HIV FORUM MEETING
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Clinical trials
for treatment naïve patients

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Do we need new ARV for naïve patients ?

Existing options :

- Low genetic barrier (NNRTI)
- Burden of the regimen (Boosted PIs)
- Metabolic adverse events (Boosted PIs)
- Mitochondrial toxicity (NRTIs)
- Lipodystrophy (common AEs)
- PK interactions (NNRTI, Boosted PIs)

=> *Obvious limitations that call for new therapeutic options*

- However, several therapeutic options available=>

  no critical time pressure for availability of new options (*contrarily to salvage therapy*)

Question : what amount of data prior to initiating studies in treatment naïve patients? 1/2

Non clinical data :

- Target organs for toxicity, QT prolongation, …
- Carcinogenicity
  - Until recently : results of carcinogenicity studies in post approval
  - EMEA Guideline on carcinogenicity evaluation for medicinal products for the treatment of HIV infection => results should be available in pre-approval

Clinical data :

- Antiviral activity
- Clinical safety (particular safety issue raised from healthy volunteers?)

Question : what amount of data prior to initiating studies in treatment naïve patients? 2/2

- To be adapted depending on whether the investigational drug belongs to an already known class or a new class of drugs, e.g.
  - Specific explorations (immune alteration, reversibility of the shift for CCR5 inhibitors)

- How to deal with potential long term uncertainties with new pharmacological class (such as tumours and raltegravir, maraviroc and host interaction and potential long term safety issues) whereas no unmet medical need ?

When/how is it acceptable to do initiate dose finding studies in treatment naive patients ?

Problem of phase II dose selection studies (raised by EU Patients Representatives in 2004) :

- First line treatment=> critical for the long term outcome
- Among tested doses => sub-optimal dose

=> Need to avoid inclusion of ARV naïve with CD4<200

F r e n c h R e p u b l i c

Conseil national du sida

Opinion on Participation in Clinical Trial Protocols On New Treatments for HIV-Infected Patients Never Having Taken Antiretroviral Medication

Adopted at the 17 March 2005 Plenary Session

EXTRACT : In a letter dated 12 November 2004, the inter-association group known as HIV-Infection Treatment and Therapeutic Research (TRT-5), alerted Conseil national du SIDA **.....** to issue an opinion on the ethical issues regarding "participation in clinical trial protocols on new treatments for HIV-infected patients never having taken antiretroviral medication".

Patients never having taken antiretroviral medication, with severe immune depression (CD4<200/mm^3) or AIDS, show a higher risk of morbidity and mortality in the three years following the start of care. This is why it is vital that they receive, as early as possible in the care cycle, treatment that offers optimal and confirmed efficacy.

For this reason, Conseil national du sida deems that promotors should first, in the early stages during which optimal doses are determined, ascertain that the new treatment, when combined with other antiretroviral medication, is both effective and well-tolerated in patients whose illness is little-advanced, e.g. with CD4 levels exceeding 200/mm^3 and viral load below 100 000 copies/ml.

Regarding the need to also obtain data regarding treatment-naïve patients[2] at a later stage of illness, CNS feels that they can be included in the assessment of the new treatment, but only later in the process, once safety and efficacy have been confirmed for lower-risk patients.

CNS reminds promotors that all patients included in a trial are entitled to the same level of monitoring as patients who are not taking part in biomedical research. Consequently, monitoring criteria for the trials must comply with the recommendations in effect in France.

[1] "The interests of those who agree to take part in biomedical research always prevail over those of science and society alone". [2] Patients having never received previous antiretroviral treatment.

When/how is it acceptable to do initiate dose finding studies in treatment naive patients ?

Specific statement in the EMEA Guideline on anti-HIV drugs :

«*Due to the importance of first-line therapy, it is of special relevance that appropriate anti-retroviral activity has been documented and that the use of the experimental compound in suboptimal dose, dose intervals, or combinations has been excluded with reasonable certainty prior to the initiation of studies in these patients. Treatment naïve patients in need of immediate therapy under current guidelines i.e. those with CD4+ T-cell count below about 200 or symptomatic patients should be included in exploratory studies only if there is a scientific rationale and if data are available from patients with higher T-cell counts. »*

What is the appropriate study duration to establish safety and efficacy ?

- The longer, the better (especially if safety signals):
  - 96 weeks being optimal for adequate efficacy/safety assessment,
  - but 48 weeks + commitment of longer term data might be acceptable

OVERALL (1/2)

- Even if still room for improvement, no unmet medical need for new therapeutic option in treatment naive patients (*contrarily to deep salvage therapy*)
- Need for some degree of reassurance *(might differ if already known class of drugs or new class)* before enrolling ARV naïve patients in clinical studies
- Problem of ARV naïve with CD4<200 and dose selection studies

OVERALL (2/2)

Moreover, referring to the EMEA guideline :

- The comparative regimen should be chosen from among those that are « strongly recommended » for the initial therapy
- Virological failure should comply with clinical guidelines

Finally,

- In non inferiority studies,the potential loss of chance has to be compensated by particular expectations of the investigational drug (genetic barrier, safety profile, adherence)