OGYÉI National Institute of Pharmacy and Nutrition

BIOSIMILARS IN PAEDIATRIC INDICATIONS:

CHALLENGING ISSUES IN EXTRAPOLATION OF TOTALITY OF EVIDENCE

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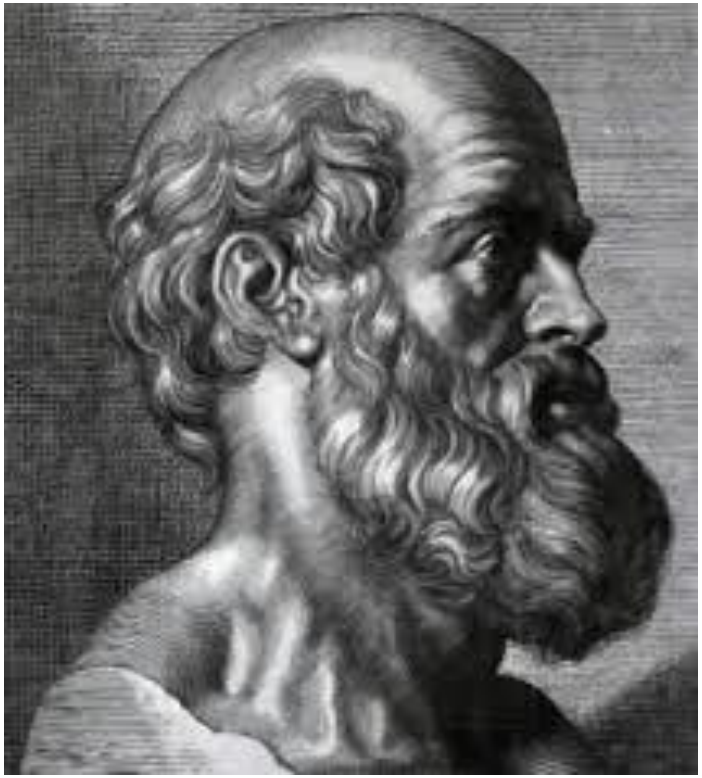

„SALUS AEGROTI SUPREMA LEX ESTO"

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No financial relationships to disclose.

European Medicines Agency (EMA)
Marketing Authorizations
47 BS for 14 INN-s

- Somatropin (1)
- Epoetin (5)
- Filgrastim (7)
- Infliximab (4)
- Follitropin alfa (2)
- Etanercept (2)
- Bevacizumab (1)
- Insulin glargine (3)
- Enoxaparin (2)
- Teriparatide (2)
- Rituximab (6)
- Adalimumab (7)
- Insulin lispro (1)
- Trastuzumab (4)

EMA Paediatric Committee (PDCO)

- Paediatric Investigation Plans (PIP) for
  - originator molecules
  - biological and chemical molecules as well
  - not evaluated: generics, biosimilars, WEU
- therapeutic areas biologics mostly used:
  - oncology
  - diabetes – insulins, GLP-1R agonists
  - immunology
    - inflammatory bowel diseases
    - rheumatoid arthritis … pJIA, sJIA
    - psoriasis, ps. arthritis
      - generally some extrapolation from adult data (Reg 1901/2006 EC)
  - paediatric only:
    - sJIA

Specific paediatric aspects

- different stages in development – physiology / disease pathology
- small patient number – feasibility of CT-s ?
- similarity of the disease to adults
  - diabetes: up to 25 y to include?
  - IBD
  - extrapolation from adults possible?
- dose determination:
  - extrapolation; Modeling&Simulation
  - e.g. BW-dependent exposure → Efficacy if influenced?
    - e.g.: clinical effects depend on obesity - but body weight is not good obesity indicator
    - → No dose adjustment needed
  - route of administration – same exposure to reach
  - if dose influenced by additional therapy
  - Safety: lower age cutoff if needed
- formulation, presentation! biologicals: devices / PreFilledSyringes
  - if available to deliver paediatric doses?
  - formulation Working Group of PDCO
- immunogenicity

extrapolation

to minimize involvement of children in clinical studies

to consider:

- what is the target exposure
  - what could be set as the limits of similarity for the target exposure based on adult data
  - was a dose/exposure - response relationship observed in adults (sufficient large range of doses/exposures investigated)?
- is the target exposure reached
  - for all subgroups in the paediatric population – if not,
  - should the dose be altered to reach sufficient exposure in all or some paediatric subpopulations?
  - are there indications that the adult target exposure is not appropriate for all subgroups in the paediatric population (need for higher/lower exposure due to efficacy/safety issues, or indications of negative benefit risk?)

Extrapolation in guidelines

- **EMA JIA guideline (2016): PK and PD data are essential**, if clear PK-PD relationship and therapeutic window has been established in adult arthritis models, a **single arm study** could be sufficient
- **EMA UC and CD guidelines** (**2016/2017**?): at least paediatric **PK and PD data are needed**. Depending on the quality and extent of available adult data - a **reduced** paediatric programme or no need for efficacy studies
- **EMA psoriasis guideline (2004):** Studies in children with plaque psoriasis can be waived if no safety concerns exist

IN SUMMARY

- biosimilars less used in paediatrics but
  - more and more in IBD e.g.
- development of paediatric use: data needed
- extrapolation
- Modeling and Simulation
- age specific characteristics might pop-up in
  - dosing / exposure e.g.
- growing confidence in healt care providers and in patients
- but: formulation, presentation :
  - if availibility of the right one?
- paediatric: rare diseases, small available sample size
- EU: ~90 000 new JIA cases/year – studies might be feasible

- Arch Dis Child2017; 102:952-957; J Dig Dis 2014; 32: 345-350