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# ROLE OF INTERFERONS IN CLINICAL PRACTICE

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**ABSTRACT:** Interferons were the first cytokines to be used therapeutically as naturally derived and as recombinant forms in humans. Their broad biological activity has resulted in clinical benefits in diseases ranging from infectious (such as viral hepatitis), autoimmune (in particular multiple sclerosis) to neoplastic (lymphomas and carcinomas). Since Interferons enhance the immune system in many ways, they are used for many diseases that involve the immune system. For example; Interferon alfa-2a (Roferon-A) is FDA-approved to treat hairy cell leukemia, AIDS-related Kaposi's sarcoma, and chronic myelogenous leukemia. Interferon alfa-2b is approved for the treatment of hairy cell leukemia, malignant melanoma, condylomata acuminata, AIDS-related Kaposi's sarcoma chronic hepatitis C, and chronic hepatitis B. Ribavirin combined with interferon alfa-2b, interferon alfacon-1 (Infergen), pegylated interferon alfa-2b, or pegylated interferon alpha-2a, all are approved for the treatment of chronic hepatitis C. Interferon beta-1b (Betaseron) and interferon beta-1a (Avonex) are approved for the treatment of multiple sclerosis. Interferon alfa-n3 (Alferon-N) is approved for the treatment of genital and perianal warts caused by human papillomavirus (HPV). Interferon gamma-1B (Actimmune) is approved for the treatment of chronic granulomatous disease and severe malignant osteopetrosis.

**INTRODUCTION:** Interferons (IFNs) are Glycoproteins made and released by host cells in response to the viruses, bacteria or parasites or tumor cells known as Cytokines. These are the first line of defence against viral infection.

They have the ability to "interfere" with viral replication within host cells. They activate natural killer cells and macrophages.

They increase recognition of infection or tumor cells by up-regulating antigen presentation to T-lymphocytes and increase the ability of uninfected host cells to resist new infection by virus. Certain host symptoms such as aching muscles and fever appear due to the production of Interferons during infection [1].

There are three types of Interferons: alpha, beta, and gamma. They fight against bacteria, viruses, fungi, tumors, and other foreign substances. They are used to treat skin cancer, Kaposi's sarcoma, and hairy cell leukemia and viral infections like hepatitis and genital warts [2]. The various clinically available Interferons are Roferon-A, Intron-A, Alferon-N, Pegintron, Avonex, Rebif, Betaseron, Infergen, Actimmune etc.

When a cell becomes infected by a virus it releases tiny amounts of ' Interferons' which then attach themselves to neighboring cells and prompt them to begin producing their own protective antiviral enzymes. The result of these actions is an impairment of the replication and growth of the attacking virus. Interferon has also been demonstrated to have some anti-tumor properties [2].

**ROFERON-A (interferon alfa-2a) injection, solution:** Roferon-A (Interferon alfa-2a, recombinant) is a sterile protein product for use by injection. Roferon-A is manufactured by recombinant DNA technology that employs a genetically engineered *Escherichia coli* bacterium containing DNA that codes for the human protein. Interferon alfa-2a, recombinant is a highly purified protein containing 165 amino acids, and it has an approximate molecular weight of 19,000 daltons. Fermentation is carried out in a defined nutrient medium containing the antibiotic tetracycline hydrochloride, 5 mg/L. However, the presence of the antibiotic is not detectable in the final product. Roferon-A is supplied in prefilled syringes. Each glass syringe barrel contains 0.5 mL of product. In addition, there is a needle, which is ½ inch in length [3].

**Clinical Studies:** Studies have shown that Roferon-A can normalize serum ALT, improve liver histology and reduce viral load in patients with chronic hepatitis C. Other studies have shown that Roferon-A can produce clinically meaningful tumor regression or disease stabilization in patients with hairy cell leukemia.[4,5] In Ph-positive Chronic Myelogenous Leukemia, Roferon-A supplemented with intermittent chemotherapy has been shown to prolong overall survival and to delay disease progression compared to patients treated with chemotherapy alone.[6] In addition, Roferon-A has been shown to produce sustained complete cytogenetic responses in a small subset of patients with CML in chronic phase. The activity of Roferon-A in Ph-negative CML has not been determined [1].

