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Interferon Therapy for Hypertrophic Scars and Keloids

Amalorpava Mary Loordhuswamy and Santhini Elango

Abstract

Interferons (IFNs) belong to the family of cytokines are widely used to treat keloids owing to their ability to increase collagenase activity thereby reducing the production of collagen and other extracellular matrix (ECM). Intralesional injection of IFN- α – 2b increases the collagenase level by inhibiting the secretion of metalloproteinases, an inhibitor of collagenase. Moreover, the anti-fibrotic activity of IFNs, interfere with fibroblast mediated collagen synthesis. On the other hand, combinatorial therapy has been preferred recently along with IFN due to its side effects observed in various clinical trials conducted only with IFN. Triamcinolone acetone (TAC) and CO₂ lasers along with IFNs are found to be the potential therapy for the treatment of scars and keloids. In this chapter, IFN mediated therapy for the treatment of scars and keloids, its benefits and limitations and the advantages of combinatorial therapy with the appropriate literature support are discussed.

Keywords: *hypertrophic* scars, keloids, interferon, collagen synthesis, combinatorial therapy

1. Introduction

Hypertrophic scars and keloids are the most common skin disease associated with aesthetically disfiguring morphology, pain, itching, discomfort as well as psychological stress and affect individual life style [1]. This disease is characterized by over production of extracellular matrix collagen and proteoglycans [2]. The development of keloids involves unpredictable irregular arrangement of collagen and other extra cellular proteins in the milieu of wound healing. Wound healing is a well orchestrated sequential process happening through the four distinct steps such as hemostasis, inflammation, proliferation and tissue remodeling [3]. In hemostasis, immediately after an injury, platelet degranulation and activation of compliments initiates blood clotting and forms fibrin network at the site of injury which act as a scaffold for wound repair [4]. Platelet degranulation is crucial step for the release and activation of cytokines including epidermal growth factor (EGF), insulin like growth factor (IGF-I), platelet-derived growth factor (PDGF) and transforming growth factor β (TGF- β). These cytokines acts as chemotactic agents for the recruitment of neutrophils, macrophages, epithelial cells, mast cells, endothelial cells and fibroblasts [5–7]. The recruited fibroblast, synthesis granulation tissue made up of procollagen, elastin, proteoglycans, hyaluronic acid and forms a structural repair framework to bridge the wound and allow vascular in growth. At that time, myofibroblast which contain actin filament initiates wound contraction. Once the

wound is closed, the abundant Extra Cellular Matrix (ECM) is then degraded and the immature type III collagen of the early wound is modified into mature type I collagen. Proper balance between ECM protein deposition and degradation is required for wound healing with minimal scarring. Once this balance is disrupted, abnormalities in scarring appear, resulting in the formation of either hypertrophic scar or keloids [8, 9]. The mechanism of *Hypertrophic* scar and keloid formation is given in the **Figure 1**. Both lesions are formed by the occurrence of imbalance between anabolic and catabolic process of wound healing, however keloids seems to be more aggressive fibrotic disorder compared to *hypertrophic* scars [10]. Keloids are more prevalent in Dark skinned individuals of Africa, Asia and Hispanic descents compared to Caucasians [11]. The occurrence of keloids in these population is found to be in the range of 5–16%. The risks of developing keloids are equal in both male and females. Due to the cosmetic procedures such as ear and nose piercing and physiological conditions like puberty and pregnancy, females have more risk for developing keloids compared to male. Persons with the age around 10 to 30 are more prone to develop keloids compared to other age groups [12, 13]. Apart from sex and age, additional risk factor include having blood group A, hyper-IgE and hormonal peaks during pregnancy and puberty also play a role in developing keloids [14]. In recent days, numbers of gene and gene loci associated with keloid development have been identified. Single nucleotide polymorphism has identified in certain loci of NEDD4 genes by genome wide association studies and admixture mapping studies which is genetically linked to keloid development. In addition to that, several human leucocyte antigen (HLA) alleles, p53, bcl-2 and fas genes have also involved in keloid development [15–17]. Studies have also reported that people with rare genetic disorders including Dubowitz syndrome, Bethlem myopathy, Rubinstein-Taybi syndrome, Noonan syndrome and Geominne syndrome have the risk of developing keloids [15].

