EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA Questions

Overview of expert responses

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An agency of the European Union

The paediatric literature on drugs in IBD remains frustrating because almost all published articles deal with retrospective and often uncontrolled studies with small patient populations.

Indeed, there is an emotional reluctance by pediatricians to use new pharmacological agents in children before they have been used successfully and safely in adults.

In addition, the pharmaceutical industry did not promote studies in children and infants because of concerns about safety and efficacy and, not least, because of an economic concern based on the fact that children can be only a small portion of the potential market for a new drug.

Thus, it does not come as a surprise that the use of drugs in children with IBD until now was guided by extrapolation from the numerous and controlled studies performed in adults without complete knowledge of dosing and side effects specific to the pediatric age.

(A.Staiano)

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- Overlapping genetic background but different clinical symptoms, treatment algorithms and underlying pathology
- Different genetic and immunological surrogate markers

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- *Q: - different treatment algorithms vs. same study design?*
- *Q: - what genetic and immunological markers can be used for clinical trials?*

2. Indetermined colitis

- Inclusion into trials may dilute the results
- Clear-cut pathologies to be studied first
- Lindberg et al., 2000: IC has worse prognosis, higher number of relapses, more aggressive character
- Peculiar clinical, laboratory, endoscopic and histological aspects
- CONSENSUS: Not to be included into clinical trials

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- *Q: Is there a need for new treatments for children with IC? Will they be probably treated with new biologics (not authorised for this indication)?*

3. Primary end point

- Endoscopic mucosal healing
- Histological remission less likely to be achieved
- Problem with repeated endoscopies in children
- Main goal – clinical remission, therefore clinical indices should be used for efficacy evaluation
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- *Q: No consensus. Clinical indices vs MH? CD/UC?*
- *Q: Definition of MH and best timing for endoscopy?*

4. Biologics in current treatment algorithm

- CD – early in selected patients – for induction of remission - step-down approach

  (Criteria for selection? Severe disease?)
- UC – after failure of steroids (and/or IS - step-up)
- Step-up or step-down approach in both
- Due to lack of knowledge currently only step-up

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- *Q.: Are result with early treatment in adults (incl. rheumatology) encouraging enough to introduce step-down approach in children (safety)?*
- *Q.: Selection criteria for step-down approach?*

5. Active comparator

- CD – 3 arms – steroid induction + IS maintanance vs bio+IS vs. bio mono or 2 different IS + bio step-up in both arms
- UC – bio in refractory disease vs. ciclosporin
- Colectomy for UC?

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- *Q.:Are active comparator controlled trials feasible?*
- *Q.: Age and ethical considerations?*

6. Extrapolation

- No extrapolation from adults.
- Partial extrapolation from adults possible. Disease more severe and better responds to therapy in children
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- *Q.: What is acceptable to extrapolate to save children from unnecessary studies?*

7. PK/PD in different diseases/age/severity

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- Probably same in CD and UC
- Patient and/or disease characteristics may influence PK
- Antimonoclonal antibodies, concomitant treatment

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- *Q.:PK/PD studies/analyses needed*
- *Q.: Modelling and simulation for PK*

Adverse events

- Depend on disease and concomitant therapy
- 8 cases HSCTL – in IBD, all treated with infliximab +AZA or 6-MP
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- *Q.:Safety monitoring as postmarketing commitment?*

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- Specific items: pubertal delay, growth retardation, concerns with placebo , but in principle yes
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Q.: What should be different – design, inclusion, exclusion criteria, endpoints? Why?

Q.: Is feasibility an issue?

Q.: Common design in different diseases?

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- Randomised placebo controlled
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- Randomised withdrawal
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