**Effects On Chronic Hepatitis C:** The safety and efficacy of Roferon-A was evaluated in multiple clinical trials involving over 2000 patients 18 years of age or older with hepatitis, with or without cirrhosis, who had elevated serum alanine aminotransferase (ALT) levels and tested positive for antibody to hepatitis C.

Roferon-A was given three times a week (TDS) by subcutaneous (s.c.) or intramuscular (i.m.) injection in a variety of dosing regimens, including dose escalation and de-escalation regimens. Normalization of serum ALT was defined in all studies as two consecutive normal serum ALT values at least 21 days apart. A sustained response (SR) was defined as normalization of ALT both at the end of treatment and at the end of at least 6 months of treatment-free follow-up.

In trials in which Roferon-A was administered for 6 months, 6 MIU, 3 MIU, and 1 MIU were directly compared. Six MIU was associated with higher SR rates but greater toxicity. In studies in which the same dose of Roferon-A was administered for 6 or 12 months, the longer duration was associated with higher SR rates and adverse events were no more severe or frequent in the second 6 months than in the first 6 months. Based on these data, the recommended regimens are 3 MIU for 12 months or 6 MIU for the first 3 months followed by 3 MIU for the next 9 months. There are no direct comparisons of these two regimens [2].

Younger patients (e.g., less than 35 years of age) and patients without cirrhosis on liver biopsy were more likely to respond completely to Roferon-A than those patients greater than 35 years of age or patients with cirrhosis on liver biopsy [4].

In the two studies in which Roferon-A was administered subcutaneously three times weekly for 12 months, 20/173 (12%) patients experienced a sustained response to therapy. Of these patients, 15/173 (9%) maintained this sustained response during continuous follow-up for up to four years. Patients who have ALT normalization but who fail to have a sustained response following an initial course of therapy may benefit from retreatment with higher doses of Roferon-A. A subset of patients had liver biopsies performed both before and after treatment with Roferon-A.

An improvement in liver histology as assessed by Knodell Histology Activity Index was generally observed. A retrospective subgroup analysis of 317 patients from two studies suggested a correlation between improvements in liver histology, durable serum ALT response rates, and decreased viral load as measured by the polymerase chain reaction (PCR) [5].

**Effects on Ph-Positive Chronic Myelogenous Leukemia (CML):** Roferon-A was evaluated in two trials of patients with chronic phase CML. Study DM84-38 was a single center phase II study conducted at the MD Anderson Cancer Center, which enrolled 91 patients, 81% were previously treated, 82% were Ph positive, and 63% received Roferon-A within 1 year of diagnosis. Study MI400 was a multicenter randomized phase III study conducted in Italy by the Italian Cooperative Study Group on CML in 335 patients; 226 Roferon-A and 109 chemotherapy.

Patients with Ph-positive, newly diagnosed or minimally treated CML were randomized (ratio 2:1) to either Roferon-A or conventional chemotherapy with either hydroxyurea or busulfan. In study DM84-38, patients started Roferon-A at 9 MIU/day, whereas in study MI400, it was progressively escalated from 3 to 9 MIU/day over the first month. In both trials, dose escalation for insufficient hematologic response, and dose attenuation or interruption for toxicity was permitted.

No formal guidelines for dose attenuation were given in the chemotherapy arm of study MI400. In addition, in the Roferon-A arm, the MI400 protocol allowed the addition of intermittent single agent chemotherapy for insufficient hematologic response to Roferon-A alone. In this trial, 44% of the Roferon-A treated patients also received intermittent single agent chemotherapy at some time during the study [6].

