CHAPTER 20

INTERFERON THERAPY IN DERMATOLOGY

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INTRODUCTION

Interferons (IFNs) are glycoprotein mediators of the human natural immune defense produced against foreign objects such as tumor cells, bacteria and antigens. The production of IFNs can be induced by antibacterial, antiviral and antitumoral activities. The INF multigene family including IFN-α, IFN-β and IFN-γ is an integral part of the cytokine network. Discovery of IFNs were credited to Isaacs and Lindenmann in 1957 although Nagona and Kojima, two Japanese virologists had noticed previously certain viral inhibitory factors that could inhibited viral growth in 1954.[1]

STRUCTURE AND CLASSIFICATION

Interferons can be classified on the basis of receptor binding and biochemical and structural features (Table 1). There are three types of IFNs according to receptor binding affinity.[1,2] Type I IFNs bind to a specific cell surface receptor complex named IFN-α receptor (IFNAR) that has two subunits known as IFNAR1 and IFNAR2 chains.[3] Type I IFN family includes seven classes: IFN-α, IFN-β, IFN-ε, IFN-κ, IFN-ω, IFN-δ and IFN-τ. All type II IFNs bind to IFN-γ receptor complex (IFNGR) that consists of IFNGR1 and IFNGR2 chains. Type III IFN group has three IFN-λ molecules called IFN-λ1, IFN-λ2 and IFN-λ3 (also known as IL29, IL28A and IL28B, respectively).4 Type II IFNs contain IFN-γ and type III IFNs include IFN-γ.[5-7]

There are more than 30 subtypes of IFN-α and they have nearly the same amino acid sequence. The difference between two approved subtypes, IFN-α2a and IFN-α2b is only a single amino acid. These subtypes can be produced by Escherichia coli by means of recombinant DNA technology.[8,9] The pegylation process attaches polyethylene glycol (peg) to IFN and provides increase time in circulation and decrease of the frequency of dosing. The pegylated form of IFN-α (pegIFN-α) has been described to have less toxicity with superior efficacy compared with non-pegylated form.[10,11] Two pegIFNs have been approved by Food Drug Administration (FDA): pegIFN-α2a (Pegasys®) and pegIFN-α2b (PEG-Intron®). These drugs have been approved for the combination therapy with ribavirin in the treatment of chronic hepatitis C. In a recent Japanese study, no significant difference was found between chronic hepatitis C patients treated with the pegIFNα-2a and pegIFNα-2b regarding sustained virologic response rates and safety profile.12 Structural homology is 29% between IFN-α and IFN-β. There is no homology between IFN-γ and IFN-α or IFN-γ and IFN-β.[8]

ACTION MECHANISMS

Recent studies showed that type I IFNs have antiproliferative effects on keratinocytes and melanocytes.[13] The main functions of IFN-α are antiproliferative, antitumoral and antiviral effects. It alters cellular transcription, translation and protein synthesis. Yaar et al. reported that seven-day administration of 2500 units/mL IFN-α or IFN-β to the cultures of human keratinocytes caused 70% growth inhibition. However IFN-α and IFN-β promoted terminal differentiation of keratinocytes reversibly.[14] Krasagakis et al. found that IFN-β caused a strong growth inhibition on normal human melanocytes although IFN-α showed no effect.[15] McCarty et al. demonstrated the antiangiogenic effects of IFN-α and IFN-β in mice.[16] Recent reports showed that IFN-α upregulated class I, but not class II, MHC antigen expression and IFN-α and IFN-β induced increased expression of class I MHC antigens in cultured human melanocytes. IFN-β had a greater effect than IFN-α in immunomodulation of keratinocytes.[13,15,17] IFN-α was found to upregulate the receptor expression of opioid growth factor that is a negative effector in the cell proliferation through DNA synthesis pathways.18 IFN-γ has been shown to inhibit TGF-β and fibrosis, via initial activation of Jak1.[19]

