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SCAR INJECTION: BEYOND TRIAMCINOLONE ACETONIDE

Introduction

Pathological scars, comprising hypertrophic scars and keloids, are both rewarding and challenging to treat in clinical practice. Beyond the cosmetic appearance and the physical reminder of the circumstances of scar formation (**Figure 1**), patients can also experience itch, pain, or even functional limitations. In many ways, the large number of available treatment options highlight that there is no globally accepted therapeutic ladder for this clinical scenario.

Modalities of treatment include scar injections, cryotherapy, surgery, and energy-based device treatments, including lasers or radiation.[1] Laser-assisted drug delivery (LADD), which is the treatment of a scar with low-density fractional ablative laser followed by immediate application of a topical agent, is associated with excellent outcomes.[2-4] However, this approach requires technology that may not be as widely available or as comprehensively reimbursed as scar injections. The objective of this article is to provide an overview of treatment options for scar injections with accessible medications to treat pathological scars, especially for dermatologists who may not have access to advanced technologies and devices for scar treatment in their practice.

Triamcinolone acetonide

Intralesional triamcinolone acetonide (TAC) is commonly used to treat pathological scars. It is widely available at pharmacies, inexpensive, and does not require specialized technology to use. A recent systematic review and meta-analysis of fifteen trials confirmed its effectiveness in the treatment of hypertrophic scars and keloids.[5] Unfortunately TAC can induce apoptosis of fibroblast and atrophy of collagen in adjacent normal skin. Potential side effects of TAC injections include atrophy, telangiectasias, hypopigmentation, and recurrences over time. Scar recurrence can be seen as frequently as in 50% of cases,[6] especially for keloids. Customizing the TAC concentration to patient skin type, size of scar, and location of scar is a strategy that can help mitigate atrophy. Empirically, in the author's practice, the first scar injection with TAC is performed with a concentration of 5-20 mg/cc. Low concentrations are used in patients with Fitzpatrick Skin Phototype V and VI who are at higher risk of hypopigmentation, as well as for treatment of cosmetically sensitive sites (face, décolleté). Careful observation of the scar is recommended during a very slow injection. This is to minimize pain and to enable stopping the injection prior to any extravasation of TAC to surrounding healthy skin. Patients are injected every 4 to 6 weeks and the concentration of TAC can be adjusted at that time – if the clinical response was modest with no adverse events, the concentration may be increased. If early signs of surrounding atrophy are noted and the scar still needs treatment, a lower concentration of TAC may be used.

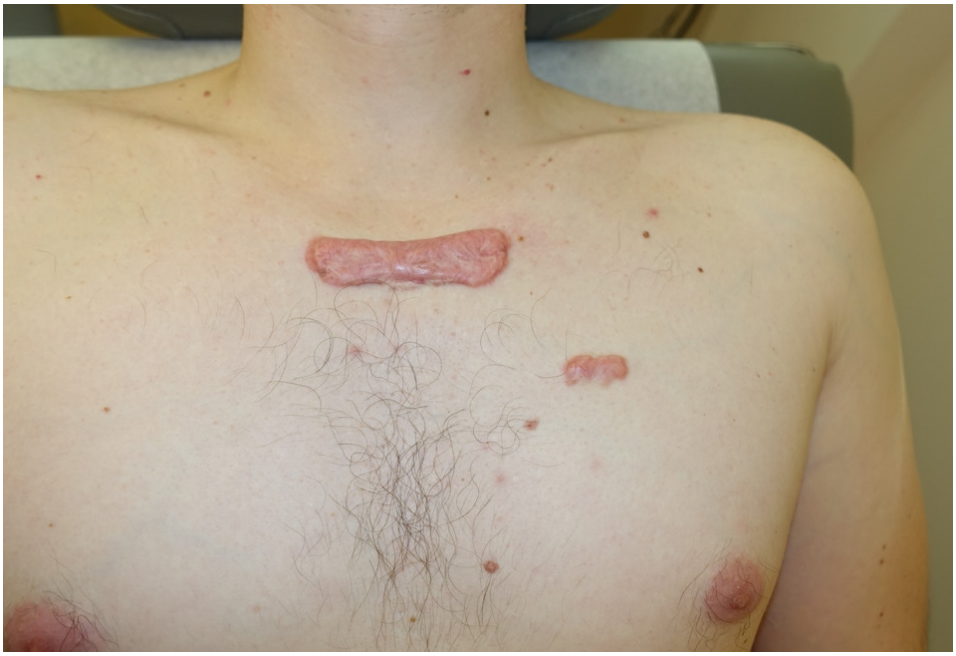

Figure 1. Close up of keloid scar on man's skin; photo courtesy of Vincent Richer, MD

5-fluorouracil

The chemotherapy agent 5-fluorouracil (5-FU) is a pyrimidine analog that suppresses deoxyribonucleic acid synthesis by inhibiting thymidine synthase, effectively halting the proliferation of fibroblasts and the fibroblast-populated collagen lattice.[7] 5-FU is commercially available in 10ml single use vials and 100ml "bulk" vials. When used in monotherapy, the performance of 5-FU at reducing scar thickness is comparable to TAC, however it does not offer the same long-term improvement in scar vascularity.[5] Moreover, injection of 5-FU alone can lead to increased pain and ulcer formation. It is generally recommended to avoid injecting more than 2 cc (e.g. 100 mg) per session to avoid significant systemic exposure and symptoms. While intralesional 5-FU and TAC have both been proven as effective monotherapy, there has been increased interest in their combined synergistic effects.

