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Interferons and Interferon Therapy

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Abstract:
Interferons(IFN) are cytokines that are responsible for the activity of the immune system . They are antiviral agents. There are mainly three types of Interferons in the humans namely Interferon Alpha (IFNA), Interferon Beta (IFNB) and Interferon Gamma (IFNG). There are also synthetically available interferons for treatment of various diseases. Interferon alpha is used to treat leukemia, cancer, Kaposi's sarcoma in relation with AIDS , multiple myeloma etc. Interferon beta is used to treat multiple sclerosis(MS) and Interferon gamma to treat chronic granulomatous disease(CGD). The route of administration is oral or parenteral in the form of injections. There are lot of precautions to be taken before the administration of the IFN as it is not tolerated by the old aged people due to the effect of the drug. Pregnant women should avoid these as it may cause complications to the fetus and the mother. The side effects caused may be flu like symptoms, head ache, joint ache, skin rashes, dryness of the mouth, dizziness, blood problems, decrease in WBC count etc.

Key Words:
Diseases, Interferons, Therapy, Treatment.

INTRODUCTION:

What are Interferons?

Interferons are small proteins belonging to the group cytokinins. They have effect on immune system and inhibit the tumor growth. They provide signaling to the immune system during viral infections. They amplify the antigen presentation to T cells. They increase the ability of the uninfected host to resist the new viral infection. They also activate the macrophages, B cells and alter the T cells and promote apoptosis. They are involved in various immune interactions as inducers, regulators and effectors of both innate immunity and acquired immunity during the viral infections.

TYPES OF IFN:

Interferons present in the humans are classified mainly into three types, 1. Alpha, 2. Beta, 3. Gamma. The interferons alpha and beta are termed to be type I and they are also called as plasmacytoid dendritic cell (pDCs) and interferon gamma is termed to be type II. Type I have a common receptor whereas type II have a distinct receptor.

Properties	INF Alpha	INF Beta	INF Gamma
Chromosomal Location	Cluster of intronless genes in 9p21	Proximity of IFN alpha cluster in 9p21	12q24
Source	Lymphocytes/ macrophages	Fibroblast/ endothelial cells	T cells
Number of proteins	22	1	1

IFN Alpha:

They are mainly involved in the innate immune response against viral infections. They come in 13 sub types namely IFNA1, IFNA2, IFNA4, IFNA5, IFNA6, IFNA7, IFN8, IFNA10 ,IFNA13, IFNA14, IFNA16, IFNA17, IFNA21. IFN alpha is also made synthetically as medications namely Pegylated IFN alpha-2a and Pegylated IFN alpha- 2b. It is monomeric with a molecular weight of 19050 to 22000

IFN Beta:

They are involved in the innate immune response as IFN alpha. The sub types namely IFNB1, IFNB2, IFNB3 are present. IFNB1 is used in the treatment of multiple sclerosis as it reduces the relapse rate. But it is not the appropriate treatment for patients with progressive, non relapsing forms of multiple sclerosis. It is momeric and a globular protein with 5 alpha helices with a molecular weight of 20kDa.

IFN Gamma:

It is involved in the regulation of immune and inflammatory responses. It also has anti- tumor effect. It is a dimer of two sub units each of molecules designated IFNGR1 and IFNGR2. Mature IFN Gamma is an anti-parallel homodimer. There is only one type of IFN Gamma.

BIOCHEMICAL FUNCTIONS OF IFN:

When a cell infected by cytolytic virus dies the virus particles gets liberated and affect the neighbouring cells. So to protect the other uninfected cells from the invaded virus the affected cells send signal to the neighbouring cells that there is a viral invasion. In order the neighbouring cells produce an enzyme called protein kinase R (PKR), phosphorylates a protein elF-2 in response to a new viral infection and this forms an inactive complex with other protein elF2B to reduce protein synthesis within the cell. Another cellular enzyme RNAse L induced by PKR activation, destroys RNA within the cells and inhibit protein synthesis and destroy the viral and host cells.

Interferons also induce the action of various other proteins such as Interferon- stimulated Genes (ISGs).

Interferons upregulate the major histocompatibility complex molecules (MHC), MHC I, MHC II , increase the immunoproteasome activity. Higher level of MHC I increases the presentation of viral peptides to cytotoxic T cells, thereby increasing the recognition and killing of infected cells. Higher level of MHC II increases the presentation of viral peptides to T helper cells, these cells release cytokines that signal to and co-ordinate the activity of other immune cells.

Other functions include increase in the p53 activity kills the viral infected cells by apoptosis. On combination with p53 it plays a protective role against cancer. IFN gamma directly activate the other immune cells such as macrophages and natural killer cells. IFN can also inflame the tongue and dysfunction or even kill the tastebuds. It inhibits angiogenesis, regulates the cell differentiation, and ha a wide variety of immunomodulatory effects.

