and promoting destruction of the local environment [126]. Fractional CO_2 lasers are found to replace irregular collagen bands with new organized collagen fibrils in the upper dermis [127, 128]. Significantly decreased TGF-β1expression is also seen following CO_2 laser therapy [127]. Clinically, fractional CO_2 lasers have demonstrated improved scar appearance, thickness, pliability, and surface relief [129–132]. Pulsed dye laser (PDL) emits light selectively absorbed by oxyhemoglobin, resulting in selective photothermolysis of vascular tissue with intact surrounding tissue [133]. Pulsed dye laser is thus used as a first-line therapy for many cutaneous vascular disorders; however, recent reports have demonstrated its effectiveness in conditions of other etiologies. The 585-nm and 595-nm PDLs are found to be a safe and effective option for the treatment of hypertrophic scars and keloids [134–136]. One comparison study between the two wavelengths found that 585 nm was preferred, having a demonstrated ability to reduce height substantially in a significant number of scars [136]. In addition to PDL, other vascular lasers such as neodymium-doped yttrium garnet lasers

have been proposed for the treatment of pathologic scars and shown to effectively reduce the Vancouver Scar Scale (VSS) score, with a notably greater effect on hypertrophic scars compared with keloids [137, 138]. Another recent study investigating the use of a 1470-nm bare-fiber diode laser found an overall VSS score improvement of 42% for hypertrophic scars and 37.9% for keloids, with no reported adverse events or recurrence [139]. Non-ablative fractional lasers are currently being studied as monotherapy and in combination with topical therapies for hypertrophic scars; however, large clinical trials to characterize its efficacy are still lacking [140–143].

International and national consensus statements have recommended the use of fractional ablative lasers as first-line therapy especially in thicker and hypopigmented hypertrophic scars, as well as in combination with other therapies such as topical agents or intralesional therapy [144, 145]. Nonetheless, the laser choice should be guided with specifics on the lesion encountered, given that certain characteristics or the type of scarring may respond better with other lasers. For instance, erythematous hypertrophic scars may respond better with PDL therapy initially with the possibility of using it in combination with ablative lasers in thicker scars [144].

5.2.1 Combination Laser Therapy

Recent evolutions in laser treatments point to more favorable outcomes and higher patient satisfaction for combination laser therapy over monotherapy for pathologic scars (Table 1). Improved efficacy of CO_2 lasers in treating keloids has been shown in combination with other local therapies such as IFN-α, 5-FU, verapamil, topical corticosteroids, and even in combination with PDL [146–150]. In vivo studies on hypertrophic scars in rabbit models found that a combination of PDL and CO_2 lasers significantly improved thickness, size, and hardness as well as suppressed the levels of TGF-β1 and the proliferating cell nuclear antigen on a histologic analysis when compared with their respective laser monotherapy [151]. One study comparing outcomes on 25 patients randomized to four treatment groups (PDL alone, CO_2 laser alone, a combined treatment of these two, and another combination with CO_2 ablative fractional resurfacing on the day of surgery) found that the best outcomes in scar appearance were seen for scars that underwent a combination treatment [150]. A retrospective study involving 35 Korean patients with keloids treated with a non-ablative fractional erbium-glass laser followed by an ablative fractional CO_2 laser, superficial cryotherapy, and an intralesional triamcinolone injection showed significant improvements in both total and subcategory VSS scores [152]. No patient experienced significant adverse effects, and most reported improvements to pain, itch, and range of motion [152].

Combinations of laser therapy and an intralesional steroid injection have also been studied for hypertrophic scar and keloid management [141, 153, 154]. A study of 38 patients with pathologic scars found that overall there were fewer treatment sessions, higher patient satisfaction, and longer remission periods for combination therapy of a non-ablative fractional laser and an intralesional triamcinolone injection versus the steroid injection alone [141]. Better results have also been reported for the ablative CO_2 laser when given in addition to intralesional triamcinolone acetonide 40 mg/mL [153, 155]. It should be noted that the efficacy of laser treatments is not widely studied in skin of color because of the increased risk of adverse events from laser therapy, such as hyperpigmentation, in higher Fitzpatrick skin types [156].