FDA-APPROVED INDICATIONS

Kaposi sarcoma in AIDS

Kaposi sarcoma (KS) is the most common AIDS-associated cancer.[20] The first-line treatment for the patients with limited AIDS-associated KS is highly active antiretroviral therapy (HAART). Interferon α2a and α2b have been approved by FDA for the treatment of AIDS-KS and hypothesized to be effective against both HIV and human herpes virus 8 as an immunomodulatory and antiviral agent. IFN-α is rarely used due to

organs.[69] Inhibition of angiogenesis is the supposed action mechanism of IFNs. Subcutaneous administration of IFN-α2a and IFN-α2b at a daily dosage of 3 MU/m2 has been recommended for a two to six-month treatment. Spastic diplegia has been reported nearly 5% with IFN-α2b and 20% with IFN-α2a.[70-74] Peng et al. carried out an experimental study in a nude mice model and found that exogenous IFN-γ injection could treat hemangioma effectively. IFN-γ has been demonstrated to inhibit hemangioma proliferation and accelerate apoptosis.[75]

ADVERSE EFFECTS

The adverse effects of IFN treatment are slight, dose-related and generally rapidly reversible after the cessation of therapy.[8] The most common adverse effects are flu-like symptoms that are often seen in doses higher than 3 MU. These symptoms including myalgia, fever, headache, chills and arthralgia can be prevented by the administration of aspirin, acetaminophen or non-steroidal anti-inflammatory drugs 1-2 hour before the injection.[8] Side effects of long-time treatment are anorexia, weight loss, fatigue and lethargy. These long-time effects are also dose-dependent. Risk of hepatotoxicity and cardiovascular, hematologic and neurologic toxicity increases at high doses. The most common side effects of IFN-α are flu-like symptoms. Injection-site reactions, diarrhea, sleep disturbances, hair thinning, hypothyroidism, hyperthyroidism, hyperglycemia, liver enzyme elevations and reversible bone-marrow suppression are other reported side effects of IFN-α. Renal failure, pulmonary infiltrates, and neurological symptoms such as paresthesia, motor-weakness, confusion and short-term memory loss are rare side effects reported of IFN-α therapy.[76] Fleming and MacKie demonstrated hair discoloration induced by IFN-α therapy.[77] IFN-α associated permanent spastic diplegia has been reported in infants.[73] IFN-α administration in children under 1 year old should be limited to physically limiting or life-threatening hemangiomas.[8,19,70,78] Besides flu-like symptoms which are the most common adverse reactions in IFN-β treatment, chest pain, back pain, abdominal pain, seizures, allergic reactions, hematologic abnormalities and cardiac abnormalities have been also described in the literature.[76] Injection-site reactions, flu-like symptoms, headache, nausea, hepatic enzyme elevations, granulocytopenia, thrombocytopenia and serum triglycerides elevation have been reported in the association with IFN-γ treatment.[79]

CONCLUSION

Interferon treatment is an expensive form of therapy, but it remains a promising therapeutic approach for severe, recurrent and refractory cases. Although IFNs have been reported to be effective in treatment of many different dermatological disorders, only four indications have been approved (Table). Further larger and controlled studies may prove the importance of IFNs in infectious and inflammatory dermatoses and malignancies. Future clinical trials may also emphasize combination therapy with other cytokines, hormones, chemotherapy, or radiation and determine optimal dosage regimes for dermatological diseases.

