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IFN-γ as a Major Antiviral Therapeutic for Viral Epidemics, Including Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): A Clinically Forgotten but Potential Antiviral Cytokine and Non-Virus-Specific Antiviral as a New Antiviral Strategy

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Abstract

IFN-γ is a type II IFN known as immune IFN that differs from virus-induced type I and III IFNs. IFN-γ has been clinically used to treat a wide variety of diseases. The original function of IFN-γ is its natural antiviral activity, and this molecule may be effective in viral infection and consequent disseminated multi-organ invasion. Despite its role as an inflammatory cytokine, IFN-γ induces regulatory T cells and antigen-specific regulatory B cells, which play a counter-regulatory role in the immune reaction, possibly preventing or controlling excessive immune responses such as cytokine storms that can result in death.

The advantages of IFN-γ are as follows: 1) IFN-γ is a non-virus-specific antiviral therapeutic and can be used in new virus infections and epidemics; 2) IFN-γ is strongly predicted to be effective in viral infection; 3) adequate clinical data for the clinical protocols of IFN-γ including dosage and period of use, are available; 4) IFN-γ is a relatively safe drug with few side effects and no rare severe side effects; 5) IFN-γ is available immediately; and 6) IFN-γ is not expensive.

New viruses have appeared every several years, causing serious epidemics to pandemic circumstances. Researchers must develop antiviral strategies against viral diseases, especially for critically serious viral epidemics. Among the IFNs, IFN-γ is regarded as suitable and strongly recommended as a major antiviral agent, at least in high-risk patients who are infected by viruses, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), when no vaccines or virus-specific antiviral therapeutics are available.

Keywords: IFN-γ, Antiviral Therapeutic, Non-Virus-Specific, Viral Epidemics, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), COVID 19

Interferon

Interferon (IFN) was first reported by Isaacs and Lindenmann in 1957 in influenza virus-infected chick cells that produced a secreted factor that mediated the transfer of a virus-resistant state active against both homologous and heterologous viruses [1]. Similar findings were described by Nagano and Kojima in 1958 [2]. Thereafter, subsequent studies began to elucidate the IFN system in detail.

Three types of IFN

IFNs are classified into three classes: type I, type II and type III [3]. Human IFN classification is based on the type of receptor through which they signal.

Type I IFNs

All type I IFNs bind to a specific cell surface receptor complex known as the IFN-α/β receptor (IFNAR) that consists of IFNAR1 and IFNAR2 chains [4]. The type I IFNs present in humans are IFN-α, IFN-β, IFN-ε, IFN-κ and IFN-ω [5]. In general, type I IFNs are produced when the body recognizes an invading virus. These molecules are produced by fibroblasts and monocytes.

Type II IFNs

Type II IFNs bind to the IFN-γ receptor (IFNGR), which consists of IFNGR1 and IFNGR2 chains [6]. Type II IFN and IFN-gamma are also known as immune IFN and are activated by interleukin-12. Type II IFN and IFN-γ are released by immune cells such as cytotoxic T cells and T helper-1 cells. These molecules block the proliferation of T helper-2 cells.

Type III IFNs

IFN type III signals through a receptor complex consisting of interleukin 10 receptor 2 and IFN-γ receptor 1 [3]. Type III IFNs, including IFN-λ1, IFN-λ2 and IFN-λ3, were previously identified as IL-29, 28a and 28b. Although type III IFNs were discovered more recently than type I and type II IFNs, type III IFNs are important in some types of virus or fungal infections [7-9]. Type III IFNs and IFN-λs are induced by infection or other stimuli and secreted by infected cells or stimulated plasmacytoid dendritic cells.

Clinical application of IFN

In 2001, IFNs were moved from the research laboratory to the clinic after they were approved as therapeutics [10]. IFN-α has been used to treat hepatitis B and C infections, while IFN-β has been used to treat multiple sclerosis [6]. IFN-γ inhibits the Th2 immune response and induces the Th1 immune response. Therefore, IFN-γ was indicated in multiple sclerosis [11].

Antiviral effects of IFN

IFNs were originally discovered as antiviral agents during studies on virus interference [1, 2]. All IFNs show antiviral activities [3]. Type I IFNs play a critical role in the innate immune response against viral infections [12]. Type II IFN and IFN-gamma have antiviral activity, and type III interferon is also involved in antiviral immunity [13, 14]. IFNs can serve as the first line of immune defence against viral infection [8]. The biological activity of IFN is evaluated by its antiviral activity [10].

Side effects of IFN

Despite its effectiveness, IFN therapy requires caution because IFNs are powerful cytokines and affect numerous cell types [15]. As a result, patients usually experience unpleasant symptoms, and some patients show systemic side effects. Constant monitoring is required for patients who are treated with IFN to suppress viral infection and maintain quality of life.

