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Re-evaluation of resistance algorithms for lopinavir/ritonavir in the TITAN trial

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Background

Genotypic algorithms used to predict the clinical efficacy of lopinavir/ritonavir (LPV/r) have included a range of mutation lists and efficacy end-points. HIV clinical trials are normally powered to detect a difference between treatment arms of 10–12% for the end-point of HIV-1 RNA suppression <50 copies/mL. The TITAN trial (TMC114-C214) evaluated LPV/r vs. darunavir/ritonavir in treatment-experienced patients with HIV-1 RNA >1000 copies/mL. Baseline genotypic resistance to darunavir was rare in the TITAN trial.

Methods

Baseline genotype data were classified using seven genotypic resistance algorithms: IAS-USA LPV mutations (cut-off = 6), Abbott 2007 (King) mutation list (cut-off = 3), ANRS mutations (cut-off = 6), FDA mutations (cut-off = 3), Stanford, REGA and IAS-USA major PI mutations. Efficacy in the TITAN trial (HIV-1 RNA <50 at week 48) was correlated with the number of mutations from each list, to show the "efficacy advantage cut-off level": the number of mutations from each list associated with a difference in efficacy between treatment arms of at least 12%. The linearity of the correlation between mutation count and efficacy of LPV/r was analysed in TITAN, with sensitivity analysis for the French LPV ATU, BMS-045 and RESIST trials.

Summary of results

In TITAN, the concordance between baseline lopinavir resistance, defined by the mutation scores, ranged from 79–95%. Multivariate analysis identified lower than previously reported genotypic cut-off levels where there was at least 12% lower efficacy for LPV/r versus darunavir/ritonavir. These "efficacy advantage cut-off levels" were: IAS-USA LPV mutations, cut-off = 3; Abbott 2007, cut-off = 2; ANRS LPV cut-off = 3; FDA LPV mutations, cut-off = 2 and major IAS-USA PI mutations, cut-off = 1, Stanford algorithm, cut-off = low level LPV resistance; REGA algorithm, cut-off = Intermediate level LPV resistance. There were linear falls in HIV-1 RNA suppression rates with rising mutation counts in the TITAN, French LPV ATU, BMS-045 and RESIST trials.

Conclusion

The analysis identified more sensitive cut-off levels for several lopinavir genotypic algorithms, below those currently used, at which there is significant efficacy advantage for treatment with darunavir/ritonavir versus lopinavir/ritonavir in the TITAN trial. These new cut-off levels also detect a higher percentage of patients with virological failure than previous cut-off levels.