INTRODUCTION

Keloids are a skin disorder in which the skin grows beyond the boundaries of the original wound, although keloids of unrecognized origin also occur. Traditionally, keloids have been seen as the result of aberrant wound healing involving excessive fibroblast participation that is characterised by hyalinised collagen bundles, although the usefulness of this characterisation has been questioned [1,2]. Keloid scars are often considered cosmetically unattractive and frustrating problems that follow injuries and cause functional and cosmetic deformities, displeasure, itching, pain, psychological stress, and patient dissatisfaction, and moreover, can possibly affect joint movement, significantly reduce quality of life, and diminish functional performance. Currently, it remains difficult to assess the effectiveness of diverse treatments for keloids because of the range of factors that influence the efficacy of treatment, including the race, age, and sex of the patient and the anatomical position of the lesion [1-3].
Numerous studies have investigated effective treatments for keloids, but the utility of these treatments and their efficacy when used in various combinations have not been clearly defined. In many cases, keloids result in fibrotic scars that are characterised by abnormal colours, textures, and thicknesses and should be corrected with surgical methods [2]. The methods that have been used to improve keloid scars vary considerably, ranging from surgical to non-surgical methods. In some cases, surgical approaches are inadvisable, and in such cases, intralesional injection treatments play an important role in the treatment of keloids.

Intralesional injection treatments have demonstrated some promising results over the years, including improvements in scar appearance that significantly benefit patients by minimizing the social and economic impacts of scarring and improving their psychological well-being in relation to both function and aesthetics [3]. Trends continue to evolve because many viable options exist for the treatment of pathological scarring, depending on the characteristics of the individual patient and institutional preferences. However, there is still no consensus regarding which intralesional injection techniques are optimal for keloid treatment. This article reviews the latest literature available on the subject and summarizes the mechanism of each treatment, its benefits and associated adverse reactions, and possible strategies to address adverse reactions.

METHODS

Review of the evidence and recent developments (Tables 1, 2) [4-14]

Corticosteroids

Since the mid-1960s, corticosteroid injections, most commonly triamcinolone acetonide, have been a popular treatment for pathological scars, and this treatment continues to play a major role in the management of keloids [14,15]. Depending on the size and site of the lesion and on the age of the patient, the dosage has varied from 10 to 40 mg/mL, and the treatment interval is administered at intervals of 4 to 6 weeks for several months or until the scar is flattened [16,17]. The corticosteroid should be injected at the correct depth in the mid-dermis to avoid irreversible atrophy of the epidermis [14]. Injections should be repeated once every 3–4 weeks depending on the bulk of the keloid and the therapeutic response [16,17].

The triamcinolone injection can suppress vascular endothelial growth factor, inhibit fibroblast proliferation, and induce scar regression, which may be the most important mechanism of action [18]. The effects of corticosteroids are primarily due to their suppressive effects on the inflammatory process in the wound and secondarily due to reduced collagen and glycosaminoglycan synthesis, the inhibition of fibroblast growth, and the enhancement of collagen and fibroblast degeneration [19]. Triamcinolone has been found to inhibit transforming growth factor (TGF)-β1 expression and to induce apoptosis in fibroblasts [18,19].

Intralesional triamcinolone injections are commonly used after surgery in combination with surgical excision of the pathological scar and decrease the recurrence rates by an average of 50%. The rates of response to intralesional corticosteroid injections vary from 50% to 100%. Triamcinolone injection alone also is effective in reducing the volume of lesions in the majority of patients [16-19]. Previous literature has reported that mean scar volumes are reduced from 0.73 ± 0.701 mL at baseline to 0.14 ± 0.302 mL after monthly intralesional injections of triamcinolone acetonide [20,21].

Side effects include the pain of the injections, thinning and atrophy of the skin and subcutaneous tissues, the development of steroid acne, capillary dilation, the development of secondary lymphogenous and linear hypopigmentation (which may be permanent), and relatively high recurrence rates of 9% to 50% [12]. Park et al. [22] concluded that the anatomic location of facial keloids could play a role in re-development, because recurrence rates were greater in perioral regions. A possible reason for this greater recurrence could be skin tension and wound strain in the highly mobile perioral region [22]. Further serious side effects include local skin necrosis, ulcer formation, and Cushing syndrome [23].