Adverse reactions to IFN-α therapy have been described in almost every organ system and are clearly dose-dependent [16]. Flu-like symptoms, pain, nausea, gastrointestinal complaints, haematological toxicity, elevated transaminases, fatigue, increased susceptibility to infections, thyroid dysfunction and psychiatric side effects and psychiatric sequelae are the most frequently encountered side effects with IFN-α [17]. When side effects occur, it is frequently necessary to interrupt IFN-α therapy or reduce the dose. Additionally, severe or even life-threatening side effects do occur, although they are not frequent. Therefore, adverse events can occur, and it is important to identify those patients who are likely to benefit from treatment without experiencing severe toxicities.

Adverse events in patients treated with IFN-β were lymphopenia, injection site reactions, asthenia, flu-like symptoms, complex headache, pain leukopenia and liver enzyme elevations, which also infrequently resulted in dose reduction or treatment discontinuation [18]. IFN-β is available only in injectable forms. IFN-β can cause reactions at the injection site that may result in cutaneous necrosis [19]. Skin reactions with IFN-β are more common with subcutaneous administration. IFN-α and IFN-β therapy is generally well tolerated, and the most common adverse events observed are flu-like symptoms such as fever, headache, chills, and myalgia [20]. However, prolonged treatment is associated with more serious adverse events, including leucopenia, thrombocytopenia, increased hepatic transaminases, and neuropsychiatric effects.

The most common adverse therapeutic events occurring with IFN-γtherapy are flu-like symptoms and signs such as fever, headache, chills, myalgia, or fatigue [21]. Other common side effects include rash, erythema or tenderness at the injection site, diarrhoea and nausea, and leukopenia [22-27].

IFN-γ

IFN-γ was first described by Wheelock EF as an immune interferon that was produced from human leukocytes stimulated with phytohemagglutinin and by others in 1965 [28]. IFN-γ is different from virus-induced type I and III IFNs. Moreover, IFN-γ is a master regulator of the immune system [29]. IFN-γ is also important in immune regulation. However, most importantly, the original activity of IFN-gamma is its natural antiviral activity.

In the 1960s, IFN-γ was discovered as an antiviral agent. However, the use of IFN-γ as a therapeutic agent was not possible due to the lack of mass production. It was not until 1986 that early clinical trials of this cytokine were first conducted [30]. The initial studies were focused on side effects and dose escalation, and later trials systematically determined its therapeutic potential against cancers and infections. In subsequent years, IFN-γ has been used in a wide variety of clinical indications.

Recombinant IFN-γ 1b has been approved by the U.S. Food and Drug Administration for the treatment of chronic granulomatous disease and osteoporosis since 1992 [31, 32]. IFN-γ clinical trials have been conducted using recombinant derived protein (IFN-γ1b, Actimmune) and adenovirus vectors that express IFN-γ cDNA (TG-1041, TG-1042) [21]. Actimmune has been used to treat a wide variety of diseases, including cancer, tuberculosis, hepatitis, chronic granulomatous disease, osteopetrosis, and scleroderma. Adeno-IFN-γ has been used to treat cutaneous lymphoma and malignant melanoma.

Although not officially approved, IFN-gamma has also been shown to be effective in treating patients with moderate to severe atopic dermatitis since 1993 [33-35]. Thereafter, IFN-γ has been investigated in several kinds of allergic diseases other than atopic dermatitis. IFN-γ therapy was successful by grouping atopic dermatitis [36]. Subsequently, IFN-γ therapy was successfully used in specific immunotherapy for allergies to inhaled allergens (house dust mites), for specific oral tolerance induction for non-IgE-mediated and IgE-mediated food allergy, and for desensitization to oral agents (aspirin and cefaclor) and injectable agents (cefazolin and lidocaine) [37-43]. Fortunately, through these clinical applications of IFN-γ in allergic diseases, extensive clinical data, especially concerning dosage and safety, have been accumulated, and the immunologic mechanisms of IFN-gamma have been revealed from basic and clinical studies.

IFN-γ therapy in allergic diseases was shown to be safe in previous reports [44]. In these reports, there were no severe side effects except flu-like syndrome, headache, fever and abdominal pain, which can be controlled by antipyretics or analgesics. From clinical experience, IFN-γ seems to be safe and suitable as an antiviral agent for general use.

Ageing, allergy and prognosis

Decreased IFN-γ levels are associated with the severity and prognosis of some diseases [45, 46]. Additionally, IFN-γ levels are decreased

with ageing [47, 48]. Susceptibility to and mortality by SARS-CoV-2 is higher in elderly patients [49]. This phenomenon may be related to the relative IFN-γ -deficient status in elderly patients due to ageing.

