EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

The European Medicines Agency (EMA) Perspective: Activities and Overview…

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An agency of the European Union

Declaration of conflict of interest

No interest to declare.

The views and opinions expressed in the following PowerPoint slides are those of the individual presenter and should not be attributed to the European Medicines Agency.

Outline

- Introduction of EMA
- Review of authorised products for IBD and IBS (trials, indications, endpoints)
- Biosimilarity
- Guidelines – current and under development
- Paediatric development
- Extrapolation
- Collaboration

Update on EMA

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Remicade – infliximab: 1st anti-TNFα monoclonal antibody authorised in the EU

- Remicade approved in 1999 for:
  - treatment of severe, active Crohn's disease, in patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/**or** an immunosuppressant
  - treatment of fistulising Crohn's disease, in patients who have not responded despite a full and adequate course of therapy with conventional treatment
- Various extensions to the GI indications:
  - 2006: treatment of patients with moderately to severely active ulcerative colitis
  - 2007: treatment of severe active Crohn's disease in children aged 6 to 17 years
  - 2011: treatment of moderately to severely active Crohn's disease
  - 2012: treatment of severely active ulcerative colitis, in paediatric patients aged 6 to 17 years, who have had an inadequate response to conventional therapy including corticosteroids and 6-MP or AZA

Humira- adalimumab, 2nd anti-TNFα monoclonal antibody in EU

- Approved in 2003 for rheumatoid arthritis
- Treatment of adult patients with severe active Crohn's disease approved in 2007
- In 2012 3 GI extension of indications:
  - moderate to severe active ulcerative colitis
  - moderate to severe active Crohn's disease
  - severe active Crohn's disease in paediatric patients (6 to 17 years of age)

Simponi- golimumab : 3rd anti-TNFα monoclonal antibody for IBD in EU

- Approved in 2009 for rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis
- 2013: moderate to severe active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy

Entyvio- vedolizumab : anti-α4β7 integrin monoclonal antibody

- Approved in EU in 2014 for patients with moderately to severely active ulcerative colitis/Crohn's diseases who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNFα) antagonist

Endpoints used for pivotal studies - Crohn's disease

Clinical Response

Reduction in CDAI ≥ 25% and ≥ 70 points

Enhanced clinical response:

An absolute decreases ≥ 100-point decrease in CDAI score from baseline

Clinical Remission

CDAI < 150

Sustained Steroid-Free Remission

CDAI < 150 at both week 30 and 54 and not receiving corticosteroids in the 3 months prior to week 54 among patients who were receiving corticosteroids at baseline

Number of fistulas

Endpoints used for pivotal studies - ulcerative colitis

Clinical response

Reduction in total Mayo score ≥3 and ≥30% plus decrease in sub-score for rectal bleeding ≥ 1 or an absolute sub-score of 0 or 1

Clinical remission

Total Mayo score of ≤2 and no individual sub-score >1

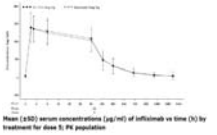
Mucosal healing

Absolute endoscopy sub-score of 0 or 1

Remsima (and Inflectra): First monoclonal biosimilar authorised in the EU

- Authorised in 2013 with clinical data on ankylosing spondylitis and rheumatoid arthritis
- Through biosimilarity efficacy extrapolated to GI indications

PK equivalence study in ankylosing spondylitis (N=250)



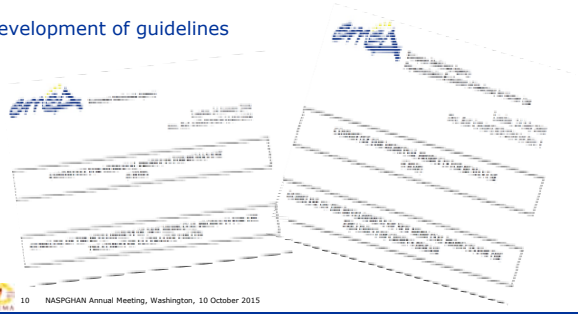
Mean (±SD) serum concentrations [µg/ml] of infliximab vs time (h) by treatment for dose 5; PK population

Safety and efficacy study in rheumatoid arthritis (N=606)

