Resident's Page

Interferons

Bharat Bhushan Mahajan, Sandeep Kaur

INTRODUCTION

Interferons (IFNs) are glycoproteins belonging to the family of cytokines and have antiviral, antitumor, and immunomodulatory activities. Nagano and Kojima, Japanese virologists, noticed viral growth inhibition in an area previously inoculated with virus and named it as "viral inhibitory factor" but their work was not fully appreciated. The main credit for discovering interferons has gone to Isaacs and Lindenmann who also coined the term "interferon."

CLASSIFICATION

Interferons are classified based on receptor binding and structural and biochemical differences [Table 1].

On the basis of receptor binding there are three types of interferons:

IFN type I: Binds to IFN-α receptor (IFNAR) that consists of IFNAR1 and IFNAR2 chains.

IFN type II: Binds to IFNGR that consists of IFNGR1 and IFNGR2 chains.

IFN type III: Signals through a receptor complex consisting of IL10R2 and IFNLR1.

Department of Dermatology, Venereology and Leprology, Guru Gobind Singh Medical College and Hospital, Faridkot, Punjab, India

Address for correspondence: Dr. Sandeep Kaur, Skin OPD, 1st Floor, OPD Block, GGS Medical Hospital, Sadiq Road, Faridkot, Punjab - 151 203, India.
E-mail: docsandeep_2005@yahoo.com

Access this article online	
Quick Response Code:	Website: www.ijdvl.com
	DOI: 10.4103/0378-6323.148570

ACTION SPECTRUM

Interferons are known to exhibit a myriad of activities which are depicted in Figure 1. These include

Antiviral activity

Interferons have potent, but non-specific antiviral activity through inhibition of virus entry, viral protein synthesis and virus maturation and through induction of assembly defects.

Anti-tumor activity

This results from modulation of cell proliferation and differentiation, tumor antigen expression, and induction of class I and II antigen expression by tumor cells. Interferons have cytostatic effect causing arrest in G1 phase of cell cycle along with inhibition of certain proto-oncogenes and induction of apoptosis.

Immunomodulating activity

Interferons induce differentiation and activation of natural killer (NK) cells, monocytes, and macrophages (interferon-γ and -λ) and dendritic cells (interferon-α and -λ). They also enhance cytotoxic T-cell activity and increase the production of immunoglobulins (interferon-γ). Interferon-β and -γ inhibit the production of interleukin-10, while interferon-λ increases it. Interferon-γ inhibits the synthesis of interleukin-4, but increases the synthesis of tumor necrosis factor alpha (TNF-α) and interleukin-2.

Other activities

Interferons also exhibit anti-angiogenic activity through inhibition of vascular endothelial cells.

Interferon-λ has been shown to inhibit keratinocyte proliferation.

PHARMACOKINETICS

Various routes of administration of interferons include subcutaneous (SC), intramuscular (IM), intralesional,

How to cite this article: Mahajan BB, Kaur S. Interferons. Indian J Dermatol Venereol Leprol 2015;81:51-5.
Received: April, 2014. **Accepted:** October, 2014. **Source of Support:** Nil. **Conflict of Interest:** None declared.

Table 1: Classification of interferons on the basis of receptor binding, structural and biochemical differences

IFN type	Receptor type	Encoding gene	Structure	Interferons	Sources
I	IFN-α receptor that consists of IFNAR1 and IFNAR2 chains	Chromosome 9	α-spiral	IFNα-2a and -2b	Leukocytes, macrophages, endothelial cells, tumor cells, keratinocytes, and mesenchymal cells
				IFN-β	Fibroblasts, endothelial cells, macrophages, and epithelial cells
				IFN-ω	T lymphocytes
				IFN-ε	Cerebral tissues
				IFN-κ	Not known yet
II	IFNGR that consists of IFNGR1 and IFNGR2 chains	Chromosome 12	Core of six α-helices and an extended unfolded sequence in the C-terminal region[1]	IFN-γ	T cells and NK cells
III	Receptor complex consisting of IL10R2 (also called CRF2-4) and IFNLR1 (also called CRF2-12)	Chromosome 19		IFN-λ	Dendritic cells and macrophages

