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Interferons as Therapeutic Agents for Infectious Diseases

Keywords: Interferon alpha (alfa), viral hepatitis, respiratory tract infection viruses, common cold, human papillomavirus, genital warts, vaccine, adjuvant

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Synopsis

Many attempts have been made to utilize interferons for the treatment or prevention of infectious diseases because of their natural antiviral and immunomodulating activity. This article explains the rationale for development of interferons as therapeutic agents and describes commercial products available today. It also provides a summary of studies that have been performed with interferons for use as exogenous biological response modifiers in viral infections. Overall the best data exist for treatment of viral hepatitis B and C where interferons are a cornerstone of therapy. While infections with human papillomavirus and common cold viruses sometimes respond favorably to interferons, their outcomes are far from ideal. Finally, the role of interferons as vaccine adjuvants is still being explored, but could be promising.

Introduction

Interferons (IFNs) are attractive biological response modifiers for use as therapeutic agents in infectious diseases because they have both antiviral and immunomodulatory activity. Their name even comes from the fact that they can “interfere” with viral replication.[1] IFN- α (“leukocyte interferon”) and IFN- β (“fibroblast interferon”) are released by human cells infected with certain viruses while IFN- γ (“immune interferon”) is produced by natural killer cells (T-cell lymphocytes) in response to antigen exposure. These cytokines then act on uninfected host tissue cells to induce a state of relative resistance to viral infections.[2] The agents bind to specific cell-surface receptors that initiate a series of intracellular events: induction of certain enzymes, inhibition of cell proliferation, and enhancement of immune activities including increased phagocytosis by macrophages and augmentation of specific cytotoxicity by T lymphocytes.[3] Further details on endogenous interferon action and an explanation of their activity as biological response modifiers, including in bacterial infections, can be found elsewhere in this issue.[4]

Even though interferons role against viruses is most prominent, they can also be induced by, and active against, rickettsia, mycobacteria and several protozoa.[1] Therapeutically, however, their use has generally been limited to treatment or prevention of viral infections. Although their potent antiviral activity is promising - inhibiting viral replication *in vitro* at concentrations as low as pg/mL – the development of interferons as clinically useful drugs has been largely disappointing. This can be attributed partly to their short half-life *in vivo* and extensive side effects. In fact, many symptoms of viral infections such as influenza can be blamed on endogenous interferon release. The adverse effects prevalent at therapeutic doses include fever, myalgia, and headache dubbed “flu-like symptoms”, along with bone marrow suppression leading to leukocytopenia and thrombocytopenia, plus central nervous system manifestations including depression.[1]

Interferons have been studied for the treatment or prevention of herpes zoster, herpes simplex, and cytomegalovirus infections, but the successful development of acyclovir and ganciclovir gave clinicians safer and more effective alternatives for dealing with these viruses.[5, 6] IFNs can also be used in the treatment of multiple sclerosis and certain cancers, but this article will review the therapeutic applications of interferons for infectious diseases, focusing on viral infections.

Interferons and IFN-inducers available commercially

Interferons are not absorbed orally because of their large amino-acid sequence which is susceptible to the proteolytic enzymes in the digestive tract. However, IFN- α is readily absorbed after both intramuscular and subcutaneous injection.[7] This rapid absorption combined with a short half-life means that frequent injections are needed to maintain adequate concentrations in the body. Both commercially available alpha interferon products in the U.S. have now been chemically attached to polyethylene glycol (PEG) to enhance their half-life and make once-weekly dosing possible. This not only

makes administration easier, but it also reduces side effects by having a predictably lower peak concentration of the exogenous cytokine.

Both pegylated IFN α -2a (Pegasys) and IFN α -2b (PegIntron) are obtained from *E. coli* by recombinant methods. They consist of naturally occurring small proteins with molecular weights of 15,000-27,600 daltons.[3] Each is considered a first-line option for the treatment of chronic hepatitis C virus infection in combination with ribavirin. More details on this use and others will be described later in the paper. Along with the list of additional FDA-approved indications in table 1, IFN- α was shown to be an effective treatment for the symptoms of an aggressive case of chronic active Epstein-Barr virus, but it did not eliminate infection entirely.[8] Therefore additional studies would need to be performed before recommendation for this use.

