Paediatric Rheumatology
International Trials Organization (PRINTO) experience with trials in paediatric rheumatology

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Overview

- PRINTO description
- Concerns in pediatric rheumatic diseases (PRD)
- Lessons learned from trials in JIA
- Proposal and conclusions
Lack of controlled trials in children

- Children used same therapies as per adults with rheumatoid arthritis
- Dosing “adjusted” according to weight/BSA
- Expert opinion/single centre efficacy studies
- Pharma companies NOT interested
  - Small market
  - Necessity to have large networks
  - Children specific formulations, outcome
2000: a radical change

- 1999 FDA “pediatric rule”
- 2007 EMA and EU parliament: pediatric legislation
- Pediatric networks
  - PRCSG: USA
  - PRINTO: Europe and ROW (>50 countries)
- PRINTO/PRCSG response to therapy standardisation
- Introduction of biologic agents
“...to foster, facilitate, and conduct high quality research in the field of paediatric rheumatology...”

PRINTO bylaws

Italy, May 1996
PRINTO

- National coordinators: 52 countries
- Centres: 308
- Official members: 600
- Mailing list: 1500 physicians
PRINTO members (52 countries)
PRINTO bottom up approach

- Standardized criteria to evaluate response to therapy in JIA, JSLE and JDM
  - ACR pediatric criteria in JIA (FDA, EMEA, ACR)
  - Expertise in consensus techniques
- Non for profit clinical trials (JIA, JDM, JSLE)
- Standardised information to families
- Training to young researchers
- Collaboration with pharma companies
- Main source of funding European Union, AIFA
## PRINTO no profit studies

<table>
<thead>
<tr>
<th>Condition</th>
<th>Western Europe</th>
<th>Eastern Europe</th>
<th>Latin America</th>
<th>North America</th>
<th>Other</th>
<th>Total</th>
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<tbody>
<tr>
<td>MTX</td>
<td>492</td>
<td>55</td>
<td>66</td>
<td>8</td>
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<td>633</td>
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<td>QOL</td>
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<td>1,388</td>
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<tr>
<td>JSLE</td>
<td>243</td>
<td>102</td>
<td>150</td>
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<td>JDM</td>
<td>162</td>
<td>37</td>
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<td>353</td>
<td>260</td>
<td>6</td>
<td>181</td>
<td>1,399</td>
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<tr>
<td>JDM</td>
<td>53</td>
<td>7</td>
<td>31</td>
<td>1</td>
<td>2</td>
<td>94</td>
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</tbody>
</table>
CHAQ (functional ability) and CHQ (quality of life)

EU grant (BMH4-983531 CA)

Translation and cross-cultural adaptation of CHAQ and CHQ in 32 languages with 6,443 patients collected

(Argentina, Austria, Belgium, Brasil, Bulgaria, Chile, Croatia, Czech Republic, Denmark, Finland, France, Georgia, Germany, Greece, Hungary, Israel, Italy, Korea, Latvia, Mexico, Netherlands, Norway, Portugal, Poland, Russia, Slovakia, Spain, Sweden, Switzerland, Turkey, United Kingdom, Yugoslavia)
Information on paediatric rheumatic diseases

To be listed on this website please download the SURVEY
For any inaccuracy CONTACT us
LINKS to related websites

Ruperto Annals Rheum Dis. 2005
Concerns in ped rheumatic diseases (PRD)

- How to define *response to therapy*
- Need to limit *time on placebo* (chronic disease)
- What are *acceptable control* groups?
- PRD are rare (*feasibility*) and therefore we need
  - a) to obtain *as much information as possible from every pts*
  - b) design trials to be as *efficient* as possible (low sample size).
- What is the standard of care?
- What we are interested in?
  - short-term
  - *long-term outcomes* (especially for safety/remission)
JIA core set and response criteria

◆ JIA core set
  1. Physician global assessment of overall disease activity
  2. Parent or patient global assessment of overall well-being
  3. Functional ability (CHAQ)
  4. Number of joints with active arthritis
  5. Number of joints with limited range of motion
  6. Index of inflammation: ESR or CRP
  7. ± fever (for systemic JIA)

