IMPACT OF NELFINAVIR (NFV) AND ITS ACTIVE METABOLITE M8 THROUGH LEVELS (TL) ON VIROLOGIC RESPONSE FROM PRIMARY HIV-1 VERTICALLY INFECTED CHILDREN TREATED WITH STAVUDINE (D4T), DIDANOSENO (DDI) AND NFV IN THE PENTA 7 STUDY.

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ABSTRACT

Background: The impact of antiretroviral combination therapy with d4T, ddi and NFV was evaluated in 20 primary HIV-1 vertically infected children aged less than 3 months. Viral load decrease was 2.06 log10 at week 4 and it was sustained up to week 12 but did not continue further. The incomplete viral suppression (HIV-1 RNA > 1000 copies) in 70% of the infants even with high doses of NFV (150 mg/kg/day) as powder or crushed tablets and the presence of genotypic resistance mutations represent a great concern. Pharmacological issues may explain virological response.

Objectives and methods: To investigate the relationship between virologic response at week 48 and early pharmacometric parameters, NFV concentrations and M8 from plasma samples taken through follow-up were analysed. M8/NFV "Metabolic ratio" (MR) was calculated. Samples taken between 0 and 1.5 hours and beyond 10.5 hours after dosing were considered as TL.

RESULTS

Demographic and baseline characteristics of the 14 infants are shown in table 1. A virological failure at week 48 was observed in 11/14 infants. At week 4, Median (range) in months: 468 (194). At W48, 11/14 were in virologic failure. In PENTA 7 we assessed the toxicity, tolerability, pharmacokinetics and activity of triple antiretroviral combination therapy with d4T, ddi and NFV in HIV-1 vertically infected children aged less than 3 months. A rapid decrease in plasma HIV-1 RNA concentrations was observed 4 weeks of therapy (the median drop was 2.06 log10) but, although this decline was sustained beyond week 12, the decline did not continue further. The presence of incomplete viral suppression in 70% of the infants, associated with genotypic resistance mutations in 30% of them represents a great concern. Even with high doses of NFV (150 mg/kg/day) attaining undetectable viral load was difficult.

OBJECTIVES

To investigate the relationship between virologic response at week 48 and early pharmacometric parameters.

METHODS

Infants initially received stavudine (d4T) suspension (2 mg/kg/day in 2 divided doses), didanosine (ddI) suspension (200 mg/m2/day in 2 divided doses) and nelfinavir (NFV) powder/crushed tablets (120 mg/kg/day in 3 divided doses taken every 8 hours). The dose of nelfinavir was increased to 150 mg/kg/day after pre-planned PK studies performed on the first 4 infants showed low AUC. In addition to this, subsequent infants received nelfinavir twice daily after data within the study showed similar AUC and troughs with BID and TID dosing. Specific instructions on food requirements or not for different drugs were given to parents/carers.

In PENTA 7, we investigated the impact of d4T, ddi and NFV in HIV-1 vertically infected children aged less than 3 months. A rapid decrease in plasma HIV-1 RNA concentrations was observed 4 weeks of therapy (the median drop was 2.06 log10) but, although this decline was sustained beyond week 12, the decline did not continue further. The presence of incomplete viral suppression in 70% of the infants, associated with genotypic resistance mutations in 30% of them represents a great concern. Even with high doses of NFV (150 mg/kg/day) attaining undetectable viral load was difficult.

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DISCUSSION

Results:

M8/NFV "Metabolic ratio" (MR) was calculated. Samples taken between 0 and 1.5 hours and beyond 10.5 hours after dosing were considered as TL. Positive values were considered as responders, and negative values as non responders. There were no differences in NFV and M8 between responders and non responders even if NFV was higher and M8 lower in non responders compared to responders. However both at W4 and between W4 and W12, the M8/NFV metabolic ratio was significantly higher in virological responders (Table 2).

In infants treated during HIV-1 primary infection, NFV TL and M8 were highly variable. A. Compagnucci, Y. Sáidi, A. Fayé, L. Ciria Calavia, D.M. Gibb, S. Girard, M. Debre, R. Weigel, V. Giacomet, J.-P. Abouiker, and E. Jacqz-Aigrain.

REFERENCES:

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Table 1:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
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<tbody>
<tr>
<td>Age (months)</td>
<td>Median (range)</td>
</tr>
<tr>
<td>Ethnic origin</td>
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</tr>
<tr>
<td>CDC disease stage</td>
<td>N</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>Median (range)</td>
</tr>
<tr>
<td>Height (m)</td>
<td>Median (range)</td>
</tr>
<tr>
<td>Pina H+1 RNA log10 copies/mL</td>
<td>Median (range)</td>
</tr>
</tbody>
</table>

Table 2: Mean (SD) of NFV, M8 and MR in responders and non responders

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
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</thead>
<tbody>
<tr>
<td>NFV</td>
<td>Median (range)</td>
</tr>
<tr>
<td>M8</td>
<td>Median (range)</td>
</tr>
<tr>
<td>MR</td>
<td>Median (range)</td>
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</table>


CONCLUSION

In infants treated during HIV-1 primary infection, NFV TL and M8 were highly variable. MR values were different between responders and non responders at week 48. These findings even with a small number of infants reinforce the need to undertake further pharmacokinetic studies in very young children. The role of this metabolic ratio in virologic response needs to be elucidated.