Interferons (IFNs) are a family of cytokine mediators that are critically involved in alerting the cellular immune system to viral infections of host cells. There are three major classes of IFNs, as follows: IFN-α, IFN-β, and IFN-γ. IFNs are being investigated and applied in various respiratory disorders, including interstitial lung diseases, lung cancer, malignant mesothelioma, malignant pleural effusions, and respiratory infections. Recent promising preliminary results concerning patients with idiopathic pulmonary fibrosis who have been treated with IFN-γ1b should prompt the performance of further confirmatory well-designed multicenter trials. IFN-γ is emerging as an important cytokine for use in the treatment of patients with infectious diseases, including multidrug-resistant pulmonary TB. A better understanding of IFN biology, indications, side effect profiles, and toxicity management will aid in optimizing its use in the treatment of patients. The purpose of this article is, therefore, to review the current clinical use of IFNs in the treatment of patients with respiratory diseases.

**Key words:** interferons; interferon-α; interferon-β; interferon-γ; pulmonary disease; therapy; treatment

**Abbreviations:** IFN = interferon; IL = interleukin; IPF = idiopathic pulmonary fibrosis; MDR-TB = multidrug-resistant pulmonary TB; MPE = malignant pleural effusion; MPM = malignant pleural mesothelioma; RA = rheumatoid arthritis; rhu-IFN = recombinant human interferon; SCLC = small cell lung cancer; TGF = transforming growth factor; Th = T helper

Interferons (IFNs) are a family of cytokine mediators that are critically involved in alerting the cellular immune system to viral infections of host cells. IFNs not only exhibit important antiviral effects but also exert a key influence on the quality of cellular immune responses and amplify antigen presentation to specific T cells.

The three major classes of IFNs are IFN-α, IFN-β, and IFN-γ. Because IFN-α and IFN-β share components of the same receptor, they are referred to as type I IFNs. IFN-γ uses a separate receptor system and is referred to as a type II IFN. Additional IFNs have been discovered, but they are not as well-characterized. Type I IFNs are secreted by virus-infected cells, while the type II IFN is secreted mainly by T cells, natural killer cells, and macrophages. IFN-α and IFN-β have a globular structure that is composed of five α-helices. Compared with class I IFNs, the gene for IFN-γ is located on a different chromosome, it binds to a different receptor, its structure is different, and it is the only IFN that is considered to be capable of activating macrophages and inducing class II antigens. The current classification of IFNs and their major characteristics is shown in Table 1. This review focuses on important clinical models and principles that serve as guidelines for future advances in cytokine therapeutics. The purpose of this article is, therefore, to review the current clinical use of IFNs in patients with respiratory diseases.

**Biological Effects of IFNs**

To understand the mechanism of action of IFNs, it is useful to begin with a brief review of their
physiology. IFNs do not normally circulate, are formed constitutively by most cells, and function physiologically by autocrine or paracrine mechanisms.⁵

The biological effects of IFNs result primarily from the enhanced expression of a group of genes and proteins in responsive cells that are involved in inflammatory and antimicrobial activities. α-IFNs constitute a family of proteins that are produced by nucleated cells, which have antiviral, antiproliferative, and immune-regulating activities. IFNs interact with cells through high-affinity cell-surface receptors. Following activation, multiple effects can be detected, including the induction of gene transcription. They inhibit cellular growth, alter the state of cellular differentiation, interfere with oncogene expression, alter cell-surface antigen expression, increase the phagocytic activity of macrophages, and augment the cytotoxicity of lymphocytes for target cells. IFNs interact with specific cellular receptors, which promote the production of second messengers, ultimately leading to the expression of antiviral and immune modulatory genes.⁶–⁸

The human IFNs are composed of a large number of genes with the type I and the type II IFNs on different chromosomes. Despite the different surface receptors, the IFNs signal through somewhat overlapping and mutually interacting pathways. IFN-α, the first cytokine to be produced by recombinant DNA technology, has emerged as an important regulator of growth differentiation, affecting cellular communication and signal transduction pathways as well as immunologic control. Originally discovered as an antiviral substance, the efficacy of IFN-α in treating patients with malignant, viral, immunologic, angiogenic, inflammatory, and fibrotic diseases suggests a spectrum of interrelated pathophysiologies. After the surprising discovery of activity in a rare B-cell neoplasm, IFN-α emerged as a prototypic tumor suppressor protein that represses the clinical tumorigenic phenotype in some malignancies that are capable of differentiation.

