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Adjuvant Interferon Gamma in the Management of Multidrug - Resistant Tuberculosis

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1. Introduction

Tuberculosis is an opportunistic infection, the minute it finds an immunocompromised host, it flourishes. The risk of tuberculosis is much higher in patients who are human immunodeficiency virus (HIV) positive. Drug resistance among microbes is testimony to their adaptive skills. In *Mycobacterium Tuberculosis* the resistance occurs due to random, single step, spontaneous mutation and is invariably induced by inadequate or incomplete therapy. This resistance was termed as Multidrug Resistant (MDR) tuberculosis when the organism was resistant to more than one anti-tuberculosis drug. The presence of MDR tuberculosis, in general population, exposes the immunodeficient patients to an MDR strain of tuberculosis, which has very serious consequences for them. The risk of tuberculosis is also higher in non-HIV immunocompromised patients such as those with genetic absence of Interferon (IFN) gamma receptors, or acquired immune defect in the elderly. In either these situations IFN gamma or its absence seems to play a major role. In addition to the pulmonary infection, immunocompromised patients (with or without HIV) fall victim to extrapulmonary tuberculosis.

IFN gamma belongs to a family of endogenously produced immunoregulators that induces an array of receptors for binding to pathogens and endothelia, degradative enzymes, transcription factors and cytokines involved in host defense. These agents have antibacterial activity against host of pathogens including *Mycobacteria* (*avium* complex, tuberculosis and *bovis*). Interferon gamma has also a potent antifibrotic effect and suggests that it can lead to pulmonary lesions improvement. Exogenously administered IFN gamma has demonstrated therapeutic effect against MDR Tuberculosis, atypical mycobacterial infections, and leprosy.

Attempts to control MDR tuberculosis, is a part of the overall strategy to finally eradicate the disease. Had it not been for the emergence of drug resistance, tuberculosis would in all

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probability been wiped off by this time. The advent of acquired immunodeficiency syndrome (AIDS) has provided new fodder for the *Mycobacterium*, which thrives in the immunocompromised and protects itself by acquired resistance. A consistent strategy to control MDR by using agents such as IFN gamma can control further spread of the disease and protect individuals at risk.

In this chapter we will focus on the role of IFN gamma as the principal macrophage-activating cytokine as well as their antifibrotic properties. Later on we will show the results of several clinical trials which recombinant IFN gamma was used as immunoadjuvant to standard chemotherapy in patients with drug-resistant tuberculosis and other mycobacterial diseases.

2. Why can Interferon gamma be used for the treatment of Multidrug Resistant (MDR) tuberculosis?

Interferon (IFN) gamma, a dimeric protein composed of 146 amino acids and variable molecular weight depending of their glycosylation patterns, was discovered in 1965. The recombinant monomeric non glycosylated form has a molecular weight of 16-17 Kd, but it is twice when the active dimeric form is formed (Schreiber & Farrar, 1993). This cytokine is secreted by CD4+, CD8+ and Natural Killers (NK) cells. Nevertheless CD4+ Th1 lymphocytes, in response to an antigenic stimulus, are the main producers (Wang et al., 1999). IFN gamma is different to other interferons regarding its physiology, activation/modulation system and genetic regulation. The most striking differences between IFN gamma and other classes of interferons concern the immunomodulatory properties of this molecule. While gamma, alpha and beta interferons share certain biological properties (e.g. antiviral, antitumoral), IFN gamma, also known as immune IFN, has potent phagocyte-activating effects not seen with other IFN preparations. IFN gamma function has been strongly conserved throughout evolution and across multiple species. The biological response to IFN gamma is mediated by a cascade of complex cytoplasm and nuclear events that presuppose as first condition the binding of the ligand (IFN gamma) to their specific surface receptor (IFNGR). This receptor is a heterodimer, with IFNGR1 and IFNGR2 chains, and is present on the surface of many inflammatory cells. Binding of IFN gamma to IFNGR leads to modulation of nuclear gene expression via the Janus kinase (JAK)-STAT signaling pathway as follows. JAK associated with IFNGR phosphorylates STAT1. This enters the nucleus, where it binds to promoter regions of IFNG-inducible genes [Schroder et al., 2004]. The rationale of the use of exogenous IFN gamma for the treatment of MDR tuberculosis is based on:

2.1 Adjunctive immunotherapy may be particularly useful in the management of difficult-to treat tuberculosis or tuberculosis in the immunodeficient host

Tuberculosis (TB) is not yet a defeated affection. Although it is a controllable infection at community level and curable in an individual manner, its eradication seems distant. TB is an endemic disease in many parts of the world steadily decimating the population. At present, at least one third of the world population is infected with the *Mycobacterium tuberculosis*. The emergency of multidrug-resistant (MDR) strains has increased this world problem, leading to a high morbidity and mortality. Global estimates showed 9.27 million

new cases of TB and 1.77 million deaths from TB in 2007 (WHO, 2009), which is the highest number of deaths attributable to a single infectious agent and corresponds to the 7th cause of death in the world. The World Health Organization (WHO) has estimated that in 2008 there were 440 000 people had MDR-TB worldwide and that a third of them died. Almost 50% of MDR-TB cases worldwide are estimated to occur in China and India (WHO, 2010). The mean survival of MDR-TB affected patients ranges from 2 to 14 months. The importance of treating MDR-TB can therefore not be overemphasized.

Directly Observed Treatment, Short-course chemotherapy (DOTS) strategy has helped prevent non-compliance and treatment failure. However drug resistance has been reduced though not eliminated, and what is been particularly worrisome is the MDR-TB. Multi drug resistance has different definitions in different countries. In the United States it is defined as resistance to rifampicin and isoniazid, while in South America it is resistance to one reserve drug in addition to rifampicin and isoniazid. It is therefore recommended that patients be classified as those resistant to the essential drugs, and those resistant to essential and reserve drugs (Mishin et al., 2002). A subset of MDR-TB strains has been identified as extensively (or extremely) drug-resistant (XDR-TB). These are now defined as being resistant not only to isoniazid and rifampin, but also to fluoroquinolones and to at least one of three injectable drugs usually employed in second-line therapy of MDR-TB: capreomycin, kanamycin and amikacin (Ginsberg, & Spigelman, 2007).

The increase in MDR-TB represents a serious set back to efforts in gaining control of tuberculosis. Resistance to drugs means a greater chance for an infected person remaining infectious and spreading the disease. It is thus imperative to control MDR-TB if we are to ever eradicate this disease. Patients of MDR-TB are difficult to treat, and mortality is significantly higher than in TB caused by susceptible organisms, as is the rate of re-infection. MDR tuberculosis poses a threat to both, the patient and the society. The patient is at risk of losing if not the life, a part of the lung permanently, while the society is at a risk of an MDR-TB epidemic (Yew, 2011). Such an epidemic is a serious threat to the life of individuals with a compromised immune system. The number of people with co-infection of HIV and TB is rising by leaps and bounds. This is a population at very high risk since, TB is the largest single cause of death in HIV infected persons (Daikos et al., 2003).

The infection is mainly transmitted by inhalation of the bacilli coming from infected secretions of the respiratory airways. Once inhaled, the bacilli are subjected to phagocytosis within the alveolar macrophages, where they can be destroyed. Nevertheless, *Mycobacterium tuberculosis* has developed mechanisms to adapt to the noxious intracellular environment of macrophages and escapes the host's innate immunity. It uses several strategies to avoid their destruction, including inhibition of the acidification/maturation of the phagosomes and phagosomal-lysosomal fusion (Pietersen et al., 2004) or by a directly inhibition of the human T cell IFN gamma production and proliferation in response to stimulation (Peng et al., 2011). Thus the *mycobacteria* can persist, replicate and disseminate, leading to new infectious foci. The emergence of resistance depends on several factors such as bacillar initial load, inadequate or incomplete chemotherapy administration, and the patient's immune condition.