5.2.2 Laser-Assisted Drug Delivery

Laser-assisted drug delivery (LADD) was proposed in 2002 for improving the delivery of topical anesthetics [157]. Generally, LADD is achieved through the use of fractional ablative lasers owing to their ability to create cylindrical micro-ablation zones that may facilitate drug absorption deeper into the affected tissue, thus improving the bioavailability of the drug [158]. Therefore, the use of LADD for the treatment of hypertrophic scarring has been evaluated in multiple studies. Waibel et al. [159] conducted a prospective case series of 15 patients with hypertrophic scars treated with CO_2 laser and immediate application of topical TAC showing significant improvements in texture, hypertrophy, and dyschromia. Similarly, a retrospective study of 23 patients with 70 keloids treated with ablative fraction lasers and topical betamethasone showed a median improvement of 50%, with recurrence in 22% of the lesions [147]. Recently, a split-face study of intralesional corticosteroids versus 2940 nm erbium-doped yttrium aluminum garnet laser therapy in conjunction with a topical corticosteroid application for the treatment of keloids showed improved VSS scores in both therapies [160]. Neither therapy was deemed to be superior in keloid management; however, patients reported significantly less pain with the laser and topical corticosteroid combination [160]. Other studies have shown improved efficacy of fractional ablative therapies in a combination of topical botulinum toxin, 5-FU, and verapamil [148, 161–163]. Although LADD is a promising emerging technology for the treatment of hypertrophic scars and keloids, more studies and consensus are needed for delineating parameters for laser settings and specific drug preparations to standardize its use in wound healing. Larger randomized controlled trials are also necessary to fully characterize its efficacy because of the large heterogeneity of current studies [145, 164]. Laser-assisted drug delivery remains an investigational therapy that shows significant promise in the treatment of hypertrophic scars and keloids.

Table 1 Current evidence for combination laser therapies

Combination therapy tested	Study design	Lesions studied	Results	Adverse events	References
CO_2 laser + IFN-α	Evaluated ultrapulse CO_2 laser (8W) combined with intralesional injections of 3 million IU of IFN-α-2b 3× per week	30 patients with keloids (16 ear; 14 trunk)	66% (20 of 30) lesions did not recur after 3 years of follow-up	Not reported	Conejo-Mir et al. [146]
CO_2 laser + 5-FU CO_2 laser + verapamil	Compared CO_2 laser followed by either topical 5-FU or topical verapamil chloride for 4 treatments each at 1-month intervals	30 patients with hypertrophic scars and keloids	Significant reduction in VSS score observed in all groups at 1 month follow-up	No significant side effects observed for either treatment	Hanan et al. [161]
CO_2 laser + triamcinolone	Compared CO_2 laser monotherapy to combination therapy with intralesional triamcinolone 40 mg/mL for patients with poor response to monotherapy	14 patients total with keloid scars; 4 later belonging to combination group	Improved response to combination therapy observed in 4 patients with poor response to monotherapy	Transient hypochromia in 1 patient. No side effects observed for all others	Verma et al. [153]
	Evaluated ultra-pulse fractional CO_2 laser [155] combined with intralesional triamcinolone 40 mg/mL over 8 sessions at 4 week intervals	41 patients with refractory keloids	All Patient and Observer Scar Assessment Scale (POSAS) components improved significantly for 38 patients with follow-up of 24 months. 10.5% (4/38) recurrence observed after 24 months	Hyperpigmentation reported in 4 patients	Wang et al. [155]
	Compared CO_2 laser monotherapy to combination therapy with either triamcinolone or trichloroacetic acid over 4 sessions at 4-week intervals	45 patients with keloid scars	Highly significant reduction in VSS for all 3 groups ($p \leq 0.001$) and a highly significant reduction in scar height for CO_2 laser + triamcinolone combination group ($p \leq 0.001$)	25 patients experienced side effects, most commonly pain, itching, ulceration, hypopigmentation, and hyperpigmentation	El-Azhary et al. [227]

Table 1 (continued)

