EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Extrapolation of dosing, efficacy and safety of biologics in JIA, IBD and psoriasis

EMA history

EMA Extrapolation workshop 17 May 2016

Presented by Richard Veselý
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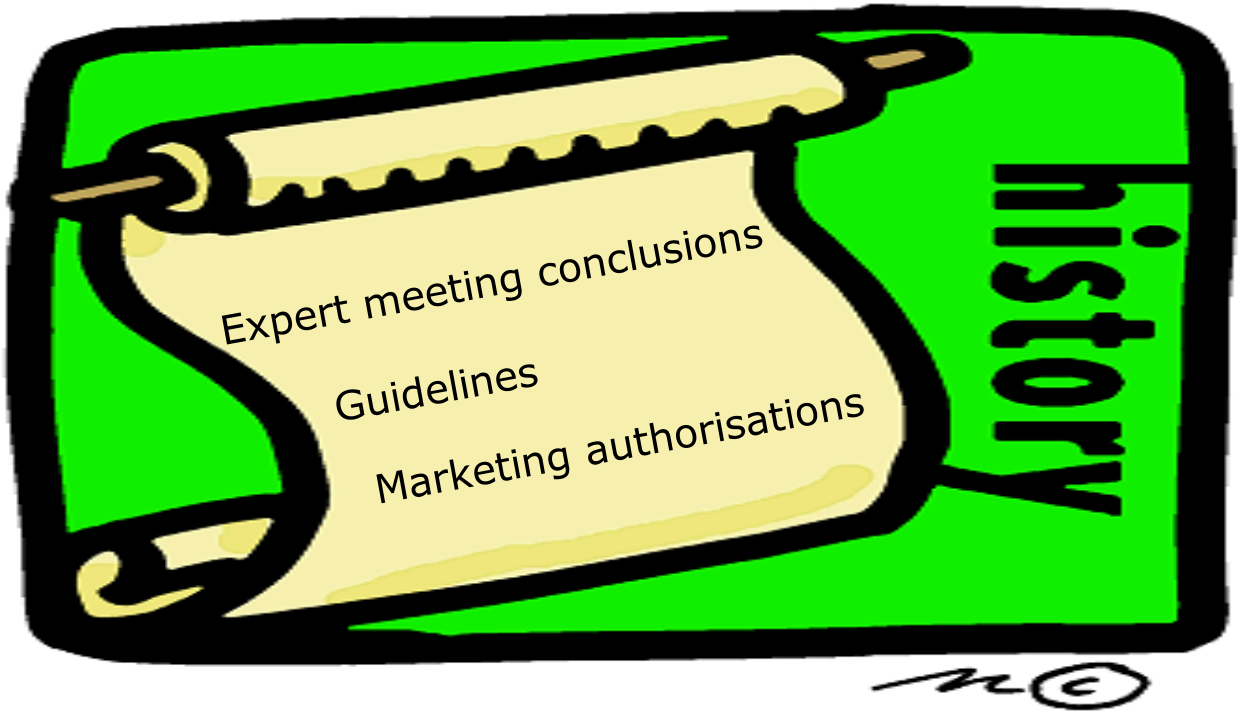
Scientific and Regulatory Management Department, EMA

Objectives for the session

- Overview of methods to support extrapolation on the basis of available efficacy safety data
- Understand the requirements for PK/PD studies
- Understand how new data can feedback into the extrapolation concept and require adaptation of the extrapolation plan

Extrapolation in JIA, IBD and psoriasis - history



EMA paediatric rheumatology expert meeting 4 December 2009

- 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.

http://www.ema.europa.eu/docs/en_GB/document_library/Other/2010/06/WC500091502.pdf

EMA paediatric rheumatology expert meeting 17 November 2010

- Extrapolation *(full)* of adult pharmacokinetic data is **not possible**. Modelling and simulation is recommended to reduce sampling burden in children but it is recognised that data are scarce in this regard.
- A standard full development with placebo-controlled randomised efficacy trial is **rarely possible**, and alternative designs may be acceptable
- The role and limits of extrapolation of efficacy need further discussion and must be addressed also within the framework of **post-marketing requirements**.

