

Recent Developments in the Use of Intralesional Injections Keloid Treatment

Aurelia Trisliana Perdanasari^{1*}, Davide Lazzeri^{2*}, Weijie Su¹, Wenjing Xi¹, Zhang Zheng¹, Li Ke¹, Peiru Min¹, Shaoqing Feng¹, Yixin Zhang¹, Paolo Persichetti³

¹Department of Plastic and Reconstructive Surgery, Shanghai Ninth People's Hospital, Shanghai JiaoTong University School of Medicine, Shanghai, China; ²Plastic Reconstructive and Aesthetic Surgery Unit, Villa Salaria Clinic, Rome; ³Plastic and Reconstructive Surgery Unit, Campus Bio-Medico University, Rome, Italy

Keloid scars are often considered aesthetically unattractive and frustrating problems that occur following injuries. They cause functional and cosmetic deformities, displeasure, itching, pain, and psychological stress and possibly affect joint movement. The combination of these factors ultimately results in a compromised quality of life and diminished functional performance. Various methods have been implemented to improve keloid scars using both surgical and non-surgical approaches. However, it has proven to be a challenge to identify a universal treatment that can deliver optimal results for all types of scars. Through a PubMed search, we explored most of the literature that is available about the intralesional injection treatment of hypertrophic scars and keloids and highlights both current (corticosteroid, 5-fluorouracil, bleomycin, interferon, cryotherapy and verapamil) and future treatments (interleukin-10 and botulinum toxin type A). The reference lists of retrieved articles were also analysed. Information was gathered about the mechanism of each injection treatment, its benefits and associated adverse reactions, and possible strategies to address adverse reactions to provide reliable guidelines for determining the optimal treatment for particular types of keloid scars. This article will benefit practitioners by outlining evidence-based treatment strategies using intralesional injections for patients with hypertrophic scars and keloids.

Keywords Keloids / Injections, intralesional / Review / Treatment outcome / Cicatrix

Correspondence: Yi Xin Zhang
Department of Plastic and Reconstructive Surgery, Shanghai Ninth People's Hospital, Shanghai JiaoTong University School of Medicine, Shanghai 200011, China
Tel: +86-21-2327-1699
Fax: +86-21-6305-1858
E-mail: zhangyixin6688@hotmail.com

*The first two authors equally contributed to this work.

No potential conflict of interest relevant to this article was reported.

Received: 21 May 2014 • Revised: 5 Sep 2014 • Accepted: 12 Sep 2014
pISSN: 2234-6163 • eISSN: 2234-6171 • <http://dx.doi.org/10.5999/aps.2014.41.6.620> • Arch Plast Surg 2014;41:620-629

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 cos-

metically 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)- β 1 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, radiation therapy, 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 acetonide

