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SHORT ANALYTICAL REVIEW

Thalidomide as an Anti-TNF-α Inhibitor: Implications for Clinical Use

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INTRODUCTION

Since the synthesis of thalidomide (α-*N*-phthalimidoglutarimide) by Kunz and others in 1956 (1) for use as a sedative, no drug has had a more tumultuous history. When first marketed in Europe, thalidomide was touted as a safe, potent, nonbarbiturate drug which was very useful in producing sound sleep (2). It was distributed throughout Europe, Australia, and Canada, but was never approved for marketing in the United States. Thalidomide also had a remarkable anti-emetic effect and was widely used to quell the nausea of first-trimester morning sickness. Then, in November 1961, after a rapid rise in reports of catastrophic fetal abnormalities in Europe and Australia associated with thalidomide use in early pregnancy, the drug was removed from the market.

EARLY USE OF THALIDOMIDE IN LEPROSY REACTIONS

While thalidomide was still available, an Israeli physician (Dr. Jacob Sheskin) had used the drug as a sedative in patients suffering from the acute reactional state of lepromatous leprosy (erythema nodusum leprosum, ENL). ENL is characterized by a painful vasculitic rash which may occur together with systemic symptoms of fever, muscle and joint pain, malaise, lymphadenopathy, insomnia, and weight loss. Peripheral neuritis is often associated with ENL and is the most important pathological manifestation of this reactional state. In 1965 Sheskin reported 6 cases of acute, severe leprosy reactions in which symptoms quickly and dramatically resolved after the use of thalidomide as a sedative (3). He then carried out a series of placebo-controlled studies and determined that thalidomide was responsible for the clinical improvements observed in patients suffering from ENL. Sheskin concluded that while thalidomide efficiently ameliorated the symptoms of moderate to severe ENL, it was not bacteriocidal nor did it cure leprosy. Within a few years of Sheskin's initial observations, thalidomide became the drug of choice for the treatment of the symptoms of ENL (4–6). However, there was no explanation for the mode of action of thalidomide in lepra reactions.

In the early 1980s, with the increasing understanding of the roles of particular cells in the developing immune response, it became clear that some diseases are actually manifestations of the host cellular immune response to an infectious agent. One of the diseases characterized by a significant immunological component was leprosy (7). The spectrum of the clinical manifestations of leprosy was found to reflect the extent of activation of antigen-specific T cells. The generation of a granulomatous response was associated with both T cell and macrophage activation at the site of infection in the skin. Patients who developed a strong cellular immune response to the infectious agent (*Mycobacterium leprae*) manifested a restricted disease (tuberculoid leprosy) with few skin lesions containing very few acid-fast bacilli. In contrast, at the other end of the spectrum were patients in whom the cellular immune response to *M. leprae* was deficient. In these patients, the infection was disseminated throughout the skin with many lesions containing numerous acid-fast bacilli (lepromatous leprosy). Superimposed on these different clinical presentations of leprosy were the reactional states, including ENL. ENL was observed predominantly in lepromatous leprosy patients, often immediately following initiation of anti-leprosy chemotherapy. The underlying mechanism for the development of ENL was unknown.

Since thalidomide had such a profound effect on the symptoms of ENL, we hypothesized that the drug had an effect on a soluble mediator or immune cell involved in the development of ENL. In an attempt to understand the factors involved in the induction of ENL, we set out to determine how thalidomide interrupts the ENL process. Using *in vitro* models of leukocyte function, we began an investigation of the immune parameters affected by thalidomide.

EFFECT OF THALIDOMIDE ON TUMOR NECROSIS FACTOR (TNF-α) PRODUCTION BY PERIPHERAL BLOOD MONOCYTES *IN VITRO*

When human monocytes were cultured and then stimulated with bacterial lipopolysaccharide (LPS), pu-

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rified protein derivative of tuberculin (PPD), or a cell wall protein extract of *M. leprae,* several cytokines were induced and secreted into the supernatant (8). These included TNF-α, IL-1β, IL-6, and GM-CSF. The addition of thalidomide to the monocyte culture medium resulted in a decrease in TNF-α production which was dose-dependent and selective (8). That is, at higher concentrations of thalidomide, the percentage inhibition of TNF-α production was increased. Under the same experimental conditions, no effect on total protein synthesis or production of the other monocyte cytokines listed above was observed. Thus, thalidomide appeared to have a direct effect on the production of TNF-α by stimulated monocytes *in vitro.* It was of interest to note that TNF-α production was never completely inhibited by thalidomide.