IFN-γ converts macrophages from a resting to an active state and induces the synthesis of an array of receptors for binding to pathogens and endothelia, degradative enzymes, transcription factors, and cytokines involved in host defense. These broad immunoregulatory activities allow IFN-γ to play an important role in controlling diseases caused by intracellular bacteria (eg, Listeria and Mycobacterium), parasites (eg, Leishmania and Toxoplasma), and fungi (eg, Cryptococcus). The broad activity of IFN-γ is still only partially understood. However, several key immunoregulatory roles of IFN-γ are known: (1) improved antigen presentation; (2) enhanced killing of intracellular pathogens, which induces the synthesis of enzymes in phagocytes that are involved in the generation of reactive oxidants (eg, superoxide, hydrogen peroxide, and nitric oxide). Both of these reactive species are involved in the killing of intracellular and some extracellular infections; (3) heightened capacity for microbial killing; and (4) enhanced recruitment of leukocyte-enhanced macrophage activity and increased intracellular concentration of antimicrobials.

### Therapeutic Applications

For the past 40 years, various forms of IFNs have been evaluated as therapy in a number of malignant and nonmalignant diseases. The major oncologic indications for IFNs include melanoma, renal cell carcinoma, AIDS-related Kaposi’s sarcoma, follicular lymphoma, hairy cell leukemia, and chronic myelogenous leukemia. IFNs have been increasingly employed in the therapy for patients with viral infections (including hepatitis C and condylomata acuminata) and multiple sclerosis. The therapeutic potential of the IFNs is currently the focus of intense attention in a number of virus-associated diseases, tumors, and autoimmune disorders.¹–⁴

### Table 1—Current Classification of IFNs*  

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Type I</th>
<th>Type II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prototypic cell origin</td>
<td>Almost all cell types</td>
<td>T cells, NK cells</td>
</tr>
<tr>
<td>Induction</td>
<td>Virus; double-stranded RNA polypeptides; cytokines</td>
<td>Not directly induced in cell by viral infection, immunologic stimuli, T-cell-specific antigens, Staphylococcus enterotoxin A, PHA</td>
</tr>
<tr>
<td>Receptor binding</td>
<td>Type I (IFN-α-R-1, IFN-α-R-2)</td>
<td>Type II (IFN-γ-R-1, IFN-γ-R-2)</td>
</tr>
<tr>
<td>Direct antiproliferative effect</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Stimulates MHC Class I</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Stimulates MHC Class II</td>
<td>No (β slightly)</td>
<td>Yes</td>
</tr>
<tr>
<td>Stimulates NK cell activation</td>
<td>Yes</td>
<td>Much less (delayed)</td>
</tr>
</tbody>
</table>

*NK = natural killer; MHC = major histocompatibility complex; PHA = phytohemagglutinin; R = receptor.
INTERSTITIAL LUNG DISEASES

Idiopathic Pulmonary Fibrosis

In contrast to normal repair, chronic inflammation in interstitial lung disease promotes fibroproliferation and the deposition of an extracellular matrix reflecting dysregulated and exaggerated tissue repair. The persistent imbalance in the expression of Th1 cytokines (ie, interferon [IFN]-γ and IL-13) vs Th2 cytokines (IL-2 and IFN-γ) in the lung is a mechanism for the progression of pulmonary fibrosis. IFN-γ is a major Th1 cytokine and possesses profound regulatory activity for collagen deposition during chronic inflammation.

Berkman et al reported that treatment with human recombinant IFN-α/2α caused a significant rise in lymphocytes in BAL fluid, and in cellularity and fibrosis fractions in lung tissue in a bleomycin-induced animal model of pulmonary fibrosis. In contrast, IFN-α/A/d had no effect in this animal model. The authors concluded that IFN-α may enhance bleomycin-induced lung injury but that this effect varies with different IFN preparations.

