Emerging Insights in Keloid Pathogenesis and Therapeutics

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Keloids are fibroproliferative lesions caused by aberrant wound healing in predisposed individuals.[1] While keloids have been reported in patients of all races and ethnicities, they most commonly develop in individuals of African or Asian descent.[2] Often associated with symptoms such as pain and itching, keloids can be disfiguring and result in poorer quality of life.[3] There is a paucity of research on keloid pathogenesis and efficacious therapeutics, particularly in patients with skin of color (SOC). Herein, we outline the current research on keloid treatment and highlight promising new therapies ranging from innovative intralesional techniques to advanced laser-based and biologic therapies.

Deficiencies in Skin of Color Research

Although keloids are 17 times more prevalent in patients with SOC,[4] there is a considerable lack of focus on this population in the literature.[5] Studies on keloids that include individuals with SOC often group patients of all skin types together, and subgroup analyses are not always performed.[6,7] As a result, dermatologists may face considerable challenges in providing effective treatments for keloids in patients with SOC. With few evidence-based options available, patients with SOC who have keloids continue to experience impairments in quality of life.

Common Keloid Therapies

There currently is no gold-standard treatment for keloids. Common therapeutic modalities include intralesional corticosteroids (ILCs), antineoplastic agents and neuromodulators, laser-based devices, and surgical therapies (eg, excision), as well as combined medical and surgical techniques.[8]

Intralesional Corticosteroids—Minimally invasive ILCs are the first-line treatment in all patients with keloids, regardless of skin phototype. Because keloid formation results from trauma to the skin, ILCs often are recommended to minimize further skin damage.[5] One meta-analysis found that ILCs have demonstrated success rates of 50% to 100%[9]; however, these studies frequently combine ILCs with other treatment modalities, and few studies have focused on the efficacy of ILC monotherapy in patients with SOC.[6,10-13]

Antineoplastic Agents and Neuromodulators—Certain antineoplastic agents (eg, 5-fluorouracil [5-FU] and bleomycin) and neuromodulators (eg, botulinum toxin A [BTA]) also have been studied in keloid management.[8]

5-Fluorouracil frequently is combined with ILCs such as triamcinolone (TAC). Combined therapy is more effective than TAC monotherapy in scar height reduction.[14,15] Rates of adverse events such as dyspigmentation, atrophy, and telangiectasias also were lower in patients who received combined therapy.[14,15] A systematic review found that intralesional bleomycin may be more effective than TAC alone, 5-FU alone, TAC combined with 5-FU, and TAC combined with cryotherapy; however, hyperpigmentation was a common adverse event, occurring in roughly 70% (42/60) of patients.[16,17] Additionally, a 2024 meta-analysis evaluated 20 randomized controlled trials comprising 1114 patients treated with intralesional TAC, 5-FU, BTA, verapamil, and/or bleomycin. Botulinum toxin A and TAC plus 5-FU were found to have outstanding therapeutic efficacy for keloids, and rates of adverse events were similar among users of TAC, 5-FU, BTA, and TAC plus 5-FU.[18]

While antineoplastic agents and BTA may be promising keloid therapies, further studies demonstrating their efficacy

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and safety profiles are necessary, particularly regarding dyspigmentation as a potential adverse event, as this may be of concern in patients with darker phototypes.

Laser Therapies—Of all treatment modalities, laser-based keloid therapies have been the most robustly studied in SOC. The 2 main types are ablative (eg, CO_2, Er:YAG) and nonablative (eg, pulsed dye, Nd:YAG) lasers. Ablative lasers rapidly heat water molecules within the skin, thereby vaporizing the skin cells in a controlled precise process that reduces scar tissue by removing layers of skin. Nonablative lasers target hemoglobin in blood vessels, reducing oxygen supply and inducing collagen remodeling without damaging the epidermis.[19]

For patients with SOC, lasers carry a risk for postinflammatory hyperpigmentation.[20] To address this risk, recent advancements in laser technology and procedural protocols have aimed to minimize the number of passes and utilize cooling devices[21]; however, many of these recommendations are based on retrospective reviews and small case series. A 2024 meta-analysis comprising 550 patients found that the combination of fractional CO_2 laser therapy and 5-FU was the most effective intervention, markedly reducing Vancouver Scar Scale and pliability scores as well as keloid thickness.[22] Conversely, pulsed dye lasers were the least effective in terms of improving scar thickness, pigmentation, and pliability when compared to other treatments.

Randomized controlled trials of laser-based therapies in patients with SOC are lacking in the literature. Future studies should focus on calibrating laser-based therapies for those with darker skin tones and examine the efficacy and adverse effects of ablative and nonablative lasers in patients with SOC.