Combination therapy tested	Study design	Lesions studied	Results	Adverse events	References
CO_2 laser + PDL	Compared CO_2 laser and PDL as separate monotherapies to a control group and to a combination group of fractional CO_2 laser and 595-nm PDL	24 rabbit models with hypertrophic surgical scars	Scar Elevation Index [46], fiber density (NA), and collagen fiber content most decreased in the combination group. Combination group also showed greatest suppression of TGF-β1 and PCNA expressions	Not reported	Zhang et al. [151]
	Compared fractional CO_2 laser combined with 595-nm PDL (treatment group) to 595-nm PDL monotherapy (control group)	56 patients with keloids divided into 2 groups (28 in each group)	VSS scores compared after 2 laser treatments showed statistically significant improvements for both; however, total score was decreased more in the control group	No severe adverse events observed for all groups	Ouyang et al. [149]
	Compared CO_2 and PDL as separate monotherapies to combined CO_2 and PDL therapy	25 patients with pathological surgical scars (mostly on the face)	At 1- to 3-month follow-ups, the best improvements in VSS and Global Evaluation Response scales were seen for combination treatment	No adverse events observed for all groups	Cohen and Geronemus [150]
CO_2 laser + erbium glass laser + cryotherapy + triamcinolone	Evaluated 1550-nm non-ablative fractional erbium-glass laser, followed by 10,600 nm ablative fractional CO_2 laser, superficial cryotherapy, and intralesional triamcinolone	35 patients with keloids	Significant improvements to both total and subcategory VSS scores, with best response seen for height and pliability scores. 5% (1/20) recurrence observed for 20 patients after a follow-up of 1 year	No significant adverse effects observed	Lee et al. [152]
Non-ablative fractional erbium laser + intralesional triamcinolone	Compared triamcinolone injection alone (control group) to triamcinolone injection combined with 1550-nm erbium-glass fractional laser (treatment group)	38 patients with hypertrophic scars or keloids (21 in control group, 17 in treatment group)	Fewer treatment sessions, higher patient satisfaction, and longer remission for combination therapy Recurrence rate 35.3% for treatment group versus 38.1% for the control	Not reported	Shin et al. [141]
Ablative fractional erbium laser + topical betamethasone	Evaluated 2940-nm ablative fractional erbium laser combined with topical betamethasone cream 2× a day under occlusion with transparent film dressings	23 patients with 70 keloids	22% (8 of 70) lesions did not recur after a mean follow-up of 8 months	Most commonly transient hypochromia in darker skin types (5/70)	Cavalié et al. [147]

CO_2 carbon dioxide, FU fluorouracil, IFN-α interferon alpha, IU international units, $PCNA$ proliferating cell nuclear antigen, PDL pulsed dye laser, TGF-β transforming growth factor beta, VSS Vancouver Scar Scale

5.3 Radiation Therapy

Radiation therapy has been widely used as an adjunctive therapy to prevent the regrowth of keloids after excision. Monotherapy is relatively limited because of higher reported recurrence rates (37%) when compared with the use after surgical excision of keloids (22%), with some studies reporting recurrence rates as low as 9.59% [165–167]. Proposed mechanisms through which radiotherapy decreases keloid formation include the inhibition of angiogenesis and the reduction in fibroblast activity [168]. Currently, three primary modalities of radiation are used as an adjunctive therapy in the treatment of pathologic scars: electron beam therapy, brachytherapy, and X-ray therapy [169]. The optimal biological effective dose (BED) that maximizes the prevention of keloid recurrence while minimizing adverse reactions is 20–30 Gy [170]. A BED of 30 Gy can be achieved by delivering four fractions of 5 Gy, three fractions of 6 Gy, two fractions of 8 Gy, one fraction of 13 Gy, or one dose of 27 Gy at a low dose rate [171].

Electron beam therapy uses a linear accelerator to deliver high-energy electrons to surface structures while minimizing the dose to underlying tissue. Advantages of this modality include the treatment of large surface areas and homogeneous dose delivery to surface structures [169]. In a study of 45 patients with chest keloids who underwent an excision followed by fractionated electron-beam radiation therapy, wounds were almost completely flattened after 12 months, with only one relapse (2.2%) within 2 years of follow-up [172]. Challenges associated with electron beam therapy include the complicated dosimetry, high cost, and inability to treat curved surfaces [169].