Figure 1.
Mechanism of Hypertrophic scars and keloid formation.

2. Currently available treatments

At present, various forms of treatment for keloids are available but no single therapeutic modality is best for all keloids. The size, location, depth of lesion, age,

S. No	Current and emerging therapies available for hypertrophic scars and keloid treatments	Types	Mode of action	Limitations
1.	Corticosteroids [19–22]	Triamcinolone acetonide (TAC), hydrocortisone acetate, dexamethasone and methyl prednisolone	Inhibit the growth of fibroblast, attenuate the synthesis of procollagen and glycosaminoglycan, reduce endothelial budding and enhance the degeneration of collagen and fibroblast, inhibit TGF - β 1 expression in fibroblast, inhibit VEGF and alphaglobulins.	Telangiectasis, atrophy, steroid acne, pigmentary changes, necrosis, ulcerations
2.	Surgical exsition [23–25]	Linear closure and flap coverage, excision with grafting, W-plasty and Z-plasty	Surgical removal of excessive fibrous tissue growth	Higher recurrence rate, needs additional treatments like intralesional injection of TAIL, Interferon, pressure therapy etc.
3.	Silicone based products [19, 26–28]	Creams, sprays, gel cushion and liquid	Enhance hydration and provide an occlusive environment which regulates proliferation of fibroblast there by decreases collagen synthesis.	Local irritation and lack of clinical trials.
4.	Pressure therapy [29–31]	Variety of materials are used to apply pressure such as adhesive plaster moulds, pressure earrings and custom-fitted splints	Applying pressure to the scar surface reduces perfusion and oxygen supply which in turn reduces collagen synthesis and angiogenesis.	Depends on patients compliance, site specific and discomfort to the patients
5.	Radiotherapy [32–34]	X ray radiation	Reduce fibroblast proliferation, induce cell senescence and apoptosis there by reducing collagen production and suppress keloid formation	Oedema, necrosis, ulceration, desquamation, erythema, pigmentary changes, atrophy, telangiectasis and alopecia

S. No	Current and emerging therapies available for hypertrophic scars and keloid treatments	Types	Mode of action	Limitations
6.	Cryotherapy [35–37]	Low temperature treatment including spray and contact probes, or Intralesional-needle cryoprobe method	Destroying the core of the keloid by sparing the surface epithelial cells including melanocytes there by reducing the volume of keloids.	Hypopigmentation, blistering, pain, delayed healing and infection
7.	Laser therapy [38–40]	Ablative laser: 2940-nm erbium doped yttrium aluminium garnet (Er:YAG) laser and the 10,600-nm carbon dioxide (CO2) laser Non ablative laser: 585-nm or 595-nm PDLs, 1064-nm neodymium-doped:yttrium-aluminium-garnet (Nd:YAG) laser, 532-nm neodymiumdoped-vanadate (Nd:Van) laser and 1064 nm Q-switched Nd:YAG laser with low fluence	Laser beam is absorbed by water present in the skin leading to local tissue destruction and reduction of lesion volume	Itching, pigmentary changes, blister formation and postoperative purpura
8.	Anti cancer drugs [41–43]	5-Flurouracil	Pyrimidine analogue that inhibits thymidylate synthase enzyme leading to suppression of nucleic acid synthesis and inhibits fibroblast proliferation	Skin erythema, pain and ulceration
9	Stem cell therapy [44–46]	Exposure of adipose derived stem cells (ASCs) by fat grafting method	Modulating fibrogenesis through increased collagen production and inhibiting fibroblast proliferation	Mechanism is not clear
10.	Anti cancer drugs [47–49]	Mitomycin C (MMC)	MMC inhibits nucleic acid and protein synthesis thereby decrease the proliferation of fibroblast	Larger randomized clinical trials are needed to elucidate the efficacy of MMC towards keloid treatment.

