Evolution of Viral Load and Genome Sequence in a Clinical Trial of Tenofovir/Emtricitabine Combination Versus Tenofovir
Monotherapy for Patients with Previous Adefovir Dipivoxil Failure
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Results

29 25  28 29  29 29  29
7 7   7 7   7 7   7
29 25  28 29  29 29  29
33 31  32 33  33 32  31
7 7   7 7   7 7   7
24 23  23 23  23 23  23
33 31  32 33  33 32  31
11 11  11 11  11 11  11
29 25  28 29  29 29  29
12 12  11 12  12 11  12
33 31  32 33  33 32  31
17 16  16 16  16 16  16
19 19  18 19  19 18  19

Methods (cont’d)

Figure 6. Median Change from Baseline in HBV DNA; All ADV-R and LAM-R by LiPA

Figure 7. Viral load evolution by type of response

Table 2. Evolution of mutant populations

Hepatitis B virus (HBV) is responsible for nearly 350 million chronic infections worldwide. More than 1 million die each year following complications of the disease (cirrhosis or hepatocellular carcinoma).

Two types of therapies are approved for treatment of chronic hepatitis B: - Immunomodulation using interferon alpha. Only one type of patients respond to this treatment and inconvenient side effects are observed - Inhibition of viral polymerase using nucleoside/nucleotide analogues. However, prolonged treatment with most nucleoside analogues results in emergence of resistant virus. Therefore, monotherapy with a nucleoside analog is associated with treatment resistance.

- Tenofovir disoproxil fumarate (TDF) is a nucleotide analogue recently approved for HBV treatment. Currently, no resistance mutation has been described for TDF but adefovir dipivoxil (ADV) resistance mutations may confer some level of cross-resistance to TDF in vivo

- Combination therapy represents an emerging strategy for treating chronic HBV infection, although its added benefit is debated

Methods

- 105 patients with chronic hepatitis B and refractory to ADV therapy were randomized and treated in a controlled trial of TDF versus TDF + FTC

- 63 patients had also been exposed to lamivudine before the trial

Background

- In patients with ADV failure, it is therefore important to determine the potential benefit of a combination therapy over a switch strategy in patients with HBV DNA greater than 1000 copies/mL, on ADV

- The aim of the present study is to compare viral kinetics and genome resistance mutation evolution during antiviral therapy with TDF or TDF + FTC in patients with HBV DNA greater than 1000 copies/mL on ADV

Methods (cont’d)

Figure 3. Median Change in HBV DNA by Baseline ADV-R (LiPA)

Table 1. Patient mutations detected either by direct sequencing or by Inno-LiPA assay

Patient Population Direct Sequencing Inno-LiPA assay

Subjects with ADV resistance mutations only

Subjects with LAM resistance mutations only

Subjects with ADV and LAM resistance mutations

All subjects with mutations

- by direct sequencing of PCR products (population sequencing) and by specific hybridization assay (LiPA) at baseline and on all samples with viral load > 1000 copies/mL.

- A simple logistic regression model was fit comparing baseline viral load between the slow and rapid responders

Objective

- To determine these potential struggles when designing new antiviral therapy regimens

- An intermediate response with a VL lower than 400 copies/mL between W12 and W24

- A slow response with a VL lower than 400 copies/mL at both W4 and W12

- Immunomodulation using interferon alpha. Only one third of patients

- A simple logistic regression model was fit comparing baseline viral load between the slow and rapid responders

Conclusions

- Inno-LiPA is significantly more sensitive to detect resistance mutations than population sequencing

- Evolution of viral load was not different whether patients received combination or monotherapy

- Baseline resistance patterns were not associated with type of response. A rapid response to < 400 copies/mL was correlated with low baseline viral load (p<0.05)

- At Week 48, ADV-R and LAM-R mutations were found to persist by LiPA in two and one patient, respectively

- 17 patients have been selected for clinical analysis. These patients have been chosen for their different type of response, treatment regimen and baseline mutations

- The viral quasi-species study and longer follow-up of these patients are ongoing to better understand viral kinetics and fitness during combination therapy and to evaluate the potential for cross resistance