Brachytherapy delivers gamma rays to target tissues using radioactive sources and catheters. Brachytherapy is classified as either interstitial or surface, depending on whether the radioactive source is placed within or on top of the wound [173]. Advantages to brachytherapy include the ability to target uneven surfaces and potentially spare more surrounding tissue. In the treatment of keloids, brachytherapy has been reported to have lower recurrence rates (15%) after surgical excision when compared with electron beam and X-ray therapy (23%) [165]. However, this modality requires high-dose rates in order to deliver the appropriate dose in short time frames [169]. A retrospective multicenter comparison of the recurrence and complications of brachytherapy for the treatment of 238 keloids at different fractionation schemes concluded that a BED of 20 Gy was effective and safe in preventing the recurrence of keloids [174]. The fractionation schemes of 2 × 9 Gy and 3 × 6 Gy were associated with more adverse reactions without being more effective in preventing keloid recurrence than a 2 × 6 Gy fractionation scheme [174].

Superficial radiation therapy (SRT) [175] delivers low-energy X-rays, generally in the 50–150 kV range, and has long been used for the treatment of superficial lesions including keloid scars [176, 177]. Past studies on its efficacy were limited, but many recent trials have led to growing evidence for the role of SRT as a practical and efficient treatment for hypertrophic and keloid scars [178–180]. One retrospective study of 96 keloid scars treated with SRT with a BED of 30 Gy found a recurrence rate of 12.7% at 18 months [181]. Another prospective study of 48 keloids treated with 18 Gy of SRT for 3 consecutive days post-resection found 81% successful remission over 12 months [180]. Prior to these studies, a consensus in 2019 had determined that SRT following keloid excision significantly reduces keloid recurrence rates with no evidence that exposing surrounding healthy skin will cause skin cancer [182]. Many studies report no adverse reactions; however, transient hyperpigmentation was reported by some as the most frequent adverse effect, the incidence and severity of which can be predicted by the location and incision length of the scar [181, 183]. Some guidelines recommend the optimal BED for SRT is 30 Gy delivered over 3 fractions with a total dose fraction of 6 Gy given on the first 3 days after surgical excision [182].

Although radiotherapy is a viable option for the treatment of keloids after surgery, there have been reports of radiation-induced carcinogenesis [184]. However, this risk is considered to be low, if any, when appropriate protective measures are taken. Radiotherapy after surgical excision is an appropriate and effective option to prevent the recurrence of keloids and hypertrophic scars.

5.4 Cryotherapy

Cryotherapy was first introduced in the early 1990s as a potential safe therapeutic modality for hypertrophic scars and keloids [185, 186]. There are various methods of delivery that can be used including spray, contact probes, and an intralesional cryoprobe. Generally, cryotherapy is carried out under local anesthesia, wherein a cryoprobe connected to a canister containing nitrogen is inserted into the core of the keloid allowing freezing to occur from the center outwards up to a 5- to 10-mm margin of normal skin. [187] Success in the treatment of keloids with cryotherapy has been highly variable with some studies suggesting full remission of the lesions, while the efficacy reported in others ranges from 32% to 74%. [186, 188] A meta-analysis of eight studies found that intralesional cryotherapy was able to decrease scar volume with a range of 51–61%, with a recurrence range of 0–24%. [189] Intralesional cryotherapy may be useful in patients with darker skin, as it can minimize the destruction of melanocytes within the epithelium. [190] Although cryotherapy may be efficacious in treating keloids, several adverse reactions have been reported

including blistering, pain, infection, hypopigmentation, and depigmentation. [187]

6 Emerging Therapies (Table 2)

6.1 Mitomycin-C

Mitomycin-C is an antibiotic derived from *Streptomyces caespitosus* that has been used as a chemotherapeutic agent and for ophthalmologic purposes [191, 192]. In vitro studies have shown that MMC is able to decrease the fibroblast concentration in keloids [193]. Earlier studies suggested that topical MMC after surgical excision of therapies showed no significant therapeutic benefit in prevention [194]. However, a recent study comparing topical and intralesional MMC showed that both preparations were able to significantly improve auricular keloids in 40 patients. [195] Similarly, other studies have shown success with topical and intralesional MMC in preventing keloid recurrence after surgical removal [196, 197]. Mitomycin-C may serve as an alternative preventive therapy for keloid recurrence; however, larger randomized clinical trials are needed to appropriately characterize its efficacy.

