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Mode of Action of SDZ NIM 811, a Non-Immunosuppressive Cyclosporin A Analog with Activity against Human Immunodeficiency Virus Type 1 (HIV-1)

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SDZ NIM 811 is a 4-substituted Cyclosporin being devoid of immunosuppressive activity while retaining full binding capacity to cyclophilin, and exhibiting potent anti-HIV-1 activity. The mechanism of action of NIM 811 is clearly different from that of all other anti-HIV agents described so far. We identified two stages in the viral life-cycle where NIM 811 interferes. During establishment of infection it prevents appearance of circular HIV DNA and viral DNA integration into the host genome, while not impairing reverse transcription. This may be due to inhibition of translocation of viral DNA to the nucleus. NIM 811 does not reduce viral antigen expression from chronically infected cell, but leads to a dose-dependent reduction of infectivity of shedded virus particles. The antiviral activity of cyclosporin derivatives correlates with their capability to bind to cyclophilin A. Cyclosporins interfere with the complex formation between cyclophilin and HIV-1 proteins, expecially with gag proteins. Sensitivity to NIM 811 covaries with cyclophilin binding of gag and incorporation of cyclophilin in virus particles. Prevention of cyclophilin/gag interactions may be the molecular basis for the antiviral effects of NIM 811.

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Cyclosporin A Modulation of Primary Simian Immunodeficiency virus (SIV) Infection in Rhesus Monkeys.

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To test the ability of cyclosporin A (CsA) to inhibit SIV by suppressing immune activation, we studied the effects of CsA on primary SIV infection in monkeys. CsA inhibits HIV-1 in two ways. 1) CsA inhibits immune activation, suppressing HIV-1 which grows best in activated cells. 2) CsA inhibits cyclophilin A interaction with the Gag polyprotein and incorporation into HIV-1. Since SIV Gag does not bind and incorporate cyclophilin A, SIV is not inhibited by CsA through the latter mechanism. Monkeys were treated intravenously for 32 days with vehicle or with 5 mg/kg of CsA twice daily beginning 5 days before SIV inoculation. Effects were measured on SIV titer, antigenemia, proviral DNA in blood and lymph node (LN) by polymerase chain reaction, and viral load in LN by *in situ* hybridization. CsA caused transient suppression of SIV in a portion of the treated monkeys compared to the controls. Reduced titers of SIV occurred in some treated monkeys 9 days postinoculation (PI), but titers were similar in both groups by day 14. The duration of antigenemia was decreased in 4 of 7 treated monkeys, 2 of which had delayed onset and delayed peak. The same 4 monkeys had decreased proviral DNA in blood and LN, and decreased numbers of infected cells in LN 7 days PI. The effects were transient, since both groups were similar by day 14. In the controls the CD4/CD8 ratio decreased by 14 days PI, but the ratio remained significantly higher in the treated group. The percentage of CD4+CD29+ (helper-inducer/memory) cells decreased in all 7 controls by day 7, but this early decrease did not occur in the 4 treated monkeys which had the greatest suppression of viral parameters. Although CsA transiently suppressed SIV in 4 of 7 monkeys, 2 of the treated monkeys had later enhancement of SIV levels. These results indicate that CsA can modulate early virologic and immunologic events in primary SIV infection.