Human leukocyte derived IFN α -n3 (Alferon N) injection contains a spectrum of alpha interferons and is only approved for the treatment of refractory or recurring condylomata acuminata in adult patients. A low dose oral version is in development for use in the treatment and prevention of influenza.[9] Both versions have been studied against HIV-1 infection, but with little success.[10, 11] Interferon alfacon-1 (Infergen) is considered the synthetic “consensus interferon” because it contains a non-natural sequence of IFN- α amino acids all chosen for the highest activity against viral hepatitis. To date, no pegylated formulation of this product has been brought to market. All the alpha interferons include a black box warning in their prescribing information about how their use “may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Therapy should be withdrawn in patients with persistently severe or worsening signs and symptoms related to side effects. In many, but not all cases, these resolve after stopping therapy.”[12, 13]

Interferon- β -1a (Avonex or Rebif) and IFN- β -1b (Betaseron) are recombinant proteins with 166- and 165-amino acids respectively. These beta interferons have antiviral and immunomodulatory properties too, but their use at this time is limited to treatment of multiple sclerosis, not infections. Interferon- γ -1b (ACTIMMUNE) injection is used regularly for the prevention of infections in patients with chronic granulomatous disease along with antibacterials and antifungals.[14] Its mechanism of action for this purpose is not entirely known, but long-term studies show a definite benefit.[15] Gamma interferon can also be used as a salvage therapy for mycobacterial infections, but it is not routinely utilized for treatment of this or other infections.[16]

Topical imiquimod 5% (Aldara) and 3.75% (Zyclara) creams do not have inherent antiviral activity alone but instead induce IFN- α , - β and - γ plus tumor necrosis factor (TNF)- α through toll-like receptors. Local application to external genital and perianal warts results in an immunomodulatory response that stimulates cytokines which have antiviral action and cause a reduction in both viral load and wart size.[3]

Use of interferons for hepatitis viruses

Chronic infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) affects over 400 million people worldwide.[17-19] Chronic viral hepatitis is a leading cause of cirrhosis, liver transplantation and hepatocellular carcinoma. With the development of a vaccination series for hepatitis B in the mid-1980's, along with increased public education and awareness, acute infection rates of both HBV and HCV in the U.S. have declined steadily.[19]

Hepatitis B virus is a double-stranded DNA virus whereas HCV is a single-stranded RNA virus, both of which are capable of significant morbidity and mortality in chronic infection. The exact mechanisms of hepatic injury from HBV and HCV infection are not completely understood. Because

asymptomatic carriers with normal liver transaminases exist, it is likely multiple immune-mediated mechanisms result in hepatocyte damage as opposed to the virus itself being directly cytotoxic.

Following acute viral infection, the innate immune response initiates formation of natural killer (NK) cells, followed by virus-specific CD4+ T cells, and CD8+ cytotoxic T lymphocytes. Natural killer cells stimulate production of IFN- α/β and promote cellular clearance of viral proteins through disruption of the replication process. Following successful clearance, either spontaneously or by treatment with IFN, peripheral cytotoxic T lymphocytes and CD4+ T cell response persists.[20] Chronic infection is likely a result of failed innate and adaptive immunity. Specifically, chronic infection with HCV has been associated with impaired T cell and NK cell response.[21-24] Genetic factors also likely influence progression of disease and predisposition to adverse effects.[25] Though an abundance of research has investigated the immune response in relation to chronic viral hepatitis, many areas of uncertainty still exist.