S. No	Current and emerging therapies available for hypertrophic scars and keloid treatments	Types	Mode of action	Limitations
11.	Anticancer drugs [50–52]	Bleomycin	Diminish TGF- β 1-induced collagen expression, decrease the levels of lysyl-oxidase, a cross-linking enzyme involved in collagen maturation and increase apoptosis	Pain at injection site, hyperpigmentation, ulceration and dermal atrophy
12	Drugs that lowers blood pressure and angina [53–55]	Verapamil	Inducing pro collagenase secretion. Alters fibroblast shape, induces TGF- β 1 apoptosis, reduces ECM production and depolymerises actin filaments	Combinational therapy such as pressure therapy, PDL, TAIL and nifedipine is needed to effectively treat keloids.
13	Botulinum toxin type A [56–58]	Intralesional Injection	Decreasing tension at the wound edge while contraction, accumulating fibroblasts in G0 and G1 of the cell cycle, reducing TGF- β 1 expression	Extensive studies need to prove the efficacy towards keloid treatment.
14	ACE inhibitors [59–61]	Intralesional injection.	Reduce the expression of Ang II, TGF- β 1, PDGF-BB, heat shock protein and inhibit fibroblast proliferation and collagen synthesis.	Extensive Clinical investigation is needed.

Table 1.
Current and emerging therapies available, mode of action and their limitations.

response to the previous treatment determines the type of therapy need to cure keloids. Treatments including corticosteroids, surgical exsition, pressure therapy, radiotherapy, cryotherapy, laser therapy, 5- flurouracil, stem cell therapy, mitomycin C application, Verapamil, Bleomycin, Botulinum toxin type A and ACE inhibitors are available [18]. The current and emerging therapy for *hypertrophic* scars and keloids are briefly discussed in **Table 1**.

3. Interferons

In 1957, Isaacs and Lindeman identified a new substance which has the capacity to interfere with viral replication and coined the term “Interferon”. Interferons are the group of naturally occurring cytokines produced by the cells upon exposure to

various stimuli such as viruses, double – standard RNA and Polypeptides. Owing to its immunomodulatory, antiviral, antiangiogenic, anti-proliferative and antitumor activities, interferons are used to treat various diseases including Hairy Cell Leukemia, Follicular Lymphoma, Renal cell carcinoma, melanoma, chronic hepatitis, AIDS-related Kaposi Sarcoma etc. In addition to their therapeutic properties, it is used to study the mechanism of mammalian signal transduction and transcriptional regulation.

4. Types of interferons

Currently, interferons are categorized in to four types namely alpha (α), beta (β), gamma (γ) and Lambda (λ) interferon [62]. More recently, IFNs were divided into three major subgroups by virtue of their ability to bind to common receptor types namely type I, type II and type III. Type I IFNs bind to a type I IFN receptor and IFN- α , IFN- β belongs to type I IFN family. IFN- γ is the sole type II IFN, and binds to a distinct type II receptor. IFN- λ belongs to Type III IFN and binds to – IFN λ R receptor [63–65]. Various types of IFN and their receptors and biological properties are given in the **Table 2**.

Alpha interferons are also called as ‘leukocyte interferon’ is a cytokine produced by innate immune system in response to external stimuli including viral infections [65–68]. Alpha interferons are categorized under type I interferons which processes antiviral, immunomodulatory as well as anti-proliferative properties. It was reported that at least 20 copies of genes which encodes alpha interferons in human genome and standard recombinant interferons alfa-2a, alfa-2b and alfa-con1 (“consensus” interferon) have been produced [69].

Beta interferons (IFN β) are type I interferon produced by fibroblasts and possesses anti viral, anti proliferative and immunomodulatory effects. There are two forms of IFN β , IFN β - 1a and, IFN β - 1b both are used therapeutically. INF β -1b SC is produced by bacterial expression system and this was the first developed recombinant interferon for clinical use [63, 70].

Gamma interferon (IFN γ) is the only interferon catergoized under type II IFNs. IFN γ is produced by CD4T helper cell type 1 (Th1) lymphocytes, CD8 cytotoxic lymphocytes, NK cells, B cells and professional antigen-presenting cells (APCs). INF γ is acid liable where as other interferons are acid stable. IFN γ involved in various biological activity such as promotes natural killer (NK) cell activity, increase

Interferon Type	Interferon categories	Receptor Type	Cell of origin	properties
Type I	Alpha (α) Beta (β)	Type I	Leukocyte Fibroblast	Direct anti proliferative effects on cells, Stimulation of MHC Class I expression and activation of Natural Killer (NK) Cells
Type II	Gamma (γ)	Type II	T cells and NK cells	Direct anti proliferative effects on cells, Stimulation of MHC Class I & II expression, delayed activation of NK cells.
Type III	Lamda (λ)	Type III	Intestinal epithelial cells	Anti tumor activity and amplify the induction of anti viral activity of type I IFN, Up regulation of MHC Class I expression

Table 2.
Interferon Classification and properties.

