2-Drug regimens in HIV treatment: pharmacological considerations

David Back[*]
Editor

Three-drug combination antiretroviral therapy (ART) based on two nucleos(t)ide reverse transcriptase inhibitors (N(t)RTIs) plus a third agent from another antiretroviral class has been the treatment paradigm that has resulted in life expectancy of HIV-infected subjects approaching that of the general population.[1] Fixed dose combinations (FDC) mean that one-pill, once-a-day is often the norm and virological suppression rates can exceed 90%. The preferred regimens for starting treatment in the major international treatment guidelines have gradually moved towards an NRTI backbone of tenofovir disoproxil fumarate/emtricitabine (TDF/FTC), tenofovir alafenamide/FTC (TAF/FTC) or abacavir/lamivudine (ABC/3TC) plus either the protease inhibitor (PI) darunavir (DRV) boosted by either ritonavir (r) or cobicistat (c), or the integrase inhibitors raltegravir (RAL), elvitegravir (ELV) or dolutegravir (DTG) or the non-nucleoside reverse transcriptase inhibitors rilpivirine (RPV) or efavirenz (EFV) – see EACS Guidelines.[2] However guidelines do not always translate into local practice, especially in relation to FDCs, due to commissioning of services and cost considerations especially in relation to the availability of generic drugs.

Since ART is life-long there is a constant desire to ensure that we minimise long term drug exposure, further reduce drug toxicity and limit cost of treatment. It is in this context that two-drug 'NRTI-sparing' regimens (2-DR) are under intense investigation. So why should we even consider a 2-DR? There are clearly a number of considerations. i) Why take 3 or 4 drugs when 2 will give the same efficacy rate? ii) the ability to potentially preserve future treatment options; iii) reduce the impact of long-term exposure to multiple ARVs and thereby the potential for adverse events; iv) fewer drugs should mean the potential to reduce drug-drug interactions (DDIs), which is especially important in aging patients with co-morbidities; v) reduce costs since there will be less active pharmaceutical ingredient (API) required.

In order for us to even consider a 2-DR we need to ensure that there is comparable efficacy with a conventional three-drug regimen which therefore requires agents with potent antiviral activity, a high barrier to resistance and a favourable pharmacokinetic (PK) and DDI profile. Currently dolutegravir (DTG) in combination with either abacavir (ABC) or rilpivirine (RPV) and the investigational integrase inhibitor cabotegravir (CAB) in combination with RPV are being studied in 2-drug regimens. From a pharmacological perspective the attraction of DTG as the core drug or the anchor drug, is that it has a rapid and potent antiviral activity, a high barrier to resistance due to both the exposure (17-fold above the protein-adjusted IC_{90}) and the long binding to wild type integrase enzyme, and a long half-life in plasma.[3] There is a vast amount of clinical trial and real-world data with DTG so that we understand that it is generally well tolerated (although we need to bear in mind some of the ongoing discussions around CNS side effects). 3TC is regarded as a well-tolerated drug which is present in all the major guidelines. It also has a long intracellular half-life and a very low potential for DDIs. The evidence for having RPV in a 2-DR is coming from the LATTE proof of principle trials in combination with CAB. RPV also has a long half-life, good tolerability (being associated with fewer

*PhD, Emeritus Professor, Department of Molecular and Clinical Pharmacology, University of Liverpool, Liverpool L693GF, UK. D.J.Back@liverpool.ac.uk

Published September 2017

ISSN 2248 – 2997
ISSN – L = 2248 – 2997

neurological and psychiatric adverse events than EFV in treatment naïve patients).

The attraction of CAB in combination with RPV is that we have the exciting possibility of a long-acting intramuscular nanoformulation. Long acting antiretroviral drugs promise new options not only for treatment but also prevention and can address poor adherence and treatment fatigue. In LATTE-2, treatment naïve patients initially received oral CAB 30 mg plus ABC/3TC 600/300 mg once daily. After a 20-week induction period patients with viral suppression were randomly assigned to intramuscular LA CAB 400 mg plus RPV 600 mg (2 x 2 mL injections) every 4-weeks, or LA CAB 400 mg plus RPV 900 mg (2 x 3 mL injections) every 8-weeks or continued oral therapy. 96-week results show that the LA combination was as effective as daily 3-drug oral therapy at maintaining HIV-1 viral suppression through 96-weeks and was well accepted and tolerated.[4]

The high satisfaction reported by patients in the LATTE-2 study suggests that LA regimens might be preferred to what can be perceived as the daily burden of oral drug intake by many patients. However there are challenges that remain to be elucidated such as injection volume, management of any adverse events occurring with the LA combination, the need for the oral lead-in and missed injections leading to low levels of drug in the circulation. Maybe one advance on the i.m. formulation will be implants containing individual drugs – since implants can be removed if any problems occur during treatment. However that is for a future discussion!

Conflicts of interest: DB has received honoraria for speaking or advising and research grants (to the institution) from AbbVie, Gilead, Janssen, Merck and ViiV.

References

1. May MT, Gompels M, Delpech V, et al. Impact on life expectancy of HIV-1 positive individuals of CD4+ cell count and viral load response to antiretroviral therapy. AIDS 2014;28:1193-202. [Crossref] [PubMed] [FullText]
2. Lundgren JD, Gatell JM, Rockstroh JK, Furrer H. EACS Guidelines, version 8.2. London: European AIDS Clinical Society (EACS), 2017.
3. Cahn P. Candidates for inclusion in a universal antiretroviral regimen: dolutegravir. Curr Opin HIV AIDS 2017;12:318-23. [Crossref] [PubMed]
4. Margolis DA, Gonzalez-Garcia J, Stellbrink H-J et al. Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomised, open-label, phase 2b, non-inferiority trial. Lancet 2017; pii: S0140-6736(17)31917-7. [Crossref] [PubMed]

Please cite this article as:
Back D. 2-Drug regimens in HIV treatment: pharmacological considerations. GERMS. 2017;7(3):113-114. doi: 10.18683/germs.2017.1115