Standard alpha interferon, the first approved IFN for viral hepatitis, lacked several desirable pharmacokinetic properties. The addition of PEG created an IFN that has a slower rate of absorption, reduced elimination and a longer half-life, necessitating less frequent dosing and fewer adverse effects. Furthermore, the PEG moiety results in reduced immunogenicity and sterically hinders the antigenic binding site.[26, 27] Although pegylated IFN has replaced standard IFN- α in treatment of chronic HBV and HCV, as many as 40 to 50% of patients still fail to respond to treatment. Successful response depends on many factors including but not limited to viral genotype, viral load and degree of liver fibrosis.[25]

Chronic hepatitis B and C are treated similarly with peginterferon (peg-IFN); however, only peginterferon α -2a is FDA approved in the U.S. for treatment of HBV. Both peg-IFN products are administered as subcutaneous injections once weekly for durations up to 48 weeks, dependent upon

viral genotype and early viral response for treatment of HCV. Peginterferon α -2b is dosed based on body weight (1.5 $\mu\text{g}/\text{kg}$ once weekly) whereas peginterferon α -2a is a fixed dose (180 $\mu\text{g}/\text{week}$). Ribavirin is used in combination with peg-IFN for treatment of HCV. The exact mechanism of action of ribavirin as an adjunctive antiviral agent in HCV is not completely understood.[12, 13] Some studies have proposed ribavirin to act as an interferon stimulated gene inducer to improve second phase viral decline.[28] Protease inhibitors (boceprevir and telaprevir) are recently approved adjunctive oral agents for the treatment of chronic HCV with peg-IFN and ribavirin. To date, all studies of protease inhibitors have been conducted in patients with HCV genotype 1, and have shown an increase in sustained virologic response (SVR) rates particularly for patients previously unresponsive to IFN therapy.[29-35].

The use of IFN for the treatment of chronic HBV and HCV has represented a mainstay of treatment for several decades. The specific mechanisms behind the antiviral effects of IFN for hepatitis are complex. Interferon stimulated genes are induced by IFN and disrupt viral replication. Hundreds of IFN-stimulated genes are thought to exist. Viperin, ISG20 and protein-kinase R (PKR) are just a few of the most commonly cited. It is also highly possible that interferon stimulated genes work synergistically to produce antiviral activities.[36, 37] A lack of PKR can lead to an environment conducive to HCV replication, though it may not be a good predictor of exogenous IFN response. The study of interferon stimulated genes and their role in determining who responds to IFN therapy has been evaluated in several studies.[25, 36, 38] Additional studies of interferon stimulated gene expression are needed in order to clarify which are directly involved in successful viral response, in what capacity they affect response, and if pharmacotherapy directed at induction of interferon stimulated genes can help improve treatment response.

Hepatitis B

Chronic HBV infection can be successfully treated with IFN monotherapy.[39] Loss of viral DNA and antibody formation are successful outcomes associated with IFN treatment. The mechanism of IFN antiviral activity varies depending on HBeAg-positive or HBeAg-negative disease. In HBeAg-positive patients, an immune response is stimulated by IFN whereas in HBeAg-negative disease, IFN acts directly as an antiviral.[5] HBeAg-negative disease tends to be more difficult to treat and is associated with a longer duration of disease and a higher likelihood of complications such as cirrhosis.[20] A number of oral non-nucleoside reverse transcriptase inhibitors are also available for treatment of HBV (entecavir, tenofovir, adefovir, lamivudine, and telbivudine). Although IFN is still considered a first line alternative and provides the advantage of defined treatment duration rather than potentially lifelong administration, these oral agents are often used in therapy because of their ease of use and reduced number of side effects associated with treatment.

Hepatitis C

The ability of HCV to evade the host immune response has produced a complex RNA virus capable of lingering infection, ultimately resulting in opportunities for increased risk of transmission and complications from advanced liver disease. Much of the research regarding the use of IFN for chronic viral hepatitis has focused on use in HCV. Following treatment with IFN, a decline in HCV RNA occurs over several phases. A rapid inhibition of RNA production within the first 1-2 days of treatment is followed by a second, slower phase associated with clearance of infected cells.[23, 40, 41] The immune response to endogenous IFN produced by innate immunity and that administered exogenously can differ in terms of antiviral activities based on the phase of viral decline.