http://www.ema.europa.eu/docs/en_GB/document_library/Other/2011/03/WC500103514.pdf

EMA paediatric gastroenterology and rheumatology expert meeting, 28 June 2010

- Extrapolation of efficacy and safety from adult studies is **limited**.
- When efficacy studies are not feasible in children, the **analysis of extrapolation** of efficacy from adults **must be performed** to support paediatric development.

http://www.ema.europa.eu/docs/en_GB/document_library/Other/2011/03/WC500103480.pdf

Centrally authorised medicinal products for pJIA

- **ENBREL (entanercept) –** EMEA/H/C/000262 **– 2000**
- **HUMIRA (adalimumab) -** EMEA/H/C/000481/II/0039 **– 2008**
- **ORENCIA (abatacept) –** EMEA/H/C/000701/II/0024 **– 2010**
- **ROACTEMRA (tocilizumab) –** EMEA/H/C/000955/II/0026 **– 2013**

Paediatric studies – results

Endpoint in Part I: % of patients with JIA ACR30 response

Part I	**% of patients with JIA ACR30 response**		duration of Part I
Enbrel	74%	51/69	13 weeks
Humira	84%	144/171	16 weeks
Orencia	65%	123/190	16 weeks
RoActemra	89%	168/188	16 weeks

Endpoint in Part II: % of patients with disease flare based on JIA ACR30 criteria

Part II	**% of patients with disease flare**						
	act. subs.		**placebo**		p value	N of patients	duration of Part II
Enbrel	24%	6/25	77%	20/26	0.0002	51	16 weeks
Humira	40%	27/68	68%	44/65	0.0017	133	32 weeks
Orencia	20%	12/60	53%	32/62	0.0003	122	24 weeks
RoActemra	26%	21/82	48%	39/81	0.0035	163	24 weeks

Paediatric studies – results

Endpoint in Part I: % of patients

Part I	% of pati… JIA AC…
Enbrel	74%
Humira	84%
Orencia	65%
RoActemra	89%

Endpoint in Part … CR30 criteria

Part II	% of patient… fl…				
	act. subs.				
Enbrel	24%	6/25			
Humira	40%	27/68	6…		
Orencia	20%	12/60	5…		24 weeks
RoActemra	26%	21/82	48…	…0035 163	24 weeks

Limitations!

- infliximab?
- golimumab?
- new class?

ROACTEMRA (tocilizumab) – Paediatric dose development

ADULTS	•extrapolation was not envisaged as given by PIP → more comprehensive clinical development was employed •adult dose 8 mg/kg applied in small supportive paediatric studies
CHILDREN Small supportive study	•dose 8 mg/kg applied in Japanese MRA318JP study (19 subjects, 12 weeks)
Dose Calculation	•PK model (two-compartment) created and a higher dose (10 mg/kg) was suggested for children weighing < 30 kg
CHILDREN Pivotal study	•≥ 30 kg → 8 mg/kg •< 30 kg → 10 mg/kg **OR** 8 mg/kg for < 30 kg •Another PK model created (two-compartment) → efficacy results and PK model confirmed the choice of doses, that were later approved: 8 mg/kg for ≥ 30kg, 10 mg/kg for < 30 kg

EMA guideline for JIA, 2016

Guideline on clinical investigation of medicinal products for the treatment of juvenile idiopathic arthritis

Draft agreed by Rheumatology Immunology Working Party and PDCO	April 2014
Adoption by CHMP for release for consultation	25 April 2014
Start of public consultation	15 May 2014
End of consultation (deadline for comments)	15 November 2014
Agreed by Rheumatology Immunology Working Party	October 2015
Adopted by CHMP	19 November 2015
Date for coming into effect	1 June 2016

The proposed guideline will replace the guideline on clinical investigation of medicinal products for the treatment of juvenile idiopathic arthritis (CPMP/EWP/422/04)

Keywords	Juvenile idiopathic arthritis, Systemic JIA, Oligoarthritis, Polyarthritis, Enthesitis related arthritis, Extrapolation