REFERENCES

1. Mahajan BB, Kaur S. Interferons. Indian journal of dermatology, venereology and leprology 2015;81:51-5.
2. Vilcek J. Novel interferons. Nature immunology 2003;4:8-9.
3. Millikan LE. Drug Therapy in Dermatology: CRC Press; 2000.
4. Lu YF, Goldstein DB, Urban TJ, Bradrick SS. Interferon-lambda4 is a cell-autonomous type III interferon associated with pre-treatment hepatitis C virus burden. Virology 2015;476:334-40.
5. Good LM, Miller MD, High WA. Intralesional agents in the management of cutaneous malignancy: a review. Journal of the American Academy of Dermatology 2011;64:413-22.
6. Kim KH, Yavel RM, Gross VL, Brody N. Intralesional interferon alpha-2b in the treatment of basal cell carcinoma and squamous cell carcinoma: revisited. Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al] 2004;30:116-20.
7. Tarhini AA, Gogas H, Kirkwood JM. IFN-alpha in the treatment of melanoma. Journal of immunology 2012;189:3789-93.
8. Berman B, Caperton CV. Interferons. In: Wolverton SE, ed. Comprehensive Dermatologic Drug Therapy. 3 ed: Saunders; 2013:269-78.
9. Pestka S, Krause CD, Walter MR. Interferons, interferon-like cytokines, and their receptors. Immunological reviews 2004;202:8-32.
10. Laguno M, Murillas J, Blanco JL, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for treatment of HIV/HCV co-infected patients. Aids 2004;18:F27-36.
11. Zeuzem S, Hultcrantz R, Bourliere M, et al. Peginterferon alfa-2b plus ribavirin for treatment of chronic hepatitis C in previously untreated patients infected with HCV genotypes 2 or 3. Journal of hepatology 2004;40:993-9.
12. Sato I, Shimbo T, Kawasaki Y, Masaki N. Comparison of peginterferon alfa-2a and alfa-2b for treatment of patients with chronic hepatitis C: a retrospective study using the Japanese Interferon Database. Drug design, development and therapy 2015;9:283-90.
13. Ismail A, Yusuf N. Type I interferons: key players in normal skin and select cutaneous malignancies. Dermatology research and practice 2014;2014:847545.
14. Yaar M, Karassik RL, Schnipper LE, Gilchrest BA. Effects of alpha and beta interferons on cultured human keratinocytes. The Journal of investigative dermatology 1985;85:70-4.
15. Krasagakis K, Garbe C, Kruger S, Orfanos CE. Effects of interferons on cultured human melanocytes in vitro: interferon-beta but not-alpha or -gamma inhibit prolifer-

ation and all interferons significantly modulate the cell phenotype. The Journal of investigative dermatology 1991;97:364-72.

