Switch to dolutegravir (DTG) from a boosted protease inhibitor (PI/r) associated with significant weight gain over 48 weeks in NEAT-022, a randomised 96-week trial

Laura Waters1, Lambert Assoumou2, Stefano Rusconi3, Pere Domingo4, Mark Gompels5, Stephane de Wit6, Francois Raffi7, Christoph Stefan8, Juergen Rockstroh9, Christine Katlama10, Georg Behrens11, Jose Gatell12, Anton Pozniak13,14, Esteban Martinez1


Background

• Several trials and cohorts report weight gain on integrase inhibitors:
  - SPRING-1 (phase 2b) showed more weight gain on all doses of DTG than efavirenz [1]; weight was not analysed in phase 3 DTG trials
  - Cohorts show weight gain on integrase inhibitors [2-4] & one cohort found significant weight gain on DTG after <12 months, most markedly in women on DTG co-formulated with abacavir & lamivudine [5]
  - We performed a post-hoc weight analysis of NEAT-022

Patient population

• 415 individuals were randomised: 205 to DTG-I and 210 to DTG-D
• Baseline characteristics were similar in both arms; key characteristics are:
  - Median age 53 years, 88% aged >50 years, 89% male, 85% white; Framingham >10% in 74%
  - Virally suppressed for median 5 years: baseline PI/r: 51% darunavir/r, 37% atazanavir/r, 9% lopinavir/r & 4% other PI/r

Weight analysis

• We assessed 48-week and 96-week changes in weight (kg) and body mass index (BMI, kg/m²)
• Factors associated with the evolution of BMI within the first 48-week on DTG (DTG-I [0-48w] and DTG-D [48-96w])

Methods

Statistical methods

• Weight/BMI change was estimated using mixed models with random effects.
• Mixed models were used to compare slopes between & within groups
• Univariable & multivariable analyses identified factors associated with BMI evolution (mixed models with random effects).
• Variables considered included: age, Framingham (≤15% vs >15%), sex, race, HIV acquisition mode, CD4, baseline HIV-, HCV IgG, duration of viral suppression, time on cART, NRTI backbone, PI/r at baseline, eGFR & CVD risk factors; Multivariable analysis was adjusted by baseline BMI
• Variables were summarised as proportions for categorical variables. median and interquartile range (IQR) for continuous baseline variables. and mean and standard error (SE) for body mass index and weight at each time point.
• All p-value are two-sided with a significance level of 5%. Analysis used SAS® statistical analysis software v9.4 and IBM SPSS statistics v24

Results

• Baseline median BMI was 25.9 (IQR: 23.7–28.3)
• Mean BMI change
  - From W0-W48: -0.272/+0.064kg in the DTG-I/DTG-D, significant for DTG-I but not DTG-D (p=0.003/0.471 respectively); difference between arms was statistically significant (p=0.008)
  - From W48-W96: -0.002/+0.332 on DTG-I/DTG-D, significant for DTG-D but not DTG-I (p=0.984/0.004 respectively); difference between arms was statistically significant (p=0.002)
• Median weight change (see figure 1)
  - From W0-W48: +0.82kg in DTG-I arm vs +0.25kg in DTG-D arm; between arm difference statistically significant (p=0.008)
  - From W48-W96: +0.03kg in DTG-I arm vs +0.08kg in DTG-D arm; between arm difference statistically significant (p=0.002)
• Factors associated with BMI gain on DTG in multivariable analysis:
  - Framingham >15% (P=0.042) & hypertension (P=0.035). Protective factors were switching from PIs other than DRV/ATV (P=0.032), current smoking (P=0.006), daily exercise (P=0.039), and HDL-Chol (P=0.001)
  - After adjustment for baseline BMI, switching from darunavir was the only independent factor associated with BMI gain (P=0.018).

Conclusions

• In virologically suppressed patients with high CV risk, switch from PI/r to DTG was associated with small but statistically significant weight & BMI gain over 48 weeks; risk of weight gain was higher amongst individuals switching from darunavir/r vs other protease inhibitors.
• These findings confirm weight gain as a potential result of integrase inhibitor-based therapy, warranting further analyses of other randomised trials, studies to elucidate body mass composition changes on DTG, and their pathogenesis.
• Weight gain is an important side effect to people with HIV and we call for all phase 3 trials to routinely include analyses of weight, an easily and routinely collected parameter, in the presentation & publication of antiretroviral trial results.

References:

Contact: lwaters@nhs.net