6.2 Botulinum Toxin

Botulinum toxin type-A (BoNT-A) has been used since the 1980s for cosmetic purposes. It is a neurotoxin derived from *Clostridium botulinum* bacteria that acts on the neuromuscular plate to cause muscular paralysis lasting up to 6 months [198]. Botulinum toxin type-A was first introduced for keloid treatment in the 2000s. By inhibiting the release of Ach, BoNT-A is thought to paralyze both muscle tissue and scar fibroblasts, reducing muscle tension and elastic fiber contracture at the site of the wound to prevent further hyperplasia of the scar [199]. The full extent of the mechanism of BoNT-A in keloids is still being studied, and has recently been suggested to involve the promotion of keloid myofibroblasts into adipocytes, leading to activation of the BMP4/Smad signaling pathway [200].

In recent years, a large number of relevant studies have examined the safety and efficacy of intralesional BoNT-A in the treatment of pathologic scars. A study of 50 patients with keloids treated with either intralesional BoNT-A or 5-FU demonstrated a significantly better therapeutic response to BoNT-A with regard to flattening of lesions [201]. The same study also found BoNT-A was significantly better at treating larger lesions, and was associated with fewer side effects than 5-FU, including less pain, pruritus, hyperpigmentation, and recurrence [201]. A systematic review and meta-analysis of 18 randomized controlled trials saw similar results, with better improvement in terms of scar width, VSS score, Visual Analogue Scale [202] score, and patient satisfaction with BoNT-A compared with the control group for 915 patients [199].

Botulinum toxin type-A has also been studied for its use in combination with intralesional corticosteroids for the treatment of keloids and hypertrophic scars. Multiple studies have suggested improved efficacy of corticosteroids combined with BoNT-A compared with corticosteroids alone [203, 204]. One meta-analysis found that corticosteroid and BoNT-A combination therapy provided faster, more effective results in terms of VSS score, VAS score, scar thickness itching, and patient satisfaction than corticosteroids alone [203]. This study also noted that combination therapy was associated with fewer adverse reactions than corticosteroid monotherapy [203]. Another meta-analysis comparing the effects of four drugs used in the treatment of pathologic scars found the greatest efficacy with BoNT-A combined with corticosteroids, followed by 5-FU combined with corticosteroids, then by BoNT-A alone [204]. A systematic review and meta-analysis of studies comparing BoNT-A with intralesional TAC for the treatment of keloids and hypertrophic scars found BoNT-A to be more effective than both TAC and placebo, and associated with decreased pain after an injection [205]. Botulinum toxin type-A has also been evaluated in combination with surgical excision of keloids and intralesional 5-FU [206]. One study on 80 patients with keloids found that combination therapy resulted in a recurrence rate of 3.75% in follow-ups that ranged from 17 to 24 months [206]. Botulinum toxin type-A has shown promise in the treatment of hypertrophic scars and keloids; however, further large-scale controlled studies are needed to determine its efficacy in monotherapy and combination therapy, as well as the most appropriate injection method, dose, spacing, and timing [199]

6.3 Hyaluronic Acid and Hyaluronidase

Hyaluronic acid is a high-molecular-weight mucopolysaccharide that is usually found in high quantities in the extracellular matrix of connective tissues and synovial fluids [207]. Hyaluronic acid is generally used in dermatology for correction and improvement in injectable filler volume and contour. Case reports have shown that hyaluronic acid injections may be useful in the treatment of keloids in combination with corticosteroids [208]. The mechanism through which this occurs is not clear. An ex vivo histological analysis of keloid samples showed that keloidal tissue contained more hyaluronic acid compared with normal dermal tissue. Additionally, ex vivo treatment of keloid fibroblasts with TAC reduced hyaluronic acid synthesis [209]. This suggests