Studies have shown that response to IFN based treatment for HCV may be affected by differences in IFN signaling and induction. It is likely that HCV has mechanisms to avoid recognition by the innate immune response, and as such inhibits the ability of HCV-infected cells to generate IFN.[25,

38, 42] Early studies conducted in non-responders to current therapy showed wide genetic diversity with many showing no common traits to predict non-response to IFN therapy.[25, 38, 43]

However, in 2009, several major studies were published associating a single nucleotide polymorphism (SNP) just upstream from interleukin-28B gene (IL28B) with IFN response in patients with HCV genotype 1.[44-48] Additional evidence points to the fact that the IL28B polymorphism is also linked to spontaneous clearance of HCV.[48, 49] The IL28B variant encodes for IFN- λ 3, a type III IFN belonging to the IL-10 superfamily, which function in a manner similar to type I IFNs resulting in interferon stimulated gene induction.[49-51]

The genome-wide association study conducted by Ge et al. evaluated over 1600 treatment-naïve HCV genotype 1 patients, the majority of which originated from the IDEAL study.[45] Results from logistic regression showed that the IL28B polymorphism was a stronger predictor of SVR than baseline viral load, ethnicity or degree of fibrosis. Further research in this area is needed to clearly identify a future role for genotype testing and further clarify whether it may influence response to therapy in other HCV genotypes.

A multicenter, randomized controlled study by Mangia et al. analyzed 268 Caucasian patients with HCV genotype 2 (n=213) and 3 (n=55). Out of 61% of patients that achieved rapid virologic response (RVR), IL28B genotype was not associated with SVR, whereas in those patients who did not achieve RVR, a significant difference in SVR was noted based on IL28B genotype.[52] At this time, genotype testing for IL28B is not routinely recommended for all HCV patients planning to undergo treatment, but it may be in the future. If done, it should not be used as the only factor when choosing a treatment strategy.[49]

Investigational IFN Therapies

The complexity of viral defense mechanisms and subsequent effect on the host response has led not only to development of chronic infections but also to a lack of a viable vaccine. HCV viral polymerase lacks a proofreading capability, creating a more diverse target for vaccine development.[18] Additional challenges include the lack of a suitable animal model to mimic a human environment and medium for viral growth.[18]

One of the major limitations to IFN therapy is adverse effects. Malaise, gastrointestinal effects, neuropsychiatric effects, neutropenia, and anemia can all limit the effectiveness of treatment by necessitating dosage reductions or treatment discontinuation. For newer IFN therapies to be successful, they must induce an antiviral response while at the same time limit adverse effects.

Albinterferon is a new IFN therapy currently in development for the treatment of chronic HCV. This product is a combination of interferon α -2b fused to recombinant human albumin. One of the advantages with this product is that it only requires once or twice monthly dosing.[53] Not much is known at this time about the immunomodulating effects of albinterferon in HCV. It has been shown to have similar SVR and adverse event rates to traditional peg-IFN when used in combination with ribavirin.[54-56]

Research into lambda IFN as an agent to treat HCV has also been initiated. It is hypothesized that lambda IFNs may be associated with less adverse effects over IFN- α because IFN- λ receptors are primarily found in hepatocytes.[49, 57] Specifically, research into new investigational pharmacotherapy in the form of pegylated IL-29 (IFN- λ 1) in patients with HCV genotype 1 who relapsed following traditional treatment with peg-IFN- α and ribavirin appears promising.[50, 57] Both IFN- λ 1 and IFN- λ 3 share a common receptor and have a similar sequence identity. [57]

A four week, open-label study conducted in 56 patients with chronic HCV genotype 1 was designed to assess peg-IFN- λ 1 in combination with ribavirin.[57] It was a dose escalation study

conducted in three parts. Parts 1 and 2 evaluated patients that relapsed following treatment with IFN- α , and part 3 included treatment-naïve patients. In part 1, pegylated lambda interferon monotherapy (1.5 $\mu\text{g}/\text{kg}$ or 3 $\mu\text{g}/\text{kg}$) was administered subcutaneously every 2 weeks or weekly. In parts 2 and 3, a range of peg-IFN- λ dosages (0.5 $\mu\text{g}/\text{kg}$, 0.75 $\mu\text{g}/\text{kg}$, 1.5 $\mu\text{g}/\text{kg}$ or 2.25 $\mu\text{g}/\text{kg}$) were administered weekly in combination with ribavirin twice daily (1000 mg for weight < 75 kg and 1200 mg if weight \geq 75 kg). The primary outcomes were safety and tolerability. Pharmacokinetics and viral load reduction were evaluated as secondary endpoints.

