

# A Novel Use for an Old Drug: The Potential for Minocycline as Anti-HIV Adjuvant Therapy

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(See the article by Szeto et al, on pages 1132–1140.)

In an interesting report in the current issue of *Journal*, Szeto et al [1] examined the ability of minocycline, a second-generation tetracycline derivative, to attenuate human immunodeficiency virus (HIV) 1 infection and replication by suppressing the activation of CD4<sup>+</sup> T cells. Minocycline mediates its antiviral effects by altering the cellular environment rather than via direct effects on HIV-1 replication. This effectively places minocycline in a new class of “anticellular anti-HIV drugs,” as the authors suggest. Minocycline decreased the expression of activation (CD25) and proliferation (Ki-67) markers and reduced the secretion of cytokines (interleukin [IL] 2, interferon- $\gamma$ , and tumor necrosis factor- $\alpha$ ). Other markers included CD45RA (increased) and CD71, CD11a, and HLA-DR (decreased). The drug did not significantly alter expression of the early activation marker CD69, and the authors suggest that minocycline may target a step downstream of early T cell activation events.

Interestingly, CCR5 expression was also reduced, which could contribute to a decrease in HIV-1 replication induced by minocycline in the presence of macrophage-tropic HIV-1.

In addition to their antimicrobial action, antibiotics have long been studied for beneficial effects attributed to immunomodulatory activity. In vitro anti-inflammatory effects have been described for almost all classes of antibiotics, but significant clinical research has been focused on the macrolides and tetracyclines. For example, the macrolides, which include erythromycin, clarithromycin, roxithromycin, and azithromycin, inhibit the production of several proinflammatory cytokines, including IL-1, IL-6, IL-8, and tumor necrosis factor- $\alpha$ . These effects are mediated by the inhibition of the transcription factors nuclear factor  $\kappa$ B and activator protein 1 [2, 3]. Clinical benefit has been seen with macrolide use among patients with cystic fibrosis [4]. Minocycline treatment markedly reduced the expression of monocyte chemoattractant protein (MCP) 1, as detected in cerebrospinal fluid in the accelerated simian immunodeficiency virus (SIV)/macaque model of HIV-1 infection [5]. MCP-1 is an inflammatory chemokine produced by macrophages and astrocytes in the brain and is implicated in the damage observed in neurodegenerative diseases. In human trials, minocycline has been shown to have neu-

roprotective effects in patients with rheumatoid arthritis [6], multiple sclerosis [7], and stroke [8]. Of special note, minocycline may be of particular use in the treatment of central nervous system (CNS) diseases among individuals with a genetic polymorphism in the MCP-1 promoter, which can result in increased MCP-1 production [9].

Using the accelerated SIV/macaque model of HIV-associated neurological disease, the authors have elsewhere demonstrated beneficial effects of minocycline, including decreases in viral load in plasma and viral RNA in the brain [5]. Minocycline treatment also reduced the severity of CNS disease. In this model a neurovirulent strain and a second immunosuppressive strain of SIV were used to generate enhanced levels of acute infection. The pigtail macaques used in the study had persistently high viral load and rapid CD4<sup>+</sup> T cell loss. In addition to anti-HIV-1 effects, minocycline treatment also had anti-inflammatory and neuroprotective effects in the CNS, reducing the incidence and severity of encephalitis. In a more recent macaque study, an examination of brain tissue demonstrated that minocycline reduced levels of astrocyte activation and neurodegenerative markers, including amyloid precursor protein and the mitogen-activated protein kinases c-Jun N-terminal kinase and p38 [10]. The authors showed that the inhibition of p38 activation by minocycline correlated with the

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suppression of HIV-1 and SIV replication in lymphocytes. However, in macrophages the minocycline-induced inhibition of p38 did not correlate with suppressed virus replication [10].

In another study, minocycline was shown to inhibit nuclear factor  $\kappa$ B activation in microglia [11]. The antibiotic was also able to inhibit HIV long terminal repeat-directed transcription in the monocytic cell line U38. Bioinformatic techniques were used to demonstrate that minocycline had high predicted affinity against HIV-1 integrase [12]. Therefore, it is apparent not only that minocycline uses >1 pathway to inhibit HIV-1 replication but also that these pathways may differ depending on the cell type examined. However, the pathway used by minocycline to inhibit HIV replication appears to be distinct from those underlying the neuroprotective effects of the drug.

Although more research is required to elucidate its antiviral mechanisms, minocycline has several advantages. It crosses the blood-brain barrier [13–15], which may be important, because current antiretroviral therapies vary in their effectiveness in controlling HIV-1 replication in the CNS [16–18]. Minocycline is inexpensive and approved by the US Food and Drug Administration. Therefore, it may be of value for treating HIV-infected individuals in developed countries, particularly in developing countries where current antiretroviral treatment may not be used owing to lack of availability or prohibitive costs. Currently, the efficacy of minocycline in reducing neurological disease in HIV-infected individuals is being examined in clinical trials in the United States and Africa.

Some questions must be resolved to define more clearly the clinical role of minocycline in HIV treatment. For example, it remains unknown whether normally prescribed doses of the antibiotic would achieve serum or cellular levels that would be effective in suppressing HIV-1 replication in vivo. This is important, because the effective dose of minocycline used in

the in vitro experiments described by Szeto et al was higher than the levels normally found in serum of treated individuals. Furthermore, it remains to be determined how minocycline may interact with currently used antiretrovirals. One report indicated that minocycline administration reduced the exposure to the protease inhibitor atazanavir [19]. The mechanism underlying this interaction is unknown, as is how potential interactions of minocycline with other antiretroviral drugs would affect the response to antiretroviral treatment. Trimethoprim-sulfamethoxazole monotherapy has clearly been shown to have beneficial therapeutic and prophylactic effects in HIV-infected children in Africa [20]. The effect of minocycline therapy for HIV infection in resource-poor countries may be difficult to distinguish from its potential antimicrobial or even antimalarial effects.

Finally, considerable research effort has been directed toward purging HIV from latent reservoirs with valproate and other small molecules, in the hope of eradicating the virus [21–24]. The approach of enhancing HIV latency, as demonstrated here by Szeto et al, seemingly runs contrary to the strategy of inducing the virus for eradication purposes. It remains to be seen which approach, if either, will result in long-term clinical benefit for those infected with HIV.

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