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Human Medicines and Evaluation

Paediatric Rheumatology Expert Meeting

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List of participants:

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CONCLUSIONS:

A. Clinical trials in Juvenile Idiopathic Arthritis (JIA)

1. ILAR classification should be used for trials in JIA taking however into account that it is an evolving concept, that some subsets need to be better defined, and that new clinical and laboratory observations will likely cause classification changes in the near future
2. “Polyarticular course” JIA has been a useful concept in previous clinical trials that have shown the efficacy of anti-TNF and anti CTL4-IG agents. It includes polyarticular JIA (both RF+ and RF-), extended oligoarthritis, and systemic arthritis without systemic features (absence of systemic features in the last 6-12 months).
3. Systemic arthritis with and without systemic manifestations should be studied separately for drugs specifically targeting the subset.
4. Development of treatments for persistent oligoarthritis, ERA, psoriatic arthritis and undefined arthritis and inclusion of patients with these JIA subtypes to clinical studies need follow-up discussions.
5. It is highly recommended to search for biological background of individual treatment responsiveness and non-responsiveness by studying genetic (gene expression profile) and biochemical disease markers as an integral part of clinical trials. Creation of trial-related bio-banks is important and related ethical and governance issues need careful consideration.
6. Withdrawal design is currently the most appropriate for clinical trials in juvenile idiopathic arthritis. The disadvantages (non-traditional efficacy outcomes, bias towards responders) is outweighed by their advantages (feasible size of population needed, short placebo exposure, investigator and patient-friendliness). However this design does not represent an ideal method for safety and efficacy confirmation and has to be seen in context with long-term post marketing observational registry studies to confirm effectiveness and evaluate safety in larger populations and longer time perspective. Innovative study designs may be introduced and tested to overcome the disadvantages of existing designs including recruitment feasibility and ethical considerations.
7. ACR Pediatric core set of criteria for JIA and definition of improvement (flare) are suitable at present for clinical trials at ACR30 level, but higher levels have to be always evaluated in parallel and reported. The tools for evaluating long-term effectiveness of all existing and new treatments

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have to be developed using long-term observational studies. ACR30 improvement is not considered sufficient long term goal for new treatments. For systemic JIA, fever has to be added to the core criteria.

8. New "me too" medicines belonging to the well-established pharmacological class might not need full efficacy to be confirmed by separate controlled clinical trial studies in children. After adult safety/efficacy results are available; dose-finding PK/PD paediatric studies with data on efficacy and safety obtained in observational studies in a limited number of patients might be sufficient to provide authorisation followed by post marketing registries for long term safety and effectiveness.
9. In general development of new treatments for JIA should be waived in children younger than 2 years for all subtypes of JIA. Although some subtypes (ERA, RF+ polyarticular JIA…) usually develop in older paediatric age groups it is not considered appropriate to set different age limit for various subtypes and children 2 years and older can be included into clinical trials.
10. B-cell depleting medicines need to be studied in children with JIA with resistant disease forms to other approved biologic agents (currently anti TNF and anti CTL4-IG). Paediatric studies should start after evaluation of safety profile in adults. Due to immune system immaturity and frequent vaccination B-cell depletion should not be applied in children below 6 years.
11. Treatments for JIA associated uveitis need to be developed. Patients with past history of uveitis should not be excluded from JIA clinical trials. Patients who need systemic therapies that might interfere with the efficacy evaluation have to be excluded.
12. To facilitate recruitment and to ensure ethical approach to the studies companies should be requested to provide study medication to patients involved in the studies until the study product is authorised in the specific patient's country

B. Systemic Lupus Erythematosus and other paediatric rheumatic diseases.

13. Studies in SLE are ongoing. Use of PRINTO/ACR criteria for disease activity is advised.
14. The participants agreed that due to complexity of SLE a separate meeting should be organised.
15. Criteria for classification criteria for childhood vasculitides are in press

C. European scientific guidelines

16. The experts in the field should be approached actively to comment on the guidelines in early stages of their preparation. Proper mailing list should be maintained by the Agency. PRINTO and PReS are recognised organisations of paediatric rheumatologists in Europe and their expertise should not be missed.
17. The minutes from this meeting will be sent to the Efficacy working party of the CHMP that is currently working on the proposal for amendment of the Guidelines for JIA. The guidelines themselves should be circulated among expert of the field (e.g. from PRINTO and PRES)

D. Pharmacovigilance

18. The need for international registry for patients with rheumatic diseases treated with biologics and methotrexate is uniformly recognised. Such a registry should overcome limitations of national, individual manufacturer and individual drug registries and allow long-term evaluation of safety and effectiveness of treatments primarily in JIA, but possibly also in other paediatric rheumatic diseases.
19. Three projects for creating the registry were proposed (PReS/PRINTO biologics registry, PRINTO methotrexate/biologics registry and US CARRA consolidated observational registry supported by FDA) and wait for funding evaluation.
20. Regulatory authorities should support creation of international independent registry as a source of unbiased information on long-term safety and efficiency evaluation. The pharmacovigilance measures are incorporated into PIP opinions.
21. Further activities can be expected after evaluation of the applications of the European FP7 projects (March 2010). European Medicines Agency has some capacities and programmes to help pharmacovigilance projects.

E. Biologics in gastroenterology

22. There is a need for future cooperation between paediatric rheumatology and paediatric gastroenterology communities towards harmonisation of the clinical trials approach. Separate meeting of experts from both fields is foreseen.

F. Future activities

1. Submission of the proceedings from the meeting and the Concept paper for amendment of European Medicines Agency JIA guidelines to the PDCO JIA Guidelines working group and Efficacy Working Party of the CHMP.
2. Follow-up meeting on the Registry for patients treated with biologics and methotrexate
3. Establishment of paediatric rheumatology expert working group
4. Expert meeting on biologics in paediatric gastroenterology and paediatric SLE