Poster 809

CROI 2007

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

N Friis-Møller[1], M Kraft[2], H Valdez[3], D Hall[3], and JD Lundgren[1]

Copenhagen HIV Programme, Hvidovre University Hospital, Hvidovre, Denmark[1]; Virology, Boehringer Ingelheim GmbH, Ingelheim am Rhein, Germany[2];Virology, Boehringer Ingelheim Pharmaceuticals, Ridgebury, Ridgefield, Connecticut, USA[3]

Nina Friis-Møller, MD, PhD
Copenhagen HIV Programme
Hvidovre University Hospital, Dept 044
Tel: +45 36 32 30 15
Fax: +45 36 47 33 40
E-mail: nfm@cphiv.dk

BACKGROUND

- The use of Tipranavir (TPV/r) is indicated in treatment-experienced patients
  - In two pivotal, phase III clinical trials — RESIST-1 and RESIST-2 — 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 responses compared to CPI/r[1]
- Elevation of lipid levels have been observed more frequently after use of TPV/r (500mg/200mg BID) than after use of other low dose ritonavir boosted PIs
- Based on data collected in the RESIST trials, we estimated the potential added risk for coronary heart disease (CHD) associated with TPV/r use compared to CPI/r

METHODS

- In treatment experienced patients, mean 5 and 10-year CHD risk was modelled according to metabolic factors observed at baseline and after 8 weeks of starting medication in the RESIST trials
  - Primary emphasis was made 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 controlling for multiple cardiovascular risk factors[2]
  - There are data to suggest that the incremental CHD risk associated with metabolic changes induced by PIs occurs without any substantial delay[3], and that
  - The Framingham score fairly reliably predicted the risk of myocardial infarction in HIV-infected individuals[4]
- The following measured covariates were introduced in to the Framingham prediction model:
  - 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
- Therefore, in the primary analyses (A) the prevalence of smoking and the average blood pressure are imputed and takes the average values observed in the D:A:D study[3] :

A. Mean systolic blood pressure 120 mmHg, and smoking prevalence 45%

- Different average values were considered in sensitivity analyses in men for the following scenarios:

B. Systolic blood pressure 120 mmHg , smoking prevalence 100%
C. Systolic blood pressure 130 mmHg, smoking prevalence 45%
D. Systolic blood pressure 130 mmHg, smoking prevalence 100%
E. Systolic blood pressure 140 mmHg, smoking prevalence 45%
F. Systolic blood pressure 140 mmHg, smoking prevalence 100%
G. Systolic blood pressure 120 mmHg, smoking prevalence 45%, diabetes prevalence 100%
H. Systolic blood pressure 140 mmHg, smoking prevalence 100%, diabetes prevalence 100%, age 60

- The numbers needed to treat to harm one person (NNTH) 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:
  - NNTH = 1/absolute risk difference

RESULTS

- 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, I and II]**
  - 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, II]**

Figure 1

Lipid Profile at Randomization and at Week 8

Figure 2

Predicted mean risk of CHD in the RESIST Trial based on risk factor profile at randomization

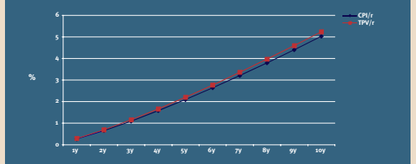
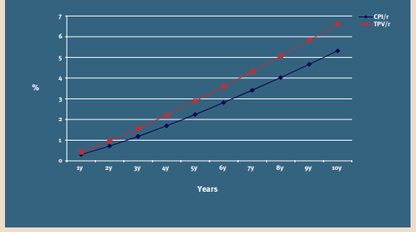


Figure 3

Predicted mean risk of CHD in the RESIST Trial based on risk factor profile at week 8



RESULTS (continued)