The complications can be eliminated by adjusting the dosage and combining the injections with other treatments. In 2002, an international panel of experts recommended that corticosteroid doses of 2.5 to 40 mg per site be used [24]. Surgical excision with intraoperative local injection of triamcinolone acetonide followed by repeated injections at weekly intervals for 2 to 5 weeks and further followed by monthly injections for 4 to 6 months yielded good results with very low rates of recurrence and other complications [21]. The combination of 5-fluorouracil (5-FU) and triamcinolone seems to be superior to intralesional steroid therapy alone in the treatment of keloids; an average reduction in 92% of the lesion size has been reported for this combination therapy compared to 73% for steroid therapy alone [13]. The results may be improved and scar recurrence reduced when corticosteroids are combined with other therapies such as surgery, pulsed-dye laser, radiotherapy, 5-FU, and cryotherapy [25,26].

Camacho-Martínez et al. [6] combined bleomycin and triamcinolone acetonide with injections every 3 months. Contrastingly, Martin et al. [5] combined treatment with a CO2 fractional laser, a Cynergy pulsed-dye laser, and triamcinolone aceton-
### Table 1. Review of the evidence and current developments in corticosteroid intralesional injection treatments

| Study                          | Type of scar | Combination therapy                                                                 | Corticosteroid dosage | Interval                        | Result                                                                 | Side effect                                                                 |
|-------------------------------|--------------|--------------------------------------------------------------------------------------|-----------------------|---------------------------------|------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Park et al. (2013) [4]         | Keloids      | Surgical excision followed NA by full-thickness skin grafting combined with postoperative steroid injections | Triamcinolone (0.5 mL, 40 mg/mL) (in a syringe of 0.5 mL) | Four corticosteroid injections (at one month intervals) postoperatively | - 78.5% experienced successful treatment                                | - Recurrence                                                                |
|                               |              | - Reduced volume of lesions                                                          |                       |                                 | - 21.5% experienced recurrence                                         | - Slight marginal elevation and redness                                   |
| Martin et al. (2013) [5]       | Keloids      | CO2 fractional laser (10,600 nm, Cynosure), Cynergy pulsed dye laser (585 nm, Cynosure), triamcinolone acetate injection | Triamcinolone acetate (0.10–0.125 mL in a syringe of 0.5 mL) | Once per month for seven sessions | - Minimal flatness                                                       | - Minimal effect on size                                                   |
|                               |              | - Decreased recurrence rates                                                         |                       |                                 | - Pruritus diminished                                                   | - Lighter pigmentation                                                    |
| Camacho-Martinez et al. (2013) [6] | Keloids and hypertrophic scars | Bleomycin and triamcinolone acetate (578 nm, 2 mg/mL for a tough bulky lesion)  | Triamcinolone acetate (0.10–0.125 mL in a syringe of 0.5 mL) | Every 3 mo                                                             | - Flattening                                                            | - Early recurrence                                                        |
|                               |              | 4–5 mg/cm² of a 40 mg/mL triamcinolone acetate (0.10–0.125 mL in a syringe of 0.5 mL) |                       |                                 | - Scar height reduction                                                | - Softening                                                               |
| Son et al. (2014) [7]          | Keloids and hypertrophic scars | Surgical excision, intralesional triamcinolone acetate injections | Triamcinolone acetate (0.10–0.125 mL in a syringe of 0.5 mL) | Combined treatment at 4-week intervals | - Reduced vascular components of scars                                 | - Telangiectasia                                                         |
|                               |              | - Decreased erythema                                                                 |                       |                                 | - Decreased fibroblast proliferation                                   | - Ulceration                                                             |
|                               |              | - Reduction of inflammatory processes                                               |                       |                                 | - Erythema                                                             | - Hemorrhage                                                             |
| Emad et al. (2010) [8]         | Keloids      | Surgical excision and immediate postoperative radiotherapy vs. cryotherapy and intralesional steroids | Triamcinolone acetate (0.10–0.125 mL in a syringe of 0.5 mL) | Every 20 day                                                            | - 66.7% satisfied                                                       | - Hypopigmentation                                                       |
| Sadeghinia et al. (2011) [9]   | Keloids      | Keloidectomy with core fillet flap and intralesional steroid injections              | Triamcinolone acetate (0.10–0.125 mL in a syringe of 0.5 mL) | Every 4 wk for 12 wk          | - Reduced erythema and pruritus                                        | - Full-flap necrosis                                                      |
| Al Aradi et al. (2013) [10]    | Keloids      | Surgical excision and immediate postoperative radiotherapy vs. cryotherapy and intralesional steroids | Triamcinolone acetate (0.10–0.125 mL in a syringe of 0.5 mL) | Monthly                     | - Efficacy 87.6%                                                       | - Alopecia                                                               |