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 by full-thickness skin grafting combined with postoperative steroid injections	NA	Four corticosteroid injections (at one month intervals) postoperatively	- 78.5% experienced successful treatment - 21.5% experienced recurrence	- Recurrence - Slight marginal elevation and redness
Martin et al. (2013) [5]	Keloids	CO ₂ fractional laser (10,600 nm, Cynosure), Cynergy pulsed dye laser (585 nm, Cynosure), triamcinolone acetonide injection	Triamcinolone acetonide (0.5 mL, 40 mg/mL 0.4 mL lidocaine with epinephrine)	Once per month for seven sessions	- Minimal flatness - Minimal effect on size - Pruritus diminished - Lighter pigmentation	NA
Camacho-Martínez et al. (2013) [6]	Keloids and hypertrophic scars	Bleomycin and triamcinolone acetonide	4–5 mg/cm ² of a 40 mg/mL triamcinolone acetonide (0.10–0.125 mL in a syringe of 0.5 mL)	Every 3 mo	- Flattening - Scar height reduction - Softening	- Erythema - Telangiectasias - Atrophy - Ulceration - Reoccurrence
Son et al. (2014) [7]	Keloids and hypertrophic scars	578 nm copper bromide laser combined with intralesional corticosteroid injections	10 mg/mL of triamcinolone acetonide	Combined treatment at 4-week intervals	- Reduced vascular components of scars - Decreased erythema - Improved pruritus - Improve telangiectasia 8% = ≤ 25% improvement 17% = 25% to 50% improvement 33% = 51% to 75% improvement 42% = ≥ 75% improvement	- Moderate pain during treatment - Transient erythema and edema - Mild hyperpigmentation
Ernad et al. (2010) [8]	Keloids	Surgical excision and immediate postoperative radiotherapy vs. cryotherapy and intralesional steroids	10 mg/mL of triamcinolone acetonide in each session (maximum 40 mg)	Every 20 day	- 66.7% satisfied - 22.2% partially satisfied - 11.1% unsatisfied	- Hypopigmentation (9.4%) - Ulceration+necrosis (31.2%) - Telangiectasia (18.8%)
Sadeghinia et al. (2011) [9]	Keloids	Intralesional triamcinolone acetonide and 5-fluorouracil tattooing	20 mg (0.5 mL) of TAC (40 mg/mL) was injected per 1 cm ² of the lesion.	Every 4 wk for 12 wk	- Reduced erythema and pruritus - Reduced surface and height	NA
Al Aradi et al. (2013) [10]	Keloids	Keloidectomy with core fillet flap and intralesional steroid injections	40 mg/mL (0.25 mL) of intralesional triamcinolone acetonide	Monthly	- Efficacy 87.6% - Immediate recurrence 9.5% - Subjectively, 82.3% patients were highly satisfied - Softness, flattening, atrophy, pigmentation, and recurrence - Scars were minimal in all patients	- Full-flap necrosis - Abscess-like nodule - Neuroma
Anthony et al. (2010) [11]	Keloids	Triamcinolone corticosteroid	- Nonbearded area of the face → mean dose of steroid of 8.75 mg - The bearded area (upper limb, earlobes, occipital area, sternum) → mean dose of 20.37 mg - Regimen 1 = 10 mg/mL of TAC - Regimen 2 = 40 mg/mL - Regimen 3 = 10 mg/mL followed by 40 mg/mL - Regimen 4 = 10 mg/mL then 40 mg/mL and then 10 mg/mL - Regimen 5 = 40 mg/mL then 10 mg/mL	4-week intervals	- Triamcinolone 10 mg/mL followed by 40 mg/mL (Regimen 3) was most effective, with the lowest recurrence rate (10%)	- Regimen 1 had 22% recurrence - Regimen 2 had 25% recurrence - Regimen 3 had 10% recurrence - Regimen 4 had 24% recurrence - Regimen 5 had 50% recurrence
Niessen et al. (1999) [12]	Keloids and hypertrophic scars	Triamcinolone corticosteroid (review)	10–40 mg/mL	Monthly	- Decreased recurrence rates - Decreased collagen and glycosaminoglycan synthesis - Reduction of inflammatory processes - Decreased fibroblast proliferation	- Atrophy - Ulceration - Necrosis - Telangiectasia - Depigmentation - Cushingoid features - Hypopigmentation
Davison et al. (2011) [13]	Keloids	5-fluorouracil and triamcinolone	0.1 mL of solution per centimeter of lesion	4-week intervals	- 92% average reduction in lesion size - Reduction of pruritus - Pain resolved	Telangiectasias
Gupta et al. (2011) [14]	Keloids and hypertrophic scars	5-fluorouracil and triamcinolone	Generally 10–20 mg/mL, 40 mg/mL for a tough bulky lesion	3–4 wk (monthly)	- Reduced volume of lesions	Irreversible atrophy

