Hypothesis

Dolutegravir (DTG) monotherapy is non-inferior to cART in maintaining viral suppression in HIV-1 infected patients.

Introduction

The use of an antiretroviral drug with a high genetic barrier against resistance may allow for a step-down to monotherapy after induction therapy with cART has led to an undetectable plasma viral load and adequate immune reconstitution.

Simplification of cART to duotherapy or monotherapy has multiple advantages (e.g., costs, toxicity, pill burden, pill-size).

DTG has a high genetic resistance barrier and development of integrase (IN) resistance in IN-naive patients has been exceedingly rare. DTG may therefore be a good candidate to be used as monotherapy for maintenance of viral suppression in HIV-1 infected individuals.

Methods

Design:

Randomized open-label multicenter non-inferiority clinical trial.

2 groups:

- DOLUMONO: direct switch to DTG monotherapy
- ConCART: continue cART for 24 weeks, followed by DTG monotherapy

Sample size/power:

N=104, P=0.95 δ=0.12 1-β=0.80 α=0.05

Inclusion criteria:

- On cART and HIV RNA <50 c/ml for >6 months with good compliance
- HIV RNA zenith <100,000 c/ml
- CD4 T-cell count >200 cells/mm³
- No baseline resistance, no previous virological failure
- HIV immune or willingness to be vaccinated before start of DTG monotherapy

Study endpoints:

For analysis of the primary endpoint, virological failure (VF) was defined as a confirmed viral load >200 c/ml.

Primary:

Comparison of the proportion of patients in the OT-population with HIV RNA <200 c/ml at W24.

Secondary:

Proportions HIV RNA <200 c/ml and <50 c/ml in the entire population on DOLUMONO at W24 and W48.

Post-hoc analysis:

Comparison of HIV RNA <200 c/ml in entire population on DOLUMONO with the 'Concurrent controls' group. This group consists of 152 patients on cART who fulfilled all inclusion criteria and exclusion criteria, but who did not participate in the study but agreed to have their data used.

OT = On Treatment analysis. This excludes patients who discontinued DTG monotherapy for adverse events at a time that HIV RNA was <200 c/ml.

Predefined study stopping rules:

Any new IN-resistance associated mutations are detected in ≥2 patients during the study.

Discontinuation of DTG for treatment failure in ≥20 patients at any time of the study.

This trial was registered at www.clinicaltrials.gov under NCT02401828

Results

Study population:

Table 2. Overview of characteristics of the patients with virological failure. TDF=Tenofovir Disoproxil Fumarate, FTC=Emtricitabine, NVP=Nevirapine, RAM=Resistance Associated Mutation.

Primary endpoint:

Figure 2. Percentages of viral suppression at week 24: on treatment analysis. 1:52 patients discontinued DOLUMONO at week 22. HIV RNA <200 c/ml for disturbed sleep.

Secondary endpoint:

Figure 3. Percentages of viral suppression in entire study population: On treatment analysis. 7/53 patients in con+cART did not switch into DOLUMONO for varying reasons.

Conclusions

- Whereas DTG monotherapy was non-inferior to cART at week 24, VF continued to occur after week 24 and led to IN-resistance associated mutations in 3 patients.
- The genetic barrier against resistance of DTG is insufficient to allow for maintenance monotherapy.
- Future studies about maintenance therapy with DTG should evaluate DTG + 3TC rather than DTG monotherapy.