|                               |              | - Abscess-like nodule                                                               |                       |                                 | - Immediate recurrence                                                  | - Hypopigmentation                                                       |
|                               |              | - Subjectively, 82.3% patients were highly satisfied                                |                       |                                 | - Mild hyperpigmentation                                                |                                                                           |
| Anthony et al. (2010) [11]     | Keloids      | Triamcinolone corticosteroid                                                         | Triamcinolone acetate (0.10–0.125 mL in a syringe of 0.5 mL) | 4-week intervals | - Triamcinolone 10 mg/mL followed by 40 mg/mL (Regimen 3) was most effective, with the lowest recurrence rate (10%) | - 21.5% experienced recurrence                                             |
|                               |              | - Nonbearded area of the face ←→ mean dose of steroid of 8.75 mg                    |                       |                                 | - Regimen 1 had 22% recurrence                                          | - Regimen 2 had 25% recurrence                                             |
|                               |              | - The bearded area (upper lip, earlobe, occipital area, sternum) ←→ mean dose of 20.37 mg |                       |                                 | - Regimen 2 had 25% recurrence                                          | - Regimen 3 had 10% recurrence                                             |
|                               |              | - Regimen 1 = 10 mg/mL of TAC                                                        |                       |                                 | - Regimen 4 had 24% recurrence                                          | - Regimen 4 had 24% recurrence                                             |
|                               |              | - Regimen 2 = 40 mg/mL                                                              |                       |                                 | - Regimen 5 had 50% recurrence                                          | - Regimen 5 had 50% recurrence                                             |
|                               |              | - Regimen 3 = 10 mg/mL followed by 40 mg/mL                                         |                       |                                 |                                                                       |                                                                           |
| Niessen et al. (1999) [12]     | Keloids      | Triamcinolone corticosteroid (review)                                               | Triamcinolone acetate (0.10–0.125 mL in a syringe of 0.5 mL) | Monthly                     | - Decreased recurrence rates                                           | - Atrophy                                                                |
|                               |              | - Decreased collagen and glycosaminoglycan synthesis                                |                       |                                 | - Decreased collagen and glycosaminoglycan synthesis                    | - Necrosis                                                               |
|                               |              | - Reduction of inflammatory processes                                               |                       |                                 | - Telangiectasia                                                       | - Telangiectasia                                                         |
|                               |              | - Decreased fibroblast proliferation                                                |                       |                                 | - Depigmentation                                                       | - Hypopigmentation                                                       |
| Davison et al. (2011) [13]     | Keloids      | Triamcinolone corticosteroid                                                         | Triamcinolone acetate (0.10–0.125 mL in a syringe of 0.5 mL) | Monthly                     | - 92% average reduction in lesion size                                  | - Telangiectasia                                                         |
|                               |              | - 0.1 mL of solution per centimeter of lesion                                        |                       |                                 | - Reduction of pruritus                                                |                                                                           |
| Gupta et al. (2011) [14]       | Keloids      | 5-fluorouracil and triamcinolone                                                    | Triamcinolone acetate (0.10–0.125 mL in a syringe of 0.5 mL) | 4-week intervals | - Reduced volume of lesions                                            | - Irreversible atrophy                                                   |
|                               |              | - Generally 10–20 mg/mL, 40 mg/mL for a tough bulky lesion                           |                       |                                 |                                                                       |                                                                           |
|                               |              | - 3–4 wk (monthly)                                                                   |                       |                                 |                                                                       |                                                                           |
| NA, none.                     |              |                                                                                  |                       |                                 |                                                                       |                                                                           |
Table 2. Review of the evidence and current developments in non-corticosteroid intralesional injection treatments