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	<ol style="list-style-type: none"> Improved scar height, erythema, and pliability Histological findings: <ul style="list-style-type: none"> - 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 	<ul style="list-style-type: none"> - Wound ulceration - Hyperpigmentation - Atrophy - Erythema - Tissue sloughing - Swelling - Pain - Molting - Telangiectasia (mostly resolved spontaneously) 	<ul style="list-style-type: none"> - Lowering or mixing the doses in cocktail therapy: <ul style="list-style-type: none"> - Mixing 1 mg/mL triamcinolone (glucocorticoids) 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	<ul style="list-style-type: none"> - Volume and functional impairment substantially reduced - Substantial flattening - Pruritus relieved 	<ul style="list-style-type: none"> - Flagellate erythema (scratch dermatitis) - Hyperpigmentation - Raynaud's phenomenon - Gangrene - Fibrosis - Neutrophil eccrine hidradenitis - Necrosis of keratinocytes - Alopecia - Oedema - Nail changes - Moderately expensive 	<ul style="list-style-type: none"> - Dosages 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 0.05 mg of IFN-c	Given twice daily over four days Injected intradermally once a week for 10 wk	<ul style="list-style-type: none"> - Reduced recurrence after excision - Reduced keloid surface area and size 	<ul style="list-style-type: none"> - Flu-like symptoms - Pain at injection site - Local erythema - Oedema - Expensive 	<ul style="list-style-type: none"> - Flu-like symptoms can be prevented by pre-treatment with 500 mg acetaminophen - The recommendation for postoperative interferon injection is 1,000,000 IU/cm 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
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	<ul style="list-style-type: none"> - Reduced volume - Improved subjective (pain, itching) and objective (hardness, color) ratings 	<ul style="list-style-type: none"> - Relatively costly - Minimal hypopigmentation 	<ul style="list-style-type: none"> - 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
Verapamil	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 1 mo after the keloid removal	<ul style="list-style-type: none"> - Reduction in fibrous tissue production - Reduced scar vascularity, pliability, height, and width - Reduced the incidence of keloid recurrence clinically after surgical excision and topical silicone application 	<ul style="list-style-type: none"> - Pain at injection sites - High recurrence rate 	<ul style="list-style-type: none"> - 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 $\geq 75\%$ 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 effi-

ciently 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. Emad

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 to 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 post-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- β 1, 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 multiple-puncture 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- α 2 is also known to increase collagenase production [42]. IFN- α 2b has been shown to prevent hypertrophic scars and keloids by inhibiting cell proliferation and TGF- β 1 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- α 2b 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- α 2b (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-c injected intradermally once a week for 10 weeks was safe and effective (almost 50% achieving \geq 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- α 2b 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 adju-