Chemotherapy is successful in most cases given that they follow thoroughly the treatment schedule, which is prolonged, costly, and needs to be directly observed. Otherwise it is inadequate to kill all the bacilli and drug resistance emerges. Toxicities are frequent as well.

Treatment for MDR-TB typically requires 18-24 months of combination therapy with second-line drugs that are less efficacious, more toxic and much more expensive than the four first-line drugs. TB treatment in HIV-positive patients is further complicated by drug-drug interactions between some of the antiretroviral agents and key antituberculous drugs, especially rifampin. As *Mycobacterium tuberculosis* drug resistance is increasing worldwide, there is an urgent need for novel interventions in the fight against tuberculosis. The main goal consist in improving capacity to treat existing drug-resistant cases effectively, in order to provide patients with the greatest opportunity for a successful outcome (Ginsberg, & Spigelman, 2007). At the global level, the rational use of existing compounds must be urgently promoted to preserve their utility in treating the most difficult tuberculosis cases and intensify efforts to develop novel interventions (including new drugs and vaccines) to fight tuberculosis more effectively.

The immunologic approach to TB treatment can be promising since only 10 - 20% of infected people develop the disease and many of them have spontaneous remission. Therefore, an alternative therapeutic target can be directed to the manipulation of the host's defenses. In patients with active tuberculosis, *M. tuberculosis*-specific T-cell responses are low, and tissue-destructive and macrophage-deactivating cytokines are upregulated. These patients have a relative weakness of production of the Th1-like cytokines Interleukin (IL-2) and IFN gamma. By contrast, the production of the immunosuppressive/macrophage-deactivating cytokines Transforming Growth Factor (TGF) beta and IL-10 is upregulated (Tomioka, 2004). These immune dysfunctions correlate with the extent of pulmonary tuberculosis, more markedly in HIV-infected patients (Zhang et al., 1994). TGF beta is produced in excess by monocytes of patients with tuberculosis, and is present at sites of tuberculous granulomas (Aung et al., 2000).

Therapies that would upregulate the host immune response and/or attenuate the effects of tissue-damaging, macrophage-deactivating and/or T-cell-suppressive cytokines may prove to be helpful in the treatment of tuberculosis, particularly MDR-TB and tuberculosis among patients with HIV infection. Enhancing host immune responses by adjunctive immunotherapy may truncate the duration of chemotherapy, and thereby abolish the need for administration of and compliance with complex drug regimens. In that sense, T helper 1 cytokines, such as IFN gamma, IL-2, and IL-12 through increment of T-cell function and macrophage activation may prove to be potent immunotherapeutic agents.

Interferons are endogenous immunomodulators that play an active role in protecting the individuals from opportunistic infections. They were first used for the treatment of hard to treat virus and fungal infections, now with the availability of recombinant IFN it is possible to use this agent for the treatment of infections caused by drug resistant organisms. IFN gamma activates macrophages and also promotes a range of host immune responses. It helps in decreasing the bacterial load by a number of intermediate messengers such as the superoxide moiety, hydrogen peroxide, etc (Mata-Espinosa & Hernández-Pando, 2008).

2.2 IFN gamma plays a key role in the modulation of immune response and is responsible for the defense against intracellular mycobacteria

Due to their pleiotrophic effects on the immune system, IFN gamma was thought to have great promise as an immunomodulatory drug. IFN gamma has been shown to be important

for the function and maturation of multiple immune cells. It is essential for Th1 immune responses and regulates T cell differentiation, activation, expansion, homeostasis, and survival. Killing of intracellular pathogens requires IFN gamma production by T cells showing to be a critical cytokine in the resistance of infected macrophages. T regulatory cell (Treg) generation and activation requires IFN gamma. This cytokine stimulates dendritic cells and macrophages to upregulate the immune response. NK cells secrete IFN gamma early in host infection, facilitating immune cell recruitment and activation. IFN gamma also activates NK cells and enhances the antibody-dependent cellular cytotoxicity (ADCC). It recruits neutrophils, stimulates them to upregulate chemokines and adhesion molecules, and triggers rapid superoxide production and respiratory burst (Miller et al., 2009).

As most of the intracellular infections, immunity to tuberculosis depends on the development of CD4+ T cells- and macrophages-mediated Th1 response. The proper formation and function of granulomas at sites of *Mycobacterium tuberculosis* infection depends on the collective activity of several cytokines. Enough evidences exist related to the action of IFN gamma on the immunoregulatory activity of macrophages, including alveolar macrophages, which are important in host immunity against *M. tuberculosis* (Tomioka, 2004). There is present certain heterogeneity in human IFN gamma responses to *M. tuberculosis* according to specific strain sensibility (Cabral et al., 2010).

The role of IFN gamma as the main macrophage-activator Th1 cytokine has been clearly established in animal models infected with *M. tuberculosis* since it was able to produce bacilli destruction. Mice rendered incapable of IFN gamma production by gene targeting develop widespread mycobacterial infection with very poor granulomatous response and succumb rapidly. Exogenously supplied IFN gamma has not able to restore normal mycobacterial resistance in these mice, suggesting that IFN gamma plays a critical development role as well (Flynn et al., 1993).

IFN gamma action on the macrophages leads to kill intracellular *Mycobacteria*. Their broad range of biological activities include stimulation of macrophages to produce Tumor Necrosis Factor (TNF) alpha, oxygen free radicals (superoxide anion and H₂O₂) and nitric oxide, increases MHC surface antigens and Fc receptors display, increases expression of costimulatory molecules and decreases lysosomal pH. IFN gamma and TNF alpha cooperate in the induction of phagocytic activity in the mononuclear cells and are also involved in the regulation of the inflammatory response. IFN gamma downregulates the production of the macrophage-inhibitory cytokines IL-4 and IL-10. Additionally, IFN gamma increases the intracellular concentration of certain antibiotics among then macrolides and quinolones (Herbst, 2011; Holland, 2001; Tomioka, 2004). Therefore, its use as adjuvant is justified since existent multidrug therapy, despite its limited efficacy, must be offered to the patients.

The general involved pathway is the following: IL-12 and the pro-inflammatory cytokines (IL-1, TNF alpha and IL-6) are produced early after the interaction of *Mycobacterium tuberculosis*-infected macrophages and CD4+ T cells, and upregulate CD4+ T-cell production of IFN gamma and IL-2. IFN gamma upregulates macrophage ability to contain the growth of *M. tuberculosis*, and IL-2 is key in the clonal expansion of specific CD4+ T cells. IL-10 and TGF beta are later products of these macrophages, and both inhibit the CD4+ T cell cytokine (IL-2, IFN gamma) response and interfere with the effects of IFN gamma. TGF beta is also auto-induced (Figure 1).