The efficacy of IFN-β-1a in the treatment of patients with idiopathic pulmonary fibrosis (IPF) has been evaluated by a multicenter, randomized, double-blind, phase II study. This study of 167 well-defined IPF patients who were treated with IFN-β-1a failed to show a significant benefit regarding pulmonary function (ie, FVC), arterial oxygenation, disease progression, or dyspnea score.

Ziesche et al reported promising results of a preliminary study comparing the treatment of patients who had IPF with IFN-γ-1b and prednisolone to treatment with prednisolone alone in 18 patients. The authors demonstrated an increase in total lung capacity and improved arterial oxygenation in the IFN-γ-1b treatment group, while the condition of patients in the prednisolone treatment group deteriorated. This objective clinical improvement coincided with decreases in messenger RNA levels of profibrotic cytokines transforming growth factor (TGF)-β and connective tissue growth factor. Therefore, it is possible that the therapeutic efficacy of IFN-γ-1b was related to its ability to shift the type 1/type 2 balance in favor of the antifibrotic type 1 response.

TGF-β1 probably has become the most important cytokine underlying progressive pulmonary fibrosis, owing to its strong activation of mesenchymal growth and its ability to modulate cellular immunity. In animal models, the administration of IFN-γ causes reduced expression of TGF-β1 together with a reduction in the amount of fibrosis.

A number of questions were raised about the study, as it was unclear that all patients who were studied had IPF, that the length of survival was atypical, and that the difference in outcome between the treated patients and those in the control group did not appear to be clinically significantly different. In a covering editorial by du Bois, it was argued that the findings of this pilot study, however promising, cannot be used as the basis of recommendations for treatment. Furthermore, the results appear to be to good to be true. For this reason, an independent expert panel reanalyzed the data. It was found that only 15 patients had definite or probable IPF, and the panel also confirmed the improvement in gas exchange and lung volumes of those treated with IFN-γ-1b.

A phase III clinical trial with a larger number of patients who have been accurately diagnosed with IPF is ongoing in the United States to evaluate the safety and efficacy of IFN-γ-1b therapy in IPF patients, using lung function as the primary objective. We are also conducting a confirmatory study in Greece comparing IFN-γ-1b and colchicine plus 10 mg prednisolone in patients with biopsy-proven usual interstitial pneumonia/IPF. The primary objective of the study is the change in the transcription level of growth factors (ie, TGF-β, connective tissue growth factor, insulin-like growth factor-1, TNF-α, and platelet-derived growth factor) and relevant ILs (ie, IL-4 and IL-5) measured in lung tissue and BAL fluid by reverse transcriptase polymerase chain reaction before and after 6-months of therapy. Secondary objectives of the study were disease outcome and mortality.

Connective Tissue Lung Diseases

The therapy for patients with rheumatoid arthritis (RA) still remains uncertain, and the rationale to study IFN-γ as a treatment for this disease is unclear. The initial studies were justified in part due to the observations of low levels of IFN-γ in the joints of patients with RA. Studies of IFN-γ have failed to demonstrate a significant degree of patient improvement at the doses used, and a high placebo response has been reported. The lack of a biological marker to adjust drug doses, the high placebo response, and the inadequate scientific rationale for using IFN-γ as therapy for patients with RA has restricted further investigation of this agent in RA patients.

IFN-γ may, however, be a promising agent in patients with other connective tissue lung diseases, such as scleroderma. The effectiveness of IFN-γ treatment on the skin and pulmonary function in patients with systemic sclerosis has been reported. In a 12-month trial of 9 patients treated with 50 µg/d IFN-γ 3 days per week subcutaneously, a significant...
improvement was observed in total skin score and arterial oxygenation. No serious adverse effects were noted.\textsuperscript{25}

Grassegger et al\textsuperscript{26} reported the results of a randomized, controlled, multicenter study on IFN-\(\gamma\) treatment for patients with systemic sclerosis as determined by skin sclerosis, renal and other organ involvement, global assessment, subjective symptoms, and quality of life. The authors concluded that IFN-\(\gamma\) therapy has mild beneficial effects on skin sclerosis and disease-associated symptoms in type I and II scleroderma with acceptable tolerability.