IFN: Interferons, IFNAR: IFN-α receptors

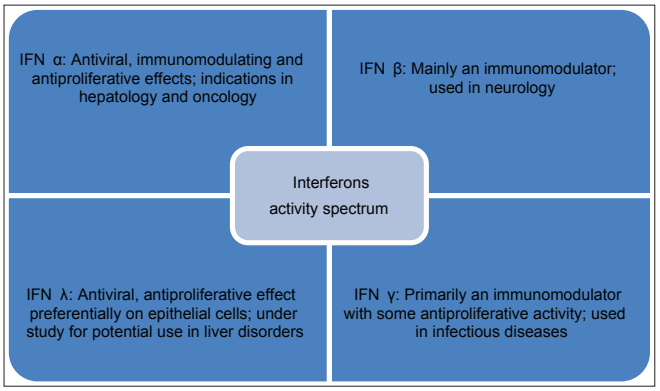

Figure 1: Action spectrum of interferons, IFN α, β, γ have been used in dermatology

aerosols, topical, and possibly intravenous. Bioavailability is over 80% for IFN-α, but only 20–40% for IFN-β and 30–70% for IFN-γ. These are metabolized in the liver and eliminated by the kidneys.

Peak plasma concentrations are achieved in 1–12 h with plasma half-life of <12 h. Nowadays, interferons are conjugated with polyethylene glycol (pegylation). This process increases their molecular weight and delays renal clearance, thereby leading to a longer half-life.

INDICATIONS IN DERMATOLOGY

Tables 2 and 3 describe the indications of interferons in dermatology.

Melanoma[2,3]

For primary melanoma stage II, low-dose subcutaneous IFN-α2a has been licensed as adjuvant treatment. High doses of interferon-α2b are recommended for lymph node involvement according to the Kirkwood study. However, subsequent studies using high dose, intermediate dose, or low dose yielded conflicting results, making it difficult to recommend a specific dose or treatment duration.

Various studies show a significant increase in progression-free survival with interferon in melanoma.[3] Most studies did not report a statistically significant difference in terms of overall survival between the treated and untreated patients.[3] Various good prognostic factors put forth include primary tumor ulceration and development of autoimmunity.[4]

Interferon-α is no longer indicated in patients with distant metastases in view of the poor response rates.[5] Interferon-γ and β are currently under trial.

Cutaneous T-cell lymphoma[6]

Interferon-α2a has been used in cutaneous T-cell lymphomas, widespread lymphomatoid papulosis, and cutaneous CD30-positive T-cell lymphomas that are refractory to or cannot be treated by conventional therapies. The response rate is about 60%, with a 20% complete remission rate. Peak efficacy is generally reached after >6 months.

Interferons can be combined with other treatments such as PUVA and extracorporeal photopheresis with higher chances of remission.

Kaposi sarcoma[7]

Interferon-α2a is used for the treatment of AIDS-related Kaposi sarcoma with a CD4 count greater than

250/mm^3 and no history of opportunistic infections or constitutional symptoms. The response rates are highly variable and depend upon patient-related factors such as CD4 count. Anti-retroviral treatments such as zidovudine and didanosine act synergistically with interferons, allowing use of lower doses of the latter.

Table 2: Indications of interferons in dermatology

Type of IFN	Uses
IFN-α	
Tumors	Adjuvant treatment of stage II and III melanoma Cutaneous T-cell lymphoma AIDS-related Kaposi sarcoma Cutaneous B-cell lymphoma Basal cell carcinoma Squamous cell carcinoma Actinic keratosis Plexiform neurofibroma
Infections	Genital warts Herpes infection
Miscellaneous	Mastocytosis Behçet's disease Hemangioma Gorham–Stout syndrome
IFN-β	Herpes infection
IFN-γ	Leishmaniasis Behçet's disease Atopic dermatitis Keloids

IFN: Interferons, AIDS: Acquired immunodeficiency syndrome

Genital warts

A meta-analysis conducted in 2009 explored the use of local (intralesional injections or gels) or systemic (subcutaneous) interferons versus placebo for genital warts.[8] Complete response rate was significantly higher ($P < 0.001$) with local IFN (44.4%) than with placebo (16.1%). The risk of recurrence was significantly lower in the local IFN group.

Leishmaniasis[9]

Interferon-γ has been used successfully in leishmaniasis due to its stimulatory effect on macrophages and NK cells with success rates of 70% in the oriental form and 40% in the American form.

Herpes infection[10]

In herpes virus infections, presently, interferons are considered inferior to antiviral agents due to the lower efficacy, higher cost, and poor tolerability.