6. Strategy and design of clinical trials

6.1. Extrapolation of efficacy

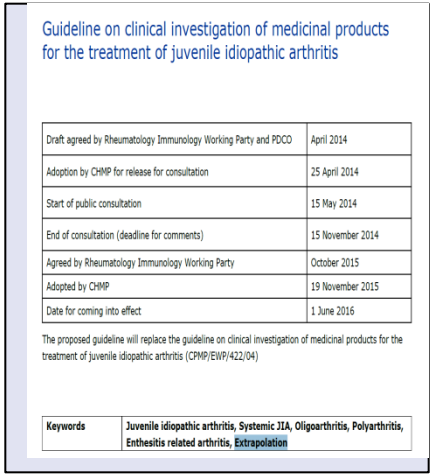
The possibility of **waiving efficacy studies** in certain subgroups of children should be considered in order to spare children from unnecessary trials, when reasonably accurate information may be obtained **by other means**.

This can be the case for example in

- well-studied pharmacological classes
- or when considerable amount of data has been collected in adults (e.g. licensed indication in one or more of the corresponding adult arthritis categories),
- or in children treated with the same medicinal product for other diseases

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/11/WC500196719.pdf

EMA guideline for JIA, 2016, ctnd.



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- Pharmacokinetic and dose finding studies in the target population **are *(always)* needed**.
- In some instances the evidence from extrapolation may obviate the need for a formal efficacy trial.
- E.g. for medicines where a clear PK-PD (pharmacokinetic/ pharmacodynamic) relationship and therapeutic window has been established in adult arthritis models, PK and dose finding studies could potentially be supported by **single arm studies**.
- The results of the extrapolation analysis, if agreed and used for marketing authorisation, would have to be supported by **post-marketing data**.

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/11/WC500196719.pdf

Approved paediatric medicines for IBD in EU

Biological treatments

Infliximab

Adalimumab (Crohn's disease only)

Conventional treatments (non-centrally authorised)

Aminosalicylates

Corticosteroids

Immunosuppressants

Efficacy of Remicade in paediatric population

CD

- **Open label study**, patients were receiving a stable dose of 6 MP, AZA or MTX and randomised to receive infliximab either at 8 or 12 week intervals
- Difference at week 30, subjects in clinical remission (CDAI score < 150 with no use of corticosteroids) were 59.6% vs 35.3% in favour of the 8-week interval group-similar results up to week 54

UC

- **Similar study**, 53% of patients receiving immunomodulator therapy
- At week 54, clinical remission, as measured by PUCAI score< 10 was in favour of the 8-week interval group: 38% vs 18% for the 12-week interval group

Delay of MA for children
(plans for completion of PIPs for non-authorised products)

Ulcerative colitis	Completion of PIP
Tofacitinib	Mar-21
Etrolizumab	Jan-24

Crohn's disease	Completion of PIP
Ustekinumab	Jun-23
Vercirnon	Jun-19
Etrolizumab	Jan-24

Global regulatory view - extrapolation in IBD

- Partial extrapolation from informative adult studies is a **necessary element** to construct a paediatric drug development program
- Studies that are keys to a paediatric development program built on a foundation of extrapolation include an initial dose-finding study that incorporates PK and preliminary efficacy assessments that support exposure-response modelling followed by a safety study that includes efficacy endpoints to explore further the exposure-response relation
- **After enough experience is accumulated, it may be possible in the future to rely on complete extrapolation instead of partial, which would make efficacy studies in children unnecessary.**
- For drugs that could be supported by complete extrapolation, **paediatric PK/dose-finding studies and safety studies would be sufficient** and yield the potential for a simultaneous adult and paediatric authorization

(JPGN 2014;58: 684–688)

Steps Toward Harmonization for Clinical Development of Medicines in Pediatric Ulcerative Colitis—A Global Scientific Discussion, Part 2: Data Extrapolation, Trial Design, and Pharmacokinetics

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See "Pediatric UC Drug Development: A GREAT Idea Now Needs a GRAND Conversation" by Rosh and Hyams on page 677 and "Steps Toward Harmonization for Clinical Development of Medicines in Pediatric UC—A Global Scientific Discussion, Part 1: Efficacy Endpoints and Disease Outcome Assessments" by Mullberg et al on page 679.

