Pentoxifylline: Clinical Application in Human Immunodeficiency Virus–associated Optic Neuropathy

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We very much enjoyed the recent article by Wilt and colleagues [1], which clearly demonstrated in vitro, that tumor necrosis factor-α (TNF-α) could enhance human immunodeficiency virus type 1 (HIV-1) replication in human microglia (without microglial toxicity) and may also induce apoptotic cell death in human oligodendrocytes. They suggested that of the various TNF-α inhibitors tried (including TNF X antibodies, soluble TNF-α-Rl fused to the Fc Ig region, and pentoxifylline), pentoxifylline produced the longest lasting and most effective blocking of HIV-1 replication in microglia [1]. Pentoxifylline has been found to be a potent in vitro and in vivo inhibitor of TNF-α [2] and has been tried in animal models of TNF-α–related diseases such as experimental allergic encephalomyelitis [3]. Wilt and colleagues [1] proposed that since pentoxifylline can interfere with TNF-α synthesis and HIV-1 replication, it may be most effective in alleviating or slowing certain neurological symptoms associated with the progression of acquired immune deficiency syndrome (AIDS), and suggested that pentoxifylline be tried in suitable animal models.

We have also been studying neurological manifestations of AIDS, in particular, HIV-related optic neuropathy. These studies have demonstrated clinical findings such as decreases in normal color discrimination and contrast threshold deficits consistent with dysfunction of the optic nerve [4]. Morphological studies have confirmed optic nerve axonal loss and degeneration, and astrogliosis suggestive of a primary HIV-related optic neuropathy [5]. We proposed that TNF-α has a major role in the pathogenesis of this optic neuropathy, and subsequently developed a rabbit model of axonal degeneration following intravitreal administration of TNF-α. When TNF-α rabbits were treated with pentoxifylline, the morphological markers of optic neuropathy (i.e., axonal loss and degeneration) were markedly decreased [6]. Finally, we have attempted, as a pilot effort, to give pentoxifylline (400 mg p.o. t.i.d.; standard rheological dose) to a few HIV patients with severe clinical symptoms of optic neuropathy. These patients actually demonstrated a recovery of some visual function; however, they quite naturally declined to participate in a crossover study. However, since HIV-associated optic neuropathy may spontaneously resolve [7], we should be careful not to make conclusions of efficacy based on such anecdotal evidence. Therefore, a large scale pentoxifylline trial for patients with HIV-associated optic neuropathy is underway in collaboration with the University of Milan, Italy.

Certainly the in vitro study of Wilt and co-workers [1] provides further justification for the use of pentoxifylline in patients with HIV-related optic neuropathy. Our rabbit model studies, in addition, support the use of pentoxifylline as a central nervous system–protective therapy in diseases such as AIDS encephalopathy and possibly multiple sclerosis.

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