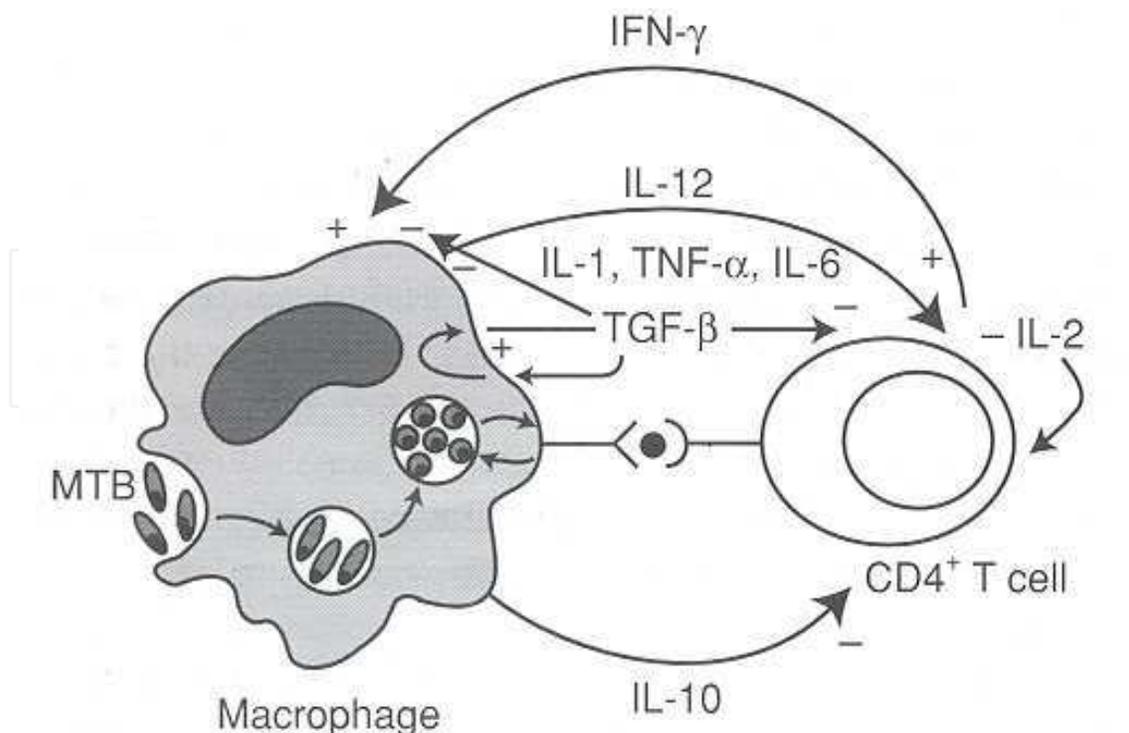


Fig. 1. Schematic representation of the known cytokine network produced by the interaction between CD4⁺ T cells and *Mycobacterium tuberculosis* (MTB)-infected macrophages.

IFN gamma and TNF alpha are present *in situ* in the paucibacillary pleural form of tuberculosis, in which the host successfully contains the replication of *M. tuberculosis*. In contrast, TGF beta increases the intracellular growth of *M. tuberculosis*. Also, neutralizing antibody to TGF beta reduce the intracellular growth of *M. tuberculosis* in monocytes. TGF beta interferes with the production of TNF alpha and IFN gamma and it also downmodulates the bactericidal effect of both cytokines in *M. tuberculosis*-infected monocytes (Hirsch et al., 1994).

The Th1 cells-mediated generation of toxic oxygen metabolites within phagocytes *in vitro* is also capable of mediating the intracellular killing of other selected bacterial or parasites microorganisms such as *Staphylococcus aureus*, *Toxoplasma gondii*, *Leishmania donovani*, *Listeria monocytogenes*, *Mycobacterium avium intracellulare*, *Mycobacterium Leprae*, *Mycobacterium ulcerans* and *Trypanosoma cruzi* (Billiau et al., 1998; El Ridi et al., 2006; Silva et al., 2009).

Mice models confirm the requirement of T CD4⁺ cells for immunity to *M. avium* strains with low or intermediate virulence. Addition of IL-4 or IL-10 to macrophages culture tried with IFN gamma inhibited the generation of oxygen free radicals (Holland, 2001; Tomioka, 2004). On the other hand, IFN gamma plays an important role in the resistance to *M. leprae* infection (Lima et al., 2000). Those individuals who present absence of IFN gamma and live in endemic areas of visceral leishmaniasis have disease progression (Carvalho et al., 1992).

The concept that IFN gamma can be useful in mycobacterial infections is supported by individuals with impaired IFN gamma action. Lack of production of this cytokine or expression of its receptor increase susceptibility to develop the disease or is associated to the infection's most lethal forms or disease progression. Recurrences or development of the

serious forms of infections with atypical *Mycobacteria* have been detected in certain families that present mutations in the gene encoding for the IFN gamma receptor binding chain (IFNGR1) (Sexton & Harrison, 2008). Patients with defects in the production of IFN gamma or partial deficiencies of IFN gamma receptor can obtain benefits with IFN gamma treatment (Hallstrand et al., 2004). Similar outcome could be obtained in patients with dysfunctions related to other Th1 cytokines and their receptors (Alangari, et al., 2011). Additionally, patients without genetic disorders but with serum anti-IFN gamma autoantibodies have a higher susceptibility to develop Mycobacteriosis (Kampitak et al., 2011). IFN gamma production appears to decline with age, and this may contribute to the increased susceptibility of the elderly to mycobacterial infection (Rink et al., 1998).

Although for many years IFN gamma have been considered as a pro-inflammatory cytokine, sometimes associated with the pathogenesis of inflammatory and autoimmune diseases, more and more evidences of their anti-inflammatory actions appeared nowadays, supposing a dual effect. It unregulated several pro-inflammatory parameters such as IL-12, TNF alpha, IFN-inducible protein 10 (IP-10), among others, but it also induces anti-inflammatory molecules as IL-1 receptor antagonist (IL-1Ra) or IL-18 binding protein (IL-18BP), modulates the production of pro-inflammatory cytokines, and induces suppressive pathways of the inflammation (Mühl & Pfeilschifter, 2003).

2.3 Interferon gamma has also a potent antifibrotic effect

Extensive tissue destruction, formation of cavities, and fibrosis are characteristic of the pathology of human tuberculosis. Although some components of the *Mycobacteria* may be directly associated in activating cellular proteases, most of the affection induced by the organism is probably cytokine-mediated.

The molecular biology of the fibrosis is characterized by a shift to increased production of Th2 cytokines and decreased production of Th1 cytokines. Th1 cytokines promote cell-mediated immunity and remove cellular antigens; decrease fibroblast procollagen mRNA, fibroblast proliferation, and fibroblast-mediated angiogenesis; and downregulate the growth mediator TGF beta. Contrarily, Th2 cytokines promote humoral immunity and produce antibody responses that can lead to fibroblast activation and fibrosis. The Th1 response is characterized by increased expression of IFN gamma, IL-2, IL-12, and IL-18. The net effect of a predominantly Th1 response is tissue restoration. The Th2 response is characterized by increased expression of IL-4, IL-5, IL-10, and IL-13. The net effect of a predominantly Th2 response is fibroblast activation and matrix deposition, leading to fibrosis (Figure 2). IFN gamma appears to restore the balance between Th1 and Th2 responses.

Enough evidences demonstrate the relevant role of IFN gamma to control the disease, since its antifibrotic properties. IFN gamma inhibits lung fibroblast proliferation and chemotaxis in a dose dependent manner. In the bleomycin-induced model of lung fibrosis, IFN gamma downregulates the transcription of the gene for TGF beta but production of IFN gamma may be decreased in patients with Idiopathic Pulmonary Fibrosis (IPF). IFN gamma reduces collagen synthesis and increases the activity of the collagenase (Tredget et al., 2000; Williams et al., 2008). Furthermore, IFN gamma contributes to the tissue repair and their remodeling (Pilette et al., 1997). This antifibrotic action agrees with that obtained with IFN gamma in IPF patients (see last paragraph on this section) and suggests that IFN gamma may have a

potential therapeutic role in the management of pulmonary fibrotic diseases, including tuberculosis (Williams & Wilson, 2008; Zhang & Phan, 1996).

