EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA Paediatric Rheumatology Expert Meeting 17 November 2010

Overview of PIPs
Overview of answers from experts to EMA questions

Presented by: Richard Veselý
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Question 1 :
Name for the condition for adults and children

- Autoimmune arthritis
- Autoinflammatory childhood arthritis
- Chronic childhood arthritis
- Juvenile idiopathic arthritis
- Chronic autoimmune arthritis in childhood
- Autoimmune/autoinflammatory arthritis
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Proposed conclusions (options to select from):

- Chronic arthritis
- Chronic autoimmune/autoinflammatory arthritis
- Autoimmune/autoinflammatory arthritis
- Chronic idiopathic arthritis

Question 2 – age subsets

- Agreed in general
- There are children below 2 years
- Especially in sJIA
- Treatment can be altering the future course
- At least PK in sJIA in 1-2 year olds
- Special concerns for B-cell depleting agents, JAK inhibitors etc.

Question 2 – age subsets

Proposed conclusions:

- Move the age limit for waiver to less than 1 year
- Don’t request specific studies in smallest children
- In sJIA (and autoinflammatory disorders) small PK study in youngest children
- For B-cell depleting agents and novel pathways individual approach to waiver depending on mechanism of action and expected adverse effects

Question 3 – Target populations

ACR 2010 guidelines

Presentation by Nicola Ruperto

Question 3 – Target populations

ACR 2010 guidelines:

1. Arthritis of 4 or fewer joints (no systemic, SI or LS)
2. Arthritis of 5 or more joints (no systemic, SI or LS)
3. Active SI or LS arthritis
4. Systemic with active systemic features
5. Systemic with active arthritis without systemic features

Disease activity, previous treatment and features of poor prognosis define more precisely the treatment group

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- Statistical concerns

Question 4 – Is systemic without systemic more like poly or more like systemic?

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- past clinical trials
- retrospective databases don’t show difference in response to treatment

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- genetic difference
- different pathogenic mechanisms

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Maybe yes, maybe not - depends on time… (1 vote)

Question 5 – Does systemic with systemic need to be further divided?

General agreement – no.

In addition systemic without systemic should be merged with systemic with systemic

Questions 3,4,5 – Target populations

Possible conclusions:

- Accept ACR treatment groups as target populations for PIPs
- Merge both systemics into one group
- Do always analysis for ILAR subtypes
- Include severity and prognostic features
- Specify in the PIP target population for each treatment
- Revise target populations after biologic background of different "subtypes" is well known and reflected in JIA classification

Question 6 – Non clinical development

Complex and divergent opinions

(clinicians admitting borderline expertise)

- Mostly support for doing juvenile animal studies
- Not in well known classes
- Use proper animals of proper age
- Avoid studies that are not necessary

Question 6 – Non clinical development

Possible conclusions:

Summarise answers from experts for

the Non clinical working group of the PDCO

Search if "standard" approach for future is possible

Question 7 – PK/PD

Options:

1. Separate full PK trial
2. PK/PD as part of efficacy study (after adult studies)
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In general options 2 and 3 supported, option 4 excluded

Divergent opinion: Option 1 – because results from pivotal phase (Option 2) may affect too much design and schedule for efficacy trial

Question 7 – PK/PD

Presentations by Nicola Ruperto and Fabrizio De Benedetti

Question 7 – PK/PD

Possible conclusions:

1. Separate full PK trial in new molecules/targets
2. PK/PD as part of efficacy study
3. Modelling and simulation with sparse sample validation

} If product/ class is better known

Question 8 – Study design for future

- Randomised controlled trials usually not feasible
- Randomised withdrawal design accepted and used successfully
- ACR30 used as target for efficacy evaluation
- Different treatments not compared
- Long term safety/efficacy not addressed in trials
- Treatment withdrawal in remission/inactivity not addressed

Question 8 – Study design for future

Do we accept current practise unchanged for future trials?

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YES……..4

NO……..6

Question 8 – Efficacy/safety evaluation for future

- Require always superiority trial for every first in the class
- Only PK/PD studies in new molecules belonging to well known classes
- Spare children from trials, extrapolate efficacy from adults
- Use post marketing studies to collect efficacy data in large populations
- Grant conditional authorisation based on PK studies and extrapolation followed by post marketing studies to confirm efficacy and safety and leading to final marketing authorisation
- Always collect data on efficacy levels higher that ACR30 and on remission
- Conduct comparative trials

Question 9 – Extrapolation

Presentation Agnes Saint Raymond

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- Always collect data on efficacy levels higher that ACR30 and on remission
- Conduct comparative trials
- Require conduct of treatment withdrawal in remission trials in the PIP

Pharmacovigilance

Presentation of Dirk Mentzer

Pharmacovigilance

Presentation of Nico Wulffraat/PRINTO on registries

Question 10 – Long term risk/benefit evaluation

What needs to be collected:

- Co-morbidities
- Medications, history, reason for discontinuation
- Growth, Tanner score, fertility
- Disease activity
- Adverse events

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What needs to be collected:

Adverse events

Focus on:

- Infections (incl. TB)
- Autoimmune diseases (Crohn, uveitis…)
- Demyelinisation
- Malignancies
- Metabolic syndrome, cardiovascular diseases…

Question 10 – Long term risk/benefit evaluation

How long?

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How long?

Lifelong…

Question 11 – Special JIA considerations

Which of the following should be addressed in the PIP:

- Bone erosions
- Osteoporosis
- Growth
- Uveitis
- Vascular involvement
- Sexual maturation
- Social impact

Question 12 – Uveitis

- Diverse opinions if uveitis should be studied within JIA trials
- Separate studies of uveitis supported if feasible.
- Separate patient group not supported

Question 13 – Future collaborations

- Do you think that standardisation of PIP requirements for new treatments in JIA is possible/desirable?

- Would you be willing to continue in efforts to standardise PIPs for JIA?

- Are facilities for videoteleconferencing or virtual teleconference meetings available for you?

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- **UNISONO YES FOR ALL!**

Question 13 – Future collaborations

Thank you!!!...

…and stay tuned…