APS and lysosome activity of macrophages, activates inducible nitric oxide synthase (iNOS), induces the production of IgG2a and IgG3 from activated plasma B cells, Promotes adhesion and binding required for leukocyte migration [71–73].

Interferon lamda (IFN λ) was discovered in early 2003 and were categorized under type III interferon. There are three different interferon genes encodes and produce three different interferon λ proteins namely IFN λ 1, INF λ 2 and INF λ 3. These proteins are also called as interleukin – 29 (IL-29), IL- 28 A and IL-28 B respectively [74]. IFN λ differ from other type I and type II interferon by signaling mechanism. IFN λ , signals through heterodimeric acceptor complex. IFN λ is responsible for the development of anti tumor immune response and amplify the induction of antiviral activity of type I interferon. IFN λ processes anti viral activity and up regulate major histocompatibility complex (MHC) class I antigen expression on many cell types [75].

5. Interferon therapy for *hypertrophic* scars and keloids

Keloid is benign fibrous growth that extends outside the original wound and invades adjacent dermal tissue due to the excessive production of extra cellular matrix, especially collagen. Histologically, keloids are characterized by disorganized deposition of thick collagen fibers along with abundant lymphocytes, eosinophils and macrophages [76]. Although numerous attempts made to understand the pathophysiology and molecular abnormalities behind keloid formation, the exact pathogenesis of keloid formation is yet to be understood. Literature reports revealed that keloid shows an elevated expression of collagen mRNA, upregulation of TGF- β genes which results in excessive production of collagen and other ECM components especially fibronectin. TGF- β , especially the TGF- β 1 isoform, is a key mediator of variety of processes including cell growth, proliferation, differentiation, apoptosis and responsible in many fibrotic diseases including keloids through its role in promoting extracellular matrix (ECM) production and tissue fibrosis [77]. TGF- β belongs to the member of cytokine family which binds and activates dimerization of TGF- β type II receptors and the subsequent phosphorylation of TGF- β type I receptors, which phosphorylate and activate Smad2/3 leading to the translocation of Smad4 to the nucleus and activate the expression of target genes [78]. TGF- β receptors and Smad proteins are over expressed in keloids and *hypertrophic* scars compared to normal skin.

Matrix metalloproteinases (MMPs) or matrix metallopeptidases are calcium dependent zinc containing endopeptidases that plays a critical role in ECM formation. The major function of MMPs is to catabolize ECM and cleave regulate the activity of many other extracellular bioactive substrates [79]. MMPs are classified into 4 subsets namely collagenases, gelatinases, stromelysins, and membrane type. The collagenases including MMP-1, MMP-8, and MMP-13, cleave types I and III collagens present in scar tissue. The activity of MMPs is regulated by tissue inhibitors of metalloproteinases (TIMPs) including TIMP-1, TIMP-2, TIMP-3, and TIMP-4, which inhibit MMPs. MMPs participate in inflammation, proliferation and remodeling phase of wound healing and MMPs involved in scars and keloid formation are also secreted by fibroblasts itself. An imbalance between MMP and TIMP leads to cause disturbance in collagen synthesis and degradation resulting in keloid and hypertrophic scar development [80–82].

Fibroblasts derived MT1-MMP and active MMP-2 play crucial roles in keloid formation and tumor invasion. Excessive synthesis and deposition of collagen contribute to the development of keloids with prolonged and excessive presence of TGF β -1. Downregulation of TIMP-2 leads to the progression of keloids because of relative increase of MT 1-MMP activity. MT 1-MMP increases the activity of TGF β -1 lead to

collagen synthesis and collagen deposition in keloid development [83]. Schematic of keloid formation with respect to TGF β -1 and MMP and role of interferon therapy in preventing TGF β -1 and MMP mediated keloid development is given in the **Figure 2**.