Promising New Keloid Therapies

Keloid disease pathogenesis is incompletely understood, but several new therapeutic targets have been highlighted in the literature, including dupilumab, pentoxifylline, sirtuin 6 (SIRT6) modulators, remdesivir, and needle-assisted electrocoagulation plus pharmacotherapy.

Dupilumab—An anti–IL-4 and IL-13 monoclonal antibody, dupilumab was first approved for the treatment of severe atopic dermatitis. Its use has broadened since its approval, and keloids have been identified as a potential therapeutic target. A 2019 case study described a 53-year-old Black man with severe atopic dermatitis and chronic keloids that regressed with systemic dupilumab therapy.[23] This prompted a follow-up case-control study using real-time polymerase chain reaction testing to evaluate Th2 gene expression (IL-4R, IL-13, and CCL18) of lesional and nonlesional tissue in 3 Black patients with chronic keloids and no concurrent atopic dermatitis vs 5 healthy Black controls. Despite the limited sample size, a significant increase in IL-13 and the Th2 chemokine CCL18 was found in patients with keloids compared to controls ($P<.05$), suggesting that the entire integument of patients with severe keloids is abnormal.[23] This finding supports the use of systemic treatments for chronic and multifocal keloid disease. Several subsequent case reports have corroborated the efficacy of systemic and/or intralesional dupilumab.[24,25] However, some studies have reported contradictory findings, suggesting the need for high-quality clinical trials.[26,27]

Pentoxifylline—Pentoxifylline is a methylated xanthine derivative and a nonspecific phosphodiesterase inhibitor used to treat claudication from peripheral artery disease. It also inhibits the proliferation and rate of collagen synthesis of fibroblasts from keloids in vitro.[28,29] A 2019 retrospective, open-label pilot study analyzed postsurgical keloid recurrence in 45 patients with 67 unique keloids that were stratified into low- and high-risk groups based on clinical factors including multiple symptomatic keloids, history of recurrence, and family history.[30] Both the low- and the high-risk groups were treated with 40 mg/mL intralesional triamcinolone acetonide monthly for 6 months; however, some of the high-risk keloids also received pentoxifylline 300 mg 3 times daily for 6 months. There was a statistically significant decrease in keloid recurrence rate between the high-risk group treated with pentoxifylline and the low-risk group for whom pentoxifylline was not prescribed ($P=.015$).

Similarly, a randomized clinical trial comparing the efficacy of combination intralesional pentoxifylline and intralesional triamcinolone vs monotherapy with pentoxifylline or triamcinolone found the most significant improvement in the combination cohort with reduction in keloid height ($P=.04$), pliability ($P=.003$), and vascularity ($P=.05$).[31] These findings highlight the need for supplementary studies on the use of pentoxifylline for keloid therapy.

SIRT6 Modulators—SIRT6 modulators are an exciting future therapeutic target. In a recent case-control study evaluating the histologic milieu of keloid tissue vs normal skin specimens, the researchers found that selective overexpression of SIRT6 via the use of a recombinant adenovirus in keloid fibroblasts attenuated proliferation, invasion, and collagen synthesis while fostering apoptosis, likely through the suppression of MAPK/ERK pathway activity.[32]

Remdesivir—The antiviral drug remdesivir has been reported to have pharmacologic activities in a wide range of fibrotic diseases, including keloids. A 2024 study explored the potential effect and mechanisms of remdesivir on skin fibrosis both in vitro and in rodents.[33] Remdesivir was found to decrease skin fibrosis and attenuate the gross weight of keloid tissues in vivo, suppress fibroblast activation and autophagy both in vivo and in vitro, dampen fibroblast activation by the TGF-β1/Smad signaling pathway, and inhibit fibroblasts autophagy by the PI3K/Akt/mTOR signaling pathway. These results demonstrate the therapeutic potential of remdesivir for keloid management.

Needle-Assisted Electrocoagulation Plus Pharmacotherapy—A novel needle-assisted electrocoagulation technique combined with pharmacotherapy (corticosteroid and 5-FU injections) was effective in a Chinese clinical trial involving 6 patients with keloids.[34] Investigators used Vancouver Scar Scale and both Patient and Observer Scar Assessment Scale scores to grade patients' scars before treatment and 1 month after the first treatment cycle. They found that ablation

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combined with pharmacotherapy significantly reduced all 3 scores without any obvious adverse events (P=.004, P=.006, and P=.017, respectively). This novel combination treatment may serve as a safe and effective therapeutic approach for keloid removal.

Final Thoughts

Emerging treatments offer promising new horizons in keloid management; however, the lack of robust, high-quality clinical trials, especially those focusing on SOC, underscores a pressing need for comprehensive and inclusive studies. There is much work to be done to close the existing knowledge gap, and future studies must be more intentional with recruitment, assuring that the patients who are disproportionately affected by these lesions are represented in study populations.

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