The two studies were analyzed according to uniform response criteria. For hematologic response: complete response (WBC $<9\times10^9$/L, normalization of the differential with no immature forms in the peripheral blood, disappearance of splenomegaly), partial response (>50% decrease from baseline of WBC to $<20\%\times10^9$/L). For cytogenetic response: complete response (0% Ph-positive metaphases), partial response (1% to 34% Ph-positive metaphases) [7].

In study DM84-38, the median survival from initiation of Roferon-A was 47 months. In study MI400, the median survival for the patients on the interferon arm was 69 months, which was significantly better than the 55 months seen in the chemotherapy control group (48 patients in study MI400 proceeded to BMT and in study DM84-38,

15 patients proceeded to BMT). Roferon-A treatment significantly delayed disease progression to blastic phase as evidenced by a median time to disease progression of 69 months to 46 months with chemotherapy [8]. By multivariate analysis of prognostic factors associated with all 335 patients entered into the randomized study, treatment with Roferon-A (with or without intermittent additional chemotherapy; p=0.006), Sokal index7 (p=0.006) and WBC (p=0.023) were the three variables associated with an improved survival, independent of other baseline characteristics (Karnofsky performance status and hemoglobin being the other factors entered into the model) [9].

In study MI400, overall hematologic responses, [complete responses (CR) and partial responses (PR)], were observed in approximately 60% of patients treated with Roferon-A (40% CR, 20% PR), compared to 70% with chemotherapy (30% CR, 40% PR). The median time to reach a complete hematologic response was 5 months in the Roferon-A arm and 4 months in the chemotherapy arm. The overall cytogenetic response rate (CR+PR), in patients receiving Roferon-A, was 10% and 12% in studies MI400 and DM84-38, respectively, according to the intent-to-treat principle.

In contrast, only 2% of the patients in the chemotherapy arm of study MI400 achieved a cytogenetic response (with no complete responses). Cytogenetic responses were observed only in patients who had complete hematologic responses. In study DM84-38, hematologic and cytogenetic response rates were higher in the subset of patients treated with Roferon-A within 1 year of diagnosis (76% and 17%, respectively) compared to the subset initiating Roferon-A therapy more than 1 year from diagnosis (29% and 4%, respectively). In an exploratory analysis, patients who achieved a cytogenetic response lived longer than those who did not [10].

Severe adverse events were observed in 66% and 31% of patients on study DM84-38 and MI400, respectively. Dose reduction and temporary cessation of therapy was required frequently. Permanent cessation of Roferon-A, due to intolerable side effects, was required in 15% and 23% of patients on studies DM84-38 and MI400, respectively [11].

Limited data are available on the use of Roferon-A in children with Ph-positive, adult-type CML. A published report on 15 children with CML suggests a safety profile similar to that seen in adult CML; clinical responses were also observed [8].

**Effects on Hairy Cell Leukemia:** A multicenter US phase II study (N2752) enrolled 218 patients; 75 were evaluable for efficacy in a preliminary analysis; 218 patients were evaluable for safety. Patients were to receive a starting dose of Roferon-A up to 6 MIU/m2/day, for an induction period of 4 to 6 months. Responding patients were to receive 12 months maintenance therapy [11].

During the first 1 to 2 months of treatment of patients with hairy cell leukemia, significant depression of hematopoiesis was likely to occur. Subsequently, there was improvement in circulating blood cell counts. Of the 75 patients who were evaluable for efficacy following at least 16 weeks of therapy, 46 (61%) achieved complete or partial response. Twenty-one patients (28%) had a minor remission, 8 (11%) remained stable, and none had worsening of disease. All patients who achieved either a complete or partial response had complete or partial normalization of all peripheral blood elements including hemoglobin level, white blood cell, neutrophil, monocyte and platelet counts with a concomitant decrease in peripheral blood and bone marrow hairy cells.