IFN-γ gamma production and blood level are also decreased with allergic status. Allergic status can result in increased susceptibility to viruses, and the allergic condition is characterized by a relative IFN-γ deficiency [36, 50, 51]. Another factor for preventive planning is the relationship between allergic tendencies and susceptibility to viral infections such as SARS-CoV-2. IFN-γ was reported to downregulate the expression of the SARS coronavirus receptor angiotensin-converting enzyme 2 in vitro [52]. Anti-histamine was also suggested for producing more IFN-γ to control the replication of SARS-CoV-2 [53]. The cytokine therapy using IFN-γ as a major antiviral therapeutic is just approaching closely from the several recent experimental and clinical reports.

Perspectives on IFN-γ therapy in viral epidemics

IFN-γ therapy showed systemic immunological effects in the circulation in tolerance induction for IgE-mediated food allergy and desensitization for injectable drug allergy [39, 42]. Poly-desensitization for multiple allergens simultaneously by IFN-γ also supports the systemic effects of this molecule [54]. In contrast to the possible elimination and defence of antiviral antibodies outside the cells in the circulation as a first line of defence, IFN-γ may arm the immune system in every organ and effectively eliminate virus-infected cells in whole organs. Additionally, from these clinical data, IFN-γ may be effective against viremia and disseminated multi-organ invasion.

In particular, cytokine storms occur in disseminated viral infections, which lead to multi-organ failure [55, 56]. IFN-γ induced regulatory T cells [57]. Additionally, IFN-γ induces antigen-specific regulatory B cells in immunotherapy. Despite the inflammatory role of IFN-γ, regulatory T cells and antigen-specific regulatory B cells, which are induced in vitro and in vivo by IFN-γ therapy, may have roles as counter-regulators in immune reactions, which may prevent or control excessive immune responses such as cytokine storms [58-60].

Clinical application of IFN-γ for non-virus-specific antiviral therapy seems to be indicated in this situation. IFN-gamma therapy may be recommended in high-risk patients who are infected by viruses, including SARS-CoV-2, which still has no vaccine or virus-specific antiviral therapeutics.

The advantages of IFN-gamma are as follows: 1) IFN-gamma is a non-virus-specific antiviral agent and can be used for new virus infections and epidemics, 2) the effectiveness of IFN-γ is strongly predicted in viral infections, at least in high-risk patients, 3) adequate (although still not sufficient) clinical data for the clinical protocols of IFN-γ, including dosage and period of use, have been obtained, 4) IFN-γ is a relatively safe drug with few side effects and no common severe side effects in the clinical data in the last decades, 5) IFN-γ is available immediately, and 6) and IFN-γ is not expensive.

IFN-γ is an option for non-virus-specific antiviral therapeutics in viral epidemics, including SARS-CoV-2

New viruses have appeared every several years, causing serious epidemics to pandemic circumstances, such as SARS, MERS or SARS-CoV-2.61 However, the development and production of virus-specific therapeutics or vaccines require a long period of time, and many people die during epidemic or pandemic periods. Researchers must develop antiviral strategies against viral diseases, especially for critically serious viral epidemics. Non-virus specific immunotherapy should be considered, and IFN-gamma is suggested as an option for non-virus-specific antiviral immunotherapy in viral epidemics, including SARS, MERS and SARS-CoV-2, for several reasons, as described above [61, 62].

However, the antiviral effects of IFN have been reported and reviewed continuously for a long time by many scientists [10, 15]. Clinical application of this molecule is not common, and the clinical data and basic research data concerning the clinical use of IFN are not sufficient. Without clear reasons, IFN-gamma has not been suggested or considered an antiviral agent in the clinical fields, even in these serious viral epidemic circumstances.

Fortunately, recombinant IFN-γ is available from several companies in several countries. The safety of IFN-γ has already been proven in recent decades. Researchers need only confirm the effectiveness of IFN-γ.

Conclusions

First, researchers should develop non-virus-specific antiviral therapy against newly appearing viruses as a new strategy. Second, the present agent, IFN-γ which is already a pre-existing agent, should be considered. IFN-γ is a well-known broad-spectrum antimicrobial and antiviral agent and can be used as a non-virus-specific antiviral therapeutic [13, 63]. Ironically, despite its prominence, the original antiviral function of IFN-γ was neglected between theory and clinical application. IFN-γ is now suggested as a potent non-virus-specific antiviral agent that can be used in new virus epidemics, especially for high-risk patients when specific drugs for new viruses are not available.

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