Short communication

The influence of the M184V mutation in HIV-1 reverse transcriptase on the virological outcome of highly active antiretroviral therapy regimens with or without didanosine

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Background: In vitro phenotypic resistance studies suggest that the presence of the M184V mutation leads to a reduction in HIV-1 susceptibility to didanosine (ddI). The relevance of this to clinical outcomes remains unclear. In this study, we compared the virological response of ddI- and non-ddI-containing regimens in the presence or absence of the M184V mutation.

Methods: Data from an observational cohort study of all HIV-1 patients who had phenotypic resistance testing following the emergence of virological failure to an existing highly active antiretroviral therapy (HAART) regimen were analysed. A total of 586 patients entered the study and were followed-up over 48 weeks; 281 (48%) were switched to ddI-containing HAART, of whom 105 had the M184V mutation at baseline. Virological efficacy of combination therapy was studied by reference to average area under the curve of viral load (VL) response and the proportion of patients attaining an undetectable VL (<400 copies/ml). Baseline characteristics and univariate analysis of changes in VL were compared using the Wilcoxon rank sum test. Multivariate analyses were performed using the Van Elteren test. Additional variables included the number of baseline nucleoside reverse transcriptase inhibitor mutations and the number of active antiretroviral drugs given to each group as compared by ‘real phenotype’ resistance test results.

Results: Amongst patients on ddI-containing HAART, median fold changes in phenotypic susceptibility to ddI were greater in patients with the M184V mutation (fold changes of 2.2 vs 1.2, \(P<0.001\)). Nonetheless, the median change in VL and percentage of patients attaining an undetectable VL were similar in those taking ddI, irrespective of whether the M184V mutation was present at baseline. In the group of patients with the M184V mutation at baseline, the virological outcome was significantly better in those treated with ddI-containing HAART than in those on HAART without ddI (\(P<0.05\)).

Conclusions: While the M184V did increase the fold resistance of HIV to ddI, these changes appeared to be lower than the clinically relevant threshold for phenotypic resistance for this drug.

Introduction

Highly active antiretroviral therapy (HAART) is accepted as the standard of care in the treatment of HIV infection with considerable reduction in morbidity and mortality since its introduction in the mid-1990s [1,2]. Failure of initial treatment regimens commonly results from the emergence of antiretroviral drug resistance caused by genetic changes in HIV-1 reverse transcriptase (RT) and protease genes, as a result of ongoing viral replication in the presence of sub-therapeutic concentrations of drugs.

The extensive use of lamivudine (3TC) as first-line triple therapy has made the M184V mutation in HIV-1 RT common in antiretroviral-experienced patients; in a group of 11 875 randomly selected HIV-1 isolates sequenced for routine drug resistance testing, 39.5% had an M184V mutation [3] and the prevalence of M184V among patients failing 3TC-containing regimens is between 84% and 100% [4–6].

In patients failing antiretroviral therapy, it is important to find alternative regimens that achieve maximal
suppression of viral load (VL) [7]. Nucleoside analogues remain an important component of such regimens and resistance testing may assist drug selection.

In vitro phenotypic resistance studies have suggested the presence of the M184V mutation leads to a reduction in HIV susceptibility to didanosine (ddI) by a factor of approximately fivefold [8,9]. However, the relevance of this on clinical outcome remains unclear.

In this study, we compare the virological response of ddI- and non-ddI-containing regimens in the presence or absence of the M184V mutation.

Methods and results

The Chelsea and Westminster Hospital HIV-1 clinical outpatient cohort was used in an observational study between 1998 and 2000. The data from all patients who had phenotypic resistance testing (Antivirogram®; Virco BVBA, Mechelen, Belgium) following the failure of an existing HAART regimen during this time were reviewed. New combination therapy regimens were allocated for each patient on the basis of clinical experience in conjunction with the results of phenotypic resistance testing. Genotyping (VircoGEN™; Virco Lab, Inc, Mechelen, Belgium) was performed and the frequency and type of RT mutations can be seen in Figure 1.

A total of 586 patients were reviewed; 281 (48%) patients were switched to a regimen containing ddI, of which 105 had the M184V mutation present at baseline. 305 (52%) patients did not switch to ddI and, of these, 65 had the M184V mutation present at baseline (Figure 2).

