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REVIEW

Triamcinolone acetonide intralesional injection for the treatment of keloid scars: patient selection and perspectives

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Abstract: Keloids are pathological scars presenting as nodular lesions that extend beyond the area of injury. They do not spontaneously regress, often continuing to grow over time. The abnormal wound-healing process underlying keloid formation results from the lack of control mechanisms self-regulating cell proliferation and tissue repair. Keloids may lead to cosmetic disfigurement and functional impairment and affect the quality of life. Although several treatments were reported in the literature, no universally effective therapy was found to date. The most common approach is intralesional corticosteroid injection alone or in combination with other treatment modalities. Triamcinolone acetonide (TAC) is the most commonly used intralesional corticosteroid. The aim of this article was to review the use of TAC, alone or in combination, in the treatment of keloid scars. The response to corticosteroid injection alone is variable with 50–100% regression and a recurrence rate of 33% and 50% after 1 and 5 years, respectively. Compared to verapamil, TAC showed a faster and more effective response even though with a higher complication rate. TAC combined with verapamil was proved to be effective with statistically significant overall improvements of scars over time and long-term stable results. TAC and 5-fluorouracil (5-FU) intralesional injections were found to achieve comparable outcomes when administered alone, although 5-FU was more frequently associated with side effects. Conversely, the combination of 5-FU and TAC was more effective and showed fewer undesirable effects compared to TAC or 5-FU alone. Several kinds of laser treatments were reported to address keloids; however, laser therapy alone was burdened with a high recurrence rate. Better results were described by combining CO_2, pulsed-dye or Nd: YAG lasers with TAC intralesional injections. Further options such as needle-less intraepidermal drug delivery are being explored, but more studies are needed to establish safety, feasibility and effectiveness of this approach.

Keywords: keloids, scars, intralesional corticosteroid injections

Introduction

Keloids are pathological scars presenting as nodular firm lesions that extend beyond the area of injury. They do not spontaneously regress, often continuing to grow over time.[1] The prevalence is high in the dark phototypes with an estimated incidence of 5–16% in the Hispanic and African-American populations.[1] The most frequently affected body areas are chest, shoulders, earlobes and upper back.[2] Symptoms often include itching and pain. Unlike hypertrophic scars, keloids do not improve over time and commonly recur following surgical excision.[3] Large lesions may lead to cosmetic disfigurement and functional impairment, thus affecting the quality of life.[2]

The abnormal wound-healing process underlying keloid formation results from the lack of control mechanisms regulating cell proliferation and tissue repair.[4]

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Histologically, keloids are characterized by haphazardly arranged hyalinized collagen bundles and a tongue-like advancing edge in the papillary dermis.[5] Despite many clinical, histological and in vitro findings, the pathogenic mechanisms underlying keloid formation have not been fully elucidated.[6,7] To date, no specific gene has been linked to the development of keloids, and it is likely that different genes contribute to their formation in different families.[7–9] Excessive matrix accumulation and cell proliferation are distinctive histological features of keloids, resulting from the increased proliferation and lower apoptotic rate of fibroblasts.[7,10,11] The change in the normal balance between extracellular matrix (ECM) deposition and degradation seen during wound healing, especially along the remodeling phase, may play a role in keloid formation. Increased local levels of PAI-1 and low levels of urokinase have been reported in keloid fibroblasts, likely leading to reduced collagen degradation.[7,12,13] Several other pathogenic theories have also been postulated, including genetic immune dysfunction, mechanical tension, increased hyaluronic acid production, sebum reaction, tissue hypoxia and abnormal epithelial–mesenchymal interaction.[7,8,12–15] Elevated levels of cytokines, such as tumor necrosis factor (TNF), interleukin (IL)-6 and IL-13, and growth factors, such as vascular endothelial growth factor (VEGF) and transforming growth factor beta (TGF-β), were proved to be involved in keloid scar formation and proliferation.[7,16] TGF-β family was associated with enhanced collagen synthesis in keloid fibroblasts. TGF-β1 treatment was shown to stimulate the production of collagen in keloid fibroblasts but not in normal skin fibroblasts.[16,17] The role of TGF-β1 was further confirmed by the observation that anti-TGF-β1 antibody suppressed collagen synthesis of keloid fibroblasts.[16,17] Moreover, TGF-β2 treatment enhanced collagen production of xenograft derived from human keloid specimens in athymic rats.[16,18] On the other hand, TGF-β2 antibody inhibited collagen generation in a xenograft model, suggesting that it could act as a potential antiscarring agent.[18] IL-13 induced a faster increase in collagen production by keloid fibroblasts compared to normal ones.[16,19] VEGF is one of the most important growth factors involved in angiogenesis, and it was previously implicated as crucial to both normal and pathological wound healing.[6,7] In vivo and in vitro studies showed that VEGF was overexpressed in keloid tissue and may play a potential role in its formation.[6,7,11] VEGF induces angiogenesis both directly, by acting as a mitogen for endothelial cells, and indirectly, by increasing vascular hyperpermeability and promoting the extravascular deposition of fibrin matrix. It is also paramount in the modulation of ECM proteolysis, an essential component of the angiogenic process.[7,20,21]