Although many treatments and therapies are available for treating *hypertrophic* scars and keloids, the most efficient and successful treatment is yet to be achieved. Interferon therapy is one of the emerging therapies which have potential therapeutic effect against keloids by decreasing the synthesis of collagen types I and III and increasing collagenase activity [84]. It has been reported that Interferon alpha and gamma decrease procollagen messenger RNA levels of fibroblasts both in normal and scleroderma patients and enhance collagenase activity. Interferon not only influences collagen synthesis in skin but also reduces the inflammatory reaction. Generally, Transforming Growth Factor (TGF) which is released by platelets at the site of injury is highly chemotactic to macrophages and monocytes during the inflammatory reaction. TGF also induces collagen and fibronectin production. Interferon antagonizing the effects of TGF- β and histamine there by reducing inflammatory reaction. Among the three isoforms of interferons, IFN- α and IFN- γ have been found to be very effective for keloid treatment since it decreases collagen and other ECM expression and increasing collagenase activity [85, 86].

Specifically, IFN - α 2b is widely used in the treatment of keloids owing to its anti-proliferative property and reduce dermal fibrosis directly or antagonizing the effects of TGF- β and histamine. In addition, it was reported that IFN - α 2b, increase collagenase levels and to inhibit the secretion of collagenase inhibitors such as metalloproteinases. Anti proliferative properties of IFN- α 2b was demonstrated by Berman and Duncan. They have intralesionally injected 1.5 million IU IFN α -2b, twice over 4 days and found that size of the keloid was reduced to 50%. Post operative injection of IFN α -2b reduce the rate of recurrence to 19% as compared with that of intralesional steroid, where the rate of recurrence was 51% [87].

Injection of IFN into the suture line of keloid excision may be prophylactic for reducing recurrences. Post operative IFN- α 2b injection treatment (5 million U, 1 million U injected per cm of scar) into keloid excision sites in 124 patients, fewer keloid recurrence rate (18%) was observed compared to excision site alone (51.1%) [88].

Figure 2.
Mechanism of IFN therapy.

Subcutaneous injection of human recombinant IFN- α 2b (1×10^6 units) for 7 days on a daily basis to patients with hypertrophic scars and then 2×10^6 units for 24 weeks in 3 times per week basis showed significant increase in the rate of scar improvement with control. Scar assessment and scar volume also improved after 3 months of treatment and no recurrences were observed after stopping IFN therapy.

Pittet et al. reported that intralesional injections of human recombinant IFN- γ 200 mcg (6×10^6 U) per injection for 4 weeks to 7 patients with *hypertrophic* scar and observed that 7 of 7 patients showed decrease in redness, swelling, firmness, and lesion area. In addition to that, the reappearance of symptoms was minimal in only 2 of 7 patients and a small increase in the lesion area occurred in 4 of 7 patients, although these lesions remained smaller than the original area was observed in 16th week [89].

IFN- γ play an important role in reducing fibrosis by inhibiting TGF- β via initial activation of Jak1, which in turn stimulates the negative regulator of collagen YB-1 (Y-box protein-1), which activates Smad7, eventually leading to TGF- β 1 suppression. Intralesional injection of IFN- γ has been shown to be effective in improving the appearance of keloids and hypertrophic scars, and also reducing keloid recurrence after excision along with variable treatment regimens [85].

6. Source and production of interferons

Commercially available interferons are human interferons manufactured by using recombinant DNA technology. There are many forms of interferons commercialized including interferon alfa-2a (Roferon-A), interferon alfa-2b (Intron-A), interferon alfa-n3 (Alferon-N), peginterferon alfa-2b (PegIntron, Sylatron), interferon beta-1a (Avonex), interferon beta-1b (Betaseron), interferon beta-1b (Extavia), interferon gamma-1b (Actimmune), peginterferon alfa-2a (Pegasys ProClick), peginterferon alfa-2a and ribavirin (Peginterferon), peginterferon alfa-2b and ribavirin, (PegIntron/Rebetol Combo Pack), peginterferon beta-1a (Plegridy). Among these interferons, interferon alfa-2b (Intron-A)

Figure 3.
Structure of human recombinant interferon (a) INTRON® A (b) ACTIMMUNE®. (Reproduced from pubchem and EMBL-EBI respectively).

and interferon gamma-1b (Actimmune) is used in the treatment of *hypertrophic* scars and keloids [90].