Responding patients also exhibited a marked reduction in red blood cell and platelet transfusion requirements, a decrease in infectious episodes and improvement in performance status. The probability of survival for 2 years in patients receiving Roferon-A (94%) was statistically increased compared to a historical control group (75%) [12].

**INTRON-A (Interferon alfa-2b): Interferon Alfa-2b Alone or in Combination with Ribavirin as Initial Treatment for Chronic Hepatitis C**

In one of the study, the efficacy and safety of recombinant interferon alfa-2b alone with those of a combination of interferon alfa-2b and Ribavirin for the initial treatment of patients with chronic hepatitis C was compared. 912 patients with chronic hepatitis C were randomly assigned to receive standard-dose of interferon alfa-2b alone or in combination with Ribavirin (1000 or 1200 mg orally per day, depending on body weight) for 24 or 48 weeks. Efficacy was assessed by measurements of serum hepatitis C virus (HCV) RNA and serum aminotransferases and by liver biopsy [13].

The rate of sustained virologic response (defined as an undetectable serum HCV RNA level 24 weeks after treatment was completed) was higher among patients who received combination therapy for either 24 weeks (70 of 228 patients, 31 percent) or 48 weeks (87 of 228 patients, 38 percent) than among patients who received interferon alone for either 24 weeks (13 of 231 patients, 6 percent) or 48 weeks (29 of 225 patients, 13 percent) (P<0.001 for the comparison of interferon alone with both 24 weeks and 48 weeks of combination treatment). Among patients with HCV genotype 1 infection, the best response occurred in those who were treated for 48 weeks with interferon and Ribavirin.

Histologic improvement was more common in patients who were treated with combination therapy for either 24 weeks (57 percent) or 48 weeks (61 percent) than in those who were treated with interferon alone for either 24 weeks (44 percent) or 48 weeks (41 percent). The drug doses had to be reduced and treatment discontinued more often in patients who were treated with combination therapy. It was concluded that initial therapy with interferon and Ribavirin was more effective than treatment with interferon alone in the patients with chronic hepatitis C. **[13]**

**Treatment of Acute Hepatitis C with Interferon Alfa-2b:** Chronic infection often develops in patients infected with hepatitis C virus and is difficult to eradicate. In this study the aim was to determine whether treatment during the acute phase could prevent the development of chronic infection or not. Between 1998 and 2001, 44 patients were identified throughout Germany who had acute hepatitis C. Patients received 5 million U of interferon alfa-2b subcutaneously daily for 4 weeks and then three times per week for another 20 weeks. Serum HCV RNA levels were measured before and during therapy and 24 weeks after the end of therapy [14]. The mean age of the 44 patients was 36 years; 25 were women. Nine became infected with HCV through intravenous drug use, 14 through a needle-stick injury, 7 through medical procedures, and 10 through sexual contact; the mode of infection could not be determined in 4.

The average time from infection to the first signs or symptoms of hepatitis was 54 days, and the average time from infection until the start of therapy was 89 days. At the end of both therapy and follow-up, 43 patients (98 percent) had undetectable levels of HCV RNA in serum and normal serum alanine aminotransferase levels. Levels of HCV RNA became undetectable after an average of 3.2 weeks of treatment. Therapy was well tolerated in all but one patient, who stopped therapy after 12 weeks because of side effects. It was concluded that the treatment of acute hepatitis C with interferon alfa-2b prevents chronic infection [14].

**ALFERON- N (interferon alfa-n3):**

**Phase I Trial of Interferon Alfa-n3 in Early-Stage Human Immunodeficiency Virus Type 1 Disease:**

**Evidence for Drug Safety, Tolerance, and Antiviral Activity:** The safety and tolerance of interferon alfa-n3 (IFN-αn3) was tested in 20 adults with asymptomatic human immunodeficiency virus type 1 (HIV-l) infection (>400 CD4Iymphocytes/mm$^3$). IFN-αn3 was self-injected three times per week for 3–6 months: 5 patients received 1 mega-IU (MIU)/dose, 10 received 5 MIU/dose, and 5 escalated to their maximum tolerated dose. Subjects were evaluated every 2–4 weeks through 2 months after cessation of treatment. Neuropsychological tests were given at 3-month intervals. Markers of IFN activity, anti-IFN neutralizing antibodies, and antiviral response were measured monthly.