| Substance | Dosage suggested | Interval | Outcomes | Adverse reactions | Possible solutions |
|-----------|-----------------|----------|----------|-------------------|-------------------|
| 5-FU      | 40–50 mg/mL     | Weekly   | 1. Improved scar height, erythema, and pliability 2. Histological findings: - Reduction of hyalinised collagen fibers - Less prominent vascularity - Flattening of the dermal papillae without any signs of atrophy - Pigmentary incontinence - Reduction of Ki-67 expression - Slight reduction of TGF-β expression | - Wound ulceration - Hyperpigmentation - Atrophy - Erythema - Tissue sloughing - Swelling - Pain - Molting - Telangiectasia (mostly resolved spontaneously) | Lowering or mixing the doses in cocktail therapy; - Mixing 1 mg/mL triamcinolone (glucocorticoid) with the 5-FU - 50 mg/mL 5-FU in combination with 10 mg/mL triamcinolone or with a very low concentration of betamethasone (5.7 mg/mL) - Triple combination of 5-FU, corticosteroids, and PDL - Above strategies result in better regression without recurrence, substantial flattening, and pruritus |
| Bleomycin | Multiple needle punctures or jet injections of bleomycin (1.5 IU/mL) | Monthly  | - Volume and functional impairment substantially reduced - Substantial flattening - Pruritus relieved | - Flagellate erythema (scratch dermatitis) - Hyperpigmentation - Raynaud’s phenomenon - Gangrene - Fibrosis - Neutrophil eccrine hidradenitis - Necrosis of keratinocytes - Alopecia - Nail changes - Nail changes - Moderately expensive | - Doses were reduced to lower than 200 IU - Multiple jet injections of 0.1 mL of bleomycin (1.5 IU/mL) were administered to each lesion - Multiple punctures were made with a 25-gauge needle and bleomycin (2 mL/cm²) was dripped onto the lesion - Bleomycin performed better than cryotherapy combined with intralesional triamcinolone injection |
| Interferon | 1.5 million IU | Given twice daily over four days | Reduced recurrence after excision | Flu-like symptoms | Flu-like symptoms can be prevented by pre-treatment with 500 mg acetaminophen - The recommendation for postoperative interferon injection is 1,000,000 IU/cm² of skin surrounding the postoperative site administered immediately after surgery and 1 to 2 weeks thereafter - In combination with intralesional corticosteroids and the CO₂ laser, the addition of interferon alpha-2b lowers recurrence rates and leads to better outcomes |
| 0.05 mg of IFN-γ | Injected intradermally once a week for 10 wk | - Reduced keloid surface area and size | - Pain at injection site - Erythema - Oedema - Expensive | - Relatively costly - Minimal hypopigmentation | |
| Cryotherapy | intralesional cryosurgery cryo-needle inserted into keloid scar and connected to a canister of liquid nitrogen, which causes the cryo-needle to freeze at 20 mm depth | Monthly | - Reduced volume - Improved subjective (pain, itching) and objective (hardness, color) ratings | - The non-response rate of this technique was less than 3%, thus representing a promising alternative scar reduction strategy - Combination treatment with surgery PDL, radiation therapy, and 5-FU leads to a better results |
| Versamyl | Intralesional verapamil (2.5 mg/mL) 0.5 mL and 2.0 mL was administered each time, depending on the size of the keloid | Once every 3–4 wk | - Reduction in fibrous tissue production - Reduced scar vascularity, pliability, height, and width | - Pain at injection sites - High recurrence rate | Combination treatment with surgery, corticosteroids, and laser therapy |

FU, fluorouracil; TGF, transforming growth factor; PDL, pulse dye laser; IU, international unit.

ide injections to treat keloids, and they reported excellent results with minimal flatness, diminished pruritus, and lighter pigmentation. Son et al. [7] showed that 42% of patients reported ≥ 75% improvement after treatment with a 578 nm copper bromide laser combined with intralesional corticosteroid injections. In 2011, Sadeghinia and Sadeghinia [9] showed that intralesional triamcinolone acetonide and 5-FU tattooing efficiently reduce erythema, pruritus, surface, and height. Moreover, Anthony et al. [11] showed that triamcinolone concentrations of 10 mg/mL followed by 40 mg/mL were most effective, with the lowest recurrence rate (10%). Park et al. [4] used a very interesting combination therapy in which surgical excisions were followed by full-thickness skin grafting along with postoperative steroid injections, achieving a 78.5% success rate. Email
et al. [8] used surgical excision and immediate postoperative radiotherapy instead of cryotherapy and intralesional steroids, but with only 66.7% satisfactory results. Al Aradi et al. [10] showed that keloidectomies combined with core fillet flaps and intralesional steroid injections resulted in 87.6% efficacy.