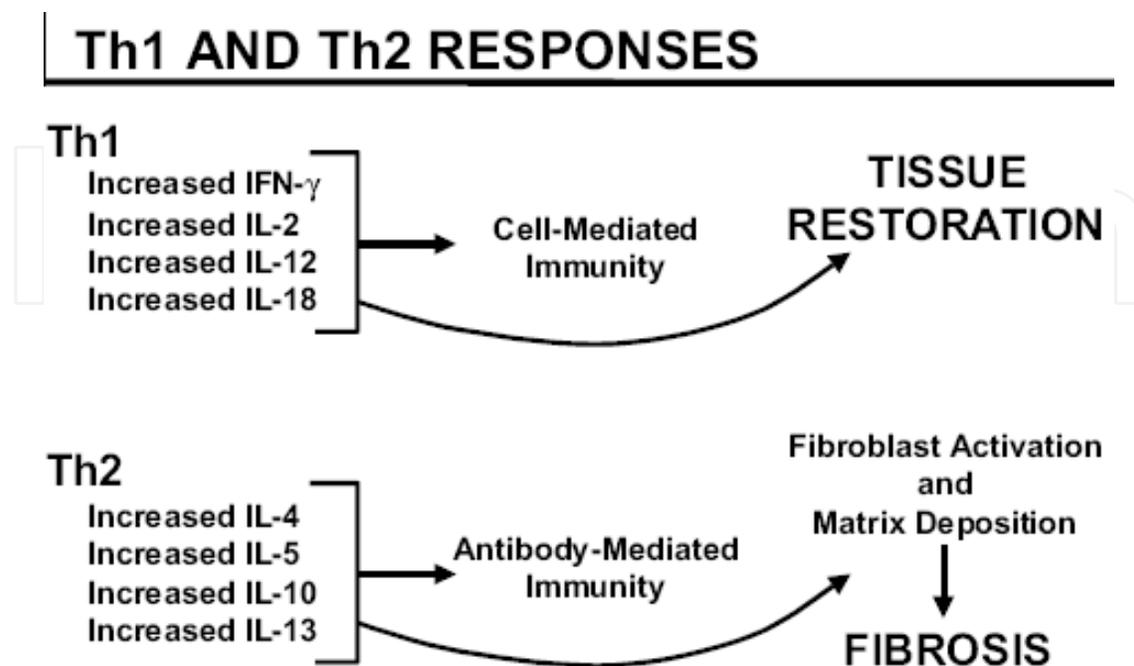


Fig. 2. Th1 and Th2 Responses and pulmonary fibrosis.

TGF beta and IFN gamma have opposite effects on diverse cellular functions and the fibrotic events are not an exception. The excessive production of TGF beta is associated with extensive fibrosis and tissue damage. TGF beta is a strong inhibitor of epithelial and endothelial cell growth, and while it promotes the production and deposition of collagen matrix, it has also shown to increase the production of macrophage collagenases. Mice injected intraperitoneally with TGF beta develop generalized fibrosis (Xu et al. 2003). IFN gamma is a potent antagonist of TGF beta (Tredget et al., 2000), involved directly in the pathogenesis of many fibrotic lung diseases (e.g. IPF, bleomycin-induced fibrosis and sarcoidosis) (Zhang & Phan, 1996).

TGF beta signals through a receptor serine kinase that phosphorylates and activates the transcription factors Smad2 and Smad3, whereas the IFN gamma receptor and its associated protein tyrosine kinase Jak1 mediate phosphorylation and activation of the transcription factor Stat1. IFN gamma inhibits the TGF beta-induced phosphorylation of Smad3 and its attendant events: the association of Smad3 with Smad4, the accumulation of Smad3 in the cell nucleus, and the activation of TGF beta-responsive genes. IFN gamma, acting through Jak1 and Stat1, induces the expression of Smad7, an antagonistic SMAD, which prevents Smad3 from interacting with the TGF beta receptor. The results indicate a mechanism of transmodulation between the STAT and SMAD signal-transduction pathways and suggest a role for IFN gamma in the treatment of pulmonary fibrosis (Ulloa et al., 1999).

The first report about the use of IFN gamma in IPF demonstrated a considerable clinical improvement in these patients treated during one year compared to those that received placebo (Ziesche et al., 1999). Afterward, a phase III study was carried out, but no significant advantages in progression-free survival, pulmonary functionality or quality of life were

observed. Nevertheless, patients with an initial less deteriorate pulmonary function impairment showed better survival (Raghu et al., 2004). Other authors indicate that IFN gamma can slow or arrested the loss of lung function, increase longevity and make possible lung transplantation (Nathan et al., 2004). Long-term treatment with this cytokine may improve survival and outcome in patients with mild-to-moderate IPF (Antoniou et al., 2006). However, the members of the recent INSPIRE trial declared that they cannot recommend one-year treatment with IFN gamma-1b since the drug did not improve survival in this disease (King et al., 2009). Our group found that in IPF a rapid clinical response could be obtained with a therapeutic schedule with IFN gamma combined with decreasing-dose prednisone (Cayón et al., 2010).

3. Clinical application of recombinant IFN gamma in multidrug – resistant tuberculosis and other mycobacterial diseases

There are reported several clinical trials where IFN gamma was used in combination with anti-TB drugs for the treatment of pulmonary TB. Some of these trials were conducted in drug-susceptible patients. Therefore, in our opinion these last studies have lower relevance or clinical impact than MDR-TB cases; despite in some of them combined treatment yielded better results than chemotherapy alone. In this review we include, in chronological order, several uncontrolled or controlled trials in patients with MDR-TB. Available communications of case report will be also included. Different routes of administration, subcutaneous, intramuscular, aerosol, have been evaluated for this immunoadjuvant cytokine. The aerosol route of administration has been proposed as organ specific delivery method, obtaining a high release to infected alveoli (Condos et al., 2004).

In spite of their high heterogeneity most of the studies refer as primary outcome the sputum negative conversion (sputum smear and/or *M. tuberculosis* culture) at a specific number of months after therapy. The secondary outcomes included chest radiographic improvement and severe adverse events. Chest radiographic improvement was defined as a decrease in the extent of lesions in the lungs, and some cases as a >50% decrease in the cavity size at a specific number of months after treatment. Other outcomes included biochemical variables reflecting immune function, and bacteriological relapse after completion of treatment. Nevertheless all trials did not have remarkably large sample sizes, which made it difficult to obtain definitive evidences.

Systemic or aerosolized IFN gammas have been reported as satisfactory in other similar intracellular infections, including other mycobacterial infections (e.g. intrinsically resistant *Mycobacterium avium*). At the end of this chapter we also show the most relevant reports regarding these species. The majority of the clinical trials here presented have been performed using Actimmune® (InterMune) or IFN gamma-1b, a genetically engineered form of human IFN gamma.

