TAJ December 2004; Volume 17 Number 2

ISSN 1019-8555
The Journal of
Teachers Association
RMC, Rajshahi

Review Article

Interferon to PEG-Interferon: A Review

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Abstract

The interferons (IFNs) are group of naturally occurring cytokines that are secreted by cells of mammalian immune system when they are stimulated by viral, bacterial and other antigens. There are number of alpha IFNs available for treatment purposes. The two most commonly used α-2a and α-2b are made by recombinant technology. When interferon Alpha-2a is combined with polyethylene glycol (PEG), it is known as pegylated interferon or PEG interferon. Polyethylene glycol (PEG) is a safe, inert and nontoxic molecule. Therapeutic benefits of altering proteins with PEG include an improvement in half-life due to reduced renal and cellular clearance, enhanced protection from proteolysis and a reduction in toxicity.

TAJ 2004; 17(2) : 113-116

The interferons (IFNs) are group of naturally occurring cytokines that are secreted by cells of mammalian immune system when they are stimulated by viral, bacterial and other antigens. They were first described in 1957 for their effect in interfering with viral activity. There are three types of IFNs, designated alpha, beta and gamma. Each has anti-proliferative, anti-viral immunomodulatory effects[1]. The class 1 IFNs, IFN-α and IFN-β, are predominantly immunomodulatory and anti-viral, whereas IFNγ has a greater anti-proliferative effect. IFN-α is, in fact, a family of at least 16 related peptides, 18-20 KD in size, coded for on chromosome 9. There is 85% homology between different members of the group. The alpha IFNs are most commonly used in the treatment of viral hepatitis, though IFN-β is also used, particularly in Japan, IFNγ is a glycosylated protein of 20-25 KD and has not been shown to have any therapeutic activity against viral hepatitis[1].

There are number of alpha IFNs available for treatment purposes. The two most commonly used α-2a and α-2b are made by recombinant technology and each is single molecular type. IFN α-2n, or Iymphoblastoid IFN, is derived from a Iymphoblastoid cell line and constraints many different molecular subspecies. Consensus IFN is a synthetic IFN, the sequence for which was derived by aligning the sequences of 12 different types of IFNs and deriving an amino acid sequence, which maximized the degree of homology between the different type 1 subspecies.

Alpha interferon 2a:

Mechanism of action:

The mechanism of action of type[1] IFNs, whether naturally occurring or administered for therapeutic purposes, is primarily one of immune stimulation[1]. All the alpha and beta IFNs act on the same cell surface receptor and have the same action on the target cell. They are secreted from activated

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lymphoblastoid cells, macrophages, B lymphocytes or fibroblasts and bind to IFN receptors on target cells. The binding of IFN to cell surface receptors stimulates the production of specific gene products within the cell within 15 minutes. These catalyze the phosphorylation of IFN-stimulated gene factor and two other proteins called STAT 1 and STAT 2, The main genes which are activated by this mechanism are the 2′5′ -oligo-adenylate synthase gene (2′5′ OAS), HLA class 1 genes, protein kinase HLA class 1 genes and β–2 microglobulin.

These gene products enhance antigen presentation by the target cell and activate anti-viral pathways within the cell. This combination of effects leads to the suppression of viral replication and also to enhanced elimination of infected cells by the immune system.

Indications: Chronic hepatitis due to hepatitis B and C virus.

Dose: 5 MU three times a week for 6-12 months.

Side effects: Anorexia, nausea, diarrhoea, flu-like symptoms-fever, headache, myalgia, arthralgia, fatigue, lethargy, impotence, bone narrow suppression, auto immune thyroiditis, alopecia, rash, depression, insomnia, dizziness, psychosis, seizure, peripheral neuropathy, neutropenia, thrombocytopenia and haemolytic anaemia[1, 2].

What is PEG-Interferon?

When interferon Alpha-2a combined with polyethylene glycol (PEG) is known as pegylated interferon or PEG interferon (PEGASYS^{R}) [2, 3]. Polyethylene glycol (PEGF), a safe, inert and nontoxic molecule when attached covalently to IFN molecule and polymerized into long, branched chains is known as pegylated inter feron^{R}. Therapeutic benefits of altering proteins with PEG include an improvement in half-life due to reduced renal and cellular clearance, enhanced protection from proteolysis and a reduction in toxicity.

