Predicted Risk of Coronary Heart Disease (CHD) with Tipranavir Exposure Compared to Conventional PI in the RESIST Trial

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Background

The use of Tipranavir (TPV)/r is indicated in treatment-experienced patients

- In two pivotal, phase III clinical trials — RESIST-I and RESIST-II — treatment-experienced patients with substantial resistance to existing PIs were randomized to receive an optimized background regimen with either ritonavir-boosted tipranavir (TPV)/r or another conventional ritonavir-boosted PI (CPI)/r.

- TPV/r showed superior treatment response compared to CPI/r.

- Median levels of total cholesterol, HDL cholesterol and triglycerides have been observed more frequently used in therapy (0.016 mg/dl above baseline).

- In treatment-experienced patients, mean 5 and 10-year CHD risk was modeled according to metabolic factors observed at baseline and after 8 weeks of starting medication in the RESIST trials.

- Primary emphasis was put to the observations at week 8, as most patients remained adherent to randomized drug assignment at this study visit.

- The CHD risk estimates were calculated using the Framingham risk equation, a parametric statistical model combining for multiple cardiovascular risk factors:

  - There are data to suggest that the incremental CHD risk associated with metabolic changes induced by PI success without any substantial delay, and that the Framingham score fairly well predicts the risk of myocardial infarction in HIV-infected individuals.

- The following measured covariates were introduced into the Framingham prediction models:

  - Age
  - Sex
  - Diabetes
  - Prior cardiovascular disease
  - The ratio of serum Total Cholesterol/HDL Cholesterol (TC/HDL)

- While the following co-variates were unavailable:

  - Blood pressure
  - Smoking

- In the primary analysis (A) the prevalence of smoking and the average blood pressure are imputed and the average values observed in the D:A:D study.

- Week 8 data were available for 630 (TPV/r) and 613 (CPI/r) individuals.

Results

The predicted risk of CHD over a 10-year period is illustrated in Figure 2. A

- Figure 2 shows the predicted risk of CHD based on baseline parameters, and illustrates that — at baseline — this predicted risk is quite similar for both arms.

- However, at 8 weeks of exposure the predicted CHD risk differ (Figure 3).

- The predicted average risk of CHD over a 5-year period in the primary analysis is 2.8% overall in the TPV/r arm versus 2.4% in the CPI/r arm (Figure 4) for a NNT of estimated 113 (95% CI: 90-138).

- Table 1 displays that in the additional analysis event over 5-year period and above what would be expected after treatment with CPI/r, 153 patients would need to be treated with TPV/r.

- However, the absolute risks vary greatly by gender.

- 3.1% for men, and 0.4% for women in the TPV/r arm versus 0.5% and 0.1% in the CPI/r arm, and thus NNT is considerably lower for men (367) than women (95).

- On top of the predictions from the primary analysis, Figures 4 and 5 also includes the sensitivity analyses (B-H) for 5-year predicted CHD risk and NNT in men.

- Among the selected scenarios, the highest absolute risk and thus the lowest estimate of NNT(40) are observed in the analysis to the right (Figure 4 and 5), illustrating the risk in diabetic men aged 60 who smokes and hypertension.

Conclusions

- In two large pivotal clinical trials conducted in highly treatment-experienced patients, TPV/r demonstrated superior treatment response in standard of care PI containing regimens.

- A difference in lipid parameters is observed in the RESIST studies by week 8, which translates into an increased predicted risk of CHD in the TPV/r arm compared to the CPI/r arm.

- However, in absolute terms, the incremental risk of CHD is modest and should be balanced against the beneficial effects of treatment in preventing progression to AIDS.

- The differences in predicted absolute risk between the TPV/r and CPI/r arms results in estimated NNT of the range of 8-15 for the men in the study over a 5-year period, and considerably higher NNT (i.e. lower absolute risks) for the women in the study.

- In certain subgroups of patients that present at baseline with well-known cardiovascular disease risk factors, and thus a higher risk of CHD, the estimated NNT is lower.

- In aggregate, these findings suggest that in future patients requiring a boosted PI regimen, the potential added harm in risk of CHD induced by TPV/r versus CPI/r is present but limited in absolute terms in most patients.

- However, there are groups of patients in whom the absolute risk of CHD over a 5-year period is as high as 15% irrespective of study arm.

- Thus, prudent evaluation of underlying cardiovascular disease risk factors and consequently absolute risk of CHD is important to assure appropriate risk assessment and patient management.

Comments

- The estimates of CHD risk presented here need to be interpreted with care.

- Risk estimates were based on the application of a conventional CHD risk equation (the Framingham score), designed for use in the US general population3.

- There are no clinical data to date on cardiovascular events in the RESIST trials.

- While the following co-variates were unavailable:

  - Blood pressure
  - Smoking

- The numbers needed to treat to harm one person (NNT) treated with TPV/r over and above the number of patients experiencing a CHD event on CPI/r were calculated from the absolute CHD risk difference between the study arms:

  - NNT = 1/absolute risk difference

- In the RESIST trials, 746 and 737 individuals were randomized to TPV/r and CPI/r, respectively (Table 1).

- Week 8 data were available for 630 (TPV/r) and 613 (CPI/r) individuals.

- Over the first 8 weeks of exposure, changes in lipid levels were observed (Figure 1).

- The TC/HDL ratio increased from 5.1(4.1-6.3) to 6.0 (4.7-7.6) in the TPV/r arm, while from 5.0 (4.1-6.2) to 5.2 (4.1-6.5) in the CPI/r arm (p-value for difference between arms at week 8: 0.0001). (Figure 1, I and II)

- The numbers needed to treat to harm one person (NNT) treated with TPV/r over and above the number of patients experiencing a CHD event on CPI/r were calculated from the absolute CHD risk difference between the study arms:

  - NNT = 1/absolute risk difference

- The predicted mean risk of CHD in the RESIST Trial based on risk factor profile at randomization and at Week 8

- The predicted mean risk of CHD in the RESIST Trial compared to Conventional PI in the RESIST Trial

- The predicted mean risk of CHD in the RESIST Trial according to study drug and risk profile

References