ABSTRACT

Objectives: To facilitate global drug development, the International Pediatric Inflammatory Bowel Disease Working Group (i-IBD Working Group) discussed data extrapolation, trial design, and pharmacokinetic (PK) considerations for drugs intended to treat pediatric ulcerative colitis (UC), and considered possible approaches toward harmonized drug development

Methods: Representatives from the US Food and Drug Administration, European Medicines Agency, Health Canada, and the Pharmaceuticals and Medical Devices Agency of Japan convened monthly to explore existing regulatory approaches, reviewed the results of a literature search, and provided perspectives on pediatric UC drug development based on the available medical literature.

Results: Although pediatric UC, when compared with UC in adults, has a similar disease progression and response to intervention, the similarity of the exposure-response relation has not been adequately established. Consequently, clinical endpoints should be selected to optimally assess efficacy in children. The inclusion of a placebo control in pediatric trials to assure assay sensitivity may be appropriate under limited circumstances. In clinical studies, although the drug under investigation could provide possible direct benefit, placebo treatment should present no more than a minor increase over minimal risk to children with UC.

Conclusions: Partial extrapolation of efficacy from informative adult studies may be appropriate. Placebo-controlled efficacy trials are:

Concept paper for UC guideline revision, 2014

Extrapolation of data from studies in adults to the paediatric situation:

…it is intended to evaluate whether more clear statements should be included into the guideline, as to what extent extrapolation of adult data is possible, and whether criteria for extrapolation can be defined.

Concept paper on the revision of the guideline on the development of new medicinal products for the treatment of ulcerative colitis (CHMP/EWP/18463/2006)

Agreed by Gastroenterology Drafting Group	September 2014
Adopted by CHMP for release for consultation	25 September 2014
Start of public consultation	1 October 2014
End of consultation (deadline for comments)	31 December 2014

The proposed guideline will replace the guideline on the development of medicinal products for the treatment of ulcerative colitis (CHMP/EWP/18463/2006).

Comments should be provided using this template. The completed comments form should be sent to gastroenterologydg@ema.europa.eu.

Keywords	Inflammatory bowel disease, Crohn's disease, medical treatment, clinical trials, study design, study endpoints, children, adults

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/09/WC500174135.pdf

Centrally authorised products for paediatric psoriasis

Enbrel - 2008 (from 4 y)

Humira - 2015 (from 4 y)

Stelara - 2015 (from 12 y)

Summary – Extrapolation in psoriasis

Substantial similarity of the disease (characteristics and prognosis, treatment strategies, response to immunomodulators).

Dose for CT based on serum concentrations corresponding to effective adult dose – later confirmed effective and recommended for children

Simpler studies (no withdrawal/re-treatment) were expected and accepted (Humira and Stelara respectively).

Long-term safety and effect in development necessary but accepted from other paediatric indications (Humira, requested for Stelara).

In general: with the **increase in experience** with biologicals in paediatric psoriasis the amount of **information extrapolated** from adults was **also increasing**

Product/ authorisation in PS (subjects)	Information from paediatric trials but assessment referred to adult as supportive	Information in AR ONLY available from adult trials.	Information in AR available from other paediatric populations	Ongoing or requested post authorisation studies
Enbrel Adult -2004 (112+652+583) Paed -2008 (211)	Complex study – equivalent to adults PK Efficacy vs PBO Safety	Not referred to.	PK in pJIA Safety in pJIA	Long-term extension (safety)
Humira Adult -2007 (1212+271) Paed-2015 (114)	Complex study – similar to adults PK Efficacy vs MTX Safety and immunogenicity	Efficacy vs PBO Long term safety (over 1 year). Post marketing experience.	PK in pJIA, ERA, CD Safety in pJIA, ERA, CD Immunogenicity in pJIA, ERA, CD PK and safety in children 4-6 yo	None
Stelara Adult -2009 (766+1230) Paed-2015 (110)	Simple study – more information from adults PK Efficacy vs PBO Safety and immunogenicity	Duration of response after discontinuation. Effects of withdrawal and retreatment. Long term safety (over 1 year). Post marketing experience.	None	CHMP requested a PAESS to evaluate long term safety and the effect on growth and development (RMP)

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- Understand the requirements for PK/PD studies
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