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

Declaration of conflict of interest

No interest to declare.

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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 ≥ 20 points

Enhanced clinical response:
An absolute decrease ≥ 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

<table>
<thead>
<tr>
<th>Treatment arm</th>
<th>Estimate of Treatment Difference</th>
<th>95% CI of Treatment Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remsima</td>
<td>0.02</td>
<td>-0.06; 0.10</td>
</tr>
<tr>
<td>Remicade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per protocol</td>
<td>0.04</td>
<td>-0.04; 0.12</td>
</tr>
<tr>
<td>Remsima</td>
<td>0.06</td>
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</table>

PK equivalence study in ankylosing spondylitis (N=250) Safety and efficacy study in rheumatoid arthritis (N=606)

Development of guidelines

- History
  - Concept papers on revision of the paediatric parts agreed by IGIDC: September 2012
  - Concept papers adopted by CHMP for 3 months public consultation: 16 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 IBD 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

Development of scientific guidelines for IBD
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

Paediatric IBD – differences

- Differences in PK seen between children and adolescents treated with the same dose/kg of infliximab (Aseunsk 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-MS, 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
  • 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
- Verciron
- Etrolizumab

**Ulcerative colitis**
- Golimumab
- Adalimumab
- Infliximab
- Tofacitinib
- Vedolizumab
- Prednisolone/mesalazine
- Etrolizumab

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

**Ulcerative colitis**

<table>
<thead>
<tr>
<th>IBD</th>
<th>Adults Approval</th>
<th>Pediatric Approval</th>
<th>Time (years elapsed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simponi (Golimumab)</td>
<td>Jul-13</td>
<td>Sep-21</td>
<td>8</td>
</tr>
<tr>
<td>Humira (Adalimumab)</td>
<td>Mar-12</td>
<td>Dec-16</td>
<td>4</td>
</tr>
<tr>
<td>Remicade (Infliximab)</td>
<td>May-06</td>
<td>Feb-12</td>
<td>6</td>
</tr>
<tr>
<td>Entyvio (Vedolizumab)</td>
<td>May-14</td>
<td>May-21</td>
<td>7</td>
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**Crohn’s disease**

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<tr>
<td>Remicade (Infliximab)</td>
<td>Aug-99</td>
<td>May-07</td>
<td>8</td>
</tr>
<tr>
<td>Humira (Adalimumab)</td>
<td>Jun-07</td>
<td>Nov-12</td>
<td>5</td>
</tr>
<tr>
<td>Simponi (Golimumab)</td>
<td>May-15</td>
<td>Sep-20</td>
<td>5</td>
</tr>
</tbody>
</table>
Delay of MA for children (plans for completion of PIPs for non-authorised products)

<table>
<thead>
<tr>
<th>Ulcerative colitis Completion of PIP</th>
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<tbody>
<tr>
<td>Tofacitinib</td>
<td>Mar-21</td>
<td></td>
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<tr>
<td>Prednisolone/mesalazine</td>
<td>Mar-16</td>
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</tr>
<tr>
<td>Extralizumab</td>
<td>Jan-24</td>
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<th>Crohn’s disease Completion of PIP</th>
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<tr>
<td>Ustekinumab</td>
<td>Jun-23</td>
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</tr>
<tr>
<td>Vedolizumab</td>
<td>Jun-19</td>
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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
<table>
<thead>
<tr>
<th>Drug</th>
<th>No of studies</th>
<th>No of patients</th>
<th>Dose in paediatric population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enbrel (etanercept)</td>
<td>adults: 4, children: 1</td>
<td>adults: 1054, children: 91</td>
<td>approximately similar to the adult dose for adults, calculated with DuBois and DuBois equation for children</td>
</tr>
<tr>
<td>Orencia (abatacept)</td>
<td>adults: 4, children: 1</td>
<td>adults: 2666, children: 122</td>
<td>approximated weight-related dose as in adults</td>
</tr>
<tr>
<td>RoActemra (tocilizumab)</td>
<td>adults: 5, children: 2</td>
<td>adults: 4556 (18.6 kg), children: 182 (13.5 kg)</td>
<td>results of small PK study suggested 2 possible doses, both investigated in main study</td>
</tr>
</tbody>
</table>

**Design of the paediatric study**

1. Randomised - withdrawal
2. All 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**

<table>
<thead>
<tr>
<th>Disease</th>
<th>No of studies</th>
<th>No of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humira (adalimumab)</td>
<td>adults: 3, children: 1</td>
<td>adults: 1470, children: 100</td>
</tr>
<tr>
<td>Entyvio (resilizumab)</td>
<td>adults: 2, children: 1</td>
<td>adults: 726, children: 45</td>
</tr>
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</table>
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, E-ECGO, 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 (ETPFA, 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

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### Thank you for your attention