3.1 Clinical trials and case report of aerosolized or systemically administered IFN gamma in patients with drug-resistant tuberculosis

In a first report (Condos et al., 1997) safety and tolerability of aerosolized IFN gamma was investigated in patients with MDR-TB in an open-label trial. In addition, its efficacy in terms of sputum-smear grades was assessed. Aerosolized IFN gamma was given to five patients

with smears and cultures positive for pulmonary MDR-TB, despite documented adherence to therapy. The patients received 500 micrograms three times a week for 1 month. IFN gamma was well tolerated by all patients. In all five, bodyweight stabilized or increased. Sputum acid-fast-bacillus smears became negative in all patients, and the time to positive culture increased (from 17 to 24 days, not significant), which suggested that the mycobacterial burden had decreased. The size of cavitory lesions was reduced in all patients, 2 months after treatment had ended. These preliminary, encourage data suggested that IFN gamma may be useful as adjunctive therapy in patients with MDR-TB who are otherwise not responding well to therapy.

Later on, a randomized, placebo-controlled, multicenter trial of inhaled adjunctive IFN gamma for MDR-TB was initiated by InterMune in 2000 (InterMune, 2000). The trial was halted prematurely because of a lack of efficacy, but its findings have never been published.

We carried out an open-label, non-randomized, non-controlled, pilot trial with the aim to evaluate IFN gamma effect on drug resistant pulmonary TB patients regarding their clinical, bacteriological and radiological evolutions (Suárez-Méndez et al., 2004). The study population was constituted by Cuban patients, both sexes, more than eighteen years old, with diagnosis of TB without a favorable response to the usual therapy, who gave their written, informed consent to participate. Patients received 1×10^6 IU of human recombinant IFN gamma (Heberon Gamma R®, Heber Biotec, Havana, produced in *Escherichia coli*, specific activity of 10^7 IU/mg protein), intramuscularly, daily during 4 weeks and then 3 times per week for the next 20 weeks. They received anti-TB drugs (WHO schemes) (Crofton et al., 1997), according to the resistance detected in each case by the antibiogram. After the end of the 6-months IFN gamma treatment period, chemotherapy continued up to 9 months if the scheme included rifampin and 18 months otherwise. Complete response was defined as total disappearance of all signs and symptoms, negative sputum acid-fast-bacilli smear and culture, and pulmonary lesions improvement at X-ray. Partial response included signs and symptoms decrease, negative sputum smear and culture and stable X-ray lesions. No response consisted in signs and symptoms persistence, positive bacteriological examinations, and lesions stabilization or progression.

Five of the eight included patients were men, six of them non-white. The age ranged between 23 and 54 years old, and Body Mass Index (BMI) between 13.2 and 22.0 Kg/m². Their main symptoms were cough, expectorations, dyspnea, stertors, distal cyanosis, and finger clubbing. Bacteriological tests codification was mostly high and all patients showed active lesions at thorax radiography. A rapid favorable evolution was obtained after treatment with IFN gamma (Table 1).

Clinical improvement was evident since the first month of treatment, when all signs and symptoms (except for finger clubbing) had disappeared in all patients and BMI increased in all but one of them. Sputum acid-fast-bacilli smears and cultures were negative since the 1 - 3 months of treatment. The eight patients had radiological improvement, with lesions size reduction (total disappearance in one case) (Figure 3). This radiological effect cannot be attributable to the antibiotics, since it is well known that DR-TB patients only develop radiological improvement long time after sputum smears and culture become negative. In many cases extensive fibrotic lesions never improve, and stay stable for life. Globular sedimentation rates decreased (2 of them normalized) in five out of 6 patients who had

abnormal values at inclusion. At the end of the IFN gamma treatment all the patients were evaluated as complete responders (Suárez-Méndez et al., 2004).

Patient	1	2	3	4	5	6	7	8
Drug regimen	ETB	RIF	ETB	ETB	RIF	ETB	RIF	RIF
	ETN	ETB	ETN	ETN	ETB	ETN	ETB	ETB
	PRZ	PRZ	PRZ	PRZ	PRZ	PRZ	PRZ	PRZ
	CPF	KAN	CPF	CPF	KAN	CPF	KAN	PRZ
	KAN		KAN	AMK		KAN		KAN
Gain BMI (Kg/m ²)	1.8	0.4	0.4	0.4	0.3	2.2	1.8	-2.1
Sputum smear status	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Sputum culture status	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Conversion time	2 mo.	3 mo.	3 mo.	1 mo.	3 mo.	2 mo.	2 mo.	3 mo.
Thorax X-ray	Residual fibrosis	Reabsorption and residual fibrosis	Residual bilateral fibrosis.	Lesions resolution	Residual fibrosis	Lesions size reduction	Residual fibrosis	Lesions size reduction
GSR (mm/h)	5	48	26	40	42	20	23	77

BMI: Body Mass Index, GSR: Globular sedimentation rate. RIF: Rifampin; ETB: Ethambutol; ETN: Ethionamide; PRZ: Pyrazinamide; CPF: Ciprofloxacin; KAN: Kanamycin; AMK: Amikacin.

Table 1. Six months follow-up data of DR-TB patients treated with IFN gamma.

The treatment with Heberon Gamma R[®] was safe and well tolerated. The adverse events were arthralgias, fever, headache and asthenia. All adverse events were mild, except for one moderate fever, which was efficiently controlled with acetaminophen. Significant differences were not detected in other clinical laboratory tests. Seven of the eight patients remained bacteriologically, clinically and radiologically negative at least twelve months after the treatment with IFN gamma concluded. Clinical practice demonstrates that these results are very difficult to obtain in such a short period of time with the chemotherapy alone. None of previous historical controls at the same hospital reached culture conversion at three months of treatment with chemotherapy and less than half had converted at six months. Their clinical outcome was also worse (Suárez-Méndez et al., 2004).

The same IFN gamma was evaluated with a similar trial design in a MDR-TB Indian outpatient setting (unpublished data). Ten patients were included, 60% were men, with a mean age of 29 years. Previous treatment all the isolations were resistant to rifampicin and isoniazid. A reduction in the number of patients with positive sputum was recorded. A significant increment (1.6 g/dL) in hemoglobin values took place. The percent of damaged left lung decreased significantly (twice). Right lung and total fibrosis were also reduced but not significantly. At the end of treatment a complete clinical response and radiological

improvement was obtained in most of the cases. All the patients presented adverse events, headache prevailed (50%). All the events were mild or moderate, and no case stop the treatment because intolerability.

