New drugs

Dolutegravir

Approved indication: HIV infection
Tivicay (ViiV Healthcare)
50 mg film-coated tablets
Australian Medicines Handbook section 5.5.4

Integrase inhibitors, such as elvitegravir and raltegravir, can be used in combination with other antiretroviral drugs to treat HIV infection. Dolutegravir also inhibits HIV integrase to disrupt viral replication. Unlike raltegravir, dolutegravir can be given once daily and unlike elvitegravir it does not need 'boosting' with other drugs to have an effect.

Dolutegravir is rapidly absorbed and although food has some effect on bioavailability it is not clinically significant. The drug's distribution includes the genital tract and cerebrospinal fluid. It is metabolised in the liver with most of the dose being excreted in the faeces. No dose adjustment is required in patients with renal impairment or mild–moderate liver impairment. The half-life is approximately 14 hours.

A combination of once-daily dolutegravir with abacavir and lamivudine was compared to a combination of efavirenz, tenofovir and emtricitabine. The 844 adults in the trial had not previously been treated for HIV and had viral RNA exceeding 1000 copies/mL. After 48 weeks, 88% of the patients who took the dolutegravir combination had less than 50 copies/mL. This was statistically superior to the 81% of patients who responded to the other combination. CD4 lymphocyte counts increased by an average of 267/microlitre with dolutegravir and by 208/microlitre in the control group. This difference was also significant.[1]

Another trial of previously untreated patients compared dolutegravir with raltegravir. The 827 adults were randomised to take the integrase inhibitors with combinations of tenofovir/emtricitabine or abacavir/lamivudine. After 48 weeks there was no significant difference between the groups. The target of less than 50 copies/mL of viral RNA in the plasma was achieved by 88% of the dolutegravir group and 85% of the raltegravir group. Both drugs increased the CD4 lymphocyte count by a median of 230 cells/microlitre.[2]

Dolutegravir and raltegravir have also been compared in patients with resistance to two or more classes of antiretroviral drugs. None of the 724 adults in the trial had previously received an integrase inhibitor. After 48 weeks, 71% of the patients treated with a regimen containing dolutegravir had plasma viral RNA concentrations below 50 copies/mL. This was statistically superior to the 64% success rate with regimens containing raltegravir. CD4 lymphocytes increased by a mean of 162 cells/microlitre with dolutegravir and 153 cells/microlitre with raltegravir. Resistance to the integrase inhibitors emerged in 1% of the dolutegravir group and 5% of the raltegravir group.[3]

Dolutegravir is also being studied in patients who are infected with HIV that is resistant to raltegravir or elvitegravir. Data from 183 patients treated for 24 weeks show that in 69% dolutegravir reduced viral RNA to below 50 copies/mL. The response rate varies depending on which genetic mutation is responsible for the viral resistance. A twice-daily dose of dolutegravir is recommended when there is resistance to integrase inhibitors.

There are insufficient data to guide the use of dolutegravir in children under 12 years old. The effect of dolutegravir in pregnancy is also unknown, but it did cross the placenta in animal studies.

Adverse events in patients infected with HIV may be caused by the treatment or the disease itself. When multiple drugs are used it can be difficult to determine which one is causing an adverse event. Some problems such as immune reconstitution syndrome may be associated with any retroviral therapy. In the studies which compared dolutegravir and raltegravir there were similar adverse effects.[2,3] These include diarrhoea, nausea and headache. Rashes may be a sign of hypersensitivity. As hypersensitivity reactions may also affect the liver, liver function should be checked.

Dolutegravir will be used in combination with other antiretroviral drugs. While there are some interactions these may not require dose adjustment. Efavirenz reduces dolutegravir concentrations so this combination should be avoided or a twice-daily dose of dolutegravir will be needed. Antacids containing magnesium, aluminium or calcium should not be taken within several hours of dolutegravir as they reduce its absorption. The combined oral contraceptive pill and methadone do not have a significant interaction with dolutegravir.

Adherence to treatment is very important in managing HIV infection. An effective once-daily drug will help adherence and it is likely that dolutegravir will be formulated with other drugs to allow patients to take a single daily dose of all their drugs. When used in previously untreated patients viral resistance to dolutegravir did not seem to be a problem.[1,2] This

Some of the views expressed in the following notes on newly approved products should be regarded as preliminary, as there may be limited published data at the time of publication, and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. Before new drugs are prescribed, the Committee believes it is important that more detailed information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

may give it another advantage over other integrase inhibitors, but the development of resistance will need to be monitored once dolutegravir is more widely used.

REFERENCES *†A

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The Transparency score (T) is explained in 'New drugs: T-score for transparency', Aust Prescr 2014;37:27.

* At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA (www.fda.gov)

† At the time the comment was prepared, a scientific discussion about this drug was available on the website of the European Medicines Agency (www.ema.europa.eu)

A At the time the comment was prepared, information about this drug was available on the website of the Therapeutic Goods Administration (www.tga.gov.au/industry/pm-auspar.htm)