IFNαn3 was safe and well tolerated: influenza-like symptoms were uncommon, laboratory toxicity was minimal, no adverse neurobehavioral side effects were evident, and no patient developed neutralizing antibodies against IFN. IFN-αn3 induced IFN-specific biologic responses and dose-related antiviral activity against HIV-1. Subjects showed stabilization of CD4 cells for > 20 months. IFN-αn3 should be studied in combination with other antiretroviral agents and in persons with more advanced HIV-1 infection [15].

**PEGINTRON:**

**Pegylated interferon alpha-2b plus Ribavirin in patients with genotype 4 chronic hepatitis C:**

**The role of rapid and early virologic response:** In patients chronically infected with hepatitis C virus (HCV) genotype 4, the optimum duration of therapy and the predictors of sustained virologic response (SVR) have not been adequately determined. In this study, 358 patients with chronic hepatitis C genotype 4 were randomly assigned to pegylated interferon (PEG-IFN) alpha-2b (1.5 µg/kg/week) plus oral Ribavirin (10.6 mg/kg/day) for a fixed duration of 48 weeks (control group, n = 50) or for a variable duration (n = 318). In the variable-duration group, patients with undetectable HCV RNA at week 4 were treated for 24 weeks (group A, n = 69), patients with undetectable HCV RNA at week 12 were treated for 36 weeks (group B, n = 79), and the rest of the patients were treated for 48 weeks (group C, n = 160).

The primary endpoint was SVR (undetectable HCV RNA 24 weeks after treatment cessation). Groups A-C and the control group had SVR rates of 86%, 76%, 56%, and 58%, respectively. After the study was controlled for predictors, a low baseline histologic grade and stage were associated with SVR ($P < 0.029$) in all groups. In addition, among patients in group C, older age ($P = 0.04$), a higher baseline body mass index ($P = 0.013$), and low baseline HCV RNA ($P < 0.001$) were also associated with SVR attainment. The incidence of adverse events and the rate of discontinuation were higher in patients in the variable-duration and fixed-duration groups treated for 48 weeks. It was concluded that in patients with chronic hepatitis C genotype 4 and undetectable HCV RNA at weeks 4 and 12, treatment with PEG-IFN alpha-2b and Ribavirin for 24 weeks and 36 weeks, respectively, is sufficient [16].

**Treating cancer with PEG Intron:** Studies in patients with chronic hepatitis C infection and malignancies had demonstrated both biologic and clinical activity of PEG Intron and had provided empiric data to compare the pharmacokinetics (PK) and pharmacodynamics of PEG Intron and IFN-α-2b. In this study, the authors conducted a review of the available data comparing the PK and pharmacodynamic effects of PEG Intron and IFN-α-2b. Safety and efficacy data from Phase I/II studies of PEG Intron in patients with chronic myelogenous leukemia (CML) and solid tumors were also reviewed.

Data from patients with chronic hepatitis C infection suggested that exposure to IFN at a PEG Intron dose of 0.25 µg/kg per week is similar to that observed after administration of IFN-α-2b at a dose of 3 million International Units, three times per week. PEG Intron at doses up to 6 µg/kg per week was well tolerated and demonstrated clinical activity in patients with CML and solid tumors, including metastatic melanoma and renal cell carcinoma [17].

It was concluded that dose intensification can be achieved safely in patients with CML and solid tumors using PEG Intron, which could improve efficacy. These results provided useful dosing guidelines to clinicians investigating the antitumor activity of PEG Intron in patients with malignancies. More data would be needed to determine the optimal dose in various oncologic indications. However, these results provide a sound rationale for further investigation of PEG Intron [17].