5-Fluorouracil

As a pyrimidine analogue, 5-FU is classified as an antineoplastic agent that inhibits normal DNA and RNA synthesis, thereby reducing thymidylate synthase activity. 5-FU has more recently been demonstrated to induce fibroblast apoptosis without necrosis and is known to inhibit TGF-β signalling in collagen I production [27]. Rapidly proliferating and metabolising cells, such as the fibroblasts in dermal wounds that are responsible for excessive collagen production, are an alternate target of 5-FU [15,27-30].

Since 1989, 5-FU has been successful in the treatment of keloids and hypertrophic scars. In 1999, Fitzpatrick [28] improvements in the majority of 1,000 patients who were treated with intralesional 5-FU injections; however, in many of these cases, other treatment modalities, including the pulsed-dye laser and radiation therapy, were combined with intralesional corticosteroid injections.

Kontochristopoulos et al. [29] treated 20 patients with intralesional injections of 5-FU (50 mg/mL) once weekly for seven weeks and followed these patients for up for 12 months. The results revealed that 85% of the patients experienced greater than 50% improvement. Biopsy specimens taken after six injections exhibited a reduction in the amount of hyalinised collagen fibres, regression of the nodular concentric arrangement of the collagen fibres, less prominent vascularity, flattening of the dermal papillae without any signs of atrophy, pigmentary incontinence, reduction of Ki-67 expression, and a slight reduction of TGF-β expression after treatment [29].

In 2009, Haurani et al. [30] conducted a prospective study to evaluate the efficacy of 5-FU in keloid treatment. The recurrence rate was only 19% at a 1-year follow-up for the keloid group, and the scar volumes ranged from 150% to 525% of the pre-excision baseline values [30].

Some authors have reported wound ulceration and hyperpigmentation, atrophy, erythema, tissue sloughing, swelling, pain, moulting, and telangiectasia as complications [27,31]. However, these complications quickly disappear [27,31].

To minimize the side effects, lower dosages of the mixture are normally administered. Currently, the majority of studies have used the high-dose version of 5-FU therapy (40–50 mg/mL), although some researchers that reported that the low-dose therapy (1.4–3.5 mg/mL) is effective [32,33]. Fitzpatrick [28] was the first to report the use of mixed 1 mg/mL triamcinolone and 5-FU, which resulted in improved efficacy and less painful injections. An intralesional injection of 50 mg/mL 5-FU in combination with 10 mg/mL triamcinolone or with a very low concentration of betamethasone (5.7 mg/mL) results in better regression, with significant flattening and pruritus, and without the recurrence of keloid scars < 2 cm in diameter [27].

There is sufficient evidence to suggest that the combination of 5-FU and triamcinolone is superior to triamcinolone alone (15% vs. 40%), as reported by Davison et al. [13]. Several studies have demonstrated that this combination results in less skin atrophy and telangiectasia than triamcinolone alone [16]. Furthermore, it has been suggested that the triple combination of 5-FU, corticosteroids, and the pulsed-dye laser is even more effective in the treatment of keloids. Fibroblast activity is suppressed by 5-FU, corticosteroids suppress inflammation and fibroblast activity, and the pulsed-dye laser suppresses angiogenesis and endothelial cells [34].

Bleomycin

Bleomycin sulphate is thought to reduce collagen synthesis, to increase degradation secondary to the inhibition of lysyl oxidase, a cross-linking enzyme involved in the maturation of collagen and TGF-β1, and to induce fibroblast apoptosis [35]. The main mode of action through which bleomycin blocks the cell cycle is via the inhibition of DNA synthesis, RNA, and protein synthesis as well as the production of reactive oxygen species [34]. Bleomycin is commonly used as a treatment for warts, hypertrophic scars, and keloids. It is administered either by intralesional injections or by multiple punctures using a 22-gauge needle [36].