**Lung Cancer**

**Small Cell Lung Cancer**

Despite high initial response rates to chemotherapy, most patients with small cell lung cancer (SCLC) relapse shortly after discontinuing therapy, and a cure remains an elusive goal, even for patients with limited-stage disease. For this reason, investigators have turned to the evaluation of alternative treatment strategies for patients with this malignancy. Different IFN preparations were used, but none of the trials showed a significant prolongation of survival.\textsuperscript{27}

IFN has been evaluated in several trials of adjuvant therapy after response to chemotherapy for SCLC. In one of these studies,\textsuperscript{28} the objective response rate to therapy with recombinant IFN-\(\gamma\) was 6.7\% (2 of 30 patients). The authors concluded that IFN-\(\gamma\) is inactive in patients with SCLC even when the tumor burden has been substantially reduced by prior chemotherapy. In a second study,\textsuperscript{29} IFN-\(\gamma\) failed to show any benefit when given as maintenance therapy to patients with SCLC who had achieved a complete or nearly complete response to induction chemotherapy.

The effectiveness of treatment with IFN-\(\alpha\)-2c in combination with standard induction chemotherapy in patients with advanced SCLC has been evaluated in a phase III trial.\textsuperscript{30} After the induction phase, patients in the IFN arm had higher rates of complete remission (30\% vs 15\%, respectively) and partial remission (42\% vs 29\%, respectively) than those who received chemotherapy alone. While there were no significant differences in time to progression, patients in the IFN arm survived longer than those in the chemotherapy arm. A similar randomized, phase II, multicenter study\textsuperscript{31} was designed to determine time to progression, the duration of the response, and the feasibility of an intensified maintenance regimen consisting of a combination of IFN-\(\alpha\) and retinoic acid after high-dose combination chemotherapy and radiotherapy in patients with SCLC.

The differences between the IFN group and the control group were not statistically significant. The patients in the IFN group lived longer after the onset of progressive disease, and the treatment was well-tolerated.\textsuperscript{31} IFN-\(\alpha\) also has been administered concomitantly with chemotherapy in patients with any stage of SCLC.\textsuperscript{32} Grade 3 and 4 leukopenia occurred more frequently in the IFN arms than in the chemotherapy-alone arm and resulted in dose reductions. Antibodies occasionally developed to recombinant IFN-\(\alpha\). The authors suggested that the drug is better used for maintenance therapy.\textsuperscript{32}

**Non-small Cell Lung Cancer**

IFN-\(\gamma\) and/or IFN-\(\alpha\) have been compared in combination with standard chemotherapy in 80 patients with previously untreated stage III-IV non-small cell lung cancer.\textsuperscript{33} The addition of IFN-\(\gamma\) alone or IFN-\(\alpha\) plus IFN-\(\gamma\) to platinum-based chemotherapy did not improve response rates or produce any significant survival benefit for the patients. Increased hematologic toxicity also was observed.

**Malignant Mesothelioma**

The natural history of malignant pleural mesothelioma (MPM) remains unchanged with a median survival time for patients of <12 months. It is resistant to both chemotherapy and radiotherapy.\textsuperscript{34}

The instillation of recombinant human IFN (rhu-IFN)-\(\gamma\) in the pleural cavity has been used with promising results to treat patients with MPM. From the original group of 22 consecutive patients, 19 could be evaluated. Four complete thoracoscopic histopathologic responses and one partial response were observed in stage I patients (56\%).\textsuperscript{35,36} Similar results were reported by the same group\textsuperscript{37} of investigators in a prospective multicenter study in 89 patients with Butchart disease stages I and II epithelial or mixed MPM. The overall response rate was 20\%, and most responses were achieved in patients with early-stage disease (response rate in patients with stage I disease, 45\%). The tolerance of IFN was good, and the treatment was performed on an outpatient basis.\textsuperscript{37}