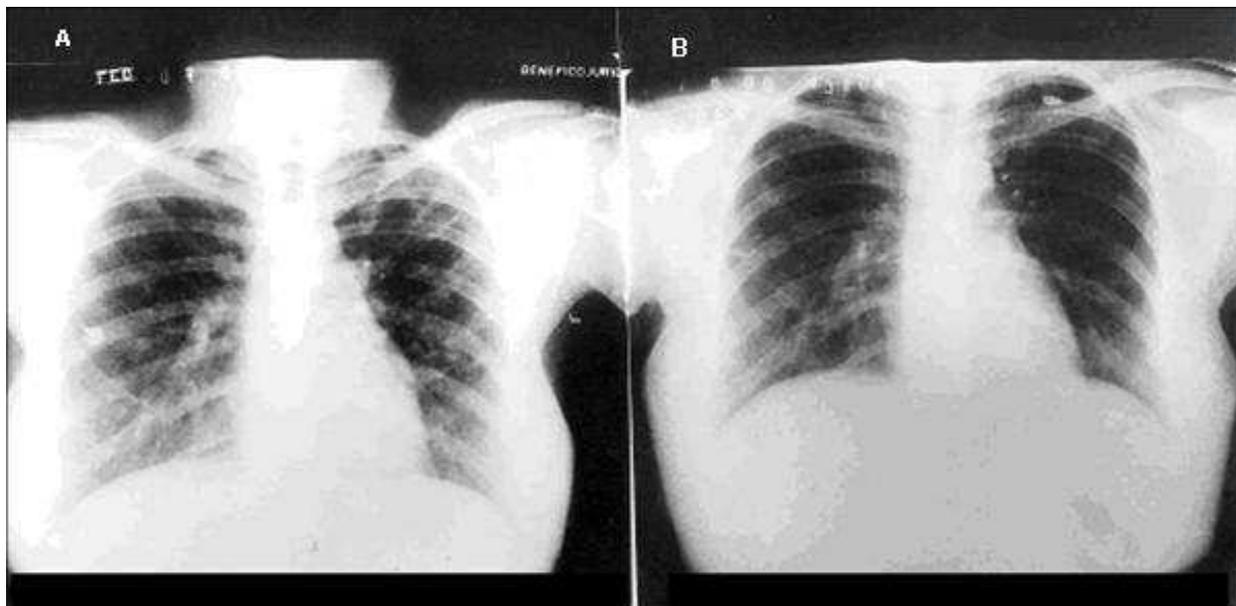


Fig. 3. Radiological improvement with IFN gamma treatment (ray-x of one patients are shown). Legend: (A), left-lung fibroexudative lesions, and (B) complete resolution after IFN gamma treatment. (Picture taken from Suárez-Méndez et al., 2004)

Aerosolized IFN gamma was given to six MDR-TB Korean patients with persistent positive smears and cultures despite long-term medical treatment (Koh et al., 2004). The patients received aerosolized 2×10^6 IU of IFN gamma three times a week for 6 months while they continued on identical antituberculous chemotherapy. Before IFN gamma inhalation therapy, the patients received a median of 6.5 (range, 4 to 7) antituberculous drugs for median duration of 29 months (range, 7 to 76). After IFN gamma inhalation therapy, sputum smears remained persistently positive in all patients throughout the study period. Sputum cultures were transiently negative at the 4th month in two patients, but became positive again at the end of 6 months of IFN gamma therapy. Five patients had radiological improvement including three patients who showed a decrease in the size of the cavitary lesions. Resectional surgery could be performed in one patient in whom substantial clinical and radiological improvement was noted after IFN gamma inhalation therapy (Figure 4).

In contrast, adjunctive subcutaneous therapy not improved the sputum culture conversion of refractory or advanced MDR-TB (Park et al., 2007). The authors evaluated the clinical and laboratory effects of subcutaneously administered IFN gamma in this class of patients. Eight patients with sputum smear and culture persistently positive MDR-TB were subcutaneously administered 2×10^6 IU of recombinant human IFN gamma three times a week for 24 weeks (72 doses total). Subjects also received a customized drug regimen containing second- and third-line antituberculosis agents based upon drug susceptibility testing and previous treatment history. Body weight remained stable or slightly decreased in all subjects during the study period, and none displayed radiographic improvement on serial chest computed

tomography scanning. Sputum smears and cultures remained positive for all patients, and there was no increase in the mean time to yield a positive culture (from 16.5 to 11.8 days). There was no enhancement of cell-mediated immune responses in terms of production of IFN gamma or IL-10, or of composition of lymphocytes among peripheral blood mononuclear cells. In four patients, therapy was discontinued because of adverse reactions. In conclusion they did not obtain improvement in clinical, radiologic, microbiologic, or immunologic parameters.

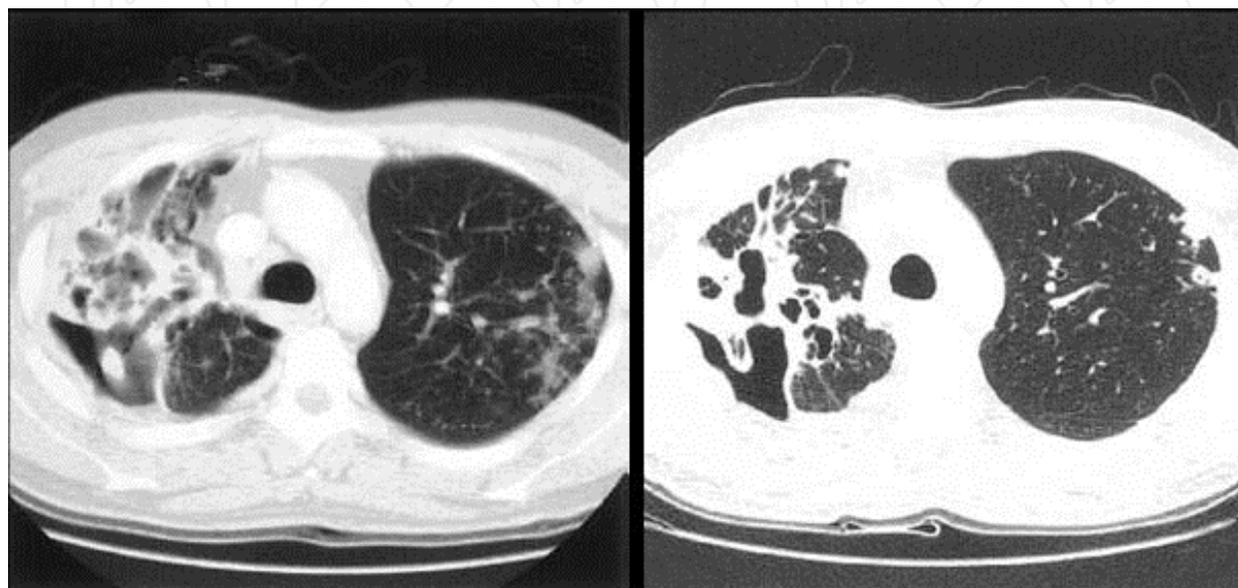


Fig. 4. 27-yr-old male patient with MDR-TB. (Left image) Computed tomographic scan of the chest showed multiple cavities in the right upper lobe and big nodular infiltrations in the left upper lobe. (Right image) After 6 months of IFN gamma inhalation therapy, computed tomographic scan showed reduction in the size of cavitary lesions and improvement of nodular infiltrates. (Picture taken from Koh et al., 2004).

In another protocol, four MDR-TB patients were treated with aerosolized recombinant IFN gamma twice weekly for 8 weeks and anti-tuberculosis drugs. Patients were monitored clinically and T-cell subpopulations were analyzed. The treatment was well tolerated. All sputum smears cleared within 6–8 weeks, and radiological signs of recovery lasted in all patients for 73–106 months (the entire follow-up period). Before treatment, a patient with a 20+ year history of TB showed no $\gamma\delta$ T-cells; these cells appeared during treatment. The proportion of natural killer (NK) cells was enhanced during treatment and remained elevated. The proportion of CD4+/CD25+ T-cells in the blood rose after treatment and remained elevated at 2 and 10 months afterwards. No significant change in T-cell levels appeared in patients with a shorter history of TB, except for a tendency toward a slight increase in $\gamma\delta$ T-cells during treatment (Grahmann & Braun, 2008).

At least two controlled clinical studies were carried out in Chinese MDR-TB patients (Yang et al., 2009; Yao, & Liu, 2003). These trials directly compared aerosolized IFN gamma plus anti-TB drugs with the same anti-TB drugs. The sample size was around 30 patients per group. Human recombinant IFN gamma was administered by aerosol at 1×10^6 IU per dose, three times weekly for 2 - 3 months. Anti-TB drug regimens varied in the trials. The follow-

up time ranged from 9 to 12 months. Both trials were open-labeled. One trial (Yang et al., 2009) was randomized and the other (Yao, & Liu, 2003) was unclear. Both studies reported higher smear conversion rates in the IFN gamma-treated group compared with the control group after 3 months of treatment or at the completion of chemotherapy, although there were no statistically significant differences. Chest radiographs demonstrated cavitory lesion reduction after 2 months of treatment.