Several strategies were suggested for keloid therapy, but, to date, no universally effective treatment was found.[22] Current therapeutic approaches fall into three broad categories: alteration of the inflammatory response; modification of collagen metabolism; surgical and physical manipulation of the keloid scar.[7] Therapeutic approaches include surgical excision, intralesional injection of steroids, verapamil, 5-fluorouracil (5-FU), cryotherapy, laser therapy (fractionated CO_2 laser, Nd:YAG laser, pulsed-dye laser), silicone sheet dressings, irradiation, retinoids, tacrolimus, imiquimod and combination therapy.

Since keloids are notoriously characterized by a high recurrence rate after surgical excision, nonsurgical approaches are recommended for primary treatment.[3,16] The most common approach is intralesional corticosteroid injection alone or in combination with other treatment modalities. Triamcinolone acetonide (TAC) is the most commonly used intralesional corticosteroid.

The aim of this review was to investigate and discuss the efficacy of TAC intralesional injection in the treatment of keloids.

Intralesional injection of TAC

The International Advisory Panel on Scar Management recommended the use of intralesional steroid injections for the treatment of keloids and hypertrophic scars.[3] Corticosteroids were proved to induce keloid regression through many different mechanisms. First, they suppress inflammation by inhibiting leukocyte and monocyte migration and phagocytosis.[23] Second, they are powerful vasoconstrictors, thus reducing the delivery of oxygen and nutrients to the wound bed.[23] Third, they have an antimitotic effect that inhibits keratinocytes and fibroblasts, slowing reepithelialization and new collagen formation. Furthermore, they may reduce plasma protease inhibitors, thus allowing collagenase to degrade collagen. TAC also induces a significant plunge in alpha-1-antitrypsin and alpha-2-macroglobulin levels, which tend to be greater in keloidal tissue and are natural inhibitors of collagenase in human skin.[24] Corticosteroids affect fibroblast proliferation and production capabilities and are responsible for their degeneration. Moreover, decreased levels of TGF-β, insulin-like growth factor-1 (IGF-1) and hydroxyproline were found in scar tissues treated with methylprednisolone.[24,25] It was shown that dexamethasone induced keloid regression via interaction with glucocorticoid receptors and

suppressed endogenous VEGF expression and fibroblast proliferation.[6,23]

Many corticosteroids are available for the treatment of keloids, but the most commonly used is TAC. Clinically, the response to corticosteroid injection alone was variable with 50–100% regression and a recurrence rate of 33% and 50% after 1 and 5 years, respectively.[3,26] Five-year recurrence rates for surgical excision followed by TAC administration were reported to be between 8% and 50%.[3]

There were considerable differences among practitioners in the dose, frequency and duration of treatment (Table 1). Rahban and Garner[27] proposed performing two to three injections of Kenalog (Bristol-Myers Squibb, Princeton, NJ, USA), at a dose of 10 mg/mL, approximately 4–8 weeks apart. Darzi et al[28] adjusted the dosage of TAC administered to patients depending on the keloid scar surface area: patients with a keloid scar surface area of 1–2 cm^2 received a total dose of 20–40 mg of TAC 0.1%, those with 2–6 cm^2 received 60–80 mg and those with 6–12 cm^2 received 80–120 mg. At 10-year follow-up, 71% of the treated keloid scars evidenced full flattening and 29% had partial flattening. Symptom relief was seen in 71% of the treated keloid scars, although this outcome measure was not defined. Four injections were given until the total dose was reached. Robles et al[9] recommended the use of TAC (Kenalog) at a concentration ranging from 10 to 40 mg/mL, depending on the size and location of the lesion. For lesions on the trunk or extremities, therapy was usually initiated at 40 mg/mL and then titrated accordingly at subsequent visits.