vant 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- α 2b 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- α 2b 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 pretreatment 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- α 2b 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]. Intralesional 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 cryosessions [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 adjuvant 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 cicatrization 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- β 1 in keloid fibroblasts [67]. Transforming growth factor β 1 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/cm³ 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.

REFERENCES

1. Huang C, Murphy GF, Akaishi S, et al. Keloids and hypertrophic scars: update and future directions. *Plast Reconstr Surg Glob Open* 2013;1:e25.

2. Ogawa R. The most current algorithms for the treatment and prevention of hypertrophic scars and keloids. *Plast Reconstr Surg* 2010;125:557-68.
3. Klinger M, Marazzi M, Vigo D, et al. Fat injection for cases of severe burn outcomes: a new perspective of scar remodeling and reduction. *Aesthetic Plast Surg* 2008;32:465-9.
4. Park TH, Park JH, Chang CH. Clinical features and outcomes of foot keloids treated using complete surgical excision and full thickness skin grafting followed by corticosteroid injections. *J Foot Ankle Res* 2013;6:26.
5. Martin MS, Collawn SS. Combination treatment of CO2 fractional laser, pulsed dye laser, and triamcinolone acetonide injection for refractory keloid scars on the upper back. *J Cosmet Laser Ther* 2013;15:166-70.
6. Camacho-Martinez FM, Rey ER, Serrano FC, et al. Results of a combination of bleomycin and triamcinolone acetonide in the treatment of keloids and hypertrophic scars. *An Bras Dermatol* 2013;88:387-94.
7. Son IP, Park KY, Kim B, et al. Pilot study of the efficacy of 578 nm copper bromide laser combined with intralesional corticosteroid injection for treatment of keloids and hypertrophic scars. *Ann Dermatol* 2014;26:156-61.
8. Emad M, Omidvari S, Dastgheib L, et al. Surgical excision and immediate postoperative radiotherapy versus cryotherapy and intralesional steroids in the management of keloids: a prospective clinical trial. *Med Princ Pract* 2010;19:402-5.
9. Sadeghinia A, Sadeghinia S. Comparison of the efficacy of intralesional triamcinolone acetonide and 5-fluorouracil tattooing for the treatment of keloids. *Dermatol Surg* 2012;38:104-9.
10. Al Aradi IK, Alawadhi SA, Alkhawaja FA, et al. Earlobe keloids: a pilot study of the efficacy of keloidectomy with core fillet flap and adjuvant intralesional corticosteroids. *Dermatol Surg* 2013;39:1514-9.
11. Anthony ET, Lemonas P, Navsaria HA, et al. The cost effectiveness of intralesional steroid therapy for keloids. *Dermatol Surg* 2010;36:1624-6.
12. Niessen FB, Spauwen PH, Schalkwijk J, et al. On the nature of hypertrophic scars and keloids: a review. *Plast Reconstr Surg* 1999;104:1435-58.
13. Davison SP, Dayan JH, Clemens MW, et al. Efficacy of intralesional 5-fluorouracil and triamcinolone in the treatment of keloids. *Aesthet Surg J* 2009;29:40-6.
14. Gupta S, Sharma VK. Standard guidelines of care: Keloids and hypertrophic scars. *Indian J Dermatol Venereol Leprol* 2011;77:94-100.
15. Chen MA, Davidson TM. Scar management: prevention