16. McCarty MF, Bielenberg D, Donawho C, Bucana CD, Fidler IJ. Evidence for the causal role of endogenous interferon-alpha/beta in the regulation of angiogenesis, tumorigenicity, and metastasis of cutaneous neoplasms. Clinical & experimental metastasis 2002;19:609-15.
17. Niederwieser D, Aubock J, Troppmair J, et al. IFN-mediated induction of MHC antigen expression on human keratinocytes and its influence on in vitro alloimmune responses. Journal of immunology 1988;140:2556-64.
18. Zagon IS, McLaughlin PJ. Opioids and the apoptotic pathway in human cancer cells. Neuropeptides 2003;37:79-88.
19. Arno AI, Gauglitz GG, Barret JP, Jeschke MG. Up-to-date approach to manage keloids and hypertrophic scars: a useful guide. Burns : journal of the International Society for Burn Injuries 2014;40:1255-66.
20. Clifford GM, Polesel J, Rickenbach M, et al. Cancer risk in the Swiss HIV Cohort Study: associations with immunodeficiency, smoking, and highly active antiretroviral therapy. Journal of the National Cancer Institute 2005;97:425-32.
21. Lane HC, Kovacs JA, Feinberg J, et al. Anti-retroviral effects of interferon-alpha in AIDS-associated Kaposi's sarcoma. Lancet 1988;2:1218-22.
22. Rokx C, van der Ende ME, Verbon A, Rijnders BJ. Peginterferon alfa-2a for AIDS-associated Kaposi sarcoma: experience with 10 patients. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2013;57:1497-9.
23. Ali H, Donovan B, Wand H, et al. Genital warts in young Australians five years into national human papillomavirus vaccination programme: national surveillance data. Bmj 2013;346:f2032.
24. Steben M, Garland SM. Genital warts. Best practice & research Clinical obstetrics & gynaecology 2014;28:1063-73.
25. Khawaja HT. Treatment of condyloma acuminatum. Lancet 1986;1:208-9.
26. von Krogh G, Lacey CJ, Gross G, et al. European guideline for the management of anogenital warts. International journal of STD & AIDS 2001;12 Suppl 3:40-7.
27. Yang J, Pu YG, Zeng ZM, Yu ZJ, Huang N, Deng QW. Interferon for the treatment of genital warts: a systematic review. BMC infectious diseases 2009;9:156.
28. Leiding JW, Freeman AF, Marciano BE, et al. Corticosteroid therapy for liver abscess in chronic granulomatous disease. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2012;54:694-700.
29. Naveen KN, Pradeep AV. Chronic granulomatous disease. Indian dermatology online journal 2015;6:64-5.
30. Errante PR, Frazao JB, Condino-Neto A. The use of interferon-gamma therapy in chronic granulomatous disease. Recent patents on anti-infective drug discovery 2008;3:225-30.
31. Roh MR, Zheng Z, Kim HS, Jeung HC, Rha SY, Chung KY. Difference of interferon-alpha and interferon-beta on melanoma growth and lymph node metastasis in mice. Melanoma research 2013;23:114-24.
32. Bolling B, Fandrey J, Frosch PJ, Acker H. VEGF production, cell proliferation and apoptosis of human IGR 1 melanoma cells under nIFN-alpha/beta and rIFN-gamma treatment. Experimental dermatology 2000;9:327-35.
33. Borden EC, Jacobs B, Hollovary E, et al. Gene regulatory and clinical effects of interferon beta in patients with metastatic melanoma: a phase II trial. Journal of interferon & cytokine research : the official journal of the International Society for Interferon and Cytokine Research 2011;31:433-40.
34. Hakansson A, Gustafsson B, Krysander L, Hakansson L. Tumour-infiltrating lymphocytes in metastatic malignant melanoma and response to interferon alpha treatment. British journal of cancer 1996;74:670-6.
35. Losinno C, Wines BD, Johns TG, Mackay IR. Natural killer cell activity against cultured melanoma cells: a dye-reduction technique with studies on augmented activity by interferon subtypes. Natural immunity 1992;11:215-24.
36. Di Pucchio T, Pilla L, Capone I, et al. Immunization of stage IV melanoma patients with Melan-A/MART-1 and gp100 peptides plus IFN-alpha results in the activation of specific CD8(+) T cells and monocyte/dendritic cell precursors. Cancer research 2006;66:4943-51.
37. Tsavaris N, Baxevanis C, Kosmidis P, Papamichael M. The prognostic significance of immune changes in patients with renal cancer, melanoma and colorectal cancer, treated with interferon alpha 2b. Cancer immunology, immunotherapy : CII 1996;43:94-102.
38. Aoyagi S, Hata H, Homma E, Shimizu H. Sequential local injection of low-dose interferon-beta for maintenance therapy in stage II and III melanoma: a single-institution matched case-control study. Oncology 2012;82:139-46.
39. Johns TG, Mackay IR, Callister KA, Hertzog PJ, Devenish RJ, Linnane AW. Antiproliferative potencies of interferons on melanoma cell lines and xenografts: higher efficacy of interferon beta. Journal of the National Cancer Institute 1992;84:1185-90.
40. Kopf J, Hanson C, Delle U, Weimarck A, Stierner U. Action of interferon alpha and beta on four human melanoma cell lines in vitro. Anticancer research 1996;16:791-8.
41. Lebwohl M, Sacks S, Conant M, et al. Recombinant alpha-2 interferon gel treatment of recurrent herpes genitalis. Antiviral research 1992;17:235-43.
42. Stevens DA, Merigan TC. Interferon, antibody, and other host factors in herpes zoster. The Journal of clinical investigation 1972;51:1170-8.
43. Merigan TC, Rand KH, Pollard RB, Abdallah PS, Jordan GW, Fried RP. Human leukocyte interferon for the treatment of herpes zoster in patients with cancer. The New England journal of medicine 1978;298:981-7.
44. Torrelo A, Harto A, Sendagorta E, Czarnetzki BM, Ledo A. Interferon-alpha therapy in atopic dermatitis. Acta dermato-venereologica 1992;72:370-2.
45. MacKie RM. Interferon-alpha for atopic dermatitis. Lancet 1990;335:1282-3.
46. Noh G, Lee KY. Successful interferon alpha therapy in atopic dermatitis of Besnier's prurigo pattern with normal serum IgE and blood eosinophil fraction: randomized case-controlled study. Cytokine 2001;13:124-8.
47. Reinhold U, Wehrmann W, Kukel S, Kreysel HW. Evidence that defective interferon-gamma production in atopic