Primary endpoint: ACR20 at Week 30

Treatment arm	n/N (%)	Estimate of Treatment Difference	95 % CI of Treatment Difference
All randomised			
Remsima	184/302 (60.9)	0.02	-0.06; 0.10
Remicade	178/304 (58.6)		
Per protocol			
Remsima	182/248 (73.4)	0.04	-0.04; 0.12
Remicade	175/251 (69.7)		

Development of guidelines



Development of scientific guidelines for IBD

- **History**
  - Concept papers on revision of the paediatric parts agreed by GDG: September 2012
  - Concept papers adopted by CHMP for 3 months public consultation: 18 October 2012
  - Start of public consultation: 14 November 2012
  - End of consultation (deadline for comments): 15 February 2013
- **Need for revision**
  - Based on the received comments from clinical experts, learned societies (ESPGHAN and ECCO), the **iIBD activities** in the background GDG/CHMP decided to reopen the public consultation for a **complete GL update**. The CPs were revised and readopted for public consultation.
- **Timelines**
  - Updated concept papers 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
  - Publication of draft guidelines for 6 months public consultation (planned): **second half of 2015**

Main issues

- Primary endpoint – morphological vs clinical score (PRO?)
- Concept of induction and maintenance of remission
- Paediatric studies
  - need
  - timing (in relationship to adult development and authorisation)
  - extrapolation from adults
  - use of endoscopy and placebo
  - dose finding
- Post-authorisation studies/patient registry

IBS and constipation GL

Name	Effective from
Points to consider on the evaluation of medicinal products for the treatment of irritable bowel syndrome	2003
Evaluation of medicinal products for the treatment of irritable bowel syndrome	2015
Clinical investigation of medicinal products for the treatment of chronic constipation	2016

Paediatric IBD – differences

- Disease presentation not different but trend to more frequent panenteric presentation in children (Vernier-Massouille et al Gastro 2008, Van Limbergen J et al. Gastro 2008, De Bie C IBD 2013, Israeli et al CGH 2014)
- Possibly more severe disease evolution (Lazarev M et al Am J Gastro 2013, Vernier-Massouille et al Gastro 2008, Pigneur et al IBD 2009, Lovasz B et al WJG 2013, Van Limbergen J et al Gastro 2008)
- Differences in PK seen between children and adolescents treated with the same dose/kg of infliximab (Adedokun et al), is this the reason for difference in response between children and adolescents (Kelsen JR et al, JPGN 2014)?

Approved paediatric medicines 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

Efficacy of Humira in Crohn's disease in paediatric patients

- **OL – clinical response week 4 :**
  - Approximately 80% in clinical response (reduction in PCDAI score of at least 15 points)
  - Clinical remission, defined as PCDAI score ≤ 10

Population	Low dose (10 or 20 mg	High dose (20 or 40 mg)	Observ diff
Total	27/95 (28.4%)	36/93 (38.7%)	10 %
No infliximab	19/54 (35.2%)	29/51 (56.9%)	22%

  - Remission week 26 - internal comparison
- **External comparison with Humira adults CD studies**
  - Results for primary endpoint at least of similar magnitude as in adults

Agreed Paediatric Investigation Plans

Crohn's disease

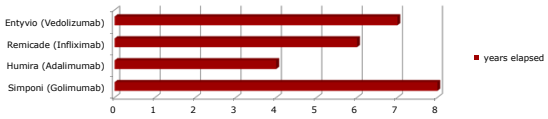
- Ustekinumab
- Adalimumab
- Infliximab
- Vedolizumab
- Vercirnon
- Etrolizumab

Ulcerative colitis

- Golimumab
- Adalimumab
- Infliximab
- Tofacitinib
- Vedolizumab
- Prednisolone/mesalazine
- Etrolizumab

Delay of MA for children from MA in adults (authorised products)

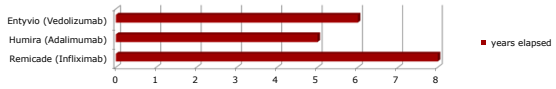
Ulcerative colitis



IBD	adults	paediatric	time (years) elapsed
Ulcerative colitis			
Simponi (Golimumab)	Jul-13	Sep-21	8
Humira (Adalimumab)	Mar-12	Dec-16	4
Remicade (Infliximab)	Feb-06	Feb-12	6
Entyvio (Vedolizumab)	May-14	Sep-21	7

