Epilepsy in the developing brain

Antiepileptic drug trials

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Current status – Bad news

• AED (RCT) trials in paediatric Epilepsies
  – are performed late (after the trials in adults)
  – are restricted to epilepsies also shared by adults (FE, LGS)
  – are designed using adult methodologies of trials

• Most EE are still therapeutic orphans
  – Among the 15 new AEDs approved since 1990, 5 for LGS, 1 for IS/DS, none for others
  – 2/3 of off-label prescriptions in EE, 90% in neonates
Current status – Good news

• **Paediatric Regulation (EU 2006)**
  – Paediatric drug development mandatory (PIP)
  – Paediatric evaluation structure (PDCO)
  – Incentive measures (orphan drugs, PUMA, ..)
  – Since 2006, 2 new AEDs for EE

• **European Framework Program (FP7)**
  – Programs for Rare Diseases
  – Public/private partnerships (SME)
  – Networks (physicians, pharmacologists, scientists, industry, patients)

• **Priority List** for off-patent paediatric drugs (EMA)
  (uncomplete)

• **Guidelines** of clinical investigation of AEDs (EMA 2010)
Paediatric trials: ethical dilemma

• Need for trials (to avoid off-label use)
  – Demand for paediatric trials (EU)
  – Demand for quality trials (EU)

• « Protect » children from research
  – Avoid useless trials (use already available data)
  – Decrease invasiveness of trials (respect children specificities)
  – Expose the minimum number of children to trials
What needs to be done

1- Adapt the current process to EE

• Promote access of EE to AED trials
  – Minimise trials in Focal E (extrapolate from adult trials) *Chiron et al 2008, Rheims et al 2008*
  – Promote early EE trials (guidelines)
  – Identifying EE candidate(s) (exploratory step) *Chiron et al 2013*

• Develop new endpoints specific for EE
  – EEG endpoints (CSWS)
  – Cognitive endpoints (scales, composite scores)
  – Adapt duration to deterioration course
What needs to be done (cont’)

2- Use innovative methodologies of trials

• Small populations
  – Homogeneous subpopulations of EE
    TS-IS/VGB n=10 Chiron et al 1997, DS/STP n=11 Kassai et al 2008
  – Enrichment withdrawal trials FE 1m-4y/LTG n=19 Pina-Garza et al 2008

• Adaptative designs
  – Sequential analysis (triangular test, bayesian)

• Modeling and simulations
  – Population PK 1m-4y: LVT Chhun et al 2009, TPM Bouillon-Pichaut et al 2011
  – Bridging dose studies 2y-10y PK/PD model: TPM Girgis et al 2010
What needs to be done (cont’)

3- Develop new therapeutic targets

- Based on **genes** identified in EE
  - DS (*SCN1A*), IS (*CDKL5, ARX,..*), MPSI (*KCNT1*), ..

- Based on **mechanisms** identified in EE
  - TS (mTOR): everolimus
  - depolarising GABA (neonate, E.surgery, autism, ..): bumetanide

- Based on **inflammation** processes associated to EE

- Considering induced-**apoptosis**
  - Pregnancy, neonates and infants
What methods to improve

- Promote **transdisciplinary** research
  - Transgenic animal models $\leftrightarrow$ humans (ex: DS,TS)
  - Computational models $\leftrightarrow$ humans/animals (ex: FE)
  - Biomarkers (basic science, imaging, neuropsycho)
  - Adults $\leftrightarrow$ children

- Promote translational **platforms** (ex: neurATRIS France)

- Promote translational **training** (ex: ESDPPP-EUDIPHARM)

- Promote translational **networks** (ex: FP7 collaborative projects)

- Promote exchanges with **patients** organisations

- Promote exchanges with **Agencies** (EMA)
Expected impact

- **Improve the quality of care in children with EE**
  - Reduce the off-label use of AEDs
  - Give therapeutic options specific to EE
- **Improve the quality of life of children with EE**
  - Improve epilepsy control
  - Improve cognitive outcome
- **Provide a model for other rare paediatric diseases**