Sirolimus—potential applications in HIV infection

Sirolimus (rapamycin, Rapamune) is currently used as an immunosuppressive medication in transplant patients. However, some research in the past several years suggests that sirolimus has several properties that may make it interesting to further study in HIV-positive people.

About sirolimus

Sirolimus exerts its immunosuppressive effect by interfering with a protein called mTOR (mammalian target of rapamycin). This interference has the effect of disabling immune system cells from fully responding to the chemical signal interleukin-2 (IL-2). T-cells exposed to sirolimus are unable to become activated and further develop their infection-fighting abilities.

Co-receptors

In addition to the CD4 receptor, HIV needs one of two co-receptors to attach itself to and gain entry to infect a cell. These co-receptors are called CCR5 and CXCR4. Some strains of HIV prefer to use CD4 and CCR5; other strains prefer to use CD4 and CXCR4. To make things even more interesting, still other strains of HIV can use CD4 and either CCR5 or CXCR4.

In the lab

Laboratory experiments with cells have found that an unexpected consequence of sirolimus’ interference with IL-2 signalling is that T-cells and other cells of the immune system are unable to display or express large numbers of CCR5 on their surface. This effect on CCR5 has been found even with very low concentrations of sirolimus, less than those used for immunosuppression in transplantation. Also, sirolimus seems to have a modest impact on protecting cells from strains of HIV that use CXCR4; exactly how sirolimus does this is not clear.

Other laboratory studies have found that sirolimus impairs the ability of HIV-infected cells to replicate (produce copies of HIV).

Monkey studies

Experiments with sirolimus in a few healthy monkeys found that the drug greatly reduced CCR5 expression on cells of the immune system and in the vagina. This latter discovery suggests that sirolimus, if formulated into a cream or gel, could be investigated for its potential to prevent the sexual transmission of SIV (simian immunodeficiency virus) in monkeys.

HIV

Small pilot studies of sirolimus have been conducted in HIV-positive people. In such studies the drug was used to provide immunosuppression for organ transplantation. According to reviewers of such studies, sirolimus appears to enhance the viral effects of HAART on HIV. However, no increase in CD4+ counts was found. Further details about one of these studies appear in the next section of TreatmentUpdate.

Future considerations

In people who have received kidney transplants, sirolimus has been prescribed at doses between 2 and 5 mg daily. At these doses, the concentration of sirolimus in the blood is between 4 and 19 nM. In laboratory experiments with cells and HIV, sirolimus at a concentration of just 1 nM can significantly impair production of HIV from infected cells. Strains of HIV used in these experiments preferred to use the CCR5 co-receptor. So a dose of sirolimus that is less
than that used in transplantation may be worth considering for testing in a pilot study of HIV-positive people. Other studies are needed to assess how sirolimus’s anti-HIV activity might be enhanced when used with drugs such as maraviroc (Celsentri), which can mask CCR5 and protect cells from HIV infection.

A major issue that needs to be explored is how sirolimus interacts with drugs used to treat HIV infection. Transplant teams have often found that the dose of immunosuppressants such as cyclosporine, sirolimus and tacrolimus require adjustment when given to HIV-positive people who are taking protease inhibitors.

Sirolimus has potential for being used in further experiments to assess its effect on the prevention and treatment of SIV in monkeys. It also has potential in HIV-positive people, particularly those who receive transplanted organs, to assess its anti-HIV activity. This potential of sirolimus is best explored in carefully designed and closely monitored studies.

REFERENCES:


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