The alpha IFNs has a short half-life of about 6 hours. Therefore, a patient on a thrice-weekly regimen of injection will only be exposed to significant drug levels for a total of 36 hours per week. More frequent administration of IFN is inconvenient and debilitating for most patients. The combination of IFN with polyethylene glycol (PEG) has helped to overcome this problem by prolonging the half-life on IFN to 48 hours. This allows once-weekly injections to be administered. Apart from the greater convenience that this offers the patient, the continuous elevated concentration of IFN achieved offers significant enhancement of anti-viral effect, particularly against HCV. Two such preparations are available: PEG (40 KD) IFN-α-2a (PEGASYS^{R}) and PEG (12KD) IFN-α-2b (PEG-INTRON). The large molecule has a longer half-life and may achieve more sustained levels of IFN[2, 4, 5].

The aim of pegylating biologically active proteins is to improve the pharmacokinetic and pharmacodynamic properties of the native protein whilst retaining their intrinsic biological activity. The structure, length and molecular weight of PEG polymer chain and the modification procedure used, are factors involved in optimizing the pharmacokinetics and pharmacodynamics of a pegylated protein order to enhance its pharmacological activity and therapeutic efficacy.

Rational and Advantages of Pegylated Interferon

Globally an estimated 170 million people, approximately 3% of the world's population, are infected with the hepatitis C virus (HCV) (WHO 1999) [6, 7]. The efficacy of interferon alpha (IFN-α) therapy for the treatment of chronic hepatitis C has been limited by protein characteristics that include poor stability, a short half-life and immunogenicity. In various studies, the half-life of interferon-α ranges from 4 t0 6 hours, with peak serum concentrations occurring at 3 to 8 hours following intramuscularly (IM) or subcutaneous (SC) administration, little or no detectable IFN-α remains in the serum. These characteristics have several important consequences.

Frequent dosing of IFN-α is required to achieve effective therapeutic concentrations of drug in the plasma. In the treatment of chronic hepatitis C, conventional IFN is administered thrice weekly, but even with regimen, large fluctuations in serum

concentrations can occur after each does, resulting in peaks and troughs in the drug concentration. The peaks in drug concentration are linked to the high incidence of adverse events, such as fever, chills, headache, myalgia and dizziness that compromise the tolerability of conventional IFN. The troughs in drug concentration represent periods of time when IFN is not in circulation and so viral suppression is not maintained which may lead to viral rebound[2].

Principle studies of other pegylated therapeutic proteins demonstrate that PEG polymers enhance the proteins pharmacological activity in comparison with the native protein. Most notably, the PEG polymers increase the half-life of the conjugated protein. This increase in half-life is related to reduce renal and intracellular clearance, as well as increased resistance to proteolytic degradation.

The large molecule has a longer half-life and may achieve more sustained levels of IFN. The side effects profile of pegylated IFN seems too similar to that of normal IFN-α, and the same precaution should be taken during administration.

Dose: 180 μg subcutaneous injection once weekly.
Advantages of pegylation

- Improved pharmacokinetics-
  - Sustained absorption
  - Restricted distribution
  - reduced renal clearance
  - Sustained therapeutic concentration
- Less fluctuation in plasma concentration
- Enhanced in vivo activity
- Decreased toxicity
- Increased compliance and patients' quality of life (QOL).
- Decreased immunogenicity and antigenicity
- Increased physiological and chemical stability
- Improved solubility
- Protection from proteolysis

Patients with genotypes 1 and 4 regarded as having a more difficult to treat disease than those infected with genotypes 2 and 3[8,9,10]. Treatment of chronic hepatitis C for 12 months with IFN monotheraphy results in sustained virological response (SVR) of 15 to 20%[12, 13, 14, and 15].

PEGASYS[R] provides sustained therapeutic concentrations allowing the therapeutic dosing interval to be lengthened to once a week. And increased SVR can be achieved by providing a near constant and adequate exposure of PEGASYS[R] to the virus, PEGASYS[R] plus ribavirin yields a 78% sustained virological response (SVR) [16]. Even in the most difficult to treat patients, genotypes 1 and 4, the PEGASYS[R] combination achieved a 51% sustained virological response[17]. The overall response of combination therapy is 61% irrespective of genotype. In addition weekly therapeutic dosing improves treatment convenience and the QOL experience of the patient[18, 19].