In a further series of experiments, the mechanism of the thalidomide-induced decrease in TNF-α production was investigated. Studies of human monocytes stimulated *in vitro* with LPS or other agonists including mycobacterial products demonstrated that there was a decrease in the accumulation of TNF-α-specific mRNA in the cells when they were cultured in the presence of thalidomide. RNA turnover experiments showed that thalidomide enhanced the degradation of TNF-α mRNA, reducing the half-life of the molecule from about 30 to about 17 min. This resulted in reduced production of the TNF-α protein, but did not eliminate the production completely. Again, the effect on TNF-α mRNA was selective, and other cytokine mRNAs including IL-1 and IL-6 were not affected. The specific and partial inhibition of TNF-α production by thalidomide suggested that the drug might be useful for the treatment of inflammatory conditions in which TNF-α production induces toxic symptoms and where the immune response must not be completely suppressed.

EFFECT OF THALIDOMIDE ON TNF-α LEVELS IN LEPROMATOUS LEPROSY PATIENTS DURING ENL

During the reactional manifestations of ENL, lepromatous leprosy patients were shown to have high levels of serum TNF-α and other cytokines (9, 10). The high serum levels of TNF-α were associated with an enhanced ability of the patients' monocytes to secrete excess TNF-α when stimulated *in vitro* with mycobacterial products or with LPS. When thalidomide was used to treat the clinical manifestations of ENL, the diminution in symptoms was accompanied by a 50–80% reduction in the serum levels of TNF-α, as well as a similar decrease in agonist stimulated TNF-α secretion *in vitro* (9, 11). The histologic appearance of skin lesions during ENL was also modified by thalidomide treatment. The mixed leukocyte infiltrate in the dermis containing polymorphonuclear leukocytes and T cells, which is characteristic of ENL, resolved during treatment. Vasculitis and the extensive expression of surface adhesion molecules and HLA Class II antigens on the endothelium and the epidermal keratinocytes were also downregulated following exposure of the patients to thalidomide. Therefore, an association between high TNF-α production by blood monocytes and the signs and symptoms of ENL was established. Furthermore, our studies suggested that high TNF-α levels in nonreactional lepromatous leprosy patients might be predictive of the future onset of ENL. More recent studies indicate that pretreatment of leprosy patients with low doses of thalidomide may actually prevent the onset of ENL episodes (11a).

THE ROLE OF TNF-α IN THE PATHOGENESIS OF TUBERCULOSIS INFECTION

The observation that TNF-α production appeared to be stimulated by *M. leprae* and its components suggested to us that TNF-α may play a pivotal role in the cellular immune response and the pathogenesis of another mycobacterial disease, tuberculosis. Tuberculosis is a chronic disease caused by infection with *Mycobacterium tuberculosis.* It is characterized by fever, weight loss, anorexia, weakness, fatigue, night sweats, and tissue necrosis. The presence of TNF-α has been documented in the pleural effusions and sera of patients with active disease (12, 13). Monocytes isolated from infected patients with systemic symptoms of tuberculosis release elevated amounts of TNF-α in response to stimulation *in vitro* with various agonists, including *M. tuberculosis* cell wall components (14–19). The TNF-α gene has also been shown to be activated in peripheral blood mononuclear cells (PBMC) from patients with active tuberculosis. TNF-α mRNA was constitutively expressed in these PBMC, while other cytokine mRNAs were variously and inconsistently affected (20).

TNF-α plays an important role in the development of the protective response against *M. tuberculosis* infection (reviewed in 21). The cytokine has been shown to induce a cascade of cellular responses in monocytes, lymphocytes, polymorphonuclear leukocytes, as well as in many nonimmune cells and tissues outside the immune system. It appears that TNF-α production is necessary for the formation and maintenance of the granulomas, which act to seal off foci of infection and limit dissemination of the bacteria (21). The cytokine has also been implicated in the activation of macrophages, rendering them more capable of killing the intracellular pathogen (21). In addition to its protective effects, TNF-α has been shown to induce cachexia or wasting (22, 23). Thus, the progressive weight loss characteristic of tuberculosis might be attributed to the chronic production of TNF-α during long-term infection with *M. tuberculosis.* To test this assumption, we asked

whether a reduction in TNF-α production in tuberculosis patients would result in changes in the rate of weight gain or loss. Since thalidomide had been shown to inhibit TNF-α production in leprosy patients, we investigated the effect of thalidomide in patients with tuberculosis.