◆ ACR Criteria: 3/6 core set variables improved ≥ 30% (50%, 70%, 90%, 100%) with no more than 1/6 worsened by >30%

◆ FDA and EMA accepted

Giannini, Ruperto et Al. Arthritis Rheum 1997
JIA inactive disease/clinical remission

- Inactive disease
  - No joints with active arthritis
  - No fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributable to JIA
  - No active uveitis (to be defined)
  - Normal ESR or CRP
  - No disease activity according to MD evaluation

- Clinical remission
  - On medication for 6 months and
  - off medication for 12 months

Wallace…Ruperto for CARRA/PRINTO/PRCSG. J Rheumatol 2004
First approach

- Non-steroidal anti inflammatory drugs
- Intraarticular steroid injections (triamcinolone acetonide)
JIA Therapy 2/2

*Second line drugs*

Methotrexate

↓

Biologic agents (Anti-TNF)

↓

Another anti-TNF **OR** anti CTL4-Ig
JIA Classification (Durban 1997)

1. **Systemic** 15%
2. **Oligoarthritis:** 50%
   - a) persistent
   - b) extended
3. **Polyarthritis (FR positive)** 3%
4. **Polyarthritis (FR negative)** 17%
5. **Psoriatic arthritis** 5%
6. **Arthritis/enthesitis** 10%
7. **Other**
   Arthritis in the first 6 months of the disease
   Oligoarthritis: \( \leq 4 \) joints
   Polyarthritis: \( >4 \) joints
Methotrexate (academic studies)

- 10 mg/m²/week oral

- 15 mg/m²/week (max 20 mg) parenteral
  - Ruperto et al for PRINTO *Arthritis Rheum* 2004

- Time to MTX withdrawal
  - Foell et al for PRINTO. *JAMA* 2010
The paradox of MTX

- Mainstream for treatment, proven efficacy and safety
- Used in combination in several biologic agents trials (infliximab, adalimumab etc)
- No interest from companies (off patent, low cost)
- Not approved for use in JIA
- Etanercept patients are required to fail MTX!!
- PRINTO dossier submitted to AIFA to approve JIA indication (and reimbursement) based on literature data
Concerns in ped rheumatic diseases (PRD)

• How to define *response to therapy*
• Need to limit *time on placebo* (chronic disease)
• What are *acceptable control* groups?
• PRD are rare (*feasibility*) and therefore we need
  • a) to obtain *as much information as possible from every pts*
  • b) design trials to be as *efficient* as possible (low sample size).
• What is the standard of care?
• What we are interested in?
  • short-term
  • *long-term outcomes* (especially for safety/remission)
BLINDED WITHDRAWAL STUDIES

All subjects receive experimental therapy for several months.

**ADVANTAGES**
- Contains a *placebo – controlled* segment
- Very user-friendly
- Allows maximum amount of info for each subject

**DISADVANTAGES**
- Estimate
  - response rate in I open segment.
  - time to “flare”
- Subjects are not virgins to experimental
- Biased towards responders
- Limited patient yrs on placebo
- Non-traditional outcomes (e.g., time to or # failures)
JIA core set and **flare** criteria

**JIA core set**

1. Physician global assessment of overall disease activity
2. Parent or patient global assessment of overall well-being
3. Functional ability (CHAQ)
4. Number of joints with active arthritis
5. Number of joints with limited range of motion
6. Index of inflammation: ESR or CRP

**ACR criteria:** 3/6 core set variables improved $\geq 30\%$ (50%, 70%, 90%, 100%) with no more than 1/6 worsened by $>30\%$

**Flare criteria:** 3/6 core set variables *worsened* $\geq 30\%$ with no more than 1/6 *improved* by $\geq 30\%$

Brunner et Al. J Rheumatol 2002
Liaisons with pharma companies

- Protocol and CRF drafting, site selection, training, monitoring, analysis, reporting
- NSAIDs: meloxicam, rofecoxib
- Biologic agents: etanercept (approved), infliximab, adalimumab, CTL4 Ig, anti IL-1, anti IL-6

- Starting point: FDA and EU legislation
## Registrative trials

<table>
<thead>
<tr>
<th></th>
<th>Western Europe</th>
<th>Eastern Europe</th>
<th>Latin America</th>
<th>North America</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Meloxicam</strong></td>
<td>130</td>
<td>94</td>
<td></td>
<td></td>
<td>224</td>
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<tr>
<td><strong>Infliximab</strong></td>
<td>61</td>
<td>10</td>
<td>28</td>
<td>11</td>
<td>110</td>
</tr>
<tr>
<td><strong>Adalimumab</strong></td>
<td>57</td>
<td>26</td>
<td></td>
<td>88</td>
<td>171</td>
</tr>
<tr>
<td><strong>CTL4-Ig</strong></td>
<td>75</td>
<td></td>
<td>108</td>
<td>31</td>
<td>214</td>
</tr>
<tr>
<td><strong>Systemic JIA</strong></td>
<td>54</td>
<td>5</td>
<td>22</td>
<td>24</td>
<td>112</td>
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</table>
### Biologic agents

<table>
<thead>
<tr>
<th>Category</th>
<th>Active principle</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF-α inhibitors</td>
<td>Etanercept, Infliximab, Adalimumab</td>
</tr>
<tr>
<td>CTLA4-Ig: inhibitor activation T lymphocytes</td>
<td>Abatacept</td>
</tr>
<tr>
<td>Anti IL-1</td>
<td>Anakinra, canakinumab, rilonacept</td>
</tr>
<tr>
<td>Anti IL-6</td>
<td>Tocilizumab</td>
</tr>
</tbody>
</table>
Etanercept in JIA: study design

**Phase 1**
- Open label
- Months: 1, 2, 3
- Randomization of responders

**Parte 2**
- Double-blind
- Months: 4, 5, 6, 7
- ENBREL (n=69)
- Placebo (n=26)
- ENBREL (n=25)

Randomization of the responders

Lovell DJ et al for PRCSG. NEJM 2000;342:763-9
Etanercept and JIA

% Responders vs. Months

- Open label
- Double-blind
- Open label extension

Etanercept
Placebo
Several safety registries

- France: Quartier P. et al. (Arthritis and R 2003)
- Italy: Ruperto et al (PRES 2005)
- The BSPAR Biologics registry on adverse events to etanercept (*T Southwood*)
- USA: Giannini et al A&R 2009
FDA black box warning

- A possible increased risk of lymphoma and other malignancies in children treated with anti-TNF agents, although the level of evidence is still not sufficient to prove this link.
  - 9 cases in registries (mainly lymphomas)
  - FDA Post-marketing 48 pediatric malignancies (20 in JIA, 28 in IBD), after a median of 2.5 years (range 1 month-7 years), 50% lymphomas, most while using other drugs (steroids, azathioprine, MTX, mercaptopurine)
## Infliximab safety

<table>
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<tr>
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<th>Placebo + MTX</th>
<th>3 mg/kg</th>
<th>6 mg/kg</th>
</tr>
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<tbody>
<tr>
<td>Total adverse events (AE)</td>
<td>49 (81.7%)</td>
<td>58 (96.7%)</td>
<td>54 (94.7%)</td>
</tr>
<tr>
<td>Discontinuation for AE</td>
<td>1 (1.7%)*</td>
<td>2 (3.3%)</td>
<td>5 (8.8%)</td>
</tr>
<tr>
<td>Infusional reaction, shock</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>3 (5.0%)</td>
<td>19 (31.7%)</td>
<td>5 (8.8%)</td>
</tr>
<tr>
<td>Infections</td>
<td>28 (46.7%)</td>
<td>41 (68.3%)</td>
<td>37 (64.9%)</td>
</tr>
<tr>
<td>Serious infections</td>
<td>2 (3.3%)</td>
<td>5 (8.3%)</td>
<td>1 (1.8%)</td>
</tr>
<tr>
<td>No. infusion with infusion reaction</td>
<td>6 (3.4%)</td>
<td>46 (9.1%)</td>
<td>13 (4.2%)</td>
</tr>
<tr>
<td>No. pts with infusion reaction</td>
<td>5 (8.3%)</td>
<td>21 (35.0%)</td>
<td>10 (17.5%)</td>
</tr>
<tr>
<td>ANA</td>
<td>0/30 (0%)</td>
<td>8/54 (14.8%)</td>
<td>1/46 (2.2%)</td>
</tr>
<tr>
<td>Anti DNA</td>
<td>0/30 (0%)</td>
<td>7/54 (13.0%)</td>
<td>0/46 (0%)</td>
</tr>
</tbody>
</table>

* death

Ruperto, Lovell for PRINTO/PRCSG. A&R 2007
Adalimumab

Open label

Extension phase

Lovell, Ruperto for PRINTO/PRCSG NEJM 2009
Abatacept

Trial design in JIA

- **Parallel design**
  - Meloxicam (Ruperto for PRINTO A&R 2004)
  - Infliximab (Ruperto for PRINTO A&R 2007)
  - Tocilizumab and canakinumab in sJIA (ongoing for PRINTO/PRCSG)

- **Withdrawal design**
  - Etanercept (Lovell for PRCSG NEJM 2000)
  - Adalimumab (Lovell, Ruperto for PRINTO/PRCSG NEJM 2008)
  - Abatacept (Ruperto, Lovell for PRINTO/PRCSG Lancet 2008)
  - Canakinumab in sJIA (ongoing for PRINTO/PRCSG)
  - Tocilizumab in poly JIA (ongoing for PRINTO/PRCSG)
  - Other to come (golimumab, certolizumab etc)
JIA populations

- Different populations similar efficacy/safety profile
- Methotrexate: **NSAIDs non responders**
- Etanercept: **MTX non responders** (NR) (MTX stopped)
- Adalimumab: (MTX NR and MTX naive)
- Abatacept: (MTX NR and biologics NR)
- Tocilizumab, canakinumab: **systemic JIA**
JIA therapy in the literature

◆ **MTX:**

◆ **Anti-TNF**
  - Infliximab Ruperto, Lovell for PRINTO/PRCSG AR 2007, ARD 2010
  - Adalimumab Lovell Ruperto for PRINTO/PRCSG NEJM 2008

◆ **Anti CTL4-Ig**

◆ **Anti IL6, IL1** Yokota et al Lancet 2008, EULAR and ACR abs 2009
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- How to define *response to therapy*
- Need to limit *time on placebo* (chronic disease)
- What are *acceptable control groups*?
- PRD are rare (*feasibility*) and therefore we need
  - a) to obtain *as much information as possible from every pts*
  - b) design trials to be as *efficient* as possible (low sample size).
- What is the standard of care?
- What we are interested in?
  - short-term
  - *long-term outcomes* (especially for safety/remission)
Pediatric rheumatology/gastroenterology link

- PRES/PRINTO Pharmachild project
  - (PI Nico Wulffraat)
  - PRINTO technical platform for data collection

Share the safety platform with gastroenterologists

- PRINTO clinical trial office

A central facility to help in planning and conduct of clinical trials under gastroenterologists leadership
Summary

- Adequate legislation
- International networks
- Appropriate outcome evaluation tools
- New drugs

- Have created the basic premises for a scientific approach to find the best available treatments for children with rheumatic diseases
PRINTO Address for new members

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Fax: +39-010-39-33-24 or +39-010-39-36-19

www.printo.it
www.pediatric-rheumatology.printo.it
BACK UP SLIDES
Back Up slides
NSAIDs open problem

- Several not approved for use in JIA
- Need to have adequate formulations
- Approval in all EU member states
- Useful in controlling inflammation and pain
  - Naproxen used as comparator for all Cox-II inhibitors (meloxicam, rofecoxib, celecoxib)
  - No difference in safety and efficacy when compared to Cox-II inhibitors

Ruperto et al Arthritis Rheum 2005
Reiff et al J Rheumatol 2006
DMARDs: the paradox of MTX

- Mainstream for treatment, proven efficacy and safety
- Used in combination in several biologic agents trials (infliximab, adalimumab etc)
- No interest from companies (off patent, low cost)
- Not approved for use in JIA
- Etanercept patients are required to fail MTX!!
- PRINTO dossier submitted to AIFA to approve JIA indication (and reimbursement) based on literature data
Beyond the pediatric legislation

- Best use of available treatments
- Biomarkers for prediction of efficacy, safety etc
- Phase IV studies in light of the new pharmacovigilance regulation
  - Etanercept sponsored phase IV registries (France, Germany, Italy, UK, USA)
The AIFA approach

- Funding from companies for no profit studies
- **2 steps approach for project selection**
- Phase III effectiveness randomised actively controlled clinical trial in new onset juvenile dermatomyositis: prednisone (PDN) versus PDN plus cyclosporine A versus PDN plus methotrexate

Ruperto Arthritis Rheum 2005
Summary

- Excellent situation for new drugs (biologic agents) thanks to the pediatric rule
- All the other drugs are not approved for use in children in many member states and lack adequate formulation
- PRINTO as model for funding support of networks dedicated to group of pediatric diseases
Proposals for discussion

- Use of data from literature to extend indication (methotrexate example)?
- Necessity to have adequate industrial partner for formulation development?
- Support for diseases related large networks
- 2 steps approach for project selection
- Beyond the pediatric legislation in research
  - Phase IV studies
  - Best use of available treatments
  - Biomarkers for prediction of efficacy, safety etc
Back up slides
JIA Classification (Durban 1997)

1. Systemic  15%
2. Oligoarthritis:  50%
   - a) persistent
   - b) extended
3. Polyarthritis (FR positive)  3%
4. Polyarthritis (FR negative)  17%
5. Psoriatic arthritis  5%
6. Arthritis/enthesitis  10%
7. Other
   Arthritis in the first 6 months of the disease
      Oligoarthritis: ≤ 4 joints
      Polyarthritis: >4 joints
Methotrexate in JIA (USA/USSR)

Giannini et al. for PRCSG NEJM 1992

Change in the articular severity score

Placebo 41 patients
MTX 5 mg/m²/w 40 pts
MTX 10 mg/m²/w 46 pts
Study design

≥ 3 mo inactive

6 months

12 months

Group 1
MTX stop 6 months

Group 2
MTX stop 12 months

Min Follow up 12 months

MRP 8/14 (S100 A9)

flare

flare

months
0  6  12  18  24
MTX: time to flare and MRP 8/14 (S100 A9)

Figure 2. Analysis of Flare-Free Survival

<table>
<thead>
<tr>
<th>Group</th>
<th>Flare-Free Survival, %</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>75 63 52 45 38 35 33 30</td>
</tr>
<tr>
<td>2</td>
<td>75 61 50 44 30 25 23 20</td>
</tr>
</tbody>
</table>

Log-rank $P = .61$
HR, 1.07 (95% CI, 0.82-1.41)

Figure 4. Analysis of Flare-Free Survival Using MRP8/14 as a Molecular Marker of Relapse Risk

<table>
<thead>
<tr>
<th>MRP8/14, ng/mL</th>
<th>Flare-Free Survival, %</th>
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</thead>
<tbody>
<tr>
<td>≥690</td>
<td>75 62 53 44 37</td>
</tr>
<tr>
<td>&lt;690</td>
<td>113 111 100 89 81</td>
</tr>
</tbody>
</table>

Log-rank $P < .001$
HR, 2.24 (95% CI, 1.39-3.62)
Canakinumab time to flare

- Large heterogeneity in relapse pattern between subjects
- Intra-subject relapse pattern exhibits periodicity
- No apparent tachyphylaxis

<table>
<thead>
<tr>
<th>Subject</th>
<th>Dose (mg/kg)</th>
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<td>5407</td>
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<tr>
<td>5218</td>
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</tr>
<tr>
<td>5408</td>
<td>1</td>
</tr>
<tr>
<td>5203</td>
<td>0.5</td>
</tr>
</tbody>
</table>

- Did not respond with 1mg/kg.