## AVONEX:

### Quality of life in Multiple Sclerosis:

**Influence of interferon-β1a (Avonex®) treatment:** Multiple sclerosis is a disease caused by the body's own defense system attacking and destroying the protective covering known as myelin that surrounds nerve fibres. Numerous data argue for initiating treatment with interferon-β (IFN-β) at an early stage in multiple sclerosis (MS). The consequences of its use may negatively influence the MS patient's quality of life (QoL). In this study, the objective was to evaluate the QoL of MS patients before and after a one-year period of treatment with IFN-β1a (Avonex®). QoL was assessed using the SF-36 in 121 relapsing-remitting MS patients. QoL was compared before and after treatment and with data from a normal population. The possible influence of disease progression on the SF-36 scores was also studied [18].

One hundred six patients completed the study (87%). Compared to a normal population, patients were, at baseline, worse off for all QoL scales, varying from a minimum decrease of 0.73 SD in mental health, to a maximum decrease of 1.55 SD in general health. After treatment, no significant changes were found in any of the QoL scores except for physical function, where a slight but significant decrease was noted (p=0.03).

Furthermore, there was no significant change either in the physical component summary (PCS) or mental component summary (MCS). The 'reported health transition' item was significantly improved compared to baseline (p=0.001). At inclusion, significant correlations were found between EDSS scores and scores of physical function (p<0.001), role - physical (p<0.01), general health and social function (both p<0.01), and with the PCS (p<0.01). Patients with clinical relapses and/or disability progression had a more significant decrease in physical function (p<0.05) and also in social function (p<0.05). It was concluded that the QoL, assessed by the SF-36 scale, is correlated with disability in MS. IFN-β1a treatment (Avonex®) has no negative effect on MS patient's QoL [18].

## REBIF:

### Subcutaneous Recombinant Interferon-β-1a (Rebif®):

**A Review of its Use in Relapsing-Remitting Multiple Sclerosis:** Subcutaneous recombinant interferon- β -1a (Rebif®) 22 or 44µg three times weekly is a valuable option in the first-line treatment in patients with relapsing-remitting multiple sclerosis (RRMS). It has shown benefits on outcome measures related to relapses, progression of disability and magnetic resonance imaging (MRI) in clinical trials. A significant efficacy advantage for subcutaneous interferon-β-1a three times weekly over intramuscular interferon- β -1a 30µg once weekly was shown at 24 and 48 weeks. The most common adverse events are generally mild and clinically manageable. Considering both direct and indirect comparative clinical trial data, an assessment suggests that subcutaneous interferon- β -1a 44µg three times weekly has the best benefit-to-risk values of the available disease-modifying drugs used to treat RRMS [19].

## BETASERON:

### Betaseron for Multiple Sclerosis:

**Implications for Therapeutics:** In one of the study, it was reported that Betaseron not only reduced the annual exacerbation rate by about 35% but also significantly slowed increasing plaque burden measured by serial magnetic resonance imaging (MRI).

Stock prices for Chiron, the manufacturer of Betaseron, fluctuated during the hearing, along with the hopes and fears of patients; but by the end of the day, the advisory panel had determined that Betaseron was both safe and effective for the treatment of exacerbating-remitting MS. Significantly, approval was heavily supported by an objective test—MRI—that corroborated the clinical findings [20].

## Systemic Recombinant Human Interferon- β Treatment of Relapsing-Remitting Multiple Sclerosis:

**Pilot Study Analysis and Six –Year Follow – Up:**
A pilot study was undertaken to test the safety and establish the side effect profile of recombinant human interferon-β lb (Betaseron, Berlex Laboratories, Richmond, CA), in patients with relapsing-remitting multiple sclerosis (RRMS). During the initial dose finding period (24 weeks), five groups of 6 patients each were treated by subcutaneous injection three times each week with either 0.8, 4, 8, or 16 million units (mil) of Betaseron or placebo (WHO Standard). Although some side effects were noted in all groups, a dose-related trend in reduction of exacerbation frequency and side-effect profile was noted.