Commonly reported adverse effects with PEG IFN- λ included fatigue (29%), nausea (12%), myalgia (11%) and headache (9%). Most adverse events were mild or moderate in severity. Four patients (7%) experienced treatment-related toxicity and required doses to be withheld. One patient experienced grade 3 thrombocytopenic purpura and another patient had elevated ALT, AST and bilirubin levels. Both events were considered to be related to treatment with peg-IFN- λ . Aminotransferase elevations occurred most often in patients who received high dose (3 $\mu\text{g}/\text{kg}$) PEG IFN- λ monotherapy. No clinically relevant decreases in absolute neutrophil count occurred. Also, hemoglobin values remained consistent with known effects in patients that received ribavirin therapy. Viral activity decreased in the majority of patients that relapsed with previous treatment, with 23 of 24 patients achieving at least a > 2-log reduction in HCV RNA. Six of 7 treatment-naïve patients achieved a similar reduction in viral load and 2 achieved undetectable HCV RNA levels. Kinetic data showed a linear relationship between dose and exposure independent of body weight, which may prompt future research into a evaluating a fixed dose of peg-IFN- λ . [57]

Larger, longer, controlled and blinded studies of lambda IFN as a viable treatment option in HCV are needed in order to define its place in therapy and benefits over existing IFN therapy. Studies in other HCV genotypes are also needed. Additionally, with the advent of protease inhibitors, more research will

be necessary to evaluate how direct antivirals and IL28B genotyping interact in guiding treatment decisions.

Adjunctive therapy with agents that induce or restore interferon stimulated gene expression has recently been evaluated in patients with HCV. S-adenosyl methionine (SAME) given orally was evaluated in an open-label study in 24 patients with chronic HCV, genotype 1 who were considered non-responders to previous IFN and ribavirin treatment.[41] SAME was administered at a dose of 800 mg twice daily in combination with peginterferon alfa-2a (180 µg/kg weekly) and weight-based ribavirin (1000 mg for weight < 75 kg and 1200 mg if weight ≥ 75 kg). The primary outcome was change in first and second phase viral decline. Treatment response and interferon stimulated gene expression were also evaluated after up to 72 weeks of treatment. Results showed significant improvement in second phase viral decline assessed at 2 weeks. Sustained virologic response (SVR) was also evaluated; however, this study was not powered to detect differences in virologic response rates. Furthermore, at the time of publication, not all patients had reached 24 weeks post-treatment so the full effects on sustained virologic response (SVR) were not fully known. The addition of SAME showed greater induction of interferon stimulated genes including, viperin, myxovirus resistance protein and ISG15, compared to control. Adverse effects noted with SAME were mild and mostly related to gastrointestinal upset, likely as a result of lactose in the tablet preparation.[41]

Additional research is aimed at investigating structure-activity relationships and preliminary pharmacokinetic studies into oral IFN inducers that act on TLRs in the treatment of HCV.[58]

Use of interferons for respiratory virus infection

Upper respiratory tract infection in the form of “the common cold” can be caused by a variety of viruses including rhinovirus, coronavirus, influenza, parainfluenza, respiratory syncytial virus, adenovirus, coxsackie, and echovirus families among others.[59] Symptoms may include rhinorrhea,

nasal obstruction, cough, fever, and sore throat. The disease is usually mild and self-limited, but a number of trials have addressed treatment or prevention of the common cold with therapeutic agents. Interferons were once one of the most popular prospects for this purpose, but the little benefit that was derived from them was counteracted by the adverse effects inflicted.[60]