Amongst patients on ddI-containing HAART, phenotypic susceptibility of HIV-1 to ddI was recorded, with comparisons made between groups with and without the M184V mutation. In the same patient group, the virological efficacy of ddI in the presence or absence of M184V was then studied by reference to median change in VL, average area under the curve over time minus baseline (AAUCMB), and the proportion of patients attaining an undetectable VL (<400 copies/ml). Finally, virological response of the M184V variant to both ddI- and non-ddI-containing regimens was compared.

The follow-up period was 48 weeks, with measurement of viral load at weeks 4, 12, 24 and 48. Study data were analysed on the basis of the treatment received by each group. Baseline characteristics and univariate analysis of changes in VL were compared using the Wilcoxon rank sum test. Multivariate analyses were performed using the Van Elteren test. Additional variables included the number of baseline
nucleoside reverse transcriptase inhibitor (NRTI) mutations and the median number of active antiretroviral drugs given to each group as compared by ‘real phenotype’ resistance test results.

In those patients on ddl-containing HAART, a greater median fold change in phenotypic resistance of HIV-1 to ddl was recorded in the presence of M184V (2.2 vs 1.2, \( P < 0.001 \)).

There was no significant difference in the median change in VL, AAUCMB (Figure 3; \( P = 0.675 \)) or percentage of patients attaining an undetectable VL (\( P = 0.035 \) at week 12; \( P > 0.05 \) at all other time points) in those taking ddl over 48 weeks, irrespective of whether the M184V mutation was present at baseline.

In patients with the M184V mutation at baseline, the virological outcome was significantly better in those treated with ddl-containing HAART than in those on HAART without ddl, when measured by AAUCMB (Figure 4; \( P = 0.007 \)) and at week 4 using median change in VL (\( P < 0.05 \)). No significant difference was shown in the proportion of patients attaining an undetectable VL.

A significant difference in the median number of active drugs used (three vs two, \( P < 0.0001 \)) was seen between those patients with the M184V mutation who were treated with a ddl-containing regimen and a non-ddl containing regimen, but the median number of RT mutations at baseline (2.0 vs 2.0, \( P = 0.259 \)) showed no difference.

**Discussion**

The value of phenotypic resistance testing in patients failing antiretroviral therapy has been evaluated in a number of randomized controlled trials with variable results [10]. Its use has been associated with a higher proportion of patients achieving an undetectable VL following the virological failure of first-line HAART regimens [11], but other studies have not shown any benefit from its use in more treatment-experienced patients [12,13]. Clinical benefit in treatment-experienced patients may be gained from the use of genotypic resistance testing [13], but the outcome of new regimens is much more dependent on the introduction of new classes of drugs.

Patients failing treatment are given a combination of drugs in subsequent regimens that makes the relationship between the effects of an individual drug and pre-existing phenotypic resistance difficult to establish.
A prolonged period of sub-optimal treatment among drug-experienced patients can result in the emergence of drug-resistant strains that can compromise the efficacy of the drugs available [14]. In particular, the M184V mutation has been shown to induce resistance to lamivudine and in vitro cross-resistance to ddI [15].

However, in vitro phenotypic studies on patient samples have shown that cross-resistance to ddI did not necessarily emerge after the amino acid substitution at codon 184 [16].

Winters [17] compared virological outcome among 104 lamivudine (3TC)-experienced HIV-1 positive patients who switched to a ddI-containing triple- or quadruple-drug regimen with those who continued receiving a 3TC-containing regimen. A significantly increased independent risk of virological failure was associated with continuing a 3TC-containing regimen. Interestingly, most patients for whom the ddI-containing regimen failed had lost the M184V/I mutation. ddI seemed to have activity against viruses with the M184V/I mutation and this study suggested that presence of this mutation should not exclude the use of ddI in nucleoside-experienced patients [17]. Eron [18] has also showed that reductions in VL among 3TC-experienced patients receiving ddI were similar in those with and without the presence of the M184V mutation.

A further study has demonstrated that phenotypic susceptibility to ddI was maintained in the majority of highly experienced patients despite the high prevalence of changes at codon 184 and prior experience of ddI. A significant 1 log_{10} decrease in VL but no significant increase in CD4 lymphocytes was observed in one group who switched 3TC for ddI after 3 and 6 months [19].

Furthermore, A1454-176, the double-blind placebo-controlled Jaguar Study showed that addition of ddI to a failing regimen in patients with four nucleoside-associated mutations produced a –0.6 log_{10} drop in VL at 4 weeks; 68% of patients had previously received ddI [20].