- and treatment strategies. *Curr Opin Otolaryngol Head Neck Surg* 2005;13:242-7.
16. Manuskhatti W, Fitzpatrick RE. Treatment response of keloidal and hypertrophic sternotomy scars: comparison among intralesional corticosteroid, 5-fluorouracil, and 585-nm flashlamp-pumped pulsed-dye laser treatments. *Arch Dermatol* 2002;138:1149-55.
 17. Mustoe TA, Cooter RD, Gold MH, et al. International clinical recommendations on scar management. *Plast Reconstr Surg* 2002;110:560-71.
 18. Wu WS, Wang FS, Yang KD, et al. Dexamethasone induction of keloid regression through effective suppression of VEGF expression and keloid fibroblast proliferation. *J Invest Dermatol* 2006;126:1264-71.
 19. Boyadjiev C, Popchristova E, Mazgalova J. Histomorphologic changes in keloids treated with Kenacort. *J Trauma* 1995;38:299-302.
 20. Muneuchi G, Suzuki S, Onodera M, et al. Long-term outcome of intralesional injection of triamcinolone acetonide for the treatment of keloid scars in Asian patients. *Scand J Plast Reconstr Surg Hand Surg* 2006;40:111-6.
 21. Atiyeh BS. Nonsurgical management of hypertrophic scars: evidence-based therapies, standard practices, and emerging methods. *Aesthetic Plast Surg* 2007;31:468-92.
 22. Park TH, Seo SW, Kim JK, et al. Clinical characteristics of facial keloids treated with surgical excision followed by intra- and postoperative intralesional steroid injections. *Aesthetic Plast Surg* 2012;36:169-73.
 23. Shaffer JJ, Taylor SC, Cook-Bolden F. Keloidal scars: a review with a critical look at therapeutic options. *J Am Acad Dermatol* 2002;46:S63-97.
 24. Ogawa R, Akaishi S, Izumi M. Histologic analysis of keloids and hypertrophic scars. *Ann Plast Surg* 2009;62:104-5.
 25. Alster TS, Williams CM. Treatment of keloid sternotomy scars with 585 nm flashlamp-pumped pulsed-dye laser. *Lancet* 1995;345:1198-200.
 26. Boutli-Kasapidou F, Tsakiri A, Anagnostou E, et al. Hypertrophic and keloidal scars: an approach to polytherapy. *Int J Dermatol* 2005;44:324-7.
 27. Apikian M, Goodman G. Intralesional 5-fluorouracil in the treatment of keloid scars. *Australas J Dermatol* 2004;45:140-3.
 28. Fitzpatrick RE. Treatment of inflamed hypertrophic scars using intralesional 5-FU. *Dermatol Surg* 1999;25:224-32.
 29. Kontochristopoulos G, Stefanaki C, Panagiotopoulos A, et al. Intralesional 5-fluorouracil in the treatment of keloids: an open clinical and histopathologic study. *J Am Acad Dermatol* 2005;52:474-9.
 30. Haurani MJ, Foreman K, Yang JJ, et al. 5-Fluorouracil treatment of problematic scars. *Plast Reconstr Surg* 2009;123:139-48.
 31. Wang XQ, Liu YK, Wang ZY, et al. Antimitotic drug injections and radiotherapy: a review of the effectiveness of treatment for hypertrophic scars and keloids. *Int J Low Extrem Wounds* 2008;7:151-9.
 32. Liu W, Wu X, Gao Z, et al. Remodelling of keloid tissue into normal-looking skin. *J Plast Reconstr Aesthet Surg* 2008;61:1553-4.
 33. Wu XL, Liu W, Cao YL. Clinical study on keloid treatment with intralesional injection of low concentration 5-fluorouracil. *Zhonghua Zheng Xing Wai Ke Za Zhi* 2006;22:44-6.
 34. Wang XQ, Liu YK, Qing C, et al. A review of the effectiveness of antimitotic drug injections for hypertrophic scars and keloids. *Ann Plast Surg* 2009;63:688-92.
 35. Vivas AC, Tang JC, Maderal AD, et al. Hypertrophic scars and keloids, part 1: conventional treatments. *Cosmet Dermatol* 2012;25:309-16.
 36. Bodokh I, Brun P. Treatment of keloid with intralesional bleomycin. *Ann Dermatol Venereol* 1996;123:791-4.
 37. Espana A, Solano T, Quintanilla E. Bleomycin in the treatment of keloids and hypertrophic scars by multiple needle punctures. *Dermatol Surg* 2001;27:23-7.
 38. Aggarwal H, Saxena A, Lubana PS, et al. Treatment of keloids and hypertrophic scars using bleom. *J Cosmet Dermatol* 2008;7:43-9.
 39. Saray Y, Gulec AT. Treatment of keloids and hypertrophic scars with dermojet injections of bleomycin: a preliminary study. *Int J Dermatol* 2005;44:777-84.
 40. Naeini FF, Najafian J, Ahmadvpour K. Bleomycin tattooing as a promising therapeutic modality in large keloids and hypertrophic scars. *Dermatol Surg* 2006;32:1023-9.
 41. Templeton SF, Solomon AR, Swerlick RA. Intradermal bleomycin injections into normal human skin. A histopathologic and immunopathologic study. *Arch Dermatol* 1994;130:577-83.
 42. Xu SJ, Teng JY, Xie J, et al. Comparison of the mechanisms of intralesional steroid, interferon or verapamil injection in the treatment of proliferative scars. *Zhonghua Zheng Xing Wai Ke Za Zhi* 2009;25:37-40.
 43. Tredget EE, Shankowsky HA, Pannu R, et al. Transforming growth factor-beta in thermally injured patients with hypertrophic scars: effects of interferon alpha-2b. *Plast Reconstr Surg* 1998;102:1317-28.
 44. Berman B, Duncan MR. Short-term keloid treatment in vivo with human interferon alfa-2b results in a selective and persistent normalization of keloidal fibroblast collagen, gly-

