EXPANDED ACCESS PROGRAMS

HIV FORUM 16 February 2007

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EXPANDED ACCESS PROGRAM

- Primary objective should be to give ACCESS to the drug to heavily pretreated patients

- EAP can also be regarded as an **observational database** close to the « real life » with descriptive safety and efficacy data

Referring to the European HIV Guidelines

- EAP is a recognized mean to supplement the safety database of the drug

- Section 4.3.3 Studies in heavily pre-treated patients with no or very limited remaining therapeutic options at time of treatment failure

  « It is recommended that the first submission for marketing authorisation should include an informative safety data package derived from such studies, supplemented with data derived from compassionate use programmes. »

Safety data : caution in the interpretation

- Heterogeneous population
- Underlying disease
- No comparator
- Unknown interactions
- ***Notification bias : physicians are less inclined to report AEs (potential reasons : advanced stage of the disease, EAP not strictly regarded as a clinical trial…)***

Safety reporting : Phase III vs Compassionate Use *e.g. Tipranavir*

	RESIST 1 TPV arm (96weeks)	CUP (EUP + EAP)
Total number of patients	311	3920
Serious adverse events	34.7% of patients	17.2% of patients
Grade 3-4 ALT/AST	12.8%	1.8%
Grade 3-4 Triglycerides	28.9%	8.6%
Intracranial haemorrhage	3 patients	3 patients

Can EAP provide more than safety data ? *Resistance, PK, PK/PD*

- Limitations :
  - Burden of the resistance testing and PK sampling
  - Various local medical practices (Resistance, Therapeutic Drug Monitoring)
  - Interpretation hampered by : heterogeneous population, questionable efficacy of the other antiretroviral agents, changes of antiretroviral agents during the treatment course, uncontrolled interactions

Potential dilemma…

- To derive reliable data from EAP would require being more drastic in the inclusion criteria and imposing specific measures in the therapeutic management of patients
- However an EAP should not constitute a burden for prescribers and patients

OVERALL

- EAP can be regarded as a way :
  - **To give access to the drug to heavily pretreated patients, answering an unmet medical need for new therapeutic options in salvage therapy**
  - **To supplement the safety database (large sample size/ rare adverse events)**
  - **To check for the consistency of the descriptive efficacy data derived from EAP as compared to well designed studies**
  - **To detect signal => considerations for the need of well-designed studies to investigate these signals**

- ***EAP should not be regarded as :***
  - ***A substitute to well-designed studies for adequately assessing efficacy, safety, resistance and PK/PD***

In EUROPE, ART 83 November 2005

In France, the Temporary Authorisation for Use (TAU)

2 types of Temporary Authorisation for Use (TAU)

Nominative TAU	Cohort TAU
■ on a named patient basis	■ for a group of patients
■ on the request and responsibility of the physician	■ Application submitted by the company/close perspective of a Marketing Authorisation
■ limited safety and efficacy	■ Substantial amount of safety and efficacy data
■ TAU for a limited time (3 months)	■ TAU for one-year duration
■ Spontaneous reporting	■ SPC, patient leaflet, labelling
	■ Follow-up of patients and data collection according to a « protocol for therapeutic use »
	■ Regular reporting to Afssaps
■ Few patients involved	■ Several hundreds patients

TAU : Safety collection

Nominative TAU	Cohort TAU
▪Same pharmacovigilance as marketed Medicinal Products (spontaneous reporting)	▪Depending to the protocol: unexpected or serious adverse reactions ; expedited and periodic reporting… ▪Collection and analysis by the company together with one regional pharmacovigilance centre (CRPV) ▪Periodic analysis and reporting to Afssaps

EAP VERSUS TAU : Not superimposable (1/2)

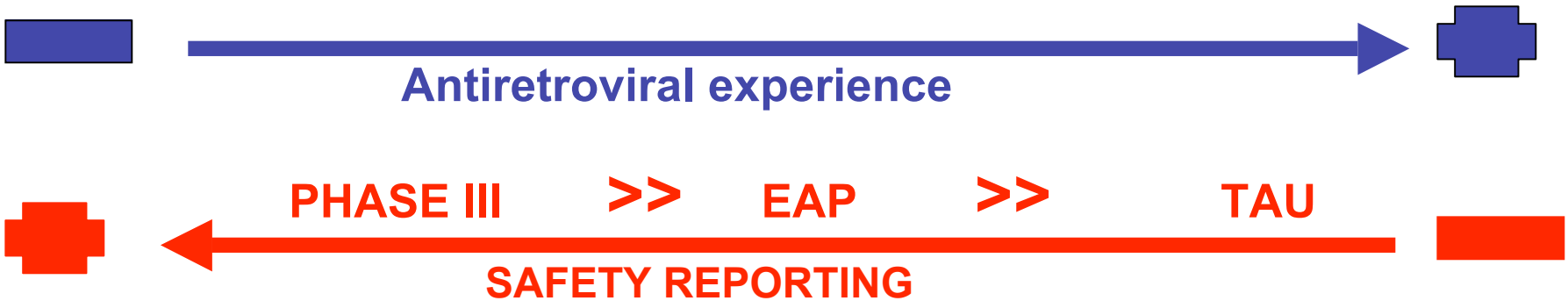
	EAP	TAU
STATUS	**CLINICAL TRIAL**	**CLINICAL PRACTICE**
Initiation	**In parallel to phase III**	***May start by the end of phase II (for the nominative TAU) as soon as the dose is selected***
Patients	Heavily pretreated patients in salvage therapy +/- **CD4 and Viral Load Criteria**	Heavily pretreated patients in salvage therapy with no CD4, no VL criteria (+/- mutational profile for the cohort TAU) ***Target : patients with no remaining options whatever their immunologic and virologic parameters***
Physicians	**Designated investigators** of the study	**Any** physician at hospital
N	Several Thousands	Several Hundreds
Primary objective	Access to the drug or Safety collection	Access to the drug
Who pay for the drug ?	Sponsor of the study	Collectivity
Are the physicians paid?	+/-	No, part of the usual therapeutic management of their patients

EAP VERSUS TAU : Not superimposable (2/2)

- EAP : access to the drug only for patients treated by designated investigators of the clinical study

- TAU : access to the drug for all patients in hospital setting

Evolution of safety reporting



e.g. Tipranavir SAEs

PHASE III >> EAP >> TAU

34.7% >> 17.2% >> 5.1%

OVERALL CONCLUSION

- EAP is a critical tool to give access to the drug to patients having exhausted the therapeutic options
- In addition EAP is of interest as an observational database closer to the « real life » than phase III studies
- Safety and (efficacy/consistency) can be derived from EAP.

  Even if their interpretation mandates caution, it may generate signals to be investigated. Given the large database, ability to detect rare AEs.
- Contrarily to the French TAU, EAP is a clinical trial with specific monitoring.

  When both options are possible for a patient, EAP is the preferred one : whereas both options answer a medical need, EAP can better supplement the safety database of the drug