dermatitis patients is due to intrinsic abnormalities. Clinical and experimental immunology 1990;79:374-9.

48. Jang IG, Yang JK, Lee HJ, et al. Clinical improvement and immunohistochemical findings in severe atopic dermatitis treated with interferon gamma. Journal of the American Academy of Dermatology 2000;42:1033-40.
49. Buechner SA, Wernli M, Harr T, Hahn S, Itin P, Erb P. Regression of basal cell carcinoma by intralesional interferon-alpha treatment is mediated by CD95 (Apo-1/Fas)-CD95 ligand-induced suicide. The Journal of clinical investigation 1997;100:2691-6.
50. Buechner SA. Intralesional interferon alfa-2b in the treatment of basal cell carcinoma. Immunohistochemical study on cellular immune reaction leading to tumor regression. Journal of the American Academy of Dermatology 1991;24:731-4.
51. Mozzanica N, Cattaneo A, Boneschi V, Brambilla L, Melotti E, Finzi AF. Immunohistological evaluation of basal cell carcinoma immunoinfiltrate during intralesional treatment with alpha 2-interferon. Archives of dermatological research 1990;282:311-7.
52. Chitwood K, Etzkorn J, Cohen G. Topical and intralesional treatment of nonmelanoma skin cancer: efficacy and cost comparisons. Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al] 2013;39:1306-16.
53. Edwards L, Levine N, Smiles KA. The effect of topical interferon alpha 2b on actinic keratoses. The Journal of dermatologic surgery and oncology 1990;16:446-9.
54. Yang WL, Lee JY. Extensive inflammation of actinic keratoses during interferon alpha therapy for chronic hepatitis C in a Taiwanese albino woman. Journal of the Formosan Medical Association = Taiwan yi zhi 2013;112:728-9.
55. Martin G. The impact of the current United States guidelines on the management of actinic keratosis: is it time for an update? The Journal of clinical and aesthetic dermatology 2010;3:20-5.
56. Clifford JL, Walch E, Yang X, et al. Suppression of type I interferon signaling proteins is an early event in squamous skin carcinogenesis. Clinical cancer research : an official journal of the American Association for Cancer Research 2002;8:2067-72.
57. Naito Y, Baba T, Suzuki H, Uyeno K. The antagonistic effect of interferon-beta on the interferon-gamma-induced expression of HLA-DR antigen in a squamous cell carcinoma line. Journal of experimental pathology 1992;6:75-87.
58. Nickoloff BJ, Basham TY, Merigan TC, Morhenn VB. Immunomodulatory and antiproliferative effect of recombinant alpha, beta, and gamma interferons on cultured human malignant squamous cell lines, SCL-1 and SW-1271. The Journal of investigative dermatology 1985;84:487-90.
59. Lopez-Albaitero A, Nayak JV, Ogino T, et al. Role of antigen-processing machinery in the in vitro resistance of squamous cell carcinoma of the head and neck cells to recognition by CTL. Journal of immunology 2006;176:3402-9.
60. Kirby JS, Miller CJ. Intralesional chemotherapy for nonmelanoma skin cancer: a practical review. Journal of the American Academy of Dermatology 2010;63:689-702.
61. Edwards L, Berman B, Rapini RP, et al. Treatment of cutaneous squamous cell carcinomas by intralesional interferon alfa-2b therapy. Archives of dermatology 1992;128:1486-9.
62. Nikolaou V, Siakantaris MP, Vassilakopoulos TP, et al. PUVA plus interferon alpha2b in the treatment of advanced or refractory to PUVA early stage mycosis fungoides: a case series. Journal of the European Academy of Dermatology and Venereology: JEADV 2011;25:354-7.