Bodokh and Brun [36] treated 31 keloids with three to five intralesional infiltrations of bleomycin and observed a total regression of 84%. The intradermal administration of bleomycin was used to treat 31 keloids, and three to five intralesional infiltrations of bleomycin were administered within one month. The keloid volumes and functional impairments were significantly reduced [36]. Espana et al. [37] administered bleomycin through multiple superficial needle punctures. In each case, the maximum dose applied was 2 mL/cm² of skin treated with a concentration of 1.5 IU/mL, and a maximum of 6 mL of bleomycin was given per session [37]. Substantial improvement occurred in 100% of lesions (n = 13), after one to five sessions of treatment with two recurrences at the 1-year follow-up [37]. In a larger 50-patient study of keloids and hypertrophic scars using the same multipuncture tattooing technique, Aggarwal et al. [38] reported that approximately 66% of lesions displayed significant or complete scar flattening with a 14% recurrence rate and that pruritus was completely relieved in 89% of the patients. In 2005, Saray and
Gulec [39] evaluated the effects of bleomycin on 15 keloids treated with intralesional multiple jet injections of 0.1 mL bleomycin (1.5 IU/mL) in each lesion. This treatment resulted in complete flattening in 73.3% of the lesions, highly significant flattening in 6.7%, significant flattening in 13.3%, and moderate flattening in 6.7% of the lesions [39]. In 2006, Naeini et al. [40] reported a multiple puncture technique performed on keloids with a 25-gauge needle through which bleomycin (2 mL/cm²) was dripped into the lesion. This technique resulted in an 88% regression of lesions with areas less than 100 mm² [40].

Cutaneous side effects, including flagellate erythema (scratch dermatitis), hyperpigmentation, Raynaud’s phenomenon, gangrene, fibrosis, neutrophil eccrine hidradenitis, necrosis of keratinocytes, alopecia, edema, nail changes, and other miscellaneous reactions have been documented [41]. It is reported that cutaneous toxicity typically occurs at total doses of 200 to 300 IU and that pulmonary fibrosis occurs at doses exceeding 400 IU [41]. The most common complications are minor ulcerations that heal within 10 days and hyperpigmentation that resolves after one year of follow-up [38,39].

Interferon
Interferon (IFN) is a cytokine with antifibrotic, antiviral, and antiproliferative properties. It is widely known to decrease the synthesis of collagen I and III. IFN-α2 is also known to increase collagenase production [42]. IFN-α2b has been shown to prevent hypertrophic scars and keloids by inhibiting cell proliferation and TGF-β1 expression but not by inducing myofibroblast apoptosis [42]. However, the limited efficacy of intralesional therapy might be related to the increase in circulating fibrogenic factors such as TGF-β or N[tau]-methylhistamine [43]. Specifically, IFN-α2b has been proposed to have antiproliferative properties, which might improve the pathologic features of dermal fibrosis directly or via the antagonism of the effects of TGF-β and histamine [43].

Intralesional injection of IFN-α2b (1.5 million IU, given twice daily over four days) resulted in a 50% reduction in keloid size after only nine days and was evidently more effective than intralesional corticosteroids [44]. Additionally, a study by Larrabee et al. [45] reported that 0.05 mg of IFN-γ injected intradermally once a week for 10 weeks was safe and effective (almost 50% achieving ≥ 50% improvement), resulting in moderate size reduction and softening of the keloid lesions. In a study conducted by Berman and Flores [46] in 1997, the injection of IFN-α2b into keloidal excision sites resulted in significantly fewer recurrences (18.7%) compared to triamcinolone acetonide (58.5%) and excision alone (51.2%). Lastly, in an uncontrolled series of 30 patients treated with CO2 laser excision of keloids and adjuvant intralesional INF-α 2b, Conejo-Mir et al. [47] reported a 66% success rate across a long-term follow-up.

Success with this modality varies and systemic side effects may occur, including flu-like symptoms and other unfavourable reactions such as pain at the injection site, local erythema, and oedema [17]. A prospective-controlled clinical trial by Davison et al. [13] investigated the efficacy of IFN-α2b as a post-excisional adjuvant therapy for keloids and reported that this approach was not effective in treating keloids. Recurrence occurred in seven of the 13 in the IFN-α2b group and four of the 26 in the triamcinolone group [13]. al-Khawajah [48] also reported two patients with severe systemic symptoms such as fever, headache, arthralgias, fatigue, chills, and confusion and found that the remainder of the patients experienced some degree of mild flu-like symptoms, which led to the conclusion that this was considered a high-cost therapy.