Gamma interferon therapy in patients co-infected with HIV and tuberculosis receiving TB medications is safe, improves clinical outcome and enhances host defense mechanism (Yola et al., 2006). Recombinant IFN gamma-1b adjuvant therapy plus DOTS in cavitory pulmonary tuberculosis can reduce inflammatory cytokines at the site of disease, improve clearance of bacilli from the sputum, and improve constitutional symptoms (Dawson et al., 2009).

The results of all these trials need to be viewed from both the individual patient's and the society's perspective. A patient of MDR-TB continues downhill, even in the presence of therapy, to finally lose a lung or even his life. From the point of view of the society, the conversion of patients from infective to non-infective is a major achievement (Noeske & Nguencko, 2002; Subhash et al., 2003).

In the literature can be also found the adjunctive treatment with IFN gamma of an immunocompromised patient who had refractory MDR-TB of the brain and spinal cord (Raad et al., 1996). Despite treatment with six antituberculous drugs for 11 months, there was no appreciable clinical or radiological improvement in the patient's condition. Within 5 months of initiating adjunctive therapy with IFN gamma and granulocyte colony stimulating factors, substantial neurological and radiological improvement was noted. Therapy with IFN gamma was continued for 12 months, resulting in complete resolution of the lesions in the brain and spinal cord.

3.2 Results from different trials and case report in other mycobacterial diseases or similar

IFN gamma has been effective as adjuvant in AIDS patients co-infected with *Mycobacterium avium* complex (MAC), where a clear decrement in the bacteremia was verified. These results were obtained in patients with low CD4+ lymphocytes counts, suggesting a non T cell-mediated effect (Squires et al., 1992). Holland and colleagues treated non-HIV patients with refractory disseminated nontuberculous mycobacterial infections. Three patients were from a family predisposed to the development of MAC infections; four patients had idiopathic CD4+ T-lymphocytopenia. Their infections were culture- or biopsy-proved, involved at least two organ systems, and had been treated with the maximal tolerated medical therapy. IFN gamma was administered subcutaneously two or three times weekly in a dose of 25 to 50 µg/m² in addition to antimycobacterial medications. In response to phytohemagglutinin, the production of IFN gamma by mononuclear cells from the patients was lower than in normal subjects (P<0.001). Within eight weeks of the start of IFN gamma therapy, all seven patients had marked clinical improvement, with abatement of fever, clearing of many lesions and quiescence of others, radiographic improvement, and a reduction in the need for paracentesis (Holland et al., 1994).

Around one year later was reported a 38-yr-old man negative for HIV, with silicosis and advanced cavitary lung disease due to *Mycobacterium avium intracellulare*, who failed to improve despite 3 yr of continuous medical therapy with three or more drugs. He received three courses of aerosolized IFN gamma (500 micrograms 3 d per week for 5 wk in two courses and 200 micrograms 3 d a week for 5 wk after a short single trial of subcutaneous IFN gamma). The numbers of bacilli decreased in the sputum during therapy, but cultures of the organism remained positive at the same level for the first two treatment periods. The patient's sputum became smear negative and the number of colonies decreased significantly after the third course of IFN gamma therapy. Cessation of IFN gamma was associated with a rapid increase in the numbers of bacilli (Chatte et al., 1995).

Fifteen patients with disseminated MAC and other nontuberculous mycobacteria infections were treated with subcutaneous IFN gamma during one year or more, 13 of them had clinical improved and 7 had even apparent disease eradication (Holland, 1996). Two human immunodeficiency virus-infected patients with refractory disseminated MAC infection were treated with recombinant IFN gamma given subcutaneously for 3 and 4 months, respectively. Although both patients demonstrated some clinical improvement initially, IFN gamma therapy did not produce sustained benefit (Lauw et al, 2001). It has been reported that a randomized trial testing this option was stopped early due to lack of efficacy (Lam et al, 2006).

A randomized, double-blind, placebo-controlled trial was done with the objective to assess the immunoadjuvant IFN gamma effect in patients with pulmonary atypical Mycobacteriosis regarding their clinical, bacteriological and radiological evolutions. Additionally, several immune response and oxidative stress markers were measured. The diagnosis comprised isolation and classification of any of the atypical Mycobacteria species three or more times in sputum-culture samples, symptoms such as cough and expectoration, and tuberculosis-like pulmonary lesions at thorax radiography. Patients were distributed to receive intramuscular IFN gamma as adjuvant to oral chemotherapy (IFN group) or chemotherapy plus placebo (placebo group) during 6 months (Milanés-Virelles et al., 2008). Patients received 1×10^6 IU of Heberon Gamma R® or placebo intramuscularly. The schedule of administration and the response criteria were similar to the referred TB study (see Suárez-Méndez et al., 2004). All the patients received the same conventional daily antibiotic schedule, as follows: azithromycin 500 mg, ciprofloxacin 1000 mg, rifampin 600 mg, and ethambutol 2000 mg.

Thirty-two patients were enrolled. Eighteen patients were included in the IFN group and 14 received placebo. Groups were homogeneous at entry; average age was 60 years, 75% men, 84% white; MAC infection prevailed (94%). At the end of treatment, 72% of patients treated with IFN gamma were evaluated as complete responders, but only 36% in the placebo group (Table 2). The difference was maintained during follow-up. A more rapid complete response was obtained in the IFN group (5 months before), with a significantly earlier improvement in respiratory symptoms and pulmonary lesions reduction. Disease-related deaths were 35.7% of the patients in the placebo group and only 11.1% in the IFN group. Three patients in the IFN group normalized their globular sedimentation rate values. Although differences in bacteriology were not significant during the treatment period, some patients in the placebo group converted again to positive during a one-year follow-up. Significant increments in serum TGF beta and advanced oxidation protein products were