EFFECT OF THALIDOMIDE ON TNF-α LEVELS IN TUBERCULOSIS PATIENTS

A two-part placebo-controlled pilot study of thalidomide in patients with tuberculosis was carried out (24). Thirty male patients with active tuberculosis (either HIV-1^+ or HIV-1^-) who were receiving multidrug antituberculosis therapy were randomly allocated to receive either thalidomide (300 mg/day) or placebo daily for 14-day cycles. After the first cycle of treatment, there was a 7-day washout period followed by up to four repeated cycles of treatment.

In general, the patients in the study tolerated the drug well. The only observed side effects were morning drowsiness, dry mouth, and constipation. Thalidomide treatment did not adversely affect the delayed type hypersensitivity response to PPD, nor was there any alteration in total leukocyte or differential cell counts. Lymphocyte proliferative responses to PPD and heat-killed mycobacteria (BCG) remained unchanged. However, thalidomide treatment caused a decrease in production of TNF-α in the sera of treated patients. In addition, analysis of mRNA isolated from unstimulated PBMCs of patients during thalidomide treatment showed a decrease in the number of copies of TNF-α mRNA, contributing to the decrease in serum TNF-α levels. IL-1 mRNA levels were also evaluated and found to be reduced in response to thalidomide treatment. Serum levels of interferon-γ (IFN-γ) were significantly enhanced after 1 week of thalidomide therapy and returned to baseline when thalidomide treatment ended. However, PBMC levels of IFN-γ mRNA were not significantly changed. When patient monocytes were stimulated *in vitro* with either LPS or PPD, monocytes from thalidomide-treated patients expressed reduced levels of TNF-α. During the study, daily administration of thalidomide resulted in a significant enhancement of weight gain (average 6% increase in body weight) in tuberculosis patients compared to placebo-treated tuberculosis patients, whether HIV-1 seropositive or HIV-1 seronegative. Upon withdrawal of thalidomide after the end of the 14-day treatment cycle, accelerated weight gain ceased or was even reversed.

The results of this pilot study suggested that thalidomide treatment may result in a decrease in TNF-α production in both uncomplicated tuberculosis and tuberculosis associated with concomitant HIV-1 infection. Also, it appeared that the weight loss of tuberculosis patients may be associated with chronic production of TNF-α. The underlying metabolic processes which may be affected by TNF-α levels are currently under investigation. Larger studies of tuberculosis patients treated with thalidomide for longer periods of time are now under way.

TNF-α IN HIV-1 INFECTION

TNF-α may have an important role in HIV-1 infection. An increase in serum TNF-α and soluble TNF-α receptor levels has been reported in HIV-1-infected individuals (13, 25–28). In addition, TNF-α enhances replication of HIV-1 in cell lines and in cells isolated from HIV-1 infected patients (29–31). TNF-α is a strong inducer of NFκB, a nuclear transcriptional factor used by the virus for replication (32). Thus, TNF-α induced by either HIV-1 infection or other simultaneous infections might stimulate HIV-1 replication by the NFκB pathway. In addition, HIV-1 infection has been shown to induce TNF-α mRNA accumulation in normal peripheral blood monocytes infected with HIV-1 *in vitro* (13), thereby stimulating the NFκB pathway and again potentially increasing HIV-1 replication. In fact, it has been suggested that AIDS might be a tumor necrosis factor disease because of the possible contribution of TNF-α to viral activation as well as to the clinical symptoms of the disease (33).

HIV-1 infection of human T cells and monocytes may be either latent or productive. Replication of latent HIV-1 in cell lines and in cells isolated from infected patients usually requires host-cell activation by an agonist such as a cytokine. When U1, a human monocytoid cell line latently infected with HIV-1, was exposed to TNF-α, viral replication occurred (34). More than a fivefold increase in reverse transcriptase activity was noted after exposure to TNF-α. The addition of thalidomide to the U1 cultures resulted in a decrease in the production of HIV-1 in a dose-dependent manner. This inhibition was associated with an inhibition of TNF-α mRNA in the U1 cell. A similar effect was observed when thalidomide was added *in vitro* to cells isolated from the peripheral blood of HIV-1-infected individuals. The drug reduced the levels of HIV-1 replication in stimulated patient cells *in vitro.* These results suggested that thalidomide might be useful in reducing TNF-α production in HIV-1 infected patients. A reduction in the levels of this cytokine could potentially reduce the TNF-α-associated symptoms of HIV-1 disease, including fever, malaise, muscle weakness, and weight loss. A reduction in TNF-α production might also result in a decrease in cytokine-induced viral replication.