Acosta et al[29] conducted a prospective clinical trial with patients aged 1–14 years. They studied keloid treatment with intralesional TAC to determine its effectiveness as a single therapy and to establish whether the affected area, the etiology of the lesion and the duration of a scar were the outcome predicting factors. Before treatment, keloid volume was calculated using soft tissue ultrasound, which was repeated after 3 months to compare volume differences attributable to therapy. If a palpable or visible lesion persisted, keloids were reinjected each month with the same dose until no volume change was perceived between sessions. Three months after the last procedure, a further ultrasound was performed to assess for any recurrence. Results showed an 82.7% reduction in size between the first and last treatments ($p < 0.001$). The median number of injections required per keloid was two (range one to five). The median dose for each session was 16 mg of TAC (range 4–40 mg), and the median dose to complete the treatment was 32 mg (range 4–80 mg). Their findings indicated a trend toward better response in those lesions caused by a trauma or a surgical scar rather than in those resulting from varicella or vaccination, although the difference was not statistically significant. Furthermore, keloids on the earlobe had a worse response than those on the arm, chest or other locations, although the difference was not statistically significant. The duration of the keloid before starting treatment had no effect on the treatment result. The authors therefore concluded that there was no relationship among clinical response and the lesion location, etiology and age of the keloid.

Despite its benefits, intralesional steroid injections may cause several adverse side effects, both local, such as telangiectasias, skin and subcutaneous fat atrophy, pigmentary changes (hypopigmentation and hyperpigmentation), skin

Table 1 Dose of TAC used by different authors when using TAC in monotherapy and in combination therapy

Study	TAC dose and/or concentration	Associated treatment	Number of injections	Interval between sessions (weeks)
Rahban and Garner[26]	10 mg/mL	–	2–3	4–8
Darzi et al[27]	10–20 mg/cm^2	–	4	–
Robles et al[9]	10–40 mg/mL	–	Multiple	4
Acosta et al[28]	4–40 mg/mL	–	1–5	4
Ahuja and Chatterjee[37]	40 mg/mL	–	Maximum 8	3
Danielsen et al[38]	1 mg/cm (maximum 5 mg)	Surgical excision (before TAC injection)	4	4
Kant et al[39]	2–4 mg of TAC 40 mg/mL	0.05–0.1 mL of verapamil 2.5 mg/mL	3	Second injection after 1 week, third injection 3 weeks later
Saha and Mukhopadhyay[43]	40 mg/mL	–	Maximum 6	1
Fitzpatrick[45]	1 mg	5-FU 45 mg	5–10	–
Khan et al[46]	4 mg	5-FU 45 mg	8	1
Tan et al[71]	40 mg/mL	–	–	4
Kassab and El Kharbotly[63]	40 mg/mL	980 nm diode laser	2–5	–
Payapvipapong et al[77]	10 mg/mL	–	3	4

Abbreviations: 5-FU, 5-fluorouracil; TAC, triamcinolone acetonide.

necrosis and ulcerations, and systemic effects, such as Cushing's syndrome. The risk of local complications is greater when inadvertent injection of surrounding normal tissue occurs.[23] Cushing's syndrome with adrenal insufficiency associated with intradermal corticosteroid injection is a rare but possible complication, usually reported in children, although a few cases were described in adults as well.[30–32] Such major adverse effect is associated with a high cumulative dose of TAC in adults, whereas in children it has been observed even after a single treatment with 40 mg of triamcinolone, thus care must be taken when administering TAC in children and patients with multiple or very large lesions.[33] Therefore, the occurrence of symptoms such as weight gain, striae rubrae, depression, moon face and amenorrhea in the course of treatment must not be underestimated but must be further investigated.

Intradermal corticosteroid injection was associated with significant injection pain, often requiring the administration of local anesthetics. Furthermore, the injection itself may be physically challenging due to the density of the lesion: the physician must be able to comfortably generate enough injection pressure to overcome this resistance.[34] Vo et al[35] investigated the effects of various syringe and needle combinations on the injection force to determine the most ergonomic combination. They found that the 1 mL polycarbonate syringe with a 25 G, 16 mm needle was the combination requiring the lowest injection force; thus, it was the most ergonomic combination for injecting into keloids.