INDUCTION OF IFN:

Interferons are produced in response to viruses and bacteria. Binding of the molecules uniquely found in microbes are viral glycoproteins, bacterial endotoxins,bacterial flagella,CpG motifs by pattern recognition receptors, such as membrane bound Toll like receptors or cytoplasmic receptors can trigger the interferon release. Toll like receptors induce the interferons in response and binds with the receptors of dsRNA. This activates the transcription factors IRF3 and NF-KB, that initiates the synthesis of many inflammatory proteins. The other factors that enhance the production of interferons are interleukin 1, interleukin 2, interleukin 3, tumor necrosis factor and colony stimulating factor.

INTERFERON THERAPY:

The immunological effects of interferons are used to treat several disease. Different types of IFN re involved in the treatment of different diseases.

For the treatment of Hairy Cell Leukemia IFN alpha type I interferon are used. Hairy cells are B cells in origin as evidence in expression of CD19, CD20, CD22 and immunoglobulin. In this the IFN alpha is reportedto the patient and the treatment is carried out for the next 2 to 3 months. Cell count gets normalized and marrow infilteration by hairy cells markedly decreased. This is the first human malignancy that was treated succefully with recombinant protein. Another mode of treatmet includes subcutaneous administration of IFN alpha every week a low dosage of 2-3 MU/m2 for a period of one year. There are also relapsing of few patients with negative result, these patients are treated with chemotherapeutic agents like 2'-deoxycoformycin or chlorodeoxyadenosine. Failure in the IFN treatment may be due to the development of neutralizing antibodies.

Chronic myelogenous leukemia is the chromosomal translocation between the long arms of chromosomes 9 and 22. Chemotherapy was the first used mode of treatment. Interferon alpha is effective at controlling CML in the chronic phase.haematologic remissions on the order of 70% have consistently been reported.About 20% of patients retreated with IFN alpha enter a complete cytogenic remission with complete elimination of Ph' positive cells. It remains to be seen if the patients with cytogenetic remission will have an overall survival advantage when compared to patients treated with conventional chemotherapy.

Multiple myeloma is a disease characterized by a neoplastic proliferation of a clonal population of plasma cells synthesizing immunoglobulin. Most of the patients with multiple myeloma respond to treatment with alkylating agents and steroids. Though there is a significant palliative benefit from treatment , no curative regimen has been found. An attempt to improve the response rate IFNs have been employed. On treating patients who have not undergone treatment previously, the response rate of 50% has been reported following treatment with IFN alpha. But the responses obtained were to be partial and so a prolonged treatment of several months has to be taken. 3 MU dose daly produces side effects and so a dose of 3 MU three times per week is well tolerated and effective. A combination of IFN alpha with cytoreductive chemotherapy appears to be aneffective induction regimen in previously untreated patients. Response rate of 80% have been approached. The use of IFN alpha involves administering the drug to the patient who have achieved partial or complete remission with cytotoxic drug combinations. There is a significant improvement seen in this strategy.

Renal cell carcinoma also known as the internists disease caused due to host of paraneoplastic phenomena such as fever,cachexia,neuromyopathy,polycythemia,the classic triad of haematuria,flank pain and palpable flank mass. The response rate of cytotoxic drug and hormonal agents were 10%. A comprehensive study and usage of IFN alpha raised the response to be upto 13%. The therapy involves anadministraton of 5 - 10 MU subcutaneously three times per week Melanoma arising from malignant transformation of melanocytes which are primarily located in skin but are also present in other organs such eye, GIT, respiratory tract and the meninges is said to be Malignant melanoma. The cytotoxic chemotherapeutic agents such as nitrosoureas ans decarbazine had the highest range of response rate upto 15%-20%.This lead to studies on IFN therapy in which IFN alpha was donstrated and the response rate was 15% out of which 5 % was a complete response. A dosage of 10-5- MU/m2 given for 3-5 days each week for a period of 6 months. Combinations with IFN alpha with cytotoxic agents have not demonstrated improved results over IFN alpha alone. and a duration of 3 months. Interferons at a high dose of 2 MU to 50 MU per week cannot be tolerated result in a poor therapeutic benefit. Interferons have also been used as a combination with the conventional chemotherapeutic drugs in kidney cancer which resulted in a disappointed response rate.

Kaposi sarcoma is the most common tumor occurring in association with AIDS. IFN alpha is the first biological agent used for the treatment of Kaposi sarcoma in relation with AIDS. The efficacy of recombinant IFN alpha for the treatment has been well documented with a response of 30% with dosage of 20 MU/m2. Median response dose for

complete responders was approximately 24 months and for partial responders 11.5 months.

