Therapeutic potential for cytokine antagonists: Thalidomide and pentoxifylline in Hansen’s disease

Therapentic potential for cytokine antagonists: Thalidomide and pentoxifylline in Hansen’s disease. Can J Infect Dis 1995;6(1):30-33. Cytokine antagonists are a group of drugs defined by their actions on specific cytokines. Cytokine antagonists can inhibit action of cytokines by acting directly on receptors, by affecting production of cytokines or by binding to cytokines and preventing their subsequent action. Recent evidence suggests that Hansen’s disease, which is characterized by reactional states, is associated with elevated serum levels of tumour necrosis factor-α (TNF-α) and interleukin-1β during these reactional states. Thalidomide, a drug used to treat reactional states in Hansen’s disease, has been reported to enhance degradation of TNF-α mRNA. Pentoxifylline has also been reported to alter TNF-α mRNA levels by inhibiting TNF-α transcription. Combination of these two drugs as cytokine antagonists may prove to be beneficial as therapeutic agents in the treatment of reactional states in Hansen’s disease. Pentoxifylline may prove to be beneficial in the treatment of reactional states in Hansen’s disease patients who are female and of childbearing age. Cytokine antagonists alone or in combination will likely fill a niche in future therapeutics.

Key Words: Antagonists, Cytokine, Hansen’s disease, Pentoxifylline, Thalidomide, Tumour necrosis factor-α.
According to a recent report, 5 million people suffer from Hansen’s disease worldwide (1). Hansen’s disease (leprosy) is characterized by two reacational states (2). Type I reactions of Hansen’s disease involve mild erythema and edema while type II reactions involve erythematous lesions lasting from several days to weeks.

Type I reactions will respond to nonsteroidal anti-inflammatory drugs (NSAIDs). Severe type I reactions involving neuropathy or neuritis, ulceration and edema of the hands, face and feet is an indication for corticosteroid therapy (2). Initially high dose prednisone 40 to 120 mg daily may be necessary, and chronic therapy is often required. In the type II reaction (erythema nodosum leprous [ENL]), cell-mediated immunity is increased (3) and circulating levels of C3 breakdown product C3D are increased (4). The reduction in interleukin (IL)-2 production observed in Hansen’s disease patients is reversed during ENL (5). ENL is subdivided into mild and severe grades for choice of therapeutics. In mild ENL NSAIDs provide symptomatic relief. In severe ENL, when neuritis, severe systemic reaction (high fever, etc), iridocyclitis or skin ulceration are present, corticosteroid or thalidomide treatment is used.

Thalidomide was originally used as a sedative in ENL and was found to improve symptoms of the reaction (6). For men and postmenopausal women, thalidomide is a drug of choice for ENL (7). The response to thalidomide therapy is rapid; within 24 to 48 h there is a decrease in fever and in numbers of lesions. ENL rapidly responds to thalidomide therapy, which may be better than long term steroid treatment (8).

On a cautionary note a recent report by Crawford (9) indicates that thalidomide itself can cause peripheral neuropathies, which can be severe and irreversible. Recently thalidomide has been reported to cause thalidomide neuropathy (10) when used in other treatment regimens (11). It is obvious that the current treatment regimens for reacational states in Hansen’s disease carry with them the potential for severe side effects.

The mechanism of action of thalidomide in ENL is not known but recent reports suggest that thalidomide selectively inhibits tumour necrosis factor (TNF-α) production (12) by enhancing degradation of TNF-α mRNA (13). Corticosteroids have anti-inflammatory action and can inhibit translation of TNF-α mRNA, ie, they act post-translationally (14); but long term steroid therapy carries with it the possibility of Cushingoïd syndrome. Delaying treatment of the reacational states of Hansen’s disease can result in irreversible nerve damage (15).

The role of cell-mediated immunity in lepromatous leprosy, particularly the importance of lymphokines and cytokines in Hansen’s disease, is the subject of much research (16). Recent studies report elevated serum levels of TNF-α and IL-1β during leprosy reacational states (17). This is in contrast to an earlier report (18) but likely reflects differences in methods of measuring cytokines (radioimmunoassay) versus cytokine activity (bioassay). Modification of cytokine production eg, IL-1 and TNF-α, can occur with currently used antilepromatous drugs, including corticosteroids (14) and thalidomide (12), and this may partially explain their mechanism of action in Hansen’s disease.