TAC intralesional injection compared and combined with other treatment modalities

Triamcinolone and verapamil

Verapamil is a calcium antagonist, which is commonly used for treating hypertension and cardiac arrhythmias. It is also able to depolymerize actin filaments, thus modifying fibroblast morphology from a bipolar to a spheroidal shape, consequently increasing the synthesis of procollagenase in the ECM, leading therefore to an increase in collagen degradation.[36,37]

Ahuja and Chatterjee[38] compared triamcinolone (40 mg/mL) and verapamil (2.5 mg/mL) intralesional injections in a non-inferiority blinded clinical trial. Injections were performed every 3 weeks until complete flattening of the scar, for a maximum of eight sessions. Scar pliability, vascularity, height and pigmentation were evaluated by Vancouver Scar Scale (VSS) score. Mean zero VSS scores were achieved with both treatments with respect to scar height, vascularity and pliability, but the response to TAC was faster and more effective, although with a higher complication rate (skin atrophy and telangiectasias). Conversely, no adverse effects were reported with verapamil, except for the injection-related pain requiring analgesia. The study, limited by the 6-month follow-up, was unable to provide data on the tendency of the scar toward hypertrophy in the longer term.

TAC was shown to be more effective than verapamil in preventing keloid recurrence after surgical excision, as found by Danielsen et al.[39] The peculiarity of the study was the paired split-scar design, each patient being their own control: 14 patients with keloid scars were enrolled; after surgical excision, one-half of the suture line was randomly allocated to receive triamcinolone 2 mg/cm (maximum total dose 10 mg), whereas the other half received verapamil hydrochloride 0.5 mg/cm (maximum total dose 2.5 mg). Intradermal injection of both drugs was performed immediately postoperatively and every 4 weeks for 3 months. Since atrophy occurred in the steroid-treated half of the scar in four patients (who were excluded from the trial), TAC dose was halved to 1 mg/cm (maximum total dose 5 mg) for new and ongoing subjects. At 12-month follow-up, a significantly higher overall risk of recurrence was found with verapamil.

From a biological standpoint, since triamcinolone acts by decreasing proteinase inhibitors and verapamil acts by increasing procollagenase secretion, the effect resulting from the association of both drugs is to increase collagenase levels, thus achieving collagen degradation within the scar.[37] Such a potential synergistic effect was investigated by Kant et al[40] in a retrospective study conducted between 2012 and 2015 on 58 patients treated with a 1:1 mixture of triamcinolone 40 mg/mL and verapamil 2.5 mg/mL. The treatment schedule consisted of a first injection, then repeated 1 and 4 weeks later. Improvements in scar surface area, pliability, relief, pain and itchiness were detected in the keloids' group (27 patients). Patient and Observer Scar Assessment Scale (POSAS) scores, with evaluation at baseline and five follow-up moments (1–3, 3–4, 4–6, 6–12 and >12 months), showed that triamcinolone combined with verapamil was effective at a relatively early stage with statistically significant overall improvements of scars over time.

Hence, verapamil, compared to TAC, is associated with a lower complication rate but higher risk of recurrence. Combined therapy is effective and offers long-term stable results.

Triamcinolone and 5-FU

5-FU is a pyrimidine analog with antimetabolite activity, which is able to block collagen synthesis in vitro by reducing fibroblast activity and to inhibit the TGF-β-induced

expression of the type I collagen gene in human fibroblasts.[41–43] Other than in chemotherapy for some kinds of metastatic cancers, it is widely used in the treatment of hypertrophic and keloid scars.

Several studies compared the efficacy of TAC and 5-FU. Saha and Mukhopadhyay[44] conducted a controlled trial over a period of 2.5 years on 44 patients, randomized into two study groups: patients of the first group were treated with intralesional 5-FU (50 mg/mL); those of the second group with TAC (40 mg/mL). Both groups received injections at weekly intervals for a maximum of six sessions. Even for bigger lesions, the maximum delivered dose never exceeded 2 mL. The reduction in keloid volume (flattening, decrease in length and width) and decrease in itching appeared to be comparable in both groups as well as the recurrence rate within 6 months from the last treatment. However, side effect rates during and after treatment were significantly higher in patients treated with 5-FU: most of them experienced pain (95% vs 4%; $p < 0.05$), hyperpigmentation (90% vs 12.5%, $p = 0.000$) and superficial ulceration (65%) at the injection site. Specifically, no ulceration was observed in any of the patients of the other group ($p = 0.000$). Although no systemic hematologic side effect was reported with 5-FU, triamcinolone was better tolerated.

