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REVIEW OF MODERN METHODS FOR TREATING KELOID SCARS.

Аннотация. *Статья представляет собой комплексный научный обзор, посвященный современным терапевтическим подходам к лечению келоидных рубцов — доброкачественных, но агрессивных фибропролиферативных образований кожи, которые вызывают физический дискомфорт (зуд, боль) и серьезно снижают качество жизни пациентов. Авторы подчеркивают, что проблема лечения келоидов остается актуальной, поскольку ни один существующий метод не гарантирует полного излечения и отсутствия рецидивов, что обусловлено сложным и до конца не изученным патогенезом заболевания, включающим генетическую предрасположенность, хроническое воспаление и нарушение регуляции роста фибробластов.*

Ключевые слова: *келоидные рубцы, триамцинолон, 5-фторурацил, компрессион терапия, криотерапия, гипертрофические рубцы, фибробласты, коллаген.*

Abstract. *This article presents a comprehensive scientific review devoted to modern therapeutic approaches to the treatment of keloid scars—benign but aggressive fibroproliferative skin growths that cause physical discomfort (itching, pain) and significantly reduce patients' quality of life. The authors emphasize that the problem of keloid treatment remains relevant, as no existing*

method guarantees a complete cure or the absence of recurrence. This is due to the complex and poorly understood pathogenesis of the disease, which includes genetic predisposition, chronic inflammation, and dysregulated fibroblast growth.

Key words: *keloid scars, triamcinolone, 5-fluorouracil, compression therapy, cryotherapy, hypertrophic scars, fibroblasts, collagen.*

1. Introduction to Keloids and Pathophysiology.

Keloid scars represent a pathological fibroproliferative disorder of the skin, characterized by an exaggerated healing response that extends beyond the original wound borders. Unlike normal scars or hypertrophic scars, keloids exhibit continuous, invasive growth and rarely regress spontaneously. They are frequently associated with significant symptoms, including pain, pruritus (itching), and stiffness, and can cause considerable psychological distress and cosmetic concern, particularly when located on visible areas.

The development of keloids is driven by a complex interplay of genetic predisposition, environmental factors, and aberrant biochemical pathways**. Key to their formation is a dysregulation in the normal wound-healing process, particularly during the proliferation and remodeling phases. This leads to an imbalance where collagen production drastically outpaces its degradation.

Core Pathogenic Mechanisms:

Fibroblast Hyperactivity: Keloid fibroblasts (KFs) demonstrate abnormal proliferation and excessive production of extracellular matrix (ECM) components, primarily type I and III collagen.

Cytokine Dysregulation: Elevated levels of growth factors, especially Transforming Growth Factor-beta (TGF-β), promote fibroblast activation and differentiation into collagen-producing myofibroblasts. A chronic inflammatory environment, sustained by cytokines like IL-6 and TNF-α, further fuels this process.

Impaired Remodeling: There is a noted reduction in the activity of enzymes (matrix metalloproteinases, MMPs) that break down collagen, coupled with an increase in their inhibitors (TIMPs), leading to the accumulation of dense, disorganized collagen bundles.

Epidemiologically, keloids show a strong genetic predisposition, with a higher prevalence in individuals of African, Asian, and Hispanic descent. They most commonly arise in areas of high skin tension, such as the chest, shoulders, and ear lobes.

2. Conventional and First-Line Treatment Modalities

The management of keloids remains clinically challenging due to high recurrence rates with monotherapy. Established treatments aim to reduce scar volume, alleviate symptoms, and prevent recurrence, often requiring a multimodal approach.

2.1 Corticosteroid Injections

Intralesional corticosteroid injections, particularly triamcinolone acetonide, are a cornerstone of keloid management. They work by suppressing inflammation, inhibiting fibroblast proliferation, and reducing collagen synthesis.

Efficacy and Protocol: A 2025 systematic review noted that triamcinolone injections achieved an average 82.2% reduction in scar severity on the Vancouver Scar Scale. Treatment typically involves monthly injections for up to six months.

Limitations: Side effects are common and can include skin atrophy (thinning), telangiectasia (spider veins), and hypopigmentation, especially in darker skin tones. Recurrence rates can be high when used alone.