Hepatits C treatment involves the treatment by IFN alpha which is the first biological agent to show significant antiviral activity. The best treatment is the combination of IFN and ribavirin. IFN is administered subcutaneously once a week while ribavirin an antiviral drug administered twice a day orally with dosage according to body weight.

Hepatitis B treatment involves the treatment by IFN alpha. The INF was dosage of 1 MU given subcutaneously per day for 4 months, 5 MU per day or prednisone followed by 5 MU daily for 4 months. The response rate was about 46% in the high dose group compared to25% in the low dose group.

Multiple sclerosis is a common neurologic disease of adults that is characterized by multiple areas of demyelination associated with inflammation in CNS resulting from autoimmune process.The first clinical trial using IFN was conducted for MS. IFN alpha was first administered subcutaneously of 5 MU for 6 months. The response rate was very poor and so the study lead to a randomized trial with IFN beta. 1 MU weekly for 4 weeks followed by monthly treatment of 5 months which also had a lower response. Then IFN beta-1b administered with a dosage od 8 MU every day for 2 years which also showed a low response report. But with a high dosage of administration there showed a high response rate than the lower dosage group. So usage of IFN beta for the trestment of MS was approved.

Chronic granulomatous disease is a rare inherited disease charaterised by a deficit in NADPH oxidase activity resulting in impaired ability of phagocytosis to kill ingested microorganisms. Therapy of CGD consists of aggressive, surgical drainage of abscess, antibiotic prophylaxis with trimethoprim- sulfamethoxazole, parenteral antibiotics. The IFN gamma was demonstrated for the therapy on CGD. IFN gamma administered subcutaneously for 3 times per week for 12 months showing a good response though thereare certain side effects like mild fever,chills,headache and cutaneous rashes which got resolved after several weeks of ongoing therapy. IFN gamma therapy is well tolerated.

Chicken pox is a viral infection caused by a virus Varicella Zoster Virus (VZV). It is a contagious disease that spreads through contact with an infected person. The therapy for cancer in children leads to death due to secondary viral infections in the course of the treatment. Children with leukemia receiving anti-cancer chemotherapy who became secondarily infected can be treated by the administration of IFN.

Herpes is a viral infection that is sexually transmitted and also spread through direct contact with the cold sores characteristic with the disease. Interferons on combination with Ribovarin gives a good response rate. IFN alpha on combination with acyclovir a treatment of 7 days eliminates the infected virus.

CLINICAL APPLICATIONS OF IFN:

The first interferon to be investigated was a natural leukocyte IFN Alpha. A mixture of acid stable IFNs produced by white blood cells exposd to Sendai cells were investigated in vitro. The clinical application of the different types of IFN are as follows

INF alpha

1. Hairy cell leukemia
2. AIDS related Kaposi's sarcoma
3. Chronic myelogenous leukemia
4. Malignant melanoma
5. Condylomata acuminate
6. Chronic hepatitis C
7. Chronic hepatitis B

INF beta

1. Multiple sclerosis

INF gamma

1. Chronic granulomatous disease

TOXICITY OF IFN:

Most of the side effects get resolved in frequency and severity with continued administration. The most side effects includes Flu like symptoms such as headache, muscle aches, joint aches, fever/chills, feeling sick vomiting, loss of appetite, feeling tired, and diarrhea,depression, mood swings, poor concentration, vagueness.Administration of Ibuprofen,acetaminophen and naproxen and intake of fluids help to alleviate these symptoms.

Less common effects include metallic taste, dry skin, dry mouth, skin rashes,loss or thinning of hair(temporary), pins and needles in the hands and toes, difficulty in sleeping, gastrointestinal upset, elevated liver function test, chronic fatigue, neurological complaints, cytopaenia. While ongoing of the treatment, temporary reduction of the WBC and platelets and thyroid problems may occur.This leads to more vulnerable infections, bleeding or bruising.The bone marrow returns to its normal state when the treatment is stopped.

PRECAUTIONS:

1. Caution should be exercised for patients with pre-existing seizure disorder.
2. Any allergies or allergic reactions that cause due to the drugs should be reported.
3. Alcoholics should be limted.
4. Should not undergo any immunization or vaccination without the consult of the physician.
5. Should stay away from patients recently taken oral polio vaccines or flu vaccines inhaled through nose.
6. Combination of IFN with Ribavirin may develop certain blood problems like anaemia and tooth and gum pain.
7. Dry mouth should be prevented with intake of water or saliva substitutes.
8. Caution should be taken for administering to older adults due to the sensitivity of the effect of drug,effect on heart,dizziness or mood changes.
9. Pregnant ladies should not be administered by this as this may end up with problems in the fetus and the mother.
10. Patients with severe neurological defects should not self administer injections without the assistance.

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