Interferon alfa-2b is commercialized under the trade name INTRON® A. It is a recombinant IFN available in the form of injection and molecular formula is $C_{16}H_{17}Cl_3I_2N_3NaO_5S$. The structure of this recombinant IFN is given in **Figure 3**. This IFN is water soluble proteins produced by recombinant DNA technology and possess molecular weight around 19000 Daltons. It is obtained from bacterial fermentation of *E.coli* bearing genetically engineered plasmid containing an interferon alfa2b gene from human leukocytes. The specific activity of this recombinant IFN (INTRON® A) is approximately 2.6×10^8 IU/mg [91].

Interferon Gamma is commercialized under the trade name ACTIMMUNE®. It is a recombinant interferon produced by cloning of hIFN γ cDNA and expressed the recombinant in *E.coli*. Production and purification of recombinant IFN γ is cost effective. Molecular weight of the recombinant IFN γ in monomeric form is around 17 kDa and dimeric form is around 35 kDa. The specific activity of this recombinant IFN γ is 3×10^6 IU/mg [92].

7. Combinatorial therapy

The most commonly employed treatment for keloid is Triamcinolone acetonide intralesional injection (TAIL). Major disadvantage of this therapy is limited success and adverse effects such as atrophy, telangiectasia, depigmentation, ulceration, and systemic effects, including cushingoid changes. In order to increase the success rate, TAIL is injected along with IFN – α 2 b. Twenty lesions (combined TAIL + IFN – α 2 b group) and 20 control lesions (TAIL-only group) were studied in 19 patients. Both groups were treated with TAIL once in 2 weeks. The combined TAIL + IFN-alpha2b group was treated with intralesional injection of IFN – α 2 b, twice a week. Lesion measurements were noted. Statistically significant decreases in depth (81.6%, $P = 0.005$) and volume (86.6%, $P = 0.002$) were observed in lesions of the combined TAIL IFN – α 2 b group. In the TAIL-only group, the decreases in depth (66.0%, $P = 0.281$) and volume (73.4%, $P = 0.245$) were less statistically significant. Hence, injection of IFN – α 2 b enhances the healing potential of TAIL [93].

Combinatorial therapy of laser ablation in conjugation with IFN – α 2 b injection, showed better healing and reduction in recurrence rate towards keloid treatment. 30 patients with keloids were chosen for the study. Among them, 16 patients have keloids on the ear and 14 patients on trunk. The duration of the study was 12 to 24 months and the size of the keloids was ranged from 1 to 3 cm in diameter. Keloids were ablated using ultra pulse carbon dioxide laser followed by sublesional and perilesional injections of 3 million IU of IFN- α 2b three times per week. By this combinatorial therapy, the recurrence rate was reduced and observed that 66% of lesions did not recur after three years. In particular, no recurrence was observed in the auricular area [94].

Though IFN therapy is successful, treatment associated adverse effects including fever, headache, arthralgias, fatigue, chills, and confusion were observed and the treatment is expensive.

8. Summary and conclusion

Keloids are problematic disfiguring scars arises due to abnormal wound healing and excessive fibrosis. Un controlled proliferation of fibroblast results in over production and deposition of collagen and other ECM components responsible for

keloid development. There are many treatments available for *hypertrophic* scars and keloids including corticosteroid injections, surgical excision, pressure therapy, radiotherapy, laser therapy etc. Efficient and successful treatment for keloids is yet to be developed. Interferon therapy is one of the emerging therapies which have potential therapeutic effect against keloids by decreasing the synthesis of collagen types I and III and increasing collagenase activity. Recombinant IFN- α 2b (INTRON® A) and IFN- γ (ACTIMMUNE®) is commercially available and used for the treatment of keloids. Significant improvement in rate of scar reduction and recurrence % was also decreased. In order to further improve the efficacy of IFN treatment, combinatorial therapy was attempted. IFN- α 2b along with TAIL injection and CO2 laser ablation showed higher success rate. Hence, IFN and/or the combinatorial therapy would be a better treatment options to the patients with *hypertrophic* scars and keloids.

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