Prioritising drug development for children with rhumatologic diseases

The Paediatric Rheumatology InterNational Trials Organization (PRINTO) perspective

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Outline

- PRINTO outline
- Liaisons with industries
Paediatric Rheumatic Diseases (PRD)

◆ PRD are rare diseases and the most common chronic illnesses in childhood
◆ PRD are highly debilitating and potentially affecting the entire life
◆ The most common diseases are
  - Juvenile Idiopathic Arthritis (JIA)
  - Juvenile Systemic Lupus Erythematosus (JSLE)
  - Juvenile Dermatomyositis (JDM) and others
Italy, May 19, 1996

“...to foster, facilitate, and conduct high quality research in the field of paediatric rheumatology...”

PRINTO bylaws

2016 new version

www.pediatric-rheumatology.printo.it

- Centres
- Family associations

~4,500 people/day from over 180 countries
## PRINTO academic not-for-profit studies

(>37,500 pts in 300 centres in 67 countries)

<table>
<thead>
<tr>
<th></th>
<th>No centres / countries 300/67</th>
<th>West Europe</th>
<th>East Europe</th>
<th>Latin America</th>
<th>North America</th>
<th>Others</th>
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<td>MTX1</td>
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<td>492</td>
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<td>JDM</td>
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<td>78</td>
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<td>85</td>
<td>4</td>
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<td>Eurofever</td>
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<td>Abirisk</td>
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## PRINTO-PRCSG Enrollment
(3349 patients in 253 centres in 39 countries)

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<th>Drug</th>
<th>West Europe</th>
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<th>Latin America</th>
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<th>Others</th>
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<td>Infliximab</td>
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<td>26</td>
<td>171</td>
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<td>Abatacept iv</td>
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<td>7</td>
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<td>58/15</td>
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<td>50</td>
<td>24</td>
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<td>Golimumab</td>
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<td>46</td>
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<td>Meloxicam</td>
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<td>96</td>
<td>226</td>
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<tr>
<td>Adalimumab regi</td>
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<td>60</td>
<td>5</td>
<td>505</td>
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<td>Abatacept registry</td>
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<td>3</td>
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<td>Rilonacept</td>
<td>59/22</td>
<td>134</td>
<td>35</td>
<td>82</td>
<td>69</td>
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<td>Tofacitinib poly</td>
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<td>7</td>
<td>17</td>
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<tr>
<td>Certolizumab Pegol</td>
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<td>44</td>
<td>39</td>
<td>80</td>
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</tr>
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</table>

>90% of the PIP successful through Phase II or III trials implemented with the PRINTO PRCSG networks
Is there a role for “academia”? Drug development: «the central paradigm»

Defined protocols «offered» to academia

- Phase I
- Phase II
- Phase III

- Phase IV and post-marketing

- No specific pediatric requests by the legislation

PIP Submission
Is there a role for “academia”?

The «broken» paradigm

PRINTO collaboration with pharmaceutical companies (independent primary outcome evaluation)

Phase I

Phase II

Phase III

Phase IV and post-marketing

No specific pediatric requests by the legislation

PRINTO pre-PIP

PIP Submission

PRINTO academic pharmacovigilance pharmacchild

Liaisons with pharma companies

◆ **Scientific collaboration:**
  - Pediatric rheumatology concerns
  - PIP/Protocol/CRF drafting
    - Study design, inclusion/exclusion criteria
  - feasibility for site selection,
  - Training and investigator certification
    - Joint assessor certificate,
  - PRINTO/PRCSG primary outcome evaluation with real time monitoring and data transfer to companies
  - Analysis and reporting
Liaisons with pharma companies

Scientific collaboration:

- Pediatric rheumatology concerns
- PIP/Protocol/CRF drafting
  - Study design, inclusion/exclusion criteria
- Feasibility for site selection,
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  - Joint assessor certificate,
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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 subject*
  - 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 remission/safety)
How to measure response

◆ JIA ACR criteria (30-50-70-100% change)
  - FDA/EMA «approved» JIA ACR 30%
  - PRINTO/ACR/EULAR criteria for juvenile SLE and JDM
    • Juvenile Arthritis Disease Activity Scores (JADAS): absolute level of disease activity
    • Inactive disease/clinical remission ACR provisional criteria and JADAS remission criteria

◆ Similar criteria for juvenile SLE, and JDM
Response to therapy
- JIA ACR 30/50-70-90 response and flare criteria (FDA and EMA approved)
- JIA clinically inactive disease/clinical remission (on or off therapy)
- Juvenile Arthritis Disease Activity Score (JADAS)
- CHAQ/CHQ and JAMAR in more than 50 languages
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 (De Benedetti/Ruperto for PRINTO/PRCSG NEJM 2012)

◆ 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 (on going for PRINTO/PRCSG)
- Tocilizumab in poly JIA (Brunner for PRINTO/PRCSG ARD 2015)
- Golimumab in poly JIA (submitted)

◆ Open Label: certolizumab pegol (5th anti-TNF) (in preparation)
**JIA population (all but one with placebo)**

- Different populations similar efficacy/safety profile
- Methotrexate: **NSAIDs non responders**
- Etanercept: **MTX non responders** (NR) (MTX stop)
- Infliximab: **MTX non responders**
- Adalimumab: **(MTX NR and MTX naive)**
- Abatacept: **(MTX NR and biologics NR)**
- Golimumab/certolizumab: **MTX non responders**
- Tocilizumab, canakinumab/sarilumab: **systemic JIA**
- Secukinumab: **spondyloarthropathies**
Liaisons with pharma companies

◆ **Scientific collaboration:**
  - Pediatric rheumatology concerns
  - PIP/Protocol/CRF drafting
    - Study design, inclusion/exclusion criteria
  - **feasibility for site selection,**
  - **Training and investigator certification**
    - Joint assessor certificate
  - PRINTO/PRCSG primary outcome evaluation with real time monitoