PEDiatric Studies Conducted Under BPCA and prea

The Pediatric Rheumatology Collaborative Study Group

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Introduction

- Pediatric Rheumatology Collaborative Study Group (PRCSG) founded in 1973
- Consortium of 148 board certified pediatric rheumatologists at 90 academic clinical pediatric rheumatology centers in the United States, Puerto Rico and Canada
- 40 trials of all phases in children with Juvenile Idiopathic Arthritis (JIA)
- Studies supported primarily by industry but also NIH, FDA Orphan Drugs, Arthritis Foundation
Background

• Juvenile Idiopathic Arthritis (JIA) most common rheumatic disease of childhood but prevalence is only 1/1000 children
• JIA has 7 subtypes but only 2-3 subtypes similar enough to adult RA to work for the BPCA
• Convergence of BPCA and proliferation of biologics in rheumatology have completely revolutionized the care of children with arthritis
• Rapidity, extent and persistence of clinical improvement able to be realized for over 80% of children with the types of JIA influenced by BPCA driven trials is nothing less than astounding but only 40-45% demonstrate complete control of the disease
• Ability to comprehensively address safety issues of biologic agents under current BPCA is limited
Etanercept in Polyarticular Forms of Juvenile Idiopathic Arthritis

% Patients

Years of Treatment

- ACR Pedi 30
- ACR Pedi 50
- ACR Pedi 70
- ACR Pedi 90
- ACR Pedi 100
Effect of etanercept on VAS, CHAQ and the Child Health Questionnaire scores
## Pediatric Rheumatology Biologic Trials in Last 15 years

<table>
<thead>
<tr>
<th></th>
<th>Polyarticular JIA</th>
<th>Systemic JIA</th>
<th>Pediatric SLE</th>
<th>Pediatric Systemic Vasculitis</th>
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</thead>
<tbody>
<tr>
<td>Etanercept</td>
<td>BPCA</td>
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<tr>
<td>Infliximab</td>
<td>BPCA</td>
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<tr>
<td>Adalimumab</td>
<td>BPCA</td>
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<tr>
<td>Abatacept</td>
<td>BPCA</td>
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<tr>
<td>Golimumab</td>
<td>BPCA</td>
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<tr>
<td>Tocilizumab</td>
<td>BPCA</td>
<td>EMA</td>
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<tr>
<td>Canakinumab</td>
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<td>EMA</td>
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<tr>
<td>Rilonocet</td>
<td></td>
<td>Orphan Drug</td>
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<tr>
<td>Belimumab</td>
<td></td>
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<td>EMA</td>
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<tr>
<td>Rituximab</td>
<td></td>
<td></td>
<td></td>
<td>EMA</td>
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# Pediatric Rheumatology Drug Trials in Last 15 years

<table>
<thead>
<tr>
<th></th>
<th>Adolescent Fibromyalgia</th>
<th>JIA</th>
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<tbody>
<tr>
<td>Celebrex</td>
<td></td>
<td>PREA</td>
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<tr>
<td>Meloxicam</td>
<td></td>
<td>PREA</td>
</tr>
<tr>
<td>Milnacipran</td>
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<td>BPCA</td>
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<tr>
<td>Leflunomide</td>
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<td>PREA</td>
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</table>
Safety Surveillance

- Under BPCA the Phase III trials generally involve 100-200 subjects with a pediatric rheumatic disease.
- The Phase IV study will include 300-500 subjects followed for up to 10 years but only a small proportion will remain on the same biologic for 10 years.
- To date, all registries are drug specific not disease specific.
  - Not large enough to detect rare events.
  - Limits ability to distinguish drug vs. class effect.
  - Not able to detect late toxicity with any reliability.
- BPCA does not contain language to require sufficient safety studies or to endorse/require consolidated drug safety registries in children.
# Numbers of Patients Needed to Detect Adverse Events of a Given Frequency

Number of Persons Required to Observe at Least One Occurrence of an Adverse Event (AE)

*Probability of observing at least one AE*

<table>
<thead>
<tr>
<th>Frequency of AE</th>
<th>95%</th>
<th>90%</th>
<th>85%</th>
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<tbody>
<tr>
<td>1 in 100</td>
<td>300</td>
<td>231</td>
<td>190</td>
</tr>
<tr>
<td>1 in 500</td>
<td>1,498</td>
<td>1,151</td>
<td>949</td>
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<tr>
<td>1 in 1,000</td>
<td>2,996</td>
<td>2,303</td>
<td>1,898</td>
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<td>1 in 5,000</td>
<td>14,979</td>
<td>11,513</td>
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<td>1 in 10,000</td>
<td>29,958</td>
<td>23,026</td>
<td>18,972</td>
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<td>1 in 20,000</td>
<td>59,915</td>
<td>46,052</td>
<td>37,943</td>
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<tr>
<td>1 in 50,000</td>
<td>149,787</td>
<td>115,130</td>
<td>94,856</td>
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<tr>
<td>1 in 100,000</td>
<td>299,574</td>
<td>230,259</td>
<td>189,712</td>
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</table>
Ongoing Challenges

• Obtaining PK data included in BPCA but critical to obtain the data prior to or very early in Phase III Trial
• Satisfying BPCA requirements vs. FDA label indication for pediatric disease
• BPCA does not apply to adult orphan disease applications and thus no pediatric studies required
• BPCA does not address pediatric focused formulations
  • Very costly to discard biologic agents
  • Accuracy of dosing
  • Redosing from same syringe raises safety issues
• Testing of 4th or more agent in class with known efficacy
  • Current BPCA has sufficient latitude to allow FDA to adjust efficacy aspects of testing and limit to PK and safety issues
Ongoing Challenges

• EMA since 2007 has had the Pediatric Regulation
  • Requires development of PIP much earlier in drug development
  • Covers orphan disease indications
  • Requires addressing pediatric focused formulations
  • Policy supports development of a consolidated safety registry
• In rare pediatric diseases, BPCA and EMA Pediatric Regulation efficacy needs to be addressed with a single trial
  • Need to think and be able to coordinate efforts globally from the very beginning
  • Requires communication between FDA and EMA much earlier than usual for FDA
  • Single trial must serve for approval in both agencies otherwise children lose out
Conclusions

- BPCA has been enormously impactful for performance of trials of biologics in children with JIA which have lead to tremendous gains in outcomes for these children
- PREA is helpful for study of drugs in children but less impactful than BPCA
- Other rheumatic diseases affecting children also need to be studied
- Studies of TNF, IL-1, and IL-6 to date but many other biologic targets need to be studied
Conclusions

• Much work remains to improve the outcomes for children with rheumatic diseases
• An international community of pediatric rheumatologists is poised and committed to doing this work
• BPCA and PREA are critically important tools to allow this work to be done