Behçet's disease

High response rates with subcutaneous interferon-α

Table 3: Route of administration and dose of interferons in various conditions

Dermatological condition	Route of administration	Recommended dose
Tumors		
Primary melanoma stage II	SC	IFNα-2a 3 million IU three times a week for 18 months, to be started not later than 6 weeks after surgery
Melanoma with lymph node involvement	IV, SC	IFNα-2b (Kirkwood regimen): 20 MIU/m^2 IV five times a week for 1 month, then 10 MIU/m^2 SC 3 times a week for 11 months
Cutaneous T-cell lymphoma	SC	Low dose of IFNα-2a (3-10 MIU) is often started with a daily injection for the first month followed by three injections a week thereafter
AIDS-related Kaposi sarcoma	SC	IFNα-2a 18-36 MIU every day for 3 months and then 3 times a week
Basal cell carcinoma	Intralesional	IFN-α 1-3 MIU 3 times a week for 3 weeks Higher doses if the tumor size is>2 cm^2
Cutaneous B-cell lymphoma	Intralesional	IFNα-2a 1-6 MIU intralesionally
Infectious diseases		
Genital warts	Intralesional, gels, SC	IFN-α 3 times a week for 4 weeks 1 MIU for local treatment 1.5-9 MIU for SC
Herpes infection	Topical or SC	-
Leishmaniasis	Intralesional	IFN-γ 1-30 μg/m^2
Miscellaneous		
Behçet's disease	SC	IFN-α 3-9 MIU 3 times a week for 6 months IFN-γ 100 μg/day
Mastocytosis	SC	IFN-α
Hemangioma	SC	IFN-α 1-3 MIU/m^2/day for 3 weeks
Atopic dermatitis	SC	IFN-γ 50 μg/m^2 once a day or 25 or 75 μg/m^2 3 times a week for 12 weeks

IFN: Interferons, AIDS: Acquired immunodeficiency syndrome, SC: Subcutaneous, MIU: Million international units, IU: International units

have been reported in mucocutaneous lesions (86%), articular lesions (96%), and eye damage refractory to conventional treatments (94%) in Behçet's disease.[11,12] Interferon-γ has a beneficial role only against cutaneous manifestations of Behçet's disease.

Mastocytosis

Subcutaneous interferon-α is one of the first-line treatments for aggressive systemic mastocytosis and is effective against the dermatological, hematological, gastrointestinal, and skeletal symptoms.[13]

Basal cell carcinoma[14]

Various studies report complete response rates of 67–86% with interferon-α in basal cell carcinoma (BCC). Its combination with imiquimod has shown better efficacy. However, it is not effective against aggressive forms such as desmoplastic BCC.

Hemangioma

Interferon-α may be tried in cases where beta-blockers and corticosteroids have failed.[15] The improvement is generally rapid with response rate of about 80%. The main adverse event observed was the rare, irreversible neurotoxicity of the spastic diplegia type.

Atopic dermatitis

IFN-γ has immunomodulating properties due to its inhibitory effect on the production of IL-4.[16] Various studies have shown response rates of approximately 45% in atopic dermatitis patients, irrespective of the dose administered.

ADVERSE EFFECTS

The adverse effects of interferons are dose-dependent and generally remit either during continued therapy or after dose reduction. The most common side effect reported is "flu-like" symptoms characterized by fever, sweats, chills, myalgias, and arthralgias. These symptoms typically resolve over the first 10 days of treatment and can be managed with paracetamol. Other side effects include hematological (neutropenia, thrombocytopenia), metabolic (hypocalcemia, hyperlipidemia), neurological (headaches, difficulties in concentration, confusion), psychiatric (depression, insomnia, anxiety, mood swings), cardiovascular (palpitations, conduction disturbances, decompensation of unstable cardiac disease), gastrointestinal (nausea, diarrhea, abdominal pain), renal toxicity, cutaneous (reversible alopecia, xerosis, injection site reactions, and pain), and sexual disturbances in the form of menstrual irregularities and decreased libido.

Uncommon side effects include anemia, lymphocytopenia, rhabdomyolysis, convulsions, suicidal ideation, aggravation of psoriasis, urticaria, Raynaud's syndrome, acrocyanosis, and autoimmune disorders like thyroid dysfunction, systemic lupus erythematosus, rheumatoid arthritis, and leukocytoclastic vasculitis.

Most of these side effects are reversible upon discontinuation, with the exception of certain autoimmune diseases.

The main absolute contraindications are known hypersensitivity to the drug or its components, severe cardiac, renal or hepatic disease, bone marrow failure, uncontrolled epilepsy, and severe psychiatric disorders. Interferons are pregnancy category C drugs with unknown safety during pregnancy and lactation.

MONITORING OF TREATMENT

Laboratory testing

- Complete blood count with differentials including platelet count
- Blood chemistries, including electrolytes and creatine phosphokinase
- Liver function tests [aspartate transaminase (AST), alanine transaminase (ALT)]
- Renal function tests [blood urea nitrogen (BUN), S. creatinine].

