Interferon therapy: the other face of the medal

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Interferons (IFNs) are naturally occurring substances first described for their ability to interfere with viral replication. The IFN cytokine family consists of a group of proteins that may be divided into two subgroups, type I (IFN-α and IFN-β) and type II (IFN-γ). IFN-α was the first cytokine to be characterized and the first to be used as a human drug. Its efficacy has been shown in various diseases of viral, malignant, allergic, inflammatory and fibrogenic etiology. At first, type I IFNs were primarily considered as viral inhibitors, whereas type II, also termed "immune IFN", was generally considered as being exclusively involved in immune reactions. Recently, both species of IFNs have been shown to have a wide array of pleiotropic effects on most components of the immune system and these data suggested that IFN-α is a multifunctional immunomodulatory cytokine that affects nearly all phases of the innate and adaptive immune responses[1-3].

Because of these properties, IFN-α has been generally used for the treatment of various diseases such as chronic myeloid leukemia, hairy cell leukemia, Kaposi's sarcoma, renal cell carcinoma, melanoma and multiple sclerosis[4], but it represents, in association with ribavirin, the treatment of choice for chronic hepatitis due to hepatitis C virus infection[5]. Since its approval for this indication, this drug has been widely used and it has been shown to induce, in therapeutic doses, immune[6] and autoimmune disorders[7]. The occasional occurrence of toxicity and severe adverse events following the administration of this drug at high doses has limited its use in clinical practice[8].

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IFN-α has been implicated in the pathogenesis of sarcoidosis, a chronic multisystem disease of unknown origin with a prevalence ranging between 10 and 47/100 000 in North America and France[9] and clinically characterized by respiratory symptoms and histologically by the formation of non-caseating granulomas. Notwithstanding the rarity of this condition, an increased incidence of pulmonary sarcoidosis has recently been reported in a cohort of patients with chronic hepatitis C treated with IFN-α and ribavirin[10]. Cough and dyspnea during IFN therapy are often considered as side effects of the drug and not as a possible sign of interstitial pulmonary disease. Hence whether the occurrence of sarcoidosis during IFN therapy is underestimated, as claimed by Salvio et al. in this issue of *Annali*[11], is still under debate. Their report briefly describes a case of pulmonary sarcoidosis occurring in a young man during IFN and ribavirin therapy for chronic hepatitis C, and evaluates some possible pathogenetic links.

Acquired or adaptive immunity requires antigen recognition by T lymphocytes. Following antigen encounter, T CD4+ cells differentiate into two main types of helper cells, Th1 and Th2, characterized by different profiles of cytokine synthesis. Th1 mainly secretes interleukin (IL)-2, IL-12 and IFN-γ. IL-12 is considered the main mediator of Th1 differentiation, whereas IFN-γ induces Th1 differentiation by activating macrophages to release IL-12 and by inducing the expression of IL-12 receptor on T lymphocytes. On the other hand, IFN-γ inhibits Th2 proliferation, thus favoring Th1 differentiation. A large number of studies have shown that IFN-α may induce the production of Th1 cells and this effect is mediated by the induction of the JAK-STAT pathway through the IL-12 receptor[12,13].

The immunopathology of sarcoidosis has been best characterized in cases of pulmonary diseases, in which the early lesion consists of an alveolitis with a high proportion of activated CD4 lymphocytes of the Th1 phenotype. These lymphocytes secrete regulatory cytokines, IL-2, IL-12, IFN-γ and tumor necrosis factor-α which appear to regulate the formation of granuloma. IFN-γ appears to play a major role, because it is the only IFN considered capable of activating macrophages and of inducing HLA class II antigens. Since both IFN-α and IFN-γ share the same signal transduction pathway, it is plausible that IFN-α could activate macrophages when given for therapeutic purposes. So far, IFN-α, as a potent stimulator of Th1-mediated immune responses, may trigger the compartimentalized Th1 reaction that has been shown to take place in sarcoidosis, determining through the inhibition of the Th2 reaction a Th1/Th2 imbalance[14-16].

IFN-α is a commonly prescribed medication, particularly in the management of chronic viral hepatitis. The side effect profile has been well described. The more frequent effects include fatigue, flu-like symptoms, gastrointestinal disorders and neuropsychiatric and neurological abnormalities. Numerous other side effects occur with a lower frequency, but may still have an impact on the patient's tolerability to antiviral therapy. Among the infrequently reported (> 1%) prominent serious adverse events associated with standard IFN are retinopathy, visual loss, tinnitus, hearing loss, cardiac arrhythmias, interstitial pneumonia, acute renal failure, autoimmune disease, hyper- and hypothyroidism, acute psychosis, panic attacks, severe depression and suicide. Because most of the side effects associated with treatment are dose-related, the adopted strategy of dose reduction and/or discontinuation of therapy has been proven to be a safe and effective way of decreasing adverse events and minimizing serious, life-threatening sequelae[8]. In fact, the concept of the "dose-response" is an aspect that needs to be analyzed. As previously reported in the literature[17] and also described by Salvio et al.[11], the temporal relationship between IFN therapy and the development of sarcoidosis has not been well established. Further, Leclerc et al.[10] recently proved that patients who presented with pulmonary or cutaneous sarcoidosis during IFN therapy, improved remarkably after IFN discontinuation or dosage reduction. Therefore, it is time to speculate that a causal association exists. This hypothesis could be strengthened by the resolution of symptoms after drug withdrawal.

The management of side effects can begin even before the first dose of medication is administered. Careful patient selection undoubtedly contributes to the low rates of serious adverse events and premature discontinuation of therapy; in fact, the available data suggest that sarcoidosis may be precipitated or exacerbated in patients receiving IFN therapy. How could we prevent the occurrence or the exacerbation of sarcoidosis in these patients? Since the angiotensin-converting enzyme (ACE) level is considered as a marker of macrophage activation in patients with sarcoidosis, ACE levels could be employed as a screening test for drug-induced macrophage activation in patients who receive IFN therapy[17]. However, it is equally important to provide the patient with regular follow-up visits, thus facilitating the early detection of adverse events and promoting rapid intervention when warranted[8].

In conclusion, all available evidences suggest that, although sarcoidosis may be a side effect in patients receiving IFN therapy, this phenomenon remains rare: in fact, among the hundreds of thousands of patients who have been treated, only 28 cases were reported in the literature[10] (since 1992 to date). It must be stressed that in over half of the reported cases, sarcoidosis-related symptoms responded to a reduction in dosage or discontinuation of IFN, and some required adjuvant treatments with corticosteroids. The association of sarcoidosis and therapeutic doses of IFN supports experimental data suggesting that IFN may be implicated in the pathogenesis of the disease and "remarks the need for a closer control and more careful evaluation of respiratory symptoms in treated patients by the application of the screening protocol" proposed by the American Thoracic Association/European Respiratory Society[18] and also reported by Salvio et al.[11].

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