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Ritonavir boosted Indinavir Treatment as a simplified maintenance "Mono"-Therapy for HIV infection

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Introduction

Mitochondrial toxicity is a newly recognized side-effect (SE) of nucleosides-RT-inhibitors (NRTI). Given the potential irreversible effect of this toxicity on mitochondrial function, these SE are a major concern of highly active antiretroviral treatment (HAART). Efforts to reduce mitochondrial SE are needed.

Rapid development of antiviral resistance is a hallmark of HIV. Due to the high error-rate of the HIV reverse transcriptase every single mutation will occur with approximately 10^{10} replication rounds per day. Combination of antiviral agents with overlapping resistance patterns is now generally used because it's extremely unlikely that a combination of 3-5 specific resistance mutations will occur after a single replication round. This is the theoretical basis for the combination of antiviral agents to treat HIV-infection.

In the study by Havlir et al [3], indinavir (IDV) monotherapy (tid) in patients who had been suppressed on an indinavir based HAART regimen was rapidly followed by an increase in HIV-RNA in 23% of patients randomised to Indinavir monotherapy. In the meantime, IDV treatment has markedly improved with the use of ritonavir boosting (IDV/r). Trough levels of IDV are several fold higher than the IC_{95} of wild-type HIV [4].

It is currently not known whether the treatment with a highly boosted PI might suffice for the maintenance of HIV suppression in patients who have reached undetectable levels of HIV-RNA under HAART.

References

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Study aim

The aim of the pilot study was to exclude a major risk of treatment failure in IDV/r-only maintenance and to evaluate biological markers to be used in future, large-scale PI-only studies.

Methods

Ethical approval of the study was obtained by the local EC.
Design: open, non comparative, observatory study

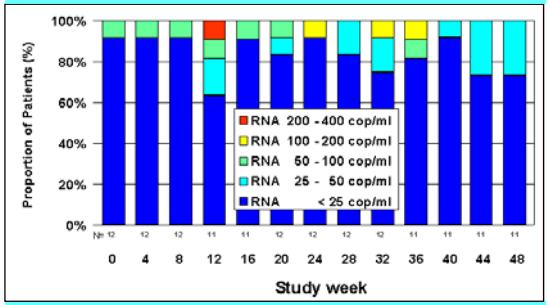
Patient entry criteria
- Patients had been on IDV/r-based HAART
- HIV-RNA <50 cop/ml over > 3 months
- No previous treatment failure

Intervention
- Patients were offered a comprehensive adherence support including MEMS-caps
- IDV dose adapted to achieve trough levels 500-2000nM/l.
- All NRTIs were stopped at baseline
- HIV-RNA blood levels were measured at 4-week intervals with an additional measurement at week 2 (Det-Limit: <20 cop/ml).

Primary endpoints
- Treatment failure was defined as:
  - 2 consequtive HIV-RNA values > 400 cop/ml
  - 3 consequtive HIV-RNA values > 200 cop/ml
  - 1 HIV-RNA value > 400 cop/ml (2 measurements)
- Predefined stopping rule for the study was two in 12 patients reaching one of the failure criteria defined above

Additional tests with limited results shown here
- DEXA-Scans were performed at baseline and week 48 and the ratio of fatty tissue of extremities and trunk was compared between BL and Wk48
- HIV-RNA measurement in semen at wk 0, 24 and 48 [7]
- CD8 activation markers (CD38 and HLA-DR) at each visit
- mtDNA:nDNA ratio in PBMC and semen at baseline and w48

Figure 1: Level of HIV-RNA Supression

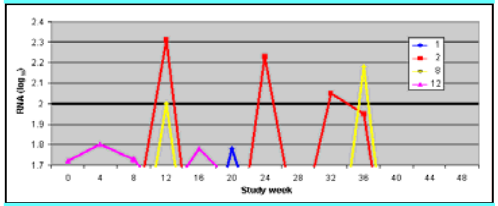


Results

Patients: n=12, 1 female
Previous treatment
- Time on previous treatment (mean): 34 months
- NRTIs: ZDV/3TC (n=9), D4T/3TC, d4T/ddI, ABC/3TC,
- Previous PI: 9 IDV/r, 1 NFV, 2 SQV/r
- Pre-treatment HIV-RNA(mean): 5.0 lg_{10}cp/ml (3.6-6.6)

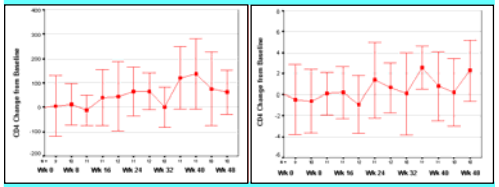
Ultrasensitive HIV-RNA follow up
- None of the patients reached a primary endpoint
- Among 138 HIV-RNA measurements (excl. wk 2), short-term HIV-RNA increases (blips) were found once >200 cp/ml, 3 times in the 100-200cp/ml range and 7 between 50-100cp/ml and 14 HIV-RNA values were between 25-50cp/ml. The vast majority (113) remained under 25cp/ml (see figure 1 and 2).
- 3 of 4 blips >100cp/ml occurred in one subject

Fig 2: HIV-RNA blips > 50cp/ml



CD4-Cell count (Fig 3)
- The mean CD4 increase over 48 weeks was 63 c/µl

Fig 3: CD4 cell courses (absolute and %)



Adverse events and other results:
- One patient developed a T-cell lymphoma of the brain (wk 24) and committed suicide at wk 33 (euthanasia)
- 4 subjects experienced nephrotoxicity (3 events of urolithiasis, 2 patients with increased creatinin level)
- DEXA-scans showed no change in fat distribution
- Activation markers remained stable over the 48 weeks

Conclusions

- **Maintenance treatment with IDV/r appears to be safe in terms of continued supression of viral load and CD4 counts.**
- **In this small pilot study, no change in fat distribution patterns was detectable using DEXA scan.**
- **Despite therapeutic drug monitoring, Indinavir demonstrated considerable renal toxicity.**
- **The importance of drug penetration in smaller compartments in not known. It remains to be seen, whether other PIs with lower compartment penetration than IDV will be able to achieve long term maintenance.**

Discussion

- **Since the introduction of protease inhibitors for HIV in 1996, HAART is usually given as a combination of at least three drugs. This paradigm, also termed the *"Vancouver paradigm"* was based on PI-treatment achieving trough levels slightly above the IC_{95} level of wild-type HIV.**
- **Boosted-PI regimens achieve drug levels considerably higher than IC_{95} of wild type virus. Theoretically, if all body compartment [6]can be reached with such a high drug level, one active drug might suffice to suppress viral load.**
- **In this pilot study evaluating the 48-week effect of IDV/r mono-therapy, the viral load suppression was maintained over the complete treatment period.**
- **Detection of HIV-RNA-"blips" (i.e. intermittent increases in HIV-RNA above 50 cop/ml) did not become more frequent over time and most patients maintained HIV-RNA concentration below 25 cp/ml in ultrasensitive RNA-PCR.**
- **The fraction of HIV-RNA blips > 50 cp/ml (5.5%) was significantly smaller than the previously [9] reported fraction of "blips" in the SHCS (34%, p<0.001), indicating that this maintenance treatment was not inferior to the general treatment in the community.**

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