These findings support the view that a VL response to ddI-containing regimens is possible in nucleoside-experienced patients with the M184V mutation.

In our study, the median fold change in phenotypic resistance of HIV-1 to ddI was significantly greater in patients with the M184V mutation, supporting previous studies [8,9]. Nonetheless, in this large cohort, ddI-containing regimens produced a similar virological response irrespective of whether the M184V mutation was present at baseline or not. This observation was reinforced by the absence of any significant difference in the number of active antiretroviral drugs between each group, although it may be confounded by the observed difference in number of RT mutations between the two groups (Table 1). There was a significantly lower median viral load in those given ddI with M184V compared with those without that did not effect virological outcome, probably because the median values were relatively low.

The study also appeared to show that ddI-containing HAART regimens produced a significantly greater virological response in patients with the M184V mutation than those not containing ddI. However, as an observational cohort study, the new regimens had been selected on the basis of phenotypic resistance tests results rather than by randomization, which might be an important source of potential confounding. Indeed, even though the baseline combinations were relatively well-matched and the frequency of thymidine analogue mutations and other RTI mutations was similar in these two groups, there was a greater number of active drugs based on phenotype available to the ddI-treated patients with the M184V mutation at baseline (Table 2) However, in both groups, the new regimens contained a similar number of active NRTIs, non-NRTIs (NNRTIs) and protease inhibitors (PIs). Switching from a PI to an NNRTI or to a boosted PI may have a very different impact on subsequent virological success and is difficult to measure, even if these strategies are both counted as a class switch. A more accurate measure of potential activity of the current regimens than the phenotypic sensitivity score is needed but it does become complex, for example, when subsequent use of boosted PIs are part of a new therapy.

In conclusion, although this study does not prove that ddI is as effective in a regimen treating people who have the M184V variant as those who do not, it does indicate that the clinical responses are often good and that the presence of the M184V mutation should not exclude the use of ddI in the treatment of HIV-1 patients.

<p>| Table 1. Baseline characteristics and HAART regimen of patient group given ddI (median values) |
|-------------------------------------------|----------------|----------------|</p>
<table>
<thead>
<tr>
<th>M184V present</th>
<th>No M184V</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>105</td>
<td>176</td>
</tr>
<tr>
<td>Viral load (log_{10})</td>
<td>4.0</td>
<td>4.6</td>
</tr>
<tr>
<td>CD4 count</td>
<td>199</td>
<td>148</td>
</tr>
<tr>
<td>Phenotypic ddI resistance</td>
<td>2.2-fold</td>
<td>1.2-fold</td>
</tr>
<tr>
<td>Number of active drugs</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Number of significant NRTI mutations excluding M184V</td>
<td>2.0</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>HAART regimen</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NNRTIs and NRTIs</td>
<td>50%</td>
<td>39%</td>
</tr>
<tr>
<td>PIs and NRTIs</td>
<td>18%</td>
<td>26%</td>
</tr>
<tr>
<td>NRTIs only</td>
<td>17%</td>
<td>24%</td>
</tr>
<tr>
<td>PIs, NNRTIs and NRTIs</td>
<td>15%</td>
<td>11%</td>
</tr>
</tbody>
</table>

7. Hogg RS, O'Shaughnessy MV, Gataric N, Yip B, Craib K.

Table 2. Baseline characteristics and HAART regimen of patient group with M184V mutation (median values)

<table>
<thead>
<tr>
<th></th>
<th>ddI-group</th>
<th>Non-ddI-group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>105</td>
<td>65</td>
<td>–</td>
</tr>
<tr>
<td>Viral load (log_{10})</td>
<td>4.0</td>
<td>4.0</td>
<td>0.945</td>
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<tr>
<td>CD4 count</td>
<td>199</td>
<td>229</td>
<td>0.564</td>
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<tr>
<td>Phenotypic ddI resistance</td>
<td>2.2-fold</td>
<td>2.3-fold</td>
<td>0.897</td>
</tr>
<tr>
<td>Number of active drugs</td>
<td>3</td>
<td>2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Number of significant NNRTI mutations excluding M184V</td>
<td>2.0</td>
<td>2.0</td>
<td>0.259</td>
</tr>
</tbody>
</table>

References


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