An early double-blind trial with IFN- α -2b intranasal drops did demonstrate that with use for several days prior to experimentally induced rhinovirus infection, common cold symptoms were significantly less in study participants compared to placebo drop users.[61] Administration of the drops four times daily was superior to a higher dose given once daily at preventing infection. Short-term use was well-tolerated, but obviously it is not realistic for everyone to use intranasal drops four times daily throughout the entire cold season. In an attempt to prevent natural infection during the period of increased acute respiratory tract virus activity, a twice daily nasal spray was studied in volunteers over 28 days.[62] There was a significant decrease in the number of rhinovirus infections noted, but not in any other types of viral respiratory tract infections including parainfluenza. Adverse events with the interferon formulation were quite common in this placebo-controlled trial. During the first week alone, 20% of participants receiving interferon spray reported nosebleeds. This number increased to 41% by the end of the study.

Providing interferon prophylaxis for family members of those infected with common cold viruses is a more targeted approach to therapy. Several studies have addressed the usefulness of IFN nasal sprays in this scenario. Seven days of use did significantly reduce rhinovirus infections in two different trials when compared to placebo for both individuals (7.9% vs 15.5%) and their families (3.3% vs. 33.3%, both $p < 0.05$), but not in two other studies when lower doses were given for a shorter five day course. [63-66] Overall, the intranasal dose of interferon needed to protect against upper respiratory tract infection appears to cause significant unwanted effects.[67] Infection with coronavirus and respiratory

syncytial virus has also been an object of investigation for IFN- α -2b nasal sprays, but with little success.[68, 69] A study of intranasal human lymphoblastoid IFN- α -n1 (Wellferon) suggested lower prophylactic activity for influenza than it did for rhinovirus.[70]

Since results of prophylactic trials with interferons for common cold viruses were not favorable, use in the treatment of infection seemed a logical application for this biological response modifier. Although some benefit was originally seen with twice daily IFN- α -2b intranasal drops for treatment of experimentally induced rhinovirus[71], no advantage was clear when an intranasal spray was used once daily for five days to treat natural infection.[72] Increased rates of blood in the mucus were again noted for participants receiving the intervention plus the interferon group experienced more secondary complications requiring prescription of antibiotics. The authors concluded that intranasal interferon was ineffective for treating the common cold and it was associated with clinically significant side effects.

Similar trials with IFN- β -serine and IFN- γ formulations, although initially positive, have shown equally disappointing clinical results.[73-76] Even though the prospects of further study on interferons for upper respiratory tract infection appear limited, one modern trial did demonstrate an added benefit of intranasal IFN α -2b in combination with an antihistamine (chlorpheniramine) and non-steroidal anti-inflammatory drug (ibuprofen) at reducing common cold symptoms – showing at least one group is still interested in studying the topic.[77] Investigators have also recently begun research on an alternative therapeutic approach for rhinovirus infections using the IFN and TNF α -inducer, imiquimod. Application of this intranasal cream in primates has shown promising results in terms of enhancing cytokine response, but human trials have not yet been published.[78]

Use of interferons for genital infections and warts

Human papillomoviruses (HPV) are now known to be the cause of cervical cancer and are also responsible for genital warts. They are non-enveloped, double-stranded DNA viruses that invade

mucosal and epithelial tissues during sexual contact with an infected partner. It is estimated that over 50% of the sexually active American population has been or will be infected with HPV at one point in their lives.[79] When hyperproliferation of infected cells occurs, this can lead to genital warts or cancer of the cervix, vagina, vulva and penis among others. There are over 100 different types of HPV and approximately 40 of them infect genital mucosa. Fifteen carcinogenic types of HPV have been identified, but two of them are associated with 70% of cervical cancers.[80] Two vaccines have recently been introduced which prevent infection with these most common high-risk types of HPV, 16 and 18.[81] One of these vaccines can also induce protection against the most prevalent HPV types that have a low-risk of malignancy, but instead cause genital warts - 6 and 11.