63. Bazarbachi A, Plumelle Y, Carlos Ramos J, et al. Meta-analysis on the use of zidovudine and interferon-alfa in adult T-cell leukemia/lymphoma showing improved survival in the leukemic subtypes. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2010;28:4177-83.
64. Mustoe TA, Cooter RD, Gold MH, et al. International clinical recommendations on scar management. Plastic and reconstructive surgery 2002;110:560-71.
65. Leventhal D, Furr M, Reiter D. Treatment of keloids and hypertrophic scars: a meta-analysis and review of the literature. Archives of facial plastic surgery 2006;8:362-8.
66. Tredget EE, Shankowsky HA, Pannu R, et al. Transforming growth factor-beta in thermally injured patients with hypertrophic scars: effects of interferon alpha-2b. Plastic and reconstructive surgery 1998;102:1317-28; discussion 29-30.
67. Granstein RD, Rook A, Flotte TJ, et al. A controlled trial of intralesional recombinant interferon-gamma in the treatment of keloidal scarring. Clinical and histologic findings. Archives of dermatology 1990;126:1295-302.
68. Larrabee WF, Jr., East CA, Jaffe HS, Stephenson C, Peterson KE. Intralesional interferon gamma treatment for keloids and hypertrophic scars. Archives of otolaryngology--head & neck surgery 1990;116:1159-62.
69. Bielenberg DR, Bucana CD, Sanchez R, Mulliken JB, Folkman J, Fidler IJ. Progressive growth of infantile cutaneous hemangiomas is directly correlated with hyperplasia and angiogenesis of adjacent epidermis and inversely correlated with expression of the endogenous angiogenesis inhibitor, IFN-beta. International journal of oncology 1999;14:401-8.
70. Garmendia G, Miranda N, Borroso S, et al. Regression of infancy hemangiomas with recombinant IFN-alpha 2b. Journal of interferon & cytokine research : the official journal of the International Society for Interferon and Cytokine Research 2001;21:31-8.
71. Rampini E, Rampini P, Occella C, Bleidl D. Interferon alpha 2b for treatment of complex cutaneous haemangiomas of infancy: a reduced dosage schedule. The British journal of dermatology 2000;142:189-91.
72. Tamayo L, Ortiz DM, Orozco-Covarrubias L, et al. Therapeutic efficacy of interferon alfa-2b in infants with life-threatening giant hemangiomas. Archives of dermatology 1997;133:1567-71.
73. Dubois J, Hershon L, Carmant L, Belanger S, Leclerc JM, David M. Toxicity profile of interferon alfa-2b in children: A prospective evaluation. The Journal of pediatrics 1999;135:782-5.
74. Zvulunov A, Metzker A. Hemangiomas and vascular malformations: unapproved treatments. Clinics in dermatology 2002;20:660-7.
75. Peng Q, Liu W, Zhou F, Wang Y, Ji Y. An experimental study on the therapy of infantile hemangioma with recombinant interferon gamma. Journal of pediatric surgery 2011;46:496-501.

76. Smith DI, Swamy PM, Heffernan MP. Off-label uses of biologics in dermatology: interferon and intravenous immunoglobulin (part 1 of 2). Journal of the American Academy of Dermatology 2007;56:e1-54.

77. Fleming CJ, MacKie RM. Alpha interferon-induced hair discolouration. The British journal of dermatology 1996;135:337-8.

78. Maguiness SM, Frieden IJ. Current management of infantile hemangiomas. Seminars in cutaneous medicine and surgery 2010;29:106-14.

79. Mahrle G, Schulze HJ. Recombinant interferon-gamma (rIFN-gamma) in dermatology. The Journal of investigative dermatology 1990;95:132S-7S.