Delay of MA for children from MA in adults (authorised products)

Crohn's disease



IBD	adults	paediatric	time (years) elapsed
Cohn's disease			
Remicade (Infliximab)	Aug-99	May-07	8
Humira (Adalimumab)	Jun-07	Nov-12	5
Entyvio (Vedolizumab)	May-14	Sep-20	6

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

Ulcerative colitis	Completion of PIP
Tofacitinib	Mar-21
Prednisolone/mesalazine	Mar-16
Etrolizumab	Jan-24

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

Extrapolation

Extending information and conclusions available from studies in one or more subgroups of the patient population (source population), or in related conditions or with related medicinal products, **to make inferences for another subgroup of the population** (target population), or **condition** or **product**, thus **reducing the need to generate additional information** (types of studies, design modifications, number of patients required) to reach conclusions for the target population, or condition or medicinal product.

On-going extrapolation activities

- EMA Extrapolation Reflection Paper
- Extrapolation Concept Paper (2012)
- EMA experts workshop September 2015
- EMA industry workshop April 2016 (TBC)
- EMA Extrapolation Group
- Handling of extrapolation in paediatric development

Extrapolation in pJIA

	No of studies	No of patients	Dose in paediatric population
Enbrel (etanercept)			
adults	4	1054	approximately similar to the adult dose
children	1	51	
Humira (adalimumab)			
adults	4	2070	calculated with DuBois and DuBois equation
children	1	133	
Orencia (abatacept)			
adults	5	2944	approximated weight-tiered dose as in adults
children	1	122	
RoActemra (tocilizumab)			
adults	5	4186	results of small PK study suggested 2 possible doses, both investigated in main study
children	2	163 (19 in PK)	
Design of the paediatric study	randomised-withdrawal		1. open-label active treatment → response assessment
			2. DB responders randomised to continue on treatment or receive placebo up until disease flare or defined period

Extrapolation in pJIA

! Partial extrapolation – in a non-structured way

Extrapolation in IBD

Paed. Crohn's disease	No of studies	No of patients
Remicade (infliximab)		
adults	5	1589
children	1	99
Humira (adalimumab)		
adults	3	1478
children	1	188
Paed. ulcerative colitis	**No of studies**	**No of patients**
Remicade (infliximab)		
adults	2	728
children	1	45

Conclusion

- Discussions on extrapolation concept in IBD are currently ongoing
- These products are used regardless the authorisation in paediatric population
- However, not everything can be extrapolated
- Dose-finding and safety studies in children should be encouraged
- The same outcome measures should be in place for both adult and paediatric population
- To be solved in the future:
  - Need to further develop algorithm(s) linking degree of similarity with reduction in data requirement
  - How to quantify the uncertainty of extrapolation assumptions?
  - How to validate assumptions in the extrapolation concept?
  - How to analyse and report post-authorisation data to support extrapolation?

Collaboration network

Scope:

Transparent interaction with all stakeholders (health care professionals, patient organisations, learned societies and academia

- to use state-of-art knowledge and expertise in the field in our evaluations and recommendations
- to support research and innovation to stimulate the development of better medicines

Adults:

UEG, ECCO

Paediatrics:

ESPGAN, P-ECCO, PIBDnet

Patients

EFCCA

Regulators: IIBD, GREAT, FDA, PMDA, HC

i-IBD group

- Convened in 2012
- EMA, FDA, Health Canada, and PMDA

The members of this group

- Considered reasons for differences in their acceptance of efficacy endpoints and disease activity indices used in paediatric IBD
- Reviewed the available literature, and developed opinions regarding approaches for evaluating outcomes in paediatric IBD trials.

IBD workshop

- Scope
  - Expert consultation in the process of development of the guidelines
  - Define way forward for paediatric development
- Participants
  - Regulators (EMA, FDA)
  - Invited clinicians/academia representatives from Europe and North America
  - Invited patient representatives
  - Industry representatives nominated by professional organisations (EFPIA, EuropaBio, EUCOPE)
- Date: 29th June 2015 at EMA, London
- Documents and broadcasting record

European Medicines Agency workshop on the development of new medicinal products for the treatment of ulcerative colitis and Crohn's disease

Thank you for your attention

Further information

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