- The predicted risk of CHD over a 10-year period is illustrated in **Figures 2-3**:
  - 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 modelled CHD risk differ **[Figure 3]**
- The predicted average risk of CHD over a 5-year period in the primary analysis (A) is 2.88% overall in the TPV/r arm versus 2.24% in the CPI/r arm **[Figure 3]**, for a NNTH estimate of 155 (1/(0.0288-0.0224))
  - That is, to observe one additional CHD event over a 5-year period over and above what would be expected after treatment with CPI/r, 155 patients would need to be treated with TPV/r
- However, the absolute risks vary greatly by gender:
  - 3.15% for men, and 1.49% for women in the TPV/r arm versus 2.38% and 1.08% in the CPI/r arm, and thus NNTH is considerably lower for men (131) than women (245)
- 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 NNTH in men
- Among the selected scenarios, the highest absolute risk and thus the lowest estimate of NNTH (41) are observed in the analysis to the right **[Figures 4 and 5**, scenario H**]**, illustrating the risk in diabetic men aged 60 who smokes and have hypertension

CONCLUSIONS

- In two large pivotal clinical trial studies conducted in highly treatment experienced patients, TPV/r demonstrated superior treatment response to standard of care PI containing regimens[1]
- A difference in lipid parameters is observed in the RESIST studies by week 8, which translates in to 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 risks between the TPV/r and CPI/r arms results in estimated NNTH in the range of 80-150 for the men in the study over a 5-year period, and considerably higher NNTH (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 à priori risk of CHD, the estimated NNTH is lower
- In aggregate, these findings suggest that in failure patients requiring a boosted PI regimen, the potential added harm on 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 population[2]
  - Although validated in HIV-infected individuals[4], a more accurate prediction model may be required for this population
  - Further, the underlying assumption for the present analyses is that the lipid levels observed in week 8 remains stable throughout the ensuing prediction period

Table 1

Baseline Characteristics in the RESIST trials

	TPV/r	CPI/r
No.of subjects	746	737
Baseline date	Aug 2003 (June-Sep)	Aug 2003 (June-Sep)
Median (IQR)		
Age (years)	43(38-49)	42(38-48)
Baseline		
BMI (kg/m²)	23.2 (21.1-25.5)	23.0 (21.2-25.2)
Log HIV-rna	4.8 (4.3-5.2)	4.8 (4.2-5.3)
CD_4 count (cells per µL)	158 (66-285)	166 (53-280)
%		
Female	15.7	11.7
Prior CVD	1.5	1.9
Diabetes	4.8	4.2
Region		
Europe	40.6	40.7
North America	41.7	41.9
South America	17.7	17.4

Figure 4

Predicted mean 5-year risk of CHD according to study drug and risk profile

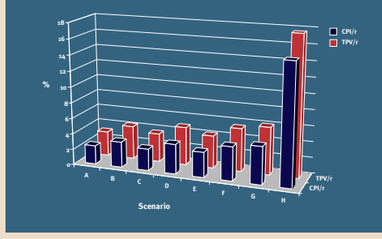
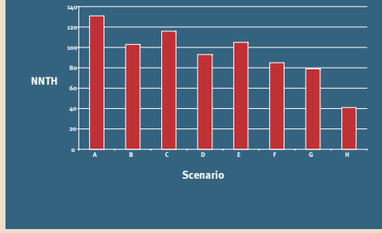


Figure 5

Predicted NNTH for 5-year CHD risk – TPV/r versus CPI/r



References

1.Hicks CB, Cahn P, Cooper DA et al. Durable efficacy of tipranavir-ritonavir in combination with an optimised background regimen of antiretroviral drugs for treatment-experienced HIV-1-infected patients at 48 weeks in the Randomized Evaluation of Strategic Intervention in multi-drug reSistant patients with Tipranavir (RESIST) studies: an analysis of combined data from two randomised open-label trials. Lancet 2006; 368(9534):466-475.
2.Anderson KM, Odell PM, Wilson PW, Kannel WB. Cardiovascular disease risk profiles. Am Heart J 1991; 121(1 Pt 2):293-298.
3.The D:A:D Study group. Risk of Myocardial Infarction in Association with Different Classes of Antiretroviral Drugs. N Engl J Med 2007; In press.
4.Law MG, Friis-Moller N, El-Sadr WM et al. The use of the Framingham equation to predict myocardial infarctions in HIV-infected patients: comparison with observed events in the D:A:D Study. HIV Med 2006; 7(4):218-230.

Download poster at: www.cphiv.dk