EFFECT OF THALIDOMIDE THERAPY IN HIV-1 INFECTED PATIENTS

We therefore conducted a randomized, placebo-controlled pilot study of thalidomide administration in pa-

tients with HIV-1-associated wasting, with or without concomitant *M. tuberculosis* infection (35). Thirty-nine HIV-1 seropositive patients who reported at least 10% loss of body weight were randomly allocated to treatment with thalidomide or placebo for 21 days. Thirty-two patients completed the study. Several important observations were made during this study. First, patients dually infected with HIV-1 and *M. tuberculosis* had significantly higher plasma levels of TNF-α (assayed by ELISA) and higher levels of HIV-1 (measured by branched-chain DNA hybridization) than patients with HIV-1 infection alone. A striking positive correlation was noted between TNF-α levels and HIV-1 levels in patient plasma: the higher the TNF-α levels, the higher the HIV-1 levels. Also, in patients dually infected with both *M. tuberculosis* and HIV-1, thalidomide treatment was associated with a reduction in both plasma TNF-α levels and HIV-1 viremia. No significant reduction in either TNF-α levels or HIV-1 viremia was observed in patients with HIV-1 infection alone. During the study, patients receiving thalidomide subjectively reported improved appetite and strength. Furthermore, thalidomide-treated patients showed a significant weight gain relative to placebo-treated patients. Coinfected patients had higher mean weight gain than patients with HIV-1 infection alone. The nature of the weight gain observed was not determined.

In the study thalidomide treatment was associated with a relatively high rate of hypersensitivity reactions. Six of the 20 patients randomized to receive thalidomide developed a drug rash between Days 7 and 14 (median Day 12), characterized by pruritic erythematous macular skin lesions over the trunk and back. The drug reaction resolved upon discontinuation of thalidomide. Patients who developed the drug reaction had more advanced HIV-1 disease with significantly lower $CD4^+$ T cell counts (mean = 17 cells/mm^3) compared to patients who did not develop a drug rash (mean = 216 cells/mm^3).

These pilot studies suggest that TNF-α may play a role in the pathogenesis of HIV-1 infection. In addition, opportunistic infections may exacerbate the course of HIV-1 infection by stimulating production of additional TNF-α, which in turn stimulates HIV-1 replication as well as contributing to the symptoms of AIDS. The anti-TNF-α activity of thalidomide and its effects on disease manifestations and viral replication are currently being further tested in a variety of clinical settings associated with HIV-1 infection, including HIV-1 wasting, aphthous ulcers, and AIDS-associated diarrheas.

CONCLUSIONS

It is becoming increasingly clear that the action of any individual cytokine is neither completely beneficial nor totally detrimental to the host. Rather, a fine balance of cytokine production and regulation must be maintained to ensure that the host can effectively react to invading microorganisms without compromising host well-being in the process. An understanding of the regulation of the network of cells and cytokines will provide us with a rational approach to designing interventions to modulate the host's response to infection and prevent damaging immune-mediated pathologies.

TNF-α is one of the cytokines which has recently been found to play a central role in the regulation of the host immune and inflammatory response to infection. Thalidomide has been shown to down-regulate the production of TNF-α both *in vivo* and *in vitro* and therefore may have a role as an immunomodulatory therapy in various clinical situations. The mechanism of the therapeutic effect of thalidomide has not yet been clearly elucidated. Through its effects on TNF-α, thalidomide may also affect other cytokines of the immunoregulatory network.

The investigation of the mechanism of action and potential clinical uses of thalidomide is illustrative of a new approach to the problem of modulating immune dysregulation and immunopathogenesis in human disease. One aspect of this approach is a program of drug analogue design and synthesis carried out in collaboration with Celgene Corp. (Warren, NJ) to produce and characterize specific TNF-α inhibitors with varying biologic activity and fewer adverse effects. Such molecules could potentially be used in a clinical setting to modulate TNF-α production to different degrees and in different tissue compartments depending on the specific disease process. There appears to be a wide range of human diseases in which TNF-α activity has been implicated in the development of symptoms, including graft-versus-host disease, rheumatoid arthritis, lupus erythematosus, multiple sclerosis, Crohn's disease, cancer cachexia, and endotoxic shock. Therapeutic agents which regulate TNF-α production are thus likely to be very important in the future in the treatment of autoimmune diseases, malignancies, and many infections, including AIDS.

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