Table 2 Summary of emerging therapies for hypertrophic scars and keloids

Therapy	Study	Treatment	Outcome	References
Mitomycin-C (MMC)	In vitro study	Keloid fibroblasts from 5 patients exposed to MMC	Decreased fibroblast concentration in keloids during 3 weeks after exposure	Simman et al. [193]
	Prospective randomized study	40 patients with auricular keloids treated with either topical or intralesional MMC	Both preparations resulted in significant improvement; better VSS scores and patient satisfaction with topical application	Mandour et al. [195]
Botulinum toxin type-A (BoNT-A)	Randomized controlled trial	50 keloid patients treated with either intralesional BoNT-A or 5-FU or both	Significantly better response to BoNT-A with regard to flattening of lesions and for larger lesions	Ismail et al. [201]
	Systematic review and meta-analysis	18 randomized controlled trials comprising 915 patients evaluated for the efficacy and safety of BoNT-A in the prevention and treatment of postoperative scars	BoNT-A demonstrated better improvement in terms of scar width, VSS score, Visual Analogue Scale [202] score, and patient satisfaction compared with the control	Yang and Li [199]
	Meta-analysis	BoNT-A and corticosteroid combination therapy was compared to corticosteroid monotherapy for at least 3 months	BoNT-A combination therapy provided faster, more effective results in terms of VSS, VAS, scar thickness itching, and patient satisfaction compared with corticosteroid monotherapy	Liu and Zhang [203]
	Meta-analysis	23 studies comprising 1513 patients evaluated to compare the effects of BoNT-A, corticosteroids, verapamil, and 5-FU	Greatest efficacy seen with BoNT-A combined with corticosteroids, followed by 5-FU combined with corticosteroids, then by BoNT-A monotherapy	Sun et al. [204]
	Systematic review and meta-analysis	15 clinical trials comprising 639 patients evaluated to compare the effects of BoNT-A and intralesional TAC versus placebo	BoNT-A was more effective than both TAC and placebo, and associated with decreased pain after injection	Bi et al. [205]
Hyaluronidase	Case report	33-year-old man with a 20-year-old ear keloid treated with HA and cortisone combination therapy	Complete resolution of the keloid with no recurrence at 12-month follow-up	Di Stadio [208]
	In vitro studies	Hyaluronan synthase, and hyaluronidase mRNA and protein levels were investigated in keloid tissue compared to normal skin	Both hyaluronan synthase and hyaluronidase mRNA levels were found to be significantly reduced in keloidal tissue ($p < 0.05$)	Sidgwick et al. [210]
	Randomized controlled trial	100 patients with keloids were divided equally into 5 treatment groups: intralesional TAC, intralesional TAC + hyaluronidase, intralesional verapamil hydrochloride, intralesional radiofrequency, and intralesional radiofrequency + TAC	Combination therapy of TAC with hyaluronidase showed 68.75% effectiveness in treating keloids with better tolerability than other regimens	Aggarwal et al. [211]
Picosecond lasers [228]	In vivo study	16 patients with 20 surgical scars treated with 3 sessions of PSL	3D imaging revealed significant improvement in texture, pigment, and vascularization of the scars	Guida et al. [175]
	Retrospective chart review	24 patients with treated with a 1064-nm picosecond Nd:YAG laser for hypertrophic scars were identified and a photographic analysis conducted	Average VSS score decreased significantly from 5.33 to 2.71 Improved cosmetic outcomes and patient satisfaction. Confocal microscopy analysis showed significant reduction in the thickness of the scars	Choi et al. (2018) [213]

Table 2 (continued)