The side effect of flu-like symptoms can be prevented by pre-treatment with 500 mg acetaminophen [49]. The recommendation for postoperative interferon injection is 1,000,000 IU/cm² of skin surrounding the postoperative site, administered immediately after surgery and one to two weeks thereafter [50]. In combination with other modalities, such as intralesional triamcinolone acetate and CO2 lasers, IFN-α2b lowers recurrence rates and leads to good outcomes [35,47].

Cryotherapy
Cryotherapy has been used to treat keloids either as a monotherapy or in combination with intralesional triamcinolone injections. In 1994, Layton et al. [51] showed in a randomized clinical trial that vascular lesions showed a significant response to cryotherapy but that this effect was limited to small regions. Histologically, intralesional cryotherapy may cause a reduction in myofibroblasts and mast cells, in addition to the normalization of collagen structure and organization [52]. Recently, intralesional cryosurgical cryoneedles have been introduced. The needle is inserted into the keloid scar and is connected to a canister of liquid nitrogen, which causes the cryoneedle to freeze and consequently freezes the scar tissue from the inside out. Significant alleviation of clinical symptoms was achieved using this technique [52]. Intraleisonal cryosurgery transforms the scar architecture: the collagen fibres become aligned in a more parallel arrangement and the structure mimics a normal, organized dermis [52].

In 2004, Zouboulis et al. [53] introduced an intralesional needle cryosurgery device for both hypertrophic scars and keloids. These authors reported a 51% average reduction in lesion volume and significantly improved subjective (pain, itching) and objective (hardness, colour) ratings [53]. This method is more effective for treating the deeper parts of scars and larger and
bulkier keloids [15]. An average of 51% scar volume reduction was achieved following a single cryogenic treatment [53]. In another recent study, scar volume reductions of 70% for ear keloids and 60% for keloids on the upper back, shoulder, and chest were achieved following single cryo-sessions [54].

Further basic research should be performed to explain these discrepancies. Although this technology is relatively costly, it appears comparatively cost-effective because a single cryo-session is frequently sufficient to induce significant improvement in keloids [51-54]. No worsening or infection of the treated scars has been noted, and only minimal hypopigmentation is evident [51-54]. The non-response rate of this technique is less than 3%; thus, this technique represents a promising alternative scar reduction strategy [54].

Verapamil

Verapamil is a phenylalkylamine calcium channel blocker anti-arrhythmic agent that alters fibroblast shape (from bipolar to spherical), induces procollagenase expression, inhibits the synthesis/secretion of extracellular matrix molecules, including collagen, glycosaminoglycans, and fibronectin, and increases collagenase [55]. Increased cytokine (interleukin) IL-6 and vascular endothelial growth factor levels have been shown to be expressed in fibroblasts from keloids and to contribute to matrix abnormalities and cell proliferation [56-58]. In cell cultures, verapamil has been observed to decrease IL-6 and vascular endothelial growth factor production in the central keloid fibroblasts, which translates to decreased cell proliferation, increased apoptosis, and increased expression of decorin, which is an inhibitor of fibroblast proliferation and migration [56]. Decorin may be present in low amounts in hypertrophic and keloid scars. When added to intralesional triamcinolone, the calcium channel blocker verapamil has been shown to augment decorin expression in animal models [59].

Lawrence [58] found that excision of keloids followed by pressure dressings and intralesional verapamil resulted in a 55% reduction in keloid scarring at an average follow-up interval of 28 months. D’Andrea et al. [59] found that adjunctive verapamil helped to reduce the incidence of keloid recurrence after surgical excision and topical silicone application. A single-blind, parallel-group study demonstrated that intralesional verapamil was comparable to intralesional triamcinolone acetonide in the treatment of keloids. Both were found to produce similar results (i.e., reductions of scar vascularity, pliability, height, and width) [60]. Intralesional triamcinolone achieved these effects faster but also had a greater incidence of adverse reactions than intralesional verapamil did [60].

Future directions of treatment

Several other modalities for the intralesional injection treatment of keloids and hypertrophic scars have been investigated, many of which are in the early stages and may prove to be viable therapies in the future.