Data from extensive clinical trial programs with PEGASYS[R] monotherapy and combination therapy indicate that it is the optimum treatment and the best chance for a cure in chronic hepatitis C. PEFASYS[R] /RBV combination therapy has been shown to be the optimum therapy for chronic hepatitis C compared with other IFN therapies[2, 20,21]. The PEGASYS[R] combination trials have established new treatment paradigms that will have significant economic, safety and adherence to treatment implications. PEGASYS[R], a yet another groundbreaking invention of the Roche, is now available in Bangladesh.

References

1. Clinicians' guide to viral hepatitis. Christopher J. Tibbs & Heather M. Smith: 116-119.
2. Remedica Issue 7, April-June 2002, 9-12.
3. Kozlowski A, Charles SA, Harris MJ, Development of pegylated interferons for the treatment of chronic hepatitis C. BioDrugs 2001; 15: 419-429.
4. Algranati NE, Sy S, Modi M. A branched methoxy 40 kDa polyethylene (PEG) moiety optimizes the pharmacokinetics (PK) pf peg IFN α-2a (PEG-IFN) and may explain its enhanced efficacy in chronic hepatitis C (CHC). Hepatology 1999; 30(4, pt 2): 190A.

5. Bailon O, Palleroni A, Schaffer CA, et al. Rational design of a potent, long lasting from of interferon: A 40 kDa branched polyethylene chem 2001; 12:1995-202.

6. EASL International Consensus on Hepatitis C, 1999.

7. European Association for the study of the liver (EASL) International Consensus Confeence on Hepatitis C. Consensus statement. J Hepatol 1999; 30: 956-961.

8. Davis GL, Lau JYN, Factors predictive of a beneficial response to therapy of hepatitis C. Hepatology 1997; 26 (suppl 1): 122S-127S.

9. Koshy A, Marcellin P, Martinot M, et al. Improved respoonse to ribavirin interferon combination compared with interferon alone in patients with type 4 chronic hepatitis C without cirrhosis Liver 2000; 20: 335-359.

10. Nishiguchi S, Ueda T, ltoh T, et al. Meyhod to detect substitutions in the interferon-sensitivity determining region of hepatitis C. virus 1b for prediction of response to interferon therapy, Hepatology 2001; 33(1): 241-247.

11. Consensus Conference. Treatment of hepatitis C. Paris, France, 2002.

12. Hoofngale, J.H (1998) Therapy of viral hepatitis. Digestion 59, 563-78.

13. Zuckerman, A.J. and lavanchy, D. (1999) Treatment options of chronic hepatitis. Antivirals look promising. Br. Med. J. 319, 799-800.

15. McHutchison JG, Poynard T. Combination therapy with interferon plus ribavirin for the initial treatment of chronic hepatitis C. Semin Liver Dis 1999: 19(suppl) 1): 57-65.

16. Nemann AU, Zeuzem S, Brunda MJ, et al. Rapid viral response to treatment with pegylated (40kDa) interferon alpha-2a (PEGASYS^{R}) is strongly predictive of a sustained virologic response in patients with chronic hepatitis C (CHC). Hepatology 2000; 32(4, pt 2): 318A.

17. Fried MW, Shiffman ML, Reddy KR, et al. Combination of peg interferon alpha-2a plus ribavirin in patients with chronic hepatitis virus infection. New Engl J Med 2002, paper accepted for publication.

18. Rasenack J, Zeuzem S, Feinman SV, et al. Therapy with pegylated (40kDa) interferon alpha-2a (PEGASYS^{R}) significantly enhances quality of life compared with conventional interferon alpha-2a (Roferon-A®) in patients with chronic hepatitis C. Hepatology 2000; 32: (4, pt 2): 307A.

19. Zeuzem S, Feinman SV, Rasenack J, et al. Evaluation of the safety and efficacy of once-weekly peginterferon alpha-2a PEGASYS^{R}) for chronic hepatitis C. A multinational randomized study. J Hepatol 2000b; 32 (suppl 2): 29.

20. Consensus conference: Treatment of hepatitis C, France 2002.

21. Lindsay KL, Therapy of hepatitis C: overview Hepatology 1997; 26 (3, suppl 1): 71S-77S.

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