Neurokinin-1 receptor antagonists: A new revolution in antiretroviral treatment?

Sir,

In the goal of complete eradication of human immunodeficiency virus (HIV), antiretroviral drug resistance seems to be a serious obstacle. It has been predicted that despite the approval of newer anti-retroviral drugs, emergence of resistance against them is almost inevitable. This necessitates the development of anti-HIV drugs with newer targets and mechanisms of action along with activity against drug-resistant viruses.

Neurokinin-1 receptor (NK1R), a receptor for the neuropeptide substance P (SP), is a member of family 1 (rhodopsin-like) of G protein-coupled receptors. These receptors are found widely distributed in both the central and the peripheral nervous systems. NK1R antagonists are drugs that interfere with binding of neuropeptide SP to NK1R. Aprepitant, an NK1R antagonist, is currently used clinically for the prevention of nausea and vomiting associated with cancer chemotherapy or following surgical procedures. Surprisingly, it also possesses novel anti-HIV properties.

SP and NK1R are known to be central mediators in the interaction between the nervous and the immune systems. SP has been shown to not only increase HIV replication but also enhance the expression of membrane-bound CD163 in monocytes. Macrophages derived from monocytes with high levels of membrane-bound CD163 have increased susceptibility to HIV infection.[1] SP also inhibits natural killer (NK) cell cytotoxicity through NK1R.[2]

Aprepitant has been found to be active against HIV drug-resistant isolates and enhance the anti-HIV activity of various anti-retroviral drugs. According to the results obtained by a phase 1B trial of aprepitant in HIV-1 infected adults, the drug was reported to decrease plasma levels of SP and soluble CD163. In addition, aprepitant treatment was also shown to be associated with decreased expression of programmed death 1 receptor which

suppresses T-cell activation; Along with a decrease in plasma levels of several pro-inflammatory cytokines such as interleukin-6 and tumor necrosis factor alpha, which when raised, are associated with poorer prognosis in chronic HIV infection. It also inhibits the negative immunomodulatory effects of SP on NK cells.[2]

In yet another study done by Wang *et al.*, aprepitant was found to inhibit infection of macrophages with zidovudine (AZT)-resistant and reverse transcriptase inhibitor-resistant viruses. It was also found to significantly increase the anti-HIV activity of antiretroviral drugs such as AZT, efavirenz, and indinavir. Both aprepitant and the non-peptide NK1R antagonist CP-96,345 inhibit CCR5 receptor expression on macrophages, which is required for the entry of HIV into macrophages.[3] Manak *et al*. showed the operation of additional antiviral mechanisms not involving CCR5 in monocytes.[4] NK1R antagonists can also help in preventing inflammatory and neurocognitive events associated with HIV infection, which remains a challenge today in most patients even after successful treatment.[5] It is a safe drug with the only significant side effect being an increase in the incidence of infection.

Therefore, aprepitant is a promising candidate that is set to revolutionize anti-retroviral treatment by not only curbing the emergence of drug resistance but also adding to the net therapeutic effect of combination antiretroviral therapy by virtue of its synergistic effects. Extensive research on this group of drugs as therapeutic and immunomodulatory agents against HIV is currently underway.

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There are no conflicts of interest.

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