HPV has the ability to persist in stratified epithelia for decades because of mechanisms that avoid immune eradication. Interferon plays a large role in this cycle.[82] Interferons are normally secreted by keratinocytes, but HPV reduces their expression. Introduction of low level IFN can actually increase early gene transcription and HPV replication which may explain why use of the agent therapeutically has had mixed results.[83] Overall outcomes have been positive more often for cases of genital warts than reduction of HPV lesions associated with cancers. A study comparing the *in vitro* activity of IFN- α -2b and IFN- α -n3 on oncogenic HPV 16, 18, and 31b demonstrated that increasing concentrations did not always correlate with a stepwise inhibition of HPV replication.[84] Meanwhile, a meta-analysis recently analyzed locally-used and systemic interferon for genital warts.[85] Seven randomized studies of interferon intralesional injection or topical gel met criteria for inclusion and overall there was a benefit in complete response rates over placebo (44.4% vs. 16.15%, RR 2.68, 95% CI 1.79 to 4.02). However there was not a difference in outcomes for trials comparing systemic interferons to placebo. In comparison, clearance of genital and perianal warts occurs in 50% of patients with the topical IFN-inducer, imiquimod, usually after 8-10 weeks of use.[3] The 5% imiquimod cream (Aldara®)

should be applied to affected areas three times a week for up to 16 weeks while the newer 3.75% cream (Zyclara) can be applied once daily for as little as 8 weeks to treat external genital warts caused by HPV.

Systemic interferon therapy may be useful when HPV affects areas of the body other than the anogenital region.[86] Successful treatment with systemic PEG IFN- α and a topical retinoid has been reported for mucosal carcinomas from epidermodysplasia verruciformis, a genetic abnormality leading to persistent and widespread HPV infection of the skin.[87] Recurrent respiratory HPV infection has also been effectively treated with IFN- α (12 out of 18 patients), although it had no effect on viral load or replication.[88] A 20-year follow-up of patients treated with IFN- α for recurrent respiratory papillomatosis confirmed better response rates for HPV-6 than type 11 which had a higher likelihood of malignant transformation.[89] For recurrent conjunctival papilloma, topical plus systemic or intralesional IFN has been effective with partial excision.[90, 91] The rapid resolution of significant HPV-associated warts on the hand, foot and face has also occurred in an HIV-infected patient on antiretrovirals while being treated for hepatitis C with PEG IFN α -2b and ribavirin.[92]

Case reports of treatment with the topical interferon inducer, imiquimod, have shown promise for its use in focal epithelial hyperplasia (Heck disease), a rare disorder caused by specific types of HPV (13, 14, 32, and 55) affecting oral mucosa primarily in children.[93] In addition to that, imiquimod 5% cream has been used successfully in the treatment of plantar warts, a smoother, flatter manifestation of HPV 1, 2, and 4 on the foot.[94] Interestingly the oral H₂-antagonist cimetidine, along with reducing stomach acid, also induces production of IFN- γ and interleukin-2 which eliminates viral warts in some patients.[95] In the future, the improved application of more effective topical interferons may become a reality.[96] This could provide a valuable treatment for HPV infections without the systemic side effects of current injectable formulations.

Use of interferons as vaccine adjuvants

Adjuvants (*adjuvare*, Latin for “to help”) are substances that augment the immunogenicity of an antigen when mixed with the antigen for use in a vaccine. Adjuvants 1) stimulate granuloma (which is a macrophage-rich mass), 2) enhance co-stimulatory signals, 3) stimulate nonspecific lymphocyte production, 4) prolong the antigen concentration in a site for lymphocyte exposure [97] and 5) induce cytokines [2, 98]

Research in vaccine development has shown that one of the most promising uses of IFNs is as an adjuvant with specific antigens in prophylactic vaccines.[99] Toporovski et al. provides a current review of the use of IFN- α , IFN- β , IFN- γ , and IFN- λ in vaccine studies that focus primarily on murine, avian, porcine, and non-human species. Regardless of the species, the use of interferons as adjuvants seems to improve the efficacy and safety of most vaccines while providing the immunomodulatory effect of stimulating the T-helper 1 response.[99]