On the other hand, Sadeghinia and Sadeghinia,[45] in a double-blind clinical trial comparing intralesional injection of triamcinolone and 5-FU administration by tattooing technique, obtained better results with 5-FU. Statistical analysis showed better results in the 5-FU group in terms of decrease in height and surface of the lesions, erythema, induration and pruritus reduction; observers' evaluation and patients' self-assessment were significantly better for the same group. At week 44, no side effects were noted in either of the two groups. The positive outcome could be related to the longer intervals between each administration session (one every 4 weeks apart) and to the peculiar method of intralesional delivery of the drug: double dripping of 5-FU (50 mg/mL) after multiple drilling of the scar by 27 G needle and subsequent occlusion of the keloid.

Even with standard intralesional delivery of the drug, the addition of triamcinolone to 5-FU may produce more effective results and reduce the injection-related pain, as reported for the first time by Fitzpatrick[46] in his 9-year experience. His formula was made by adding 1 mg of TAC to 45 mg of 5-FU. Injections were repeated for a mean of 5–10 times.

Khan et al[47] compared the use of intralesional TAC alone and its combination with 5-FU for the treatment of keloidal and hypertrophic scars. The combination used, 45 mg of 5-FU (0.9 mL of 250 mg/5 mL) and 4 mg of TAC (0.1 mL of 40 mg/1 mL), was administered weekly for 8 weeks. This combination had already been reported as effective.[48] The study found that the combination therapy was superior to TAC alone in reducing the initial height of the scar, also offering a faster response, with fewer undesirable effects, such as skin atrophy and telangiectasias. Similar findings were reported in other studies.[49–51]

It is important to understand that a dose of 10–40 mg/mL of TAC is usually required to have any effect in keloid or hypertrophic scar reduction. The small amount of TAC used in combination with 5-FU is not therapeutic, but it might play an important role in reducing 5-FU-induced inflammation. Side effects such as erythema, hyperpigmentation and ulceration are common when pure 5-FU is used. A small concentration of TAC may reduce the risk of such local side effects.[47]

Triamcinolone and laser therapy

Different kinds of laser treatments were described to address keloids. Laser therapies for keloids fall into two categories: ablative and non-ablative. Ablative lasers, such as the 2940 nm erbium:YAG laser and the 10600 nm CO_2 laser, emit energy absorbed by water in skin resulting in local tissue destruction. Non-ablative lasers target skin chromophores, such as hemoglobin or melanin, according to the principle of selective photothermolysis. The 585 or 595 nm pulsed-dye lasers, the 980 nm diode laser and the 1064 nm Nd:YAG laser cause selective damage to blood vessels that supply the scar.[52] The heat energy produced by lasers causes collagen denaturation, dissociating disulfide bonds and realigning collagen fibers.[53–55] Therefore, it is plausible that non-ablative lasers may interact directly with and affect the biological function of keloidal fibroblasts. However, laser therapy alone (pulsed dye, CO_2, Nd:YAG) is burdened with a high recurrence rate at 6–24 months.[56–60] For CO_2 laser, better results were reported in association with 2 mL of triamcinolone 40 mg/mL injection.[61] In a clinical study on 17 patients, whose keloids had been previously treated by Nd:YAG laser, complete resolution and full flattening in seven patients were achieved only by intralesional TAC, following the laser procedures.[62] In a retrospective study, combined therapy of 300 µs 1064 nm Nd:YAG laser plus intralesional triamcinolone proved more effective than corticosteroid alone in reducing thickness and erythema of the keloid scars. No hyperpigmentation nor hypopigmentation was detected, even in Fitzpatrick skin types IV to VI.[63]

Kassab and El Kharbotly[64] described successful treatment of ear lobule keloids with 980 nm diode laser (single mode,

4-second duration, 5 W power, 20 J/cm^2 energy fluence). In each laser treatment session, five to nine pulses were delivered, depending on the lesion size and darkness degree. Each laser session was followed by intralesional injection of 1 mL of 40 mg/mL TAC. An effective response, or rather a decrease in the keloid size of 75% or more, was achieved in 12 out of 16 lesions. The number of sessions needed to achieve the best result ranged from two to five. Skin erythema was observed immediately in all patients, whereas persistent minimal hyperpigmentation was recorded in four lesions.

