NEW DRUGS

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Cabotegravir

Approved indication: HIV
(ViiV Healthcare)
30 mg film-coated tablets (Vocabria)
vials containing 200 mg/mL suspension (Cabenuva)

Adherence to therapy is vital for viral suppression in people living with HIV.[1] Therapy is lifelong so there is a need for regimens that are easy to adhere to and well tolerated. Early regimens had a high pill burden and current combination regimens still require daily doses. A longer acting drug that requires less frequent dosing may therefore help with adherence.

Cabotegravir is an analogue of dolutegravir, an integrase inhibitor. By binding to HIV integrase, cabotegravir blocks viral replication. To maintain viral suppression, cabotegravir is given with rilpivirine, a non-nucleoside reverse transcriptase inhibitor which has been available for many years. Both drugs can be formulated for oral or intramuscular administration.

Following injection into gluteal muscle, cabotegravir is slowly absorbed into the circulation. It can remain in the plasma for at least a year after a single injection. The mean half-life of intramuscular cabotegravir is 5.6–11.5 weeks with most of the dose being metabolised, mainly by uridine diphosphate glucuronosyltransferase 1A1. Although patients with severe impairment have not been studied, no dose adjustments are recommended for patients with liver or renal impairment.

The intramuscular formulation of rilpivirine is also slowly absorbed from the gluteal muscle. It is metabolised, mainly by cytochrome P450 3A, and has a mean half-life of 13–28 weeks. Like cabotegravir most of the dose is excreted in the faeces.

Cabotegravir and rilpivirine have many possible interactions with other drugs. Some are potentially serious and therefore the combination is contraindicated with anticonvulsants, antimycobacterial drugs, glucocorticoids and St John's wort.

An open-label phase II trial (LATTE-2) investigated whether injections of cabotegravir and rilpivirine were as effective as oral cabotegravir with abacavir and lamivudine at suppressing HIV in previously untreated adults. All patients took the oral regimen for 20 weeks. A total of 286 patients then entered a maintenance period in which they were randomised to receive injections of cabotegravir and rilpivirine every four or eight weeks, or to continue the oral regimen. After 32 weeks of maintenance therapy, the plasma concentration of HIV RNA was below 50 copies/mL in most patients. This viral suppression was achieved by 94% (108/115) of the patients injected every four weeks and 95% (109/115) of those given a higher dose every eight weeks. The virus was suppressed in 91% (51/56) of the patients taking oral maintenance therapy. After 96 weeks of maintenance there was viral suppression in 87% of the four-weekly injection group and 94% of the eight-weekly injection group compared with 84% of the oral group.[2]

Previously untreated patients were also studied in the subsequent open-label, phase III FLAIR trial. After a 20-week oral induction period, 283 patients were randomised to long-acting therapy while 283 continued oral therapy with dolutegravir, abacavir and lamivudine. Long-acting therapy began with four weeks of oral cabotegravir and rilpivirine. The patients were then given loading doses of the two drugs, followed by monthly maintenance doses. At 48 weeks after randomisation the viral RNA concentration was below 50 copies/mL in 93.6% of the patients receiving monthly injections and 93.3% of the oral maintenance group.[3]

The phase III ATLAS trial enrolled patients who were already being treated with antiretroviral drugs. This open-label trial randomised 308 patients to continue their usual oral treatment and 308 to switch to long-acting therapy. This regimen began with four weeks of oral cabotegravir and rilpivirine followed by a loading dose and then monthly injections. After 48 weeks of the maintenance regimen 92.5% of the patients had less than 50 copies/mL. This concentration of viral RNA was also present in 95.5% of those who continued oral treatment.[4]

Patients completing the ATLAS trial could enrol in the ATLAS-2M trial along with other previously treated patients. This open-label phase III trial compared monthly injections with higher doses given every eight weeks. After 48 weeks of therapy viral RNA had been suppressed below 50 copies/mL in 93% (489/523) of the patients injected monthly and 94% (492/522) of the patients injected every eight weeks.[5]

Long-acting therapy can have long-lasting adverse effects. This is why the regimen begins with at least 28 days of oral therapy to assess if the patient can tolerate cabotegravir and rilpivirine. When intramuscular administration begins, the two drugs should be given at separate sites. Most patients will experience injection-site reactions with some developing a fever. Other common adverse events in the trials included headache, diarrhoea, nausea, back pain and upper respiratory tract infections.[2-5] The incidence of adverse effects was similar for the four-week and eight-week regimens with 2% of the patients in each group discontinuing because of adverse events.[5] Liver function should be monitored

as some patients may develop hepatitis. Patients with viral hepatitis were excluded from the trials. There has also been no study of long-acting therapy in pregnancy.

Like oral therapy, it is important for patients receiving cabotegravir and rilpivirine to adhere to the schedule of injections to reduce the risk of virological failure. In the ATLAS-2M trial, virological failure was confirmed in two patients having monthly injections and eight patients having injections every eight weeks.[5] Patients who miss scheduled injections by more than a few days will need oral therapy. This is to try and reduce the risk of developing viral resistance.

Although there are problems with injection-site reactions, cabotegravir and rilpivirine offer a new option for people living with HIV. In the FLAIR and ATLAS trials most patients preferred the long-acting injectable drugs to oral therapy.[3,4]

T manufacturer provided the product information

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The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA, the European Medicines Agency and the Therapeutic Goods Administration.