Evaluation	Month	IFN gamma	Placebo	P (test)		
Overall response						
Responders ^(a) (intention-to- treat)	6	13/18 (72.2%)	5/14 (35.7%)	0.037 (χ^2)		
	18	12/18 (66.7%)	4/14 (28.6%)	0.030 (χ^2)		
	Responders (last evaluation)	15/18 (83.3%)	5/14 (35.7%)	0.005 (χ^2)		
Clinical						
Dyspnea	0	15/18 (83.3%)	13/14 (92.9%)			
	6	1/15 (6.7%)	3/9 (33.3%)	0.27 (FE)		
	18	1/13 (7.7%)	3/8 (37.5%)	0.25 (FE)		
Good general status (intention-to-treat)	0	3/18 (16.7%)	4/14 (28.6%)			
	6	13/18 (72.2%)	5/14 (35.7%)	0.037 (χ^2)		
	18	12/18 (66.7%)	4/14 (28.6%)	0.03 (χ^2)		
Improvement ^(b) (intention-to-treat)	6	13/18 (72.2%)	5/14 (35.7%)	0.037 (χ^2)		
	18	12/18 (66.7%)	4/14 (28.6%)	0.03 (χ^2)		
Radiological						
Lesion extension	0	Adv	12 (66.7%)	11(78.6%)		
		Mod	5 (27.8%)	3 (21.4%)		
		Min	1 (5.6%)	0		
	6	Adv	2 (13.3%)	5 (55.6%)		
		Mod	12 (80.0%)	3 (33.3%)	1.00 ^(c) (FE)	
		Min	1 (6.7%)	1 (11.1%)		
	18	Adv	1 (7.7%)	2 (25.0%)		
		Mod	5 (38.5%)	5 (62.5%)	0.085 ^(c) (FE)	
		Min	7 (53.8%) ^(d)	1 (12.5%)		
Improvement (intention to treat)	6	12/18 (66.7%)	6/14 (42.8%)	0.32 (χ^2)		
	18	13/18 (72.2%)	4/14 (28.6%)	0.036 (χ^2)		
Cavitary lesions disappearance		5/12 (41.7%)	1/12 (8.3%)	0.15 (FE)		
Bacteriological						
Sputum- Direct (+)	0	Cod.	14/18 (77.8%)	10/14 (71.4%)		
			7 ± 4	8 ± 8		
		6	1/15 (6.7%)	2/10 (20.0%)	0.54 (FE)	
	18	Cod.	0 ± 0	0 ± 2	0.28 (MW)	
			1/13 (7.7%)	3/8 (37.5%)	0.253 (FE)	
		Cod.	0 ± 0	0 ± 7	0.112 (MW)	
	Relapse		1/13 (7.7%)	3/8 (37.5%)	0.25 (FE)	
	Sputum- Culture (+)	0	Cod.	18 (100%)	14 (100%)	
				8 ± 2	9 ± 4	
6			2/15 (13.3%)	2/10 (20.0%)	1.00 (FE)	
18		Cod.	0 ± 0	0 ± 2	0.60 (MW)	
			1/13 (7.7%)	4/8 (50.0%)	0.11 (FE)	
		Cod.	0 ± 0	0 ± 8	0.042 (MW)	
Relapse			1/13 (7.7%)	3/8 (37.5%)	0.25 (FE)	

(St): Student's t test; (MW): Mann-Whitney's U test; all binary variable comparisons were with the Fisher's exact test. ^(a) All overall responses were complete except for one IFN group case at month 6 with partial response. ^(b) General clinical status improvement if the patient passed from "bad" to "moderate" or from "moderate" to "good". Adv: Advanced; Mod: Moderate; Min: Minimum; ^(c) Combining advanced-moderate; ^(d) One of them had lesions disappearance at this time.

Table 2. Clinical, radiological, bacteriological and overall outcomes during the trial.

observed in the placebo group but not among IFN receiving patients. Treatments were well tolerated. Flu-like symptoms predominated in the IFN gamma group. No severe events were recorded. This report constituted the first and largest randomized, controlled clinical study, using an immunomodulating agent systemically in pulmonary or disseminated atypical Mycobacteriosis (Milanés-Virelles et al., 2008).

Use of a combination of IFN gamma and IL-2 resulted in a remarkable improvement in a 5-year-old girl presented with disseminated *Mycobacterium avium* complex infection during advanced HIV infection, together with an increase in circulating CD4+ T cells (Sekiguchi et al., 2005). A highly unusual case suggests that IFN gamma may be effective in patients with *M. chelonae* infection that fails to respond adequately to antimicrobials (Jousse-Joulin et al., 2007). Short-term IFN gamma-1b and IL-2 might be considered as therapeutic options in refractory mycobacterial infections in patients with idiopathic CD4 lymphopenia (Sternfeld et al., 2010).

The disseminated mycobacterial infection after *Bacillus Calmette-Guerin* (BCG) vaccination is a very rare disorder that appears mainly in immunocompromised patients. Two pediatric patients with adverse reactions induced by the BCG vaccine, both expressed by suppurative and abscessed regional lymphadenitis, one month after birth, were successfully treated with recombinant IFN gamma (6 months as minimum) after failed courses of chemotherapy (Abreu-Suárez et al., 2008). They showed a marked improvement of lesions after IFN gamma treatment. The evolution of the lesions in the case No.1 is showed in Figure 5. She had imperceptible lesions after 6 months of treatment.

During IFN gamma treatment, only few febrile episodes occurred, well-controlled with antipyretic medication. Both children conserved good general status, normal bodyweight, and no other adenopathies or visceromegaly appeared. During or after IFN gamma treatment no other infections were detected. The first case had a familiar history of tuberculosis (maternal great-grandfather, maternal grandmother and mother), which clearly increases susceptibility to mycobacterial infections by inherited recessive genetic defects. However, the second case did not present those antecedents and an IFNGR1 deficiency was not perceived (Abreu-Suárez et al., 2008).

IFN gamma has been shown efficacy (decrease in acid-fast bacilli) and safety in the treatment of patients with *Mycobacterium leprae*, where immunological pathways for killing intracellular pathogen are similar (Gallin et al., 1995; Nathan et al., 1986). In the 90s IFN gamma was administered to Cuban patients with lepromatous leprosy. Five patients received 1×10^6 IU of IFN gamma three times per week during six months and other five received placebo solution with the same schedule. Those patients treated with IFN gamma showed better clinical and histological evolution. These patients remained with sensibility damage but all the infiltrated cutaneous lesions were clarified. They had less granuloma and reduced greatly the number of bacilli, which look mostly fragmented. Lepromin skin test and lymphoblastic proliferation test didn't have changes in these patients (unpublished data).

In visceral leishmaniasis, patients treated with short courses of recombinant IFN gamma and pentavalent antimony exhibit favorable results such as decrease of the splenic parasitic load, improvement of the symptoms, gain of body weight and reduction of the spleen size, without relapses after several months of follow-up. Doses up to 8×10^6 UI/m² of body surface has been used for 20 days without important toxic effects (Badaro et al., 1990; Squires et al., 1993; Sundar et al., 1994).



Fig. 5. BCGitis Case No.1: Suppurative axillary and supraclavicular adenopathies after BCG vaccination in a nursing girl. (Left photo): before IFN gamma treatment, (Right photo): complete healing after only 3 months of treatment. (Picture taken from Abreu-Suárez et al., 2008).

4. Conclusions

There is a scientific rationale for the use of recombinant IFN gamma in difficult-to treat cases of tuberculosis and other mycobacterial diseases. By activating macrophages and promoting a range of host immune and antifibrotic responses, IFN gamma may provide an effective adjunct to antimycobacterials in patients not responding to conventional courses of therapy.

Clinical and laboratory experience suggest that adding IFN gamma to established treatment regimens may upregulate macrophage function and decrease mycobacterial load in pulmonary, disseminated and cutaneous infections. Prospective, randomized, more extensive, controlled clinical trials are necessary to confirm previous clinical reports.

Combination with second-line drugs can reduce the time of treatment, diminishing toxicities and possible relapses; in many cases could reduce the application of recessional surgery. Adjunctive immunotherapies, including IFN gamma, will likely play a role in the treatment of mycobacterial disease in the years ahead.

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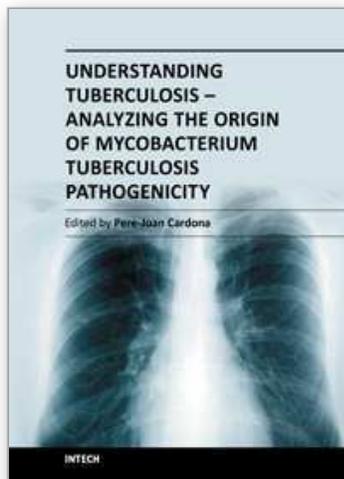
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Mycobacterium tuberculosis in an attempt to understand the extent to which the bacilli has adapted itself to the host and to its final target. On the other hand, there is a section in which other specialists discuss how to manipulate this immune response to obtain innovative prophylactic and therapeutic approaches to truncate the intimal co-evolution between Mycobacterium tuberculosis and the Homo sapiens.

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