Raltegravir-Isentress, An Important Antiretroviral in HIV/AIDS Treatment

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Introduction
Even though there were registered major progresses in HAART therapy (Highly Active Antiretroviral Therapy) – complex of several ARVs (antiretroviral) used together – the HIV infection still remains an important problem with more than 33 million patients all over the world and a global incidence of 2.6 million new infections discovered every year.

Starting with 2007 there is rumour around a brand new drug therapy for the HIV, the integrase inhibitors.

Raltegravir received in 2011 the FDA approval (US Food and Drug Administration) for being used on children and teenagers (from 2 to 18 years old), not only on adults.

The efficiency of this drug was demonstrated thru several studies involving treatment of different kind of patients. It is a special type of anti-HIV drug called integrase inhibitor which works by blocking the integrase, an HIV enzyme. This prevents the HIV replication and reduces the quantity of virus in the blood cell.

Raltegravir does not cure the HIV/AIDS infection and it can not be demonstrated that it reduces the risk of HIV transmission to other persons. Raltegravir represents a brand new and important therapeutic option, especially on patients with high resistance to antiretroviral therapy but recently it is being used even on naïve patients.

There is data regarding using Raltegravir on patients who are concomitantly infected with the HIV and hepatitis B or with hepatitis C. Cronical patients infected with hepatitis B or C whom received classic combined ARV therapy present a highly risk for adverse severe hepatical reactions or even deadly adverse reactions.

Even though in osteonecrosis the ethiology is multiple (including the use of corticosteroids, alcohol consumption, severe imunosupression, high body weight) there were reported cases of osteonecrosis more frequent to advanced HIV patients with long-term exposure to combined ARV therapy.

At the HIV patients with severe immune deficiency at the starting moment of the combined ARV therapy, it can appear an inflammatory reaction for asymptomatic infections or residual with opportunistic infection resulting severe clinical symptoms. This type of reactions were seen over the first weeks or months of the combined ARV therapy.

On the cases where Raltegravir is administrated concomitantly with powerful inductors of uridine diphosphate glucuronosyltransferase (UGT) – for example Rifampicin – the medication needs a special attention. Rifampicin decreases the plasmatic concentrations of Raltegravir and when the concomitantly administration of Raltegravir with Rifampicin is needed it must be considered doubling the Isentress dose.

Preventing and curing the HIV infection still remains two major objectives for the HIV scientific community. We are now in a new era of HIV infections when the main focus is on reducing the worldwide spread and exploring new therapeutic approaches for curing and eradication.

There are 6 classes of ARV:

NRTIS - nucleoside reverse transcriptase inhibitors
NNRTIS - non-nucleoside reverse transcriptase inhibitors
PIS – protease inhibitors
FI – fusion inhibitors
II – integrase inhibitors
IR – R5 coreceptor inhibitors (CCR5)

On what regards the experience in using Raltegravir we are now following and treating 12 patients with RLV in therapy:
- most of them have associated the TB infection
- they have at least 3 previous ARV experiences
- they have positive both immunological and virological evolution after starting the RLV treatment
- ISENTRESS is indicated in association with other ARV drugs for HIV-1 treatment on adult patients treated before with the proof of HIV-1 replication. From our patients on whom it was prescribed in the treatment RLV, 9 of them are in the C3 stage and the rest in C2.
- 6 of them are monitored since the childhood
- RLV treatment started on 2010, 2011 and 2012
- following their evolution we observed a progressive increasing of CD4 and a decrease in viremia

Patient I
- male, 39 years old, AIDS C2, discovered in 2012
- first treatment scheme – KIV + KLT
- evolution of pulmonary TB, low CD4, high VL
- RAL treatment started -> after 3 months CD4 over 500 cel/mm and VL below 34 copies/ml
- positive clinical evolution

Patient II
- female, 38 years old, AIDS C3
- 3 previous ARV schemes
- decreasing CD4, very high VL
- 2013 – pulmonary TB, very severe condition
- RAL treatment started in association with T20 (integrase inhibitor along with fusion inhibitor)- 2 completely active ARV- viral suppression – saved
- positive clinical, immunological and virological evolution

Patient III
- male, 23 years old, AIDS C3
- suffering from TB when diagnosed
- naïve patient with initial treatment with RAL+CBV
- very positive evolution – initial CD4 17 cel/mm; after 1 year of treatment, over 400 cel/mm; initial VL 51,000 copies/ml; after 1 year of treatment – untraceable

Patient IV
- female, 45 years old, AIDS C3
- diagnosed when she was 30 years old, 15 years of treatment as experienced patient with 6 therapeutic schemes
- in 2011 diagnosed with pulmonary TB – RAL treatment started in association with DRV+RTV+ETR (2 protease inhibitors + non-nucleoside reverse transcriptase inhibitors)
- positive evolution, VL untraceable and CD4 782 cel/mm

Patient V
- female, 23 years old, HIV B3
- diagnosed when she was 11 years old
- 4 previous ARV therapeutic schemes
- in 2011 – CD4 242 cel/mm and VL 3916 copies/ml
- treatment started with RAL+DRV+RTV+ETR
- positive evolution – increasing CD4, VL below 34 copies/ml after 1 year

Patient VI
- male, 25 years old, HIV B3
- diagnosed when he was 4 years old
- 6 previous ARV therapeutic schemes
- in 2012, when he had CD4 375 cel/mm and VL 335,014 copies/ml, we started the ARV treatment with RAL+DRV+RTV+ETR
- positive evolution
- after 6 months – CD4 551 cel/mm and VL – untraceable

Raltegravir proves to have high efficiency, thereby in mono therapy the VL decreases with 1.7 – 2.2 logi in 10 days. Its tolerance is very good. Very rare appeared adverse reactions like rhabdomiolise, hepatitis, rash, insomnia. It is important to know that this drug has a moderate effect on CNS.

Raltegravir recommendations:
- naïve – first line
- TB as associate infection if there is intolerance to Efavirenz
- experienced – in saving therapy (it does not have crossover resistance with other classes)

If the evolution is not positive we can consider a failure which can be determined by:
- traceable viremia – any positive viremia = virological failure
- CD4 value – decreasing CD4 = immunological failure
- resistance test – if not possible then it will be assessed patient’s therapeutic history

Nowadays because of the patient tracking and the ARV treatment, there is an increasing number of old patients with 1 out of 5 being more than 50 years old. The HAART had a dramatic impact in approaching AIDS, the infection rate decreased and as well the death rate. There are millions of people infected worldwide and a global incidence of 2.6 milion of new infections each year. HAART still remains throughout patient’s life a...
permanent challenge in what means toxicity, adherence, the resistance risk and the social stigma.