The mechanisms of action of rhu-IFN-\(\gamma\) in the pleura are poorly understood. Mesothelial cells can produce cytokines, coagulation, and fibrinolytic factors that are involved in processes like inflammation, tissue repair, immunologic reactions, and coagulation. The intrapleural production of IL-6 in patients with mesothelioma and its modulation by IFN-\(\gamma\) treatment were evaluated in 17 patients with MPM.\textsuperscript{38} The results of the study indicated that the systemic manifestations of MPM may be related to...
The production of IL-6 by malignant cells and that local IFN-γ infusion may alter the behavior of malignant cells. In addition to potential antitumor properties, the inhibiting effect of rhu-IFN-γ on intrapleural IL-6 production may abrogate systemic manifestations that are associated with mesothelioma, including fever and cachexia.38

A recent study43 evaluated a combined regimen of cisplatin, doxorubicin, and IFN-α-2b in the treatment of patients with advanced MPM. In the 35 patients who were assessable for response, the overall response rate was 29% and the 1-year and 2-year survival rates were 45% and 34%, respectively. However, toxicity, particularly myelosuppression and fatigue, is not negligible and may limit its application.

**Malignant Pleural Effusions**

Malignant pleural effusions (MPEs) remain a distressing and symptomatic problem in cancer patients. In one postmortem series,40 MPEs were found in 15% of patients who died with malignancies. MPEs also are one of the leading causes of exudative effusions. Studies40 have demonstrated that 77% of exudative effusions are secondary to a malignancy. Once an MPE is diagnosed, appropriate therapy may provide symptomatic relief and improved quality of life.

MPEs cause severe symptoms in patients with lung cancer. Since pleural exudate cells are thought to play a role in the host defense against cancer cells, the intrapleural administration of biological response modifiers has been conducted to augment the host defense against cancer and to control malignant pleurisy. The treatment of MPEs with bacterial preparations and cytokines, such as IFN-α and IFN-β, has been reported.41,42 It has been demonstrated that the daily intrapleural administration of IL-2 results in the in vivo generation of killer activity of mononuclear cells in the MPE, leading to an effective clinical control.43

Several treatment modalities are currently available for patients with MPEs. These modalities are associated with variable degrees of success and substantial side effects. Wilkins et al44 reported a 100% success rate in 15 patients who were treated with intrapleural IFN-α-2b for symptomatic malignant MPEs. Previous series45,46 have been reported success rates from 38 to 70%. The technique used by Wilkins et al44 (ie, closed chest tube thoracostomy drainage until a complete resolution of the MPE occurs before instilling the IFN) has probably played an important role in obtaining the promising results.

Different agents have been compared for the treatment of patients with MPEs. The therapeutic effect of the intrapleural instillation of bleomycin and IFN-α in 24 consecutive patients was compared.45 It was found that pleurodesis with intrapleural bleomycin was effective in 71.5% of patients and that it gave better results than treatment with IFN-α. The same group of investigators48 compared the effectiveness and safety of two different IFNs (ie, IFN-α and IFN-γ). The authors suggested that IFN-γ is more effective (71.5% vs 53.5%, respectively) for the control of MPEs.

The effect of the intrapleural instillation of IFN-γ at increasing doses (1 to 12 × 10^6 U) was examined in six patients who had MPEs due to lung cancer. Although the clinical control of pleural effusions by this IFN-γ treatment schedule was not generally satisfactory, the instillation of IFN-γ caused the disappearance of lung cancer cells from the pleural effusions in two patients.49 Further studies, using combinations with other fibrogenic cytokines, are warranted to examine the effect of local therapy with IFN.

**Respiratory Infections**

More than a century after the discovery of *Mycobacterium tuberculosis*, mycobacterial infections are resurgent. Therapy, which until recently had seemed simple and straightforward, is now complicated by the emergence of drug-resistant organisms and immunocompromised hosts. Multidrug-resistant tuberculosis (MDR-TB) is a serious, life-threatening condition that is associated with a high degree of morbidity and mortality (about 70%).50 Adjunct cytokines such as IL-2, IFN-γ, IL-12, and granulocyte-macrophage colony-stimulating factor hold great promise for shortening the duration of treatment and overcoming drug resistance.