Recently, Kraeva et al[1] suggested an alternative method of administration of the corticosteroid: laser-assisted drug delivery of topical TAC, following each session of CO_2 laser, was successfully employed for a keloid on the posterior scalp in an African-American man. According to the authors, the laser enhanced the drug delivery to the dermis, avoiding painful injections; on the other hand, the steroid decreased the risk of post-inflammatory hyperpigmentation, following the laser procedure.

More advanced possibilities of needle-less intraepidermal drug delivery are being explored: Singhal et al[65] created polymeric microparticles containing TAC, which were prepared using a freeze fracture technique employing cryomilling. These microparticles can be deposited in cutaneous micropores following ablation with fractional erbium:YAG laser. This technique could provide high-dose intraepidermal drug reservoir systems, resulting in a sustained and localized action, with minimal transdermal permeation. Further preclinical and clinical studies are needed to establish safety, feasibility and effectiveness of this approach.

Triamcinolone and silicone gel sheet

Topical silicone gel sheet was first reported as an effective treatment for burn scars by Perkins et al.[66] Gold[67] showed that 12 weeks of treatment with silicone dressing was effective in improving hypertrophic scars and keloids, recommending it as the optimal duration of treatment. The mechanisms of silicone gel sheet on keloids are only partially known. It has been shown that occlusion decreases IL-lα mRNA, which results in a reduction in pro-inflammatory IL-1α and IL-6 and subsequent human fibroblast synthesis and activation.[68,69]

Many authors, such as Fulton[70] and Katz,[71] investigated the efficacy of silicone gel sheeting in the treatment of keloids, reporting a high success rate, although lacking a comparison to other treatment modalities.

Tan et al[72] compared the effectiveness of silicone gel sheet and intralesional TAC injections. They reported that only two of the 17 lesions treated with silicone gel sheet showed a reduction in size greater than 50%. This result, however, was not statistically significant ($p < 0.05$) when compared to the untreated control lesions. Conversely, 16 of the 17 lesions treated with intralesional TAC injections at a concentration of 40 mg/mL and 4 weeks of time interval showed a significant reduction in size, and this result was statistically significant ($p < 0,05$) when compared to the untreated lesions.

Only three articles comparing silicone gel sheet and TAC intralesional injections for the treatment of keloids were found in the literature.[72–74] Further comparative studies with a higher population for each group would be useful for a better understanding.

Excision and radiation

The combination of surgical excision plus postoperative irradiation is another option for treating keloids. The recurrence and efficacy rates reported in the literature vary significantly. The recurrence rate ranges from 10% to 100%.[3]

Yamawaki et al[75] showed their experience with the combination of surgical excision and radiation therapy. They treated 91 keloids with extralesional excision and irradiation 72 hours after the operation. The total dose was 20 Gy delivered in five fractions of 4 Gy per every other day, except for ear keloids which were given a total dose of 16 Gy in four fractions. During the follow-up period, they detected signs of recurrence in 46 of 91 keloids that were treated with intralesional TAC injections. At the end of follow-up time, 5 years after the surgical excision and radiation therapy, 81 of 91 keloids showed excellent or good results.

Kuo et al[76] showed that irradiation and intralesional corticosteroid injections can suppress the synthesis of type I collagen and fibronectin by keloid fibroblasts. However, the underlying molecular mechanisms remain largely unknown. Irradiation is likely to damage the majority of keloid cells but may not be strong enough to completely remove all cells. This might explain the high recurrence rate of this treatment modality and the need to administer intralesional TAC injections to inhibit re-propagation of the keloid from certain cell types that are resistant to irradiation. One of the major concerns about radiation therapy is its potential carcinogenic effect that depends on the dose, organ and age. The authors, in fact, in their protocol, administered a dose not greater than 20 Gy and did not irradiate patients aged <10 years.

Triamcinolone and bleomycin

Bleomycin is a water-soluble glycopeptide antibiotic with anticarcinogenic, antibacterial and antiviral effects.

Bodokh and Brun[77] first used bleomycin to treat keloids, showing complete remission in 47% of cases. Further studies demonstrated the efficacy of intralesional bleomycin injections.[78–80]

Payapvipapong et al[78] compared the efficacy of intralesional bleomycin injections (1 IU/mL) to intralesional TAC (10 mg/mL) injections; 26 patients were included in the study and divided into two groups, each treated either with bleomycin or with TAC injections once every 4 weeks for three consecutive sessions. They assessed results with both objective measures, such as photography and ultrasonography, and subjective measures, such as POSAS and self-rated patient satisfaction score. No difference between the two groups was reported. The authors reported, however, a high rate of hyperpigmentation (71.4%), partially due to the population being Fitzpatrick type III–IV. For this reason, TAC is recommended over bleomycin in darker skin populations.

