Abstracts

New class of HIV drug

Increasing concerns about the long-term effects of the current classes of antiretroviral drugs and problems with resistance, have led to efforts to identify a new class of antiretroviral drugs. This report in the *Lancet* looks at new treatment options that target HIV entry into the cell. Currently, most regimens are combinations of inhibitors of two viral enzymes—reverse transcriptase and protease. Nevertheless, several steps in the HIV replication cycle are potential targets for intervention. These steps can be divided into entry steps, in which viral envelope glycoproteins and their receptors are involved, and postentry steps, involving viral accessory gene products and the cellular proteins with which they interact.

HIV surface proteins bind to CD4, so anchoring the virus to the surface of the host cell. This allows additional interactions with co-receptors, in the case of HIV-1, mainly chemokine receptors CCR5 and CXCR4. The viral surface proteins gp120 is highly variable in HIV-1 isolates, with five variable and four constant regions identified. The expression of CCR5 or CXCR4 on different CD4+ target cells defines their susceptibility to infection by the corresponding CCR5 (R5) or CXCR4 (X4) HIV-1 strain.

All the steps in viral entry have long been regarded as relevant targets for anti-HIV intervention. The most promising of these are those targeting HIV co-receptors.

The most promising new drug so far is enfuvirtide (also known as Fuzeon, T-20, or ENF), which is the first HIV entry inhibitor approved for use in treatment-experienced patients. Unfortunately the drug is costly and has to be injected.

CCR5 antagonists have progressed from target discovery to description to the clinical assessment of new candidate drugs in less than 10 years. There are currently at least three candidate drugs in phase III clinical trials or beyond. Maraviroc (Celsentri, UK-427,857; Pfizer, New York, NY, USA) is at present in an expanded access programme for drug-experienced patients. Two other candidate drugs that target CCR5, Pro140 (Progenics, Tarrytown, NJ, USA) and INCB9471 (Incyte Corporation, Wilmington, Delaware, USA), are at present in phase II trials. Pro140 is regarded as a fast-track product by the US Food and Drug Administration.

The first low-molecular-weight anti-HIV agent targeting a co-receptor was the CXCR4 antagonist AMD3100, which showed that CXCR4 antagonists can have antiviral activity. Since then, several agents have been tested and some have advanced to clinical trials, but most of them have failed.

However, overall, the development of a new class of antiretroviral drugs is a major success. According to the authors, the possibility of blocking HIV entry by fusion inhibitors and co-receptor antagonists proves the value of basic research on the viral life cycle.

Esté JA, Telenti A. *Lancet* 2007; 370: 91-98.

Reducing the risk of diabetes with anti-arthritis drugs

An article in the *Journal of the American Medical Association* suggests that patients using the anti-rheumatoid arthritis drug, hydroxychloroquine, may have a reduced risk of diabetes.

The drug which is used to treat rheumatoid arthritis, has hypoglycaemic effects. The authors of this paper set out to look at any association between hydroxychloroquine and the incidence of self-reported diabetes among patients using the drug. In the study, 4 905 adults were followed up for just over 21 years. Of these patients, 1 808 had taken hydroxychloroquine and 3 097 had not. None had been diagnosed or treated for diabetes at the start of the study.

During the follow-up period, 54 patients who had taken hydroxychloroquine and 171 patients who had never taken the drug reported diabetes. This difference was statistically significant, confirming that taking hydroxychloroquine for a long period of time is associated with a reduced risk of diabetes.

Wasko MCM, *et al. JAMA* 2007; 298: 187-193.

Is rosiglitazone safe?

Recent analysis of clinical trials has suggested that rosiglitazone, used in the treatment of type 2 diabetes, is associated with an increased risk of myocardial infarction and death from cardiovascular causes. However, a recent paper in the *New England Journal of Medicine* suggests that, while the drug may be associated with an increased risk of heart failure, there are not yet enough data to show a clear link between rosiglitazone and myocardial infarction.

As the authors point out, cardiovascular causes are the leading causes of death among type 2 diabetics, which means that these patients already have an elevated risk of cardiovascular disease – probably through factors that increase the progression of atherosclerosis. Using data from the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) trial these authors provided an interim report on the deaths and outcomes from the RECORD trial so far. Their analysis involved 4 447 patients with type 2 diabetes who had poor glycaemic control while receiving metformin or sulphonylurea. Of these patients, 2 220 were assigned to receive add-on rosiglitazone and 2 227 to receive a combination of metformin and sulphonylurea – the control group.

The mean follow-up period was just under 4 years, making the analysis limited in its statistical power to detect treatment differences. At this stage, the analysis did not show a statistical difference between the rosiglitazone group and the control group. However, there were more patients with heart failure in the rosiglitazone group.

The authors conclude that, at present, the data are inconclusive, although the drug is associated with an increased risk of heart failure.

Home PD, *et al. NEJM* 2007; 357: 28 - 38.

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