Several recent reports suggest that pentoxifylline can inhibit the synthesis and action of TNF-α (19-21). Pentoxifylline reduces TNF-α mRNA by inhibiting TNF-α transcription, thus suppressing TNF-α gene expression (22). These actions are distinct from the actions of thalidomide or corticosteroids on TNF-α synthesis, suggesting the possibility of synergy when these drugs are used in combination. Pentoxifylline has also been reported to inhibit IL-1-mediated functions (23,24). Inhibition of phosphodiesterase by pentoxifylline would elevate cAMP (25) and thereby reduce transcription of TNF-α (26). Due to its effects on TNF-α and IL-1, pentoxifylline may be an effective therapeutic agent in the treatment of reacational states in Hansen’s disease alone or when used in combination with thalidomide.

In addition to its effects on TNF-α and IL-1, pentoxifylline inhibits neutrophil function (27,28). Neutrophils play an important role in ENL (29), so this effect of pentoxifylline may prove to be an added benefit in Hansen’s disease, particularly ENL.

Pentoxifylline appears to be a very safe drug when used in chronic treatment of other disorders (30). Chronic use of pentoxifylline for up to one year carries a low instance of side effects, which include gastrointestinal disturbances in 2.6% of patients treated, while fewer than 0.25% of patients treated experience cardiovascular, psychological, neurological, hepatic or dermatological effects (31).

In reacational states of Hansen’s disease, pentoxifylline may prove to be an effective therapeutic agent, with particular indication in women of childbearing age where thalidomide use is contraindicated. In the subgroup of Hansen’s disease patients in whom thalidomide is currently used, the combination of thalidomide with pentoxifylline will likely provide additional therapeutic benefit. Both drugs affect TNF-α transcription, but at different sites, thus providing the possibility of synergistic activity. It is understood, however, that a certain level of cytokine production (eg, TNF-α) can be beneficial (32), so careful titration of cytokine inhibition will likely be necessary to achieve optimum results.

The role of cytokine antagonism by pentoxifylline in the treatment of other cytokine-mediated diseases, disorders and injury is becoming increasingly evident in the literature. Pentoxifylline has been shown to prolong survival in animal models of peritonitis (33) and bacteremia (34), potentially through a mechanism whereby pentoxifylline inhibits TNF-α-induced polymorphonuclear leukocyte activation including polymorphonuclear leukocyte adherence, degranulation and superoxide production (35). Pentoxifylline improves the hemodynamic and histological changes, as well as a decrease in neutrophil adhesiveness, in a pig fecal peritonitis model (36).

Reports in the literature suggest that pentoxifylline also reduces both septic- and TNF-α-induced acute lung injury and multiple organ damage in the guinea pig (37-39). They also suggest that pentoxifylline attenuates edema formation in proteolytic enzyme-induced lung injury (40).

Hoffman and co-workers (41) report that pentoxifylline attenuates Escherichia coli-induced acute lung injury in guinea pigs.
pigs. Further reports by Gibson et al (42) indicated that group B streptococcus induces TNF-α in neonatal piglets and that pentoxifylline treatment both attenuates group B streptococcus-induced TNF-α production and provides some improvement in pulmonary hemodynamics and hypoxemia in the piglet model. Noel et al (43) report that pentoxifylline inhibited lipopolysaccharide-induced serum TNF-α and protected the animals from the lethal effects of an intravenous challenge with lipopolysaccharide.

TNF has been implicated in the pathogenesis of sepsis, cancer cachexia (44), the cachexia of chronic heart failure (45), IL-2 toxicity (46), ischemia/reperfusion injury (47,48), cerebral malaria (49), pulmonary fibrosis (50) and acid aspiration-induced lung injury (51). The blockade of TNF-α action with neutralizing anti-TNF antibodies has improved some of these conditions, including septic shock and IL-2 toxicity. This suggests that there may be an important role for cytokine antagonists in these and other conditions in which TNF appears to have a deleterious effect. It has clearly been shown that pentoxifylline blocks TNF-α at the mRNA level (52) and can be used successfully in vivo for the treatment of diseases with high endogenous TNF-α levels (39,43,53-56).

The release and/or action of other cytokines has recently been reported to be inhibited by pentoxifylline treatment (57-60), thus providing further roles for pentoxifylline as a cytokine antagonist in diseases and disorders involving other cytokines (61,62).

The future application of pentoxifylline and thalidomide, alone or in combination, as well as other cytokine inhibitors has wide implications in therapeutics.

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