Patients given 16 mU had no exacerbations during the initial dosing period, but associated side effects led to dose reduction or dropout. An 8 mU dose was selected for further study after 24 weeks, and continuous dosing at 8 mU in 15 patients has now exceeded 6 years. Side effects abated over time. Neutralizing antibody developed in most patients, but titers were variable, fluctuated independently of clinical course, and tended to fall with prolonged treatment.

A dose-dependent rise in neopterin levels was observed during the initial dosing period. This pilot study has demonstrated responsiveness to Betaseron, shown a stable safety profile over time, and established guidelines for a dosing regimen to evaluate and optimize further the efficacy of Betaseron in RRMS [21].

**INFERGEN (Interferon Alfacon-1):**

**Interferon Alfacon-1:**

**A Review of its Pharmacology and Therapeutic Efficacy in the Treatment of Chronic Hepatitis C:** Interferon alfacon-1 (consensus interferon) is a non-naturally occurring, synthetic, type I interferon (IFN)α that is used for the treatment of patients with chronic hepatitis C. In one of the study, the efficacy of subcutaneously administered interferon alfacon-1 has been demonstrated in clinical trials during the treatment of IFN-naive patients (interferon alfacon-1 9μg 3 times a week for 24 weeks) and retreatment of non-responders and relapsers to previous interferon therapy (interferon alfacon-1 15μg 3 times a week for up to 48 weeks). Higher and more frequent interferon alfacon-1 dosages have also been investigated [22].

Results from a pivotal double-blind randomized trial in 704 patients with chronic hepatitis C showed that interferon alfacon-1 9μg 3 times a week achieved virological and biochemical response rates of 34.9 and 42.2%, respectively, at treatment end-point (week 24). Sustained virological and biochemical responses (week 48) were reported in 12.1 and 20.3% of the patients, respectively. In general, response rates in recipients of interferon alfacon-1 9μg 3 times a week were similar to those achieved with IFN-α2b 3 MIU 3 times a week.

However, interferon alfacon-1 was more effective in the subgroup of patients infected with hepatitis C virus (HCV) genotype 1 at end-point (virological response, 24 *vs* 15%; p < 0.05) and post-treatment observation period (8 *vs* 4%) although the difference between treatment groups was statistically significant only at treatment end-point. The sustained virological response rate achieved in patients with high baseline levels of serum HCV RNA receiving interferon alfacon-1 was statistically superior to that exhibited in the IFN-α2b treatment group (7 *vs* 0%; p < 0.05) [22].

Interferon alfacon-1 also showed efficacy during the retreatment of non-responders and relapsers to previous IFN therapy in a large nonblind multicentre trial. Sustained virological response (week 72) was observed among 13 and 58% of non-responders and relapsers, respectively, after 48 weeks of treatment with interferon alfacon-1 15μg 3 times a week [22].

Interferon alfacon-1 has been generally well tolerated in clinical trials. As with other IFNs, adverse events were reported frequently but were usually considered of mild to moderate severity,

decreased with time and caused a small percentage of patients to withdraw from the treatment. Fever, fatigue, arthralgia, myalgia, headache and rigors were the most frequently reported adverse events. Psychiatric adverse events appeared to be dose-related and caused the majority of treatment withdrawals [22].

It was concluded that Interferon alfacon-1 was generally well tolerated and was an effective agent in the treatment of patients with chronic hepatitis C. Comparative data from a pivotal randomized trial indicated that the drug has at least equivalent efficacy to IFNα-2b, and a statistically significant advantage was demonstrated at treatment end-point in patients infected with HCV genotype 1. A number of ongoing trials with interferon alfacon-1 are evaluating issues such as the optimal dosage regimen and duration of therapy in an effort to improve sustained virological response to therapy, a goal for IFNs in general [22].