In humans, IFN- α , predominantly produced by plasmacytoid dendritic cells, plays a large role in the body’s immune response against viruses. [100] It induces plasma cell differentiation from B-cells, causing an increase in the serum level of influenza specific immunoglobulins and channels antigen presenting cells (APC’s) to the site of infection.[101] Most research on IFN- α adjuvant activity and its subsequent use in approved vaccines seems to indicate that it is a potent adjuvant.[99] When mixed with the influenza vaccine and injected intramuscularly, it is a highly effective adjuvant.[100] Oromucosal administration of recombinant IFN- α , like that of natural oromucosal IFN production, has been shown to provide immunity against viral infection and tumor cell growth. [102] Non- or low-responders to a previous vaccine showed an improved immunoglobulin response with a recombinant IFN- α and HBV vaccine.[103]

While research is also focused on the other classes of IFNs as adjuvants, thus far they haven't yielded results as promising as that of IFN- α . The use of IFN- β has yielded mixed results; IFN- γ has been used primarily in DNA vaccines; even less is known about the use of IFN- λ in vaccines.[99] Nevertheless, the use of IFNs as adjuvants shows great promise in augmenting vaccine efficiency and should continue to be a top priority in the development of vaccines.

Conclusion

Interferons have been tested repeatedly against infectious diseases, but injections are used mostly for the treatment of viral hepatitis C and prevention of infections in patients with chronic granulomatous disease clinically. Intralesional IFN and topical inducers are effective for reducing the manifestations of genital warts, but they do not eliminate cancer-causing HPV from the body. IFN has not proven to be consistently effective for treatment of respiratory tract infections from the common cold or influenza viruses and prophylactic use is not currently feasible. The severity and quantity of adverse effects from systemic IFN therapy make it unattractive for many uses. Several infections, including herpes simplex, herpes zoster, cytomegalovirus and even viral hepatitis B have other effective pharmacological treatments. IFN has been successfully utilized as a vaccine adjuvant and further research may allow for additional use of it for that application in the future.

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Table 1: Commercially available interferon products

Product	Brand names	FDA-approved indications	Usual doses in adults for treatment of indicated infections
Interferon alfa-2a & PEG Interferon α -2a injection	Roferon-A Pegasys	Chronic HCV, hairy cell leukemia and AIDS-related Kaposi's sarcoma Chronic HBV, HCV	3 million units SC three times weekly 180 mcg SC q week x 24 or 48 weeks
Interferon alfa-2b & PEG Interferon α -2b injection	Intron A PegIntron, Sylatron	Chronic HBV, chronic HCV, condylomata acuminata, hairy cell leukemia, follicular lymphoma, and AIDS-related Kaposi's sarcoma Chronic HCV, melanoma	3 million units SC three times weekly 1.5 mcg/kg SC q week x 24 or 48 weeks
Interferon alfacon injection	Infergen	Chronic HCV	15 mcg SC daily with ribavirin for retreatment of IFN refractory disease
Interferon alfa-n3 injection	Alferon N	Refractory or recurring external condylomata acuminata	Intralesional injection of 250,000 IU (0.05 mL) per wart twice weekly for up to 8 weeks.
Interferon beta-1a	Avonex,	Relapsing multiple sclerosis	Not indicated for infection

injection	Rebif		
Interferon beta-1b injection	Betaseron	Relapsing multiple sclerosis	Not indicated for infection
Interferon gamma-1b injection	ACTIMMUNE	Reduction in the frequency and severity of serious infections associated with CGD or treatment of severe, malignant osteopetrosis	50 mcg/m ² (1 million IU/m ²) for patients whose BSA is greater than 0.5m ² SC three times weekly
Imiquimod 5% topical cream	Aldara	Actinic keratoses of the face or scalp, superficial basal cell carcinoma, external genital and perianal warts/condyloma acuminata	Apply topically three times per week until total clearance of warts or a maximum of 16 weeks
Imiquimod 3.75% cream	Zyclara	Actinic keratoses of the full face or balding scalp, external genital and perianal warts/condyloma acuminata	Apply once daily to the warts until total clearance or up to 8 weeks.

HBV = Hepatitis B Virus infection, HCV = Hepatitis C Virus Infection, SC = subcutaneously, q= every, AIDS = Acquired Immunodeficiency Syndrome, CGD = chronic granulomatous disease, IU = international units, BSA = body surface area