Special testing

- ECG is recommended in patients with preexisting cardiac disease
- Thyroid function tests and thyroid autoantibodies like thyroid peroxidase, thyroglobulin, and thyroid stimulating hormone receptor antibodies are recommended on a yearly basis.

Monitoring frequency

- Prior to start of treatment
- Two weeks after initiation of therapy
- Monthly thereafter while on therapy.

DRUG INTERACTIONS

Drugs that increase the hematological toxicity of interferons are angiotensin converting enzyme

inhibitors, methotrexate, zidovudine, cidofovir, and imatinib.

Interferons decrease the clearance of theophylline, thereby increasing its serum levels.

Nonsteroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids inhibit the activity of interferons.

Vinca alkaloids (vinblastine, vincristine), when used along with interferons increase the risk of neurotoxicity.

CNS depressants like narcotics, hypnotics, and sedatives increase the risk of neurological adverse effects when used concomitantly with interferons.

CONCLUSION

Interferons have a variety of biological activities. There is an ever-expanding list of their indications in dermatologic diseases. However, it should be kept in mind that interferons are a double-edged sword since they can exert useful anti-inflammatory and immunomodulatory effects while also having the potential to induce or exacerbate autoimmune disorders.

REFERENCES

1. Ealick SE, Cook WJ, Vijay-Kumar S, Carson M, Nagabhushan TL, Trotta PP, *et al*. Three-dimensional structure of recombinant human interferon-gamma. Science 1991;252:698-702.
2. Garbe C, Eigentler TK, Keilholz U, Hauschild A, Kirkwood JM. Systematic review of medical treatment in melanoma: Current status and future prospects. Oncologist 2011;16:5-24.
3. Mocellin S, Pasquali S, Rossi CR, Nitti D. Interferon alpha adjuvant therapy in patients with high-risk melanoma: A systematic review and meta-analysis. J Natl Cancer Inst 2010;102:493-501.
4. Eggermont AM, Suciu S, Testori A, Kruit WH, Marsden J, Punt CJ, *et al*. Ulceration and stage are predictive of interferon efficacy in melanoma: Results of the phase III adjuvant trials EORTC 18952 and EORTC 18991. Eur J Cancer 2012;48:218-25.
5. Ives NJ, Stowe RL, Lorigan P, Wheatley K. Chemotherapy compared with biochemotherapy for the treatment of metastatic melanoma: A meta-analysis of 18 trials involving 2,621 patients. J Clin Oncol 2007;25:5426-34.
6. Prince HM, Whittaker S, Hoppe RT. How I treat mycosis fungoides and sezary syndrome. Blood 2009;114:4337-53.
7. Krown SE. AIDS-associated Kaposi's sarcoma: Is there still a role for interferon alfa? Cytokine Growth Factor Rev 2007;18:395-402.
8. Yang J, Pu YG, Zeng ZM, Yu ZJ, Huang N, Deng QW. Interferon for the treatment of genital warts: A systematic review. BMC Infect Dis 2009;9:156-64.
9. Smith DI, Swamy PM, Heffernam MP. Off-label uses of biologics in dermatology: Interferon and intravenous immunoglobulin (part 1 of 2). J Am Acad Dermatol 2007;56:e1-54.
10. Viera MH, Amini S, Huo R, Konda S, Block S, Berman B. Herpes simplex virus and human papillomavirus genital infections: New and investigational therapeutic options. Int J Dermatol 2010;49:733-49.
11. Mendes D, Correia M, Barbedo M, Vaio T, Mota M, Gonçalves O, *et al*. Behcet's disease-a contemporary review. J Autoimmun 2009;32:178-88.
12. Onal S, Kazokoglu H, Koc A, Akman M, Bavbek T, Direskeneli H, *et al*. Long-term efficacy and safety of low-dose and dose-escalating interferon alfa-2a therapy in refractory Behcet uveitis. Arch Ophthalmol 2011;129:288-94.
13. Pardanani A. Systemic mastocytosis in adults: 2011 update on diagnosis, risk stratification, and management. Am J Hematol 2011;86:362-71.
14. Good LM, Miller MD, High WA. Intralesional agents in the management of cutaneous malignancy: A review. J Am Acad Dermatol 2011;64:413-22.
15. Mabeta P, Pepper MS. Hemangiomas-current therapeutic strategies. Int J Dev Biol 2011;55:431-7.
16. Walling HW, Swick BL. Update on the management of chronic eczema: New approaches and emerging treatment options. Clin Cosmet Investig Dermatol 2010;3:99-117.