Triamcinolone and pressure therapy

Pressure therapy was introduced in the 1970s when clinicians noted that pressure stockings applied on lower extremity wounds reduced erythema and scar thickness.[81] Pressure causes localized hypoxia, decreased intercollagenous cohesion, increased collagenase activity and, hence, fibroblast degeneration.[3,82] Furthermore, it induces reorientation of the scar collagen fibers (that become parallel to skin surface), increases hyaluronic acid levels and decreases chondroitin sulfate levels, promoting flattening of the initially elevated scar tissue and reducing the recurrence rates.[14,83–84]

The minimum effective pressure to cause collagen fragmentation and fibroblast degradation should be at least 24 mmHg to exceed the capillary pressure, but it should remain under 30 mmHg to avoid a decrease in peripheral blood circulation resulting in tissue necrosis.[83,85] Although the precise mechanism of compression is not fully understood, success rates of 60–85% were reported from pressure therapy in monotherapy. These rates increased to 90–100% when pressure therapy was applied in combination with surgical excision of keloids.[86]

Carvalhaes et al[87] developed a device similar to an earring to treat auricular keloids with pressure therapy. They treated 81 earlobe keloids with TAC intralesional injections (20–40 mg/mL) once a month for 3 months. They subsequently performed surgical excision and perioperative infiltration in the 4th month, followed by two more TAC injections in the following 2 months. After surgical excision, patients applied pressure earrings on the scar 18 hours/day for 4 months. The earrings exerted a pressure of 30 mmHg but were well tolerated by patients. Results showed very good outcomes with only three recurrences in less than a year. The authors therefore suggested pressure therapy as a very effective method to improve the quality of the scar.

Bran et al[88] developed a similar auricular compression device in 2012 made of two transparent subunits fabricated with acrylate and custom made for every patient. They treated seven auricular keloids with surgical excision and TAC intralesional injection followed by the application of the auricular compression device overnight for at least five nights per week until the scar level matched the level of the surrounding healthy skin. They observed no recurrence during a mean 24-month follow-up time. This device had the advantage of controlling adequately intralesional blood circulation during treatment, thanks to its transparency.

Pressure is more difficult to attain in other body parts, but it should be considered as a good adjuvant therapy for auricular keloids, because it is noninvasive and well tolerated by patients.

Conclusion

TAC intralesional injection is the most widely used treatment for keloid scars, primarily or after surgical excision, alone or in combination with 5-FU, verapamil and bleomycin. It is considered the gold standard in nonsurgical management of hypertrophic and keloid scars. It was proved to be effective in reducing keloid scar dimensions, alleviating symptoms such as itching and pain and preventing recurrence. Alone, it is more effective than verapamil and better tolerated than 5-FU and bleomycin. However, local complications such as delayed wound healing, hypopigmentation, dermal atrophy, telangiectasias, widening of the scar and systemic adverse effects such as Cushing's syndrome may occur. Care must be taken when administering triamcinolone in children and patients with multiple or very large lesions: in such cases, intralesional steroid injection may be unviable since the pain of injection is considerable and large doses of corticosteroids are needed.

Combined treatments are usually associated with better outcomes and higher patients' satisfaction. Association of triamcinolone and verapamil was proved to be effective in ensuring significant overall improvements of the scars over time and long-term stable results. Combined administration of triamcinolone and 5-FU may reduce injection-site 5-FU-related undesirable effects, such as pain, erythema and superficial ulceration.

Triamcinolone reduces keloid recurrence after surgical excision, followed or not by radiation therapy or

laser (pulsed dye, Nd: YAG, CO_2) ablation. It can also prevent post-inflammatory hyperpigmentation after laser treatments.

In the treatment of earlobe keloids, pressure devices may play an important role, in combination with triamcinolone intralesional injection.

New mechanisms of intraepidermal needle-less delivery of the drug are being explored: they might improve the efficacy and limit the risk of adverse reactions, in particular those related to systemic exposure. However, further preclinical and clinical trials are needed to establish safety and efficacy of this kind of administration.

Disclosure

The authors report no conflicts of interest in this work.

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