2.2 Surgical Excision

Surgical removal is generally reserved for large, symptomatic keloids that have not responded to less invasive treatments. Crucially, surgery alone is associated with recurrence rates of 45% to 100%. Therefore, it is almost always

performed as part of a combined modality strategy, with immediate post-operative adjuvant therapy (e.g., corticosteroid injections, radiation, or silicone therapy) to prevent recurrence.

2.3 Laser Therapy

Various lasers target different aspects of keloid pathology.

Pulsed Dye Laser (PDL): Primarily targets the microvasculature, reducing redness (erythema) and improving pliability and height.

Ablative Fractional Lasers (CO_2, Er:YAG): Create microscopic channels in the scar tissue. This approach can be used for laser-assisted drug delivery (LADD), where topical medications (like triamcinolone ointment) are applied immediately after laser treatment to enhance penetration and efficacy.

Nd:YAG Laser: Shown to be effective, with one review citing a 65.4% efficacy in reducing scar severity.

2.4 Other Established Modalities

Cryotherapy: Freezing the keloid with liquid nitrogen can reduce the size of small lesions. It can cause blistering, pain, and permanent hypopigmentation. A clinical pearl is to use cryotherapy briefly to soften a firm keloid before injection, making it more amenable to treatment.

Radiation Therapy: Used as an adjuvant, typically after surgical excision, to inhibit fibroblast proliferation and reduce recurrence risk. Concerns exist about potential long-term carcinogenic risk.

Silicone-Based Therapies: Silicone gel sheets or gels are a first-line, non-invasive option for both prevention and treatment. They improve hydration, reduce collagen synthesis, and are recommended for use over new scars for at least 3 months.

Pressure Therapy: Involves wearing customized garments or devices for 12-24 hours daily for many months. It is more effective when started early and is often used post-operatively or in combination with silicone products.

3. Emerging and Investigational Therapies.

Recent research has shifted toward targeting the specific molecular pathways underlying keloid fibrosis, yielding promising new therapeutic candidates.

3.1 Targeted Molecular and Pharmacologic Agents

Prolyl-tRNA Synthetase (PRS) Inhibitors: This represents a novel, first-in-class approach. The drug DWN12088 inhibits PRS, an enzyme essential for incorporating proline into collagen. By downregulating de novo collagen synthesis at its source, it effectively reduced keloid formation in preclinical models.

Hedgehog-Interacting Protein (HHIP) Inhibitors: Identified as a driver of keloid formation, HHIP can be targeted with topical inhibitors to block abnormal growth signaling, leading to reduced inflammation and collagen production.

5-Fluorouracil (5-FU) and Bleomycin: These antineoplastic agents are increasingly used as intralesional injections, often in combination with triamcinolone. They inhibit fibroblast proliferation and have shown improved efficacy over steroids alone in some studies.

Botulinum Toxin A (BTA): Injected intralesionally, BTA may improve scars by reducing wound tension and downregulating TGF-β expression in fibroblasts.

Intralesional Verapamil: A calcium channel blocker with antifibrotic properties, showing promise with a reported 57.7% efficacy in one analysis.

3.2 Energy-Based and Biophysical Modalities

Photobiomodulation Therapy (PBMT): Also known as low-level laser therapy (LLLT), PBMT uses non-thermal red or near-infrared light to modulate cellular activity. It enhances mitochondrial function, reduces inflammatory cytokines (IL-6, TNF-α), and inhibits TGF-β1 expression, leading to reduced collagen deposition and scar size with minimal side effects.

Light-Emitting Diode (LED) Red Light: Similar to PBMT, LED red light has been shown in laboratory studies to inhibit keloid fibroblast proliferation in a dose-dependent manner and is being investigated for clinical use.

Extracorporeal Shockwave Therapy (ESWT): A non-invasive treatment using acoustic pulses. It may improve keloids by modulating inflammation, enhancing tissue perfusion, and breaking down dense collagen fibers.

3.3 Advanced Biological Therapies

Mesenchymal Stem Cell (MSC) Therapy: Investigated for its immunomodulatory and regenerative potential, MSC therapy aims to reprogram the local wound environment to promote normal rather than fibrotic healing.

