The ability of four genotypic resistance algorithms to predict HIV-RNA responses to boosted PI-containing regimens after 4 and 12 weeks follow-up

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BACKGROUND

Limited information is available on the relationship between PI resistance and viremic response.

OBJECTIVES

To investigate:

• Concordance between predicted PI resistance levels using four genotypic interpretation systems (IS) and virological response at week 4 and at week 12

• To assign a genotypic sensitivity score (GSS) to the rest of the regimen and explore the relationship between this GSS and virological response

DATA

We used combined data from three international, 48-week, multi-centre trials (MaxCmin1, MaxCmin2, COLATE).

METHODS

Reverse transcriptase and protease mutations were identified for all patients with baseline viral load >500 cps/ml.

RESULTS

Baseline HIV-1 genotypic resistance tests were available for 368 patients (94% (n=358) indinavir/r, 96% (n=355) lopinavir/r, and 86% (n=311) saquinavir/r).

At baseline, 9 (10%), 3 (2%) and 6 (4%) patients had full resistance and 74 (83%), 110 (87%) and 142 (93%) were sensitive to saquinavir/r, lopinavir/r and indinavir/r, respectively (Using the REGA IS – Figure 1).

Overall, 3 (9%) patients were susceptible to ≥2 ARVs other than the PI/r.

Virological response

Median (IQR) baseline viral load was 4.7 (3.9 to 5.2) log10 cps/ml. At week 12, the median (IQR) decrease in viral load from baseline was:

• 0.8 (0.5 to 1.2) log10 cps/ml (REGA) to 0.4 (0.1 to 1.1) log10 cps/ml (DMC) and 1.8 (0.6 to 2.7) log10 cps/ml (Stanford).

Similar viral load reductions were seen for all of the PI/r studied at both time-points.

• Reductions in viral load between baseline and week 4, were associated with PI resistance levels (pro.10 for all ISs), but not the number of other active drugs in the regimen in unadjusted analysis (Figure 2).

• Reductions in viral load between baseline and week 12 were associated with both the PI/r resistance levels (pro.01 for all ISs) and the number of other active drugs in the regimen (pro.01 for all ISs) in unadjusted analysis (Figure 3).

• After adjustments, none of the ISs predicted viral load reductions to week 4 when looking at resistance to PI/r or the number of other active drugs in each patient’s regimen at baseline (Figure 3).

• In multivariable analysis only DMC and Stanford showed significantly greater reductions as sensitivity to PI/r increased (Figure 4).

Using Stanford, patients sensitive to the PI/r had a 0.62 greater log10 reduction between baseline and week 12 compared to patients with full resistance.

• The number of other active drugs in the regimen did not predict response further.

SUMMARY AND CONCLUSIONS

• Concordance between ISs was moderate.

• Virological outcomes were used to test the clinical value of the ISs.

• In our study baseline resistance to the PI/r did not show a difference in viral load responses until week 12.

• A change needs to be reached on how we would expect resistance to impact on viral load response.

• This study included patients with high levels of viral load sensitivity, limiting our ability to assess the association with virological response.

• At week 4, the level of baseline resistance to the PI/r produced a 0.8 log 10 cps/ml difference between sensitive and resistant viruses after adjustments for baseline viral load, the number of other active drugs, gender and PI-naivity.

• A surprising 1.5 log 10 cps/ml reduction in viral load was still seen for patients with a fully resistant virus.

• Potency of the ISs may be such that virologic benefit is seen even in the presence of resistance.

• ISs need to be improved so that they capture the magnitude of these viral load changes more accurately for PI/r.

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