Therapy	Study	Treatment	Outcome	References
Dupilumab	Case report	53-year-old African American man with severe AD given 300-mg subcutaneous dupilumab injections every 2 weeks	Shrinkage of a large keloid and complete disappearance of a smaller keloid after 7 months of treatment	Diaz et al. [28]
	Case report	37-year-old South Asian woman given initial 600-mg subcutaneous injection of dupilumab, followed by 300 mg every 2 weeks	No physical reduction in keloid size, but patient reported markedly improved symptoms after 3 months of treatment that allowed for better tolerance of intralesional steroid injections	Wong and Song [215]
	Case report	80-year-old woman with a symptomatic hypertrophic scar on her chest treated with dupilumab 300 mg every 14 days after an initial 600-mg loading dose	Itch from the hypertrophic scar improved within 3 months and the size was reduced after 10 months	Peterson et al. [216]
	Case reports	Two 17-year-old patients with diffuse keloids treated with intramuscular dupilumab 300 mg every 2 weeks for 12 weeks	No improvement after 3 months, with one patient experiencing an increase in both size of existing lesions and number of new keloids	Luk et al. [217]
	Case reports	Reports on eight patients treated with dupilumab, 300 mg, subcutaneously every 2 weeks for 2 months to 1 year	Disease progression reported as the most common response, with only one patient willing to continue the treatment	Tirgan and Uitto [29]
Pentoxifylline	In vitro study	Keloid fibroblasts were cultured in the presence and absence of pentoxifylline (100–1000 µg/mL)	Exposure to pentoxifylline resulted in non-lethal dose-dependent reductions in keloid fibroblasts with reduced amounts of collagen up to 95%	Berman et al. [219]
	Retrospective pilot study	Identified recurrence rates in patients who underwent keloid excision treated with postoperative oral pentoxifylline	Statistically significant decrease in keloid recurrence rates for groups treated with pentoxifylline	Tan et al. [218]
	Randomized controlled trial	30 patients with keloids divided equally into three treatment groups: intralesional pentoxifylline, intralesional TAC, or their combination. Injections repeated every 3 weeks until lesion flattening or for a maximum of 5 sessions	Efficacy of pentoxifylline alone was lower than that of TAC alone; however, more satisfactory results with less TAC-induced side effects were seen with combination therapy	Serag-Eldin [221]
Oral tranilast	Randomized controlled trial	40 patients with surgical chest scars received 5 mg/kg/day of tranilast for 3 months while 34 patients with the same scars did not receive tranilast	Hypertrophic scar incidence was similar for tranilast administered patients (28%) and those who did not receive tranilast (29%); however, redness scores were significantly less for those who received tranilast ($p < 0.01$)	Nakamura et al. [225]
	Retrospective study	42 patients prescribed oral tranilast for more than 3 months were assessed for scar improvement using the VSS	Significant improvement of total VSS score was noted (9.50 vs 5.62, $p < 0.001$) with no specific side effects	Kim et al. [226]

3D three-dimensional, BoNT-A botulinum toxin type-A, FU fluorouracil, HA hyaluronic acid, IFN interferon, MMC mitomycin-C, mRNA messenger RNA, Nd:YAG neodymium-doped yttrium aluminum garnet, PSL picosecond laser, TAC triamcinolone, VSS Vancouver Scar Scale

that a decrease in hyaluronic acid may affect keloid formation. Other more recent in vitro studies have shown that hyaluronic acid is decreased in keloidal tissue [210]. Additionally, hyaluronan synthase and hyaluronidase messenger RNA levels were found to be reduced in keloidal tissue [210]. A study using a combination of TAC with hyaluronidase showed 68.75% effectiveness in treating keloids with better tolerability than other regimens [211]. The role of hyaluronic acid in wound healing has not been fully elucidated. The current literature shows conflicting evidence in regard to the impact of hyaluronic acid in the treatment of keloids. Some data suggest hyaluronic acid plays a role in the downregulation of fibroblastic signaling factors, while clinical evidence suggests that hyaluronidase therapy is efficacious in keloid treatment [5, 211]. Further research is needed to characterize the role of hyaluronidase and hyaluronic acid therapy in the wound-healing process.

6.4 Picosecond Lasers

Picosecond lasers have been used for a wide variety of dermatologic conditions including tattoo removal, Nevus of Ota and Hori's macules, solar lentigines, and freckles, among others [212]. Picosecond lasers offer several advantages in that they are associated with reduced discomfort and downtime [212]. Guida et al. recently showed that picosecond lasers can be efficacious in treating atrophic and hypertrophic scars [175]. Their reflectance confocal microscopy analysis showed a significant reduction in the thickness of the scars [175]. A retrospective study of 24 patients with hypertrophic scars treated with a 1064-nm-picosecond neodymium-doped yttrium aluminum garnet laser showed improved cosmetic outcomes and patient satisfaction [213]. Taken together, these studies provide some evidence that picosecond laser treatment of hypertrophic scars may become a viable option in the future. Larger split-face studies are needed in order to characterize their efficacy more clearly.

6.5 Dupilumab

Dupilumab, an IL-4 receptor-α monoclonal antibody that blocks type 2-driven inflammation via inhibition of IL-4/IL-13 signaling, is the first biological agent approved for treatment of moderate-to-severe AD [214]. Recently, there have been inconsistent reports over the ability of dupilumab to treat keloid scaring. In 2020, Diaz et al. reported the case report of a 53-year-old African American man with severe AD who experienced shrinkage of a large keloid and complete disappearance of a smaller keloid after 7 months of treatment with dupilumab [28]. The following year, another case study of a 37-year-old South Asian woman found no physical reduction in keloid size, but markedly improved symptoms after 3 months of dupilumab treatment that