- cosaminoglycan, and collagenase production in vitro. *J Am Acad Dermatol* 1989;21:694-702.
45. Larrabee WF Jr, East CA, Jaffe HS, et al. Intralesional interferon gamma treatment for keloids and hypertrophic scars. *Arch Otolaryngol Head Neck Surg* 1990;116:1159-62.
 46. Berman B, Flores F. Recurrence rates of excised keloids treated with postoperative triamcinolone acetonide injections or interferon alfa-2b injections. *J Am Acad Dermatol* 1997;37:755-7.
 47. Conejo-Mir JS, Corbi R, Linares M. Carbon dioxide laser ablation associated with interferon alfa-2b injections reduces the recurrence of keloids. *J Am Acad Dermatol* 1998;39:1039-40.
 48. al-Khawajah MM. Failure of interferon-alpha 2b in the treatment of mature keloids. *Int J Dermatol* 1996;35:515-7.
 49. Jones GJ, Itri LM. Safety and tolerance of recombinant interferon alfa-2a (Roferon-A) in cancer patients. *Cancer* 1986;57:1709-15.
 50. Kelly AP. Medical and surgical therapies for keloids. *Dermatol Ther* 2004;17:212-8.
 51. Layton AM, Yip J, Cunliffe WJ. A comparison of intralesional triamcinolone and cryosurgery in the treatment of acne keloids. *Br J Dermatol* 1994;130:498-501.
 52. Har-Shai Y, Amar M, Sabo E. Intralesional cryotherapy for enhancing the involution of hypertrophic scars and keloids. *Plast Reconstr Surg* 2003;111:1841-52.
 53. Zouboulis CC, Rosenberger AD, Forster T, et al. Modification of a device and its application for intralesional cryosurgery of old recalcitrant keloids. *Arch Dermatol* 2004;140:1293-4.
 54. Tziotzios C, Profyris C, Sterling J. Cutaneous scarring: Pathophysiology, molecular mechanisms, and scar reduction therapeutics Part II. Strategies to reduce scar formation after dermatologic procedures. *J Am Acad Dermatol* 2012;66:13-24.
 55. Copcu E, Sivrioglu N, Oztan Y. Combination of surgery and intralesional verapamil injection in the treatment of the keloid. *J Burn Care Rehabil* 2004;25:1-7.
 56. Giugliano G, Pasquali D, Notaro A, et al. Verapamil inhibits interleukin-6 and vascular endothelial growth factor production in primary cultures of keloid fibroblasts. *Br J Plast Surg* 2003;56:804-9.
 57. Yang JY, Huang CY. The effect of combined steroid and calcium channel blocker injection on human hypertrophic scars in animal model: a new strategy for the treatment of hypertrophic scars. *Dermatol Surg* 2010;36:1942-9.
 58. Lawrence WT. Treatment of earlobe keloids with surgery plus adjuvant intralesional verapamil and pressure earrings. *Ann Plast Surg* 1996;37:167-9.
 59. D'Andrea F, Brongio S, Ferraro G, et al. Prevention and treatment of keloids with intralesional verapamil. *Dermatology* 2002;204:60-2.
 60. Margaret Shanthi FX, Ernest K, Dhanraj P. Comparison of intralesional verapamil with intralesional triamcinolone in the treatment of hypertrophic scars and keloids. *Indian J Dermatol Venereol Leprol* 2008;74:343-8.
 61. Liechty KW, Kim HB, Adzick NS, et al. Fetal wound repair results in scar formation in interleukin-10-deficient mice in a syngeneic murine model of scarless fetal wound repair. *J Pediatr Surg* 2000;35:866-72.
 62. Hanasono MM, Kita M, Mikulec AA, et al. Autocrine growth factor production by fetal, keloid, and normal dermal fibroblasts. *Arch Facial Plast Surg* 2003;5:26-30.
 63. Liu RK, Li CH, Zou SJ. Reducing scar formation after lip repair by injecting botulinum toxin. *Plast Reconstr Surg* 2010;125:1573-4.
 64. Viera MH, Amini S, Valins W, et al. Innovative therapies in the treatment of keloids and hypertrophic scars. *J Clin Aesthet Dermatol* 2010;3:20-6.
 65. Gassner HG, Brissett AE, Otlely CC, et al. Botulinum toxin to improve facial wound healing: a prospective, blinded, placebo-controlled study. *Mayo Clin Proc* 2006;81:1023-8.
 66. Zhibo X, Miaobo Z. Botulinum toxin type A affects cell cycle distribution of fibroblasts derived from hypertrophic scar. *J Plast Reconstr Aesthet Surg* 2008;61:1128-9.
 67. Zhibo X, Miaobo Z. Intralesional botulinum toxin type A injection as a new treatment measure for keloids. *Plast Reconstr Surg* 2009;124:275e-277e.
 68. Xiao Z, Zhang F, Lin W, et al. Effect of botulinum toxin type A on transforming growth factor beta1 in fibroblasts derived from hypertrophic scar: a preliminary report. *Aesthetic Plast Surg* 2010;34:424-7.
 69. Xiao Z, Zhang F, Cui Z. Treatment of hypertrophic scars with intralesional botulinum toxin type A injections: a preliminary report. *Aesthetic Plast Surg* 2009;33:409-12.
 70. Haubner F, Leyh M, Ohmann E, et al. Effects of botulinum toxin A on patient-specific keloid fibroblasts in vitro. *Laryngoscope* 2014;124:1344-51.
 71. Maderal AD, Tang JC, Vivas AC, et al. Hypertrophic scars and keloids, part 2: newer and investigational therapies. *Cosmet Dermatol* 2012;25:373-9.