Combination triamcinolone acetonide and 5-fluorouracil

Compared to TAC alone, using combination TAC and 5-FU produces significant improvement in scar height, pliability, and pigmentation. Additionally, the combination is associated with increased long-term responses (24+ weeks) when compared to TAC alone, suggesting lower rates of scar recurrence.[5] Many combination dosages and treatment intervals have been examined, however, there is currently no consensus on any of them. It is likely that the patient's skin type as well as the size and location of the scar will affect the dosing strategy. Empirically, in the author's practice, up to 2 mL of 50 mg/mL 5-FU are used to dilute down TAC to its desired concentration and patients are injected every 4 to 6 weeks. Dilution of TAC can be as low as 2.5 to 3.3 mg/mL for first-time treatment of small keloids at risky sites for iatrogenic atrophy (e.g. the presternal region). The concentration of TAC may be increased with subsequent treatments or started at 5 to 20 mg/mL for larger keloids at more forgiving anatomical sites (e.g. the helix).[7] Injections are delivered slowly to minimize pain until the scar appears temporarily blanched. Clinicians should take care to interrupt injection if diffusion occurs into adjacent normal skin.

Botulinum toxin-A

Botulinum toxin-A (BTX-A) is a neurotoxin that acts on neurons to inhibit the release of acetylcholine, which inhibits muscle contraction. BTX-A is more expensive than TAC but is widely available and stocked by many dermatologists who offer cosmetic services. Dermatologists are familiar with its cosmetic use to treat dynamic rhytides and its medical indications such as primary hyperhidrosis, but may not be aware that it can also reduce inflammatory stimuli involved in wound healing, thereby affecting scar formation.[8] Moreover, BTX-A may directly regulate the activity of fibroblasts by changing apoptosis, migration, and fibrosis.[6] Since hypertrophic scars and keloids occur at areas of high skin tension, it stands to reason that minimizing these forces in surrounding skin by relaxing muscle tissue may be beneficial. A recent systematic review and meta-analysis concluded that BTX-A was more effective than saline at prevention of postsurgical facial scars.[8] Monotherapy of pathological scars with BTX-A has been studied and shows favorable outcomes when compared with TAC.[6] However, the dosing and treatment sequence reported in the literature are highly heterogeneous.

Combination triamcinolone acetonide and botulinum toxin-A

In a recent network meta-analysis, botulinum toxin-A combined with TAC had the highest predicted efficacy, followed by combination TAC and 5-FU.[6] Further analysis reveals this is based on a handful of studies that compared combination TAC and BTX-A to either treatment as monotherapy.[9] Nonetheless, the evidence supporting BTX-A monotherapy is encouraging,

and adding BTX-A to TAC or TAC + 5-FU combination injections is a viable treatment option. As mentioned above, the optimal dosing and treatment sequence for BTX-A to treat pathological scars has not been determined. Empirically, in the author's practice, 2 units of onabotulinum toxin-A are injected per cm^2 of scar, with injection points extending beyond the scar periphery. Treatment is performed immediately after TAC or TAC + 5-FU combination scar injection during the same visit.

Other drugs for scar injection

Verapamil has also been extensively studied for the treatment of pathological scars. It appears to have comparable efficacy to TAC in improving scar height over time, however it may not achieve similar outcomes on the domains of scar vascularity and pliability.[5] In the network meta-analysis mentioned previously, verapamil had the lowest order of efficacy as compared to the above treatment options.[6] The body of evidence to support the use of bleomycin, hyaluronic acid, hyaluronidase, platelet rich plasma or collagenase is less robust and beyond the scope of this article.[1]

Scar injection versus laser-assisted drug delivery

With the advent of LADD, has scar injection been fully supplanted? A large number of peer-reviewed articles compare ablative fractional laser (AFLX) alone versus AFLX with LADD.[2] However, data comparing intralesional (IL) injection versus LADD of a medication are scarce. Only two studies comparing IL injection to LADD of a medication were found in the literature. Abd El-Dayem et al.[10] compared four IL TAC treatment sessions at 4-week intervals vs fractional Er:YAG-assisted delivery of topical betamethasone in 30 keloids. While both treatments showed significant improvement three months after the last treatment, there was no significant difference between the outcomes and there was a higher incidence of telangiectasia, dermal atrophy and dyspigmentation with IL TAC, although this difference was not statistically significant. Sabry et al.[11] compared once-monthly treatments of IL BTX-A for four consecutive months to four sessions of fractional CO2-assisted delivery of topical BTX-A in 10 keloids and 10 hypertrophic scars. In the hypertrophic scars group, both treatments showed overall significant improvement at the six-month follow-up mark, with more improvement on the LADD-treated side than the IL injection side. Interestingly, in the keloid group, IL injections were favored over LADD of BTX-A for vascularity and pliability. The limitations of these studies include a small sample size as well as scoring by evaluators who were not blinded. While these two studies help support the role of LADD in the management of pathological scars and potentially elucidate a better safety profile compared to IL injections of TAC, they do not obviate the role of scar injections.

Conclusion

Of the many treatment options available to treat pathological scars, scar injection is widely available and requires no specialized technology. Though TAC is most commonly used for scar injection, 5-FU and BTX-A have been studied as monotherapy and in combination with TAC. Notably, duration of treatment response may be longer with combination TAC and 5-FU. Both 5-FU and BTX-A carry the added benefit of reducing the risk of skin atrophy associated with high-concentration TAC. Combining 5-FU and/or BTX-A with TAC may allow for effective treatment of pathological scars while maintaining lower concentrations of TAC to minimize side effects. Additional randomized trials are necessary to further optimize combination scar injection therapy and to guide resource allocation.

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