Interleukin-10

IL-10 is a cytokine that reduces inflammatory responses. IL-10 is necessary for scarless wound repair, and its anti-inflammatory effects are mediated through reductions of IL-6 and IL-8, which are proinflammatory cytokines [61]. The absence of IL-10 leads to an amplified inflammatory response and abnormal collagen deposition. An adult murine model of wound healing revealed that injection of IL-10 48 hours before wounding led to decreased inflammation and decreased expression of proinflammatory mediators compared to controls [62]. At 3 weeks, the treated wounds showed decreased inflammation, normal dermal architecture, and no abnormal collagen deposition [62].

Botulinum toxin type A

Botulinum toxin type A (BTX-A) is a potent neurotoxin derived from Clostridium botulinum that causes the flaccid paralysis of striated muscle by inhibiting acetylcholine release at the neuromuscular junction. BTX-A is an accepted standard treatment for upper face rejuvenation [63]. BTA immobilises local muscles and reduces skin tension caused by muscle pull, thus decreasing microtrauma and subsequent inflammation [64]. The reduction of the tensile force during the course of cicatrisation and the effective regulation of the balance between fibroblast proliferation and cellular apoptosis may represent a novel therapeutic option for the aesthetic improvement of post-surgical scars.

In 2006, Gassner et al. [65] demonstrated that BTX injections into the musculature adjacent to the wound (15 IU of BTX-A, Allergan) resulted in enhanced wound healing and less noticeable scars. In one in vitro study, fibroblasts from eight keloids were treated with BTX-A. Measurements of the cell cycle distributions demonstrated that notably higher numbers of experimental fibroblasts (64%) were in the non-proliferative phases (G0 and G1) compared to the control (36%) [66]. The same author conducted a prospective, uncontrolled study to evaluate the effects of BTA in the treatment of ear keloids with a 24-gauge needle [67]. Per session, 70–140 IUs of BTX-A were injected intralesionally into 12 ear keloids in three sessions once a month. The results were excellent in three patients, good in five patients, and fair in four patients after 1 year of follow-up. However, there was no failure of therapy or signs of recurrence. In 2008, another study confirmed the ability of BTX-A to reduce the expression
of TGF-β1 in keloid fibroblasts [67]. Transforming growth factor β1 is thought to be the main regulator of the pathogenesis of keloids and is associated with an excessive deposition of scar tissue and fibrosis [68]. In a 2009 study by Xiao et al. [69], single-dose treatments with BTX-A at 2.5 IU/cm² of lesion at 1-month intervals (not exceeding 100 IU per patient) were used in 19 patients. At six months post-treatment, all patients reported decreases in erythema, itching sensations, and pliability. Haubner et al. [70] recently tested patient-specific keloid tissue in a cell culture model to determine the effects of BTX-A incubation on cell proliferation and the expression of cytokines and growth factors such as IL-6, vascular endothelial growth factor, and TGF-β. They showed that none of the tested parameters of human keloid tissue were affected by BTX-A incubation and concluded that there was no evidence to suggest a significant therapeutic role for BTX-A injections in the treatment of keloids [70]. BTX-A also has analgesic properties that are not yet completely understood, but may disrupt the neuropathic painful symptoms that are present in some keloids [71].

No serious adverse reactions of this treatment have been reported. BTX-A appears to be a safe and effective potential treatment option that can influence cellular apoptosis and proliferation to favour a cellular state that ultimately leads to the prevention and treatment of keloids.

**CONCLUSIONS**

The present overview summarizes current intralesional treatment strategies for keloid and hypertrophic scars along with future perspectives. This overview will benefit practitioners by providing evidence-based treatment strategies using intralesional injections for patients with hypertrophic scars and keloids.

Many treatment options have already been described in the literature, although there is no universally accepted treatment resulting in permanent hypertrophic or keloid scar ablation. Nonetheless, although no definitive conclusions could be presented about the relative effectiveness of various techniques, we highlighted some results with implications for routine clinical practice. Recent studies combining various traditional treatments and ongoing investigations of novel modalities may provide new perspectives on the treatment of scarring. Further investigation will shed light on the mechanism of scarring and will offer more techniques to effectively prevent and treat pathological scars.

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