There is a scientific rationale for the use of IFN-γ-1b in difficult-to-treat cases of mycobacterial disease. By activating macrophages and promoting a range of host immune responses, IFN-γ-1b may provide an effective adjunct to antimycobacterial agents in patients who are not responding to conventional courses of therapy. IFN-γ enhances antigen processing and presentation to lymphocytes through the induction of major histocompatibility complex class II antigens. It also acts on T lymphocytes, stimulating a differentiation toward a Th1-type of immune response.51–53

Condos et al51 investigated the safety and tolerability of therapy with aerosolized IFN-γ in patients with MDR-TB and assessed its efficacy in terms of sputum-smear grades. In this open-label trial, five patients with severe, advanced MDR-TB received inhaled IFN-γ-1b three times weekly for 1 month.
concomitant with their unchanged, previously ineffective antimycobacterial drugs. This treatment was associated with an improvement in the findings of sputum acid-fast-bacillus smears, the stabilization of weight or weight gain, and the lengthening of the time to a culture positive for \( M \) \textit{tuberculosis} from sputum samples, suggesting that the mycobacterial burden had decreased. There was stabilization or improvement of radiographic findings on CT scans in two patients, and cavitary lesions diminished in three other patients. The IFN-\( \gamma \) was well-tolerated by all patients.

IFN-\( \gamma \) therapy also has been evaluated in combination with conventional antituberculous therapy in patients with severe disseminated infection due to nontuberculous mycobacteria (mostly \textit{Mycobacterium avium} complex) showing symptomatic and clinical improvement in seven patients. Another group of investigators demonstrated that IFN-\( \gamma \) is required for the induction of anti-\( M \) \textit{tuberculosis} activity in cocultures of macrophages and lymphocytes. These data confirm the critical role of IFN-\( \gamma \) in defense against \( M \) \textit{tuberculosis}. A randomized, double-blind, placebo-controlled, phase II study is currently being performed for the evaluation of the safety and efficacy of inhaled IFN-\( \gamma \)-1b with antimycobacterial agents in previously treated or moderate-to-severe pulmonary \textit{M avium} complex infection.

**TOXICITY**

IFNs, when used as a systemic pharmacologic agent, have certain toxic effects. Skin, neurologic, endocrine, and immune toxicities have been reported. IFN-\( \alpha \) therapy may result in fatigue, fever, weight loss, and appetite loss. In addition, it can induce autoimmune diseases due to its immunomodulatory properties. Furthermore, there are some reports in the literature that describe the development of sarcoidosis associated with IFN-\( \alpha \) treatment.

Less commonly, various autoimmune processes have developed. Specifically, IFN-\( \alpha \) has been associated with hypothyroidism and hyperthyroidism, diabetes mellitus, idiopathic thrombocytopenic purpura, RA, a lupus syndrome, and nonspecific polyarthropathy. These phenomena are not surprising given the diverse immunomodulatory effects of IFNs, which could upset the balance between self-tolerance and autoimmunity when exogenously administered. Moreover, there is evidence that exogenously administered IFN-\( \alpha \) and IFN-\( \beta \) can activate macrophages in vitro. Therefore, the possibility exists that IFN-\( \alpha \) could cause macrophage activation when it is given for therapeutic reasons. Maybe such a mechanism (acting either in combination with an inherent predisposition or in isolation) was involved in the clinical development of sarcoidosis.

Similarly, adverse reactions to IFN-\( \gamma \) occur, including fever, fatigue, malaise, myalgias, and headache. The incidence of these side effects appears to be greater with IM administration of therapy compared to subcutaneous administration. We have reported a case of a patient who developed deep venous thrombosis after receiving treatment with IFN-\( \gamma \) for bronchiolitis obliterans-organizing pneumonia.

**CONCLUSION**

IFNs are being investigated and applied in patients with various respiratory disorders, including interstitial lung diseases, lung cancer, malignant mesothelioma, malignant pleural effusions, and respiratory infections. Recent promising preliminary results for IPF patients treated with IFN-\( \gamma \)-1b should prompt further confirmatory, well-designed, multicenter trials. IFN-\( \gamma \) is emerging as an important cytokine for use in the treatment patients with infectious diseases, including pulmonary MDR-TB. A better understanding of IFN biology, indications, side effects profiles, and toxicity management will aid in optimizing its use in the treatment of patients.

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