allowed for better tolerance of intralesional corticosteroid injections [215]. Improvement of a symptomatic hypertrophic scar in an 80-year-old woman was also reported after 10 months of dupilumab therapy [216]. Meanwhile, further studies of two 17-year-old patients found no improvement after 3 months of dupilumab treatment, with one patient experiencing an increase in both the size of existing lesions and the number of new keloids [217]. Another study of eight patients treated with dupilumab 300 mg subcutaneously every 2 weeks saw disease progression as the most common response, with only one patient willing to continue the treatment [29]. All eight patients in this study were advised to stop treatment. In their paper, Diaz et al. also reported on how the efficacy of dupilumab against keloid scars they observed may suggest an underlying type 2-centered pathogenesis shared by AD and keloids, and found increased IL-4/IL-13 signaling in nodules to confirm this rationale [28]. However, Tirgan et al. pointed out that an established diagnosis of AD would increase IL-4/IL-13 signaling independently [29]. Despite these conflicting reports, future studies on dupilumab will help determine its role in the treatment of pathologic scars and may enhance the current pathophysiological understanding. A phase IV clinical trial investigating the use of dupilumab for keloids is currently underway (NCT04988022).

6.6 Pentoxifylline

Pentoxifylline is a methylated xanthine derivative and phosphodiesterase inhibitor used in the treatment of the peripheral artery as a vasodilator, anti-inflammatory, and antifibrotic agent [218]. It has been shown that pentoxifylline can inhibit the rate of collagen synthesis in fibroblasts of keloids, thereby halting growth [219]. In severely symptomatic keloids, pentoxifylline has also been shown to decrease pain and itch [220]. The use of pentoxifylline for the treatment of keloids is not fully established but has recently been studied as both an adjunctive systemic agent and intralesional injection [218, 221]. Tan et al. [218] published a retrospective study in 2020 where they found a statistically significant decrease in keloid recurrence rates after surgical excision for groups treated with pentoxifylline, supporting the use of pentoxifylline as an adjunctive systemic agent to decrease keloid recurrence. Another recent study comparing the efficacy and safety of intralesional pentoxifylline, TAC, and their combination for the treatment of keloids found pentoxifylline to be helpful, safe, and well tolerated [221]. The efficacy of pentoxifylline alone was lower than that of TAC alone; however, more satisfactory results with less TAC-induced side effects were seen with combination therapy [221]. Pentoxifylline is a safe option that appears potentially helpful for both keloid management and the prevention of

scar recurrence, warranting future studies to explore its role as both an adjunctive and stand-alone treatment.

6.7 Oral Tranilast

Oral tranilast, an analog of a tryptophan metabolite, is an anti-allergic agent known to improve inflammatory disease with few adverse effects [222]. Tranilast was first suggested for the treatment of pathologic scars in the late 1980s after investigators discovered its ability to inhibit fibroblast proliferation in vitro and suppress collagen deposition in vivo [223]. Since then, this drug has been used for many years in Japan to treat keloids and hypertrophic scars and shown in randomized controlled trials to reduce the redness of postsurgical hypertrophic scars [224, 225]. However, clinical studies on the efficacy and safety of oral tranilast for the treatment of hypertrophic and keloid scars remain limited. One recent retrospective study found a significant improvement of total VSS scores with no specific side effect in 42 patients with keloids who were treated with oral tranilast for more than 3 months [226].

7 Conclusions

Hypertrophic scar and keloid management remains a multistep endeavor involving careful identification of patient risks factors as well as a comprehensive perioperative approach to optimize patient outcome and satisfaction. Newer treatment modalities may offer promising alternatives in the use as monotherapy or in combination with more established treatment modalities such as surgical excision, lasers, radiotherapy, and injectables. Regardless of the treatment modality, patient expectation and education are of utmost importance to establish understanding of the therapeutic options, their adverse reactions, and efficacy rates. Additionally, patient education cannot be understated especially when pursuing a prophylactic approach in scar management. Preventive strategies such as priming of the skin prior to surgery with lasers and topical agents show promise, but further studies are needed to characterize its efficacy. Future efforts should focus on delineating guidelines and parameters for laser-assisted drug delivery specifically in regard to drug formulations and duration of treatment.

Declarations

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