RNA Interference (RNAi) and MicroRNA Therapies: These experimental strategies seek to silence the expression of specific genes responsible for the fibrotic cascade (e.g., profibrotic cytokines or collagen genes) at the transcriptional level.

4. Combination and Protocol-Based Approaches.

Given the complexity of keloids, combination therapy is the rule rather than the exception. Modern protocols strategically sequence different modalities to attack the scar through multiple mechanisms.

Example of an Advanced Protocol:

One clinic describes an "Advanced Sequential Approach Protocol (ASAP)" involving four stages:

1. Assessment: Molecular and genetic analysis of the keloid.
2. Targeted Molecular Therapy: Application of topical pathway inhibitors (e.g., HHIP inhibitors).
3. Precision Intervention: Combination laser and injection therapy.
4. Stabilization & Prevention: Long-term maintenance with silicone and molecular therapies.

Common Effective Combinations Include:

Surgical Excision + Post-op Adjuvant: This is critical. Adjuvants include steroid injections, radiation, or immediate application of silicone sheets/ pressure therapy.

Laser-Assisted Drug Delivery (LADD): Fractional ablative laser immediately followed by topical triamcinolone ointment.

Cryotherapy + Injection: Brief cryotherapy to soften the keloid, followed by intralesional steroid injection.

Steroid + 5-FU Injection: A common intralesional cocktail that improves efficacy and may reduce steroid-related side effects.

To help visualize how these treatments compare in a clinical context, here is an overview of their key characteristics:

Treatment Modalities for Keloid Scars

Corticosteroid Injections (e.g., Triamcinolone)

Mechanism of Action: Anti-inflammatory, inhibits fibroblast proliferation

Typical Efficacy: High (e.g., ~82% reduction per VSS)

Common Side Effects: Skin atrophy, hypopigmentation, telangiectasia

Recurrence Risk without Adjuvant: High

Surgical Excision (with adjuvant therapy)

Mechanism of Action: Physical removal of scar tissue

Typical Efficacy: Variable, depends heavily on adjuvant

Common Side Effects: Pain, infection, new scar formation

Laser Therapy (e.g., PDL, Fractional CO2)

Mechanism of Action Vascular targeting, collagen remodeling, LADD

Typical Efficacy: Moderate to High

Common Side Effects: Hyper/hypopigmentation, blistering (skin type dependent)

Recurrence Risk without Adjuvant: Moderate

Silicone Gel Sheets

Mechanism of Action: Hydration, occlusion, signaling modulation

Typical Efficacy: Moderate (first-line for prevention/early treatment)

Common Side Effects: Local irritation, pruritus

Recurrence Risk without Adjuvant: Data limited; best for prevention

Emerging Therapies (e.g., PRS inhibitors, PBMT)

Mechanism of Action: Target-specific molecular pathways (collagen synthesis, cellular metabolism)

Typical Efficacy: Promising in preclinical/early clinical studies

Common Side Effects: Generally minimal reported in studies

Recurrence Risk without Adjuvant: Under investigation

5. Future Directions and Conclusion.

The future of keloid management lies in personalized, precision medicine. Advances in genomic profiling and artificial intelligence (AI) are paving the way for predictive models that can select optimal treatment protocols based on an individual's keloid biology and genetic predisposition. The integration of molecular diagnostic tests to identify upregulated pathways (e.g., TGF-β, HHIP) in a patient's specific keloid will allow for tailored selection of targeted inhibitors.

Furthermore, the focus of research is expanding beyond mere reduction to true scar regeneration. Therapies involving stem cells, microRNA modulators, and growth factor reprogramming aim to fundamentally alter the wound-healing process toward a regenerative rather than a fibrotic outcome.

In conclusion, while keloids remain a therapeutically challenging condition, the modern treatment arsenal has moved far beyond singular interventions. The current standard of care emphasizes early, combination therapy rooted in an understanding of scar pathophysiology. The horizon is bright with novel targeted agents and biotechnologies that promise not only improved efficacy and lower recurrence but also a move toward personalized treatment regimens. Successful management requires careful patient selection,

realistic goal setting, and often long-term follow-up to ensure sustained outcomes.

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