**Actimmune (interferon gamma 1b):** Actimmune is used for treatment of the following conditions:

- Chronic granulomatous disease

- Osteopetrosis

- Idiopathic pulmonary fibrosis (IPF) in the following situations; where the diagnosis of IPF has been confirmed by a pulmonologist and where the patient has early disease i.e., forced vital capacity (FVC) $\geq$ 50% [23].

Interferon gamma is a member of the interferon class of drugs. Gamma Interferons activate phagocytes, cells capable of ingesting microorganisms. This activation mediates the killing of certain bacteria. Chronic granulomatous disease is an inherited disorder characterized by malfunctioning phagocytes. Interferon gamma is used to reduce the frequency and severity of serious infections in patients with chronic granulomatous disease [24].

Osteopetrosis is a life-threatening, congenital disorder in which an overgrowth of bony structures leads to blindness, deafness and increased susceptibility to infections. Interferon gamma helps to reduce the number of infections, improve bone marrow function and prolong the lives of children with the disease [25].

Idiopathic Pulmonary Fibrosis (IPF) is a life-threatening disease of unknown cause leading to progressive inflammation, injury, and fibrosis (scarring) of the lungs which can prevent the lungs from providing oxygen to tissues in the body.IPF may result from either an autoimmune disorder, a condition in which the body's immune system attacks its own tissues, or the after effects of an infection.

The severity of IPF is evaluated by pulmonary lung testing to determine the rate of airflow through the lungs. FVC (forced vital capacity) is the total volume of air expired after a full inspiration. FEV1 (forced expiratory volume) is the volume of air expired in the first second during maximal expiratory effort.

Patients with IPF develop more rapid shallow breaths as the disease progresses; therefore their FVC and FEV1 are decreased due to the decrease in lung volume. Even in the absence of a complicating disease, the median survival after the diagnosis of IPF is less than three years. Approximately 40% of patients eventually die from respiratory failure. Early symptoms of IPF are usually similar to those of other lung diseases such as dry cough and/or dyspnea (shortness of breath). Enlargement (clubbing) of the fingertips is also a symptom that may develop [26].

Corticosteroids (prednisone) and cytotoxic agents (cyclophosphamide) are used in the management of IPF with response rates of 10-40%. Oxygen administration and, in special cases, lung transplantation is an alternative treatment for patients in severe, final stages of IPF. Treatment with interferon gamma is believed to slow the progression of IPF by suppressing the proliferation of fibroblasts and preventing further lung tissue damage. Interferon gamma is administered by subcutaneous injection [26].

**CONCLUSION:** Interferons are currently the most widely used biological response modifiers. They are of high clinical value in hematological malignancies (chronic myelogenous leukemia, multiple myeloma, non-Hodgkin lymphoma), in solid tumors (malignant melanoma, hypernephroma, pancreas neoplasms, carcinoid tumors, Kaposi's sarcoma, glioma, in ovarium, cervix and bladder carcinoma, and in basalioma) and in infectious diseases (chronic hepatitis B,

chronic non-A/non-B hepatitis, chronic delta hepatitis, AIDS, Papova virus and Rhinovirus infections, leishmaniasis, leprosy) and some other conditions.

The various clinically available Interferons are Roferon-A, used in chronic hepatitis, hairy cell leukemia, etc., Intron-A used in hairy cell leukemia, malignant melanoma, follicular lymphoma, condylomata acuminate, chronic hepatitis C , chronic hepatitis B etc., Alferon-N used for genital warts (condylomata acuminata), Pegintron in chronic hepatitis C etc. , Avonex, Rebif, Betaseron all are used in multiple sclerosis, Infergen used in chronic hepatitis C and Actimmune in chronic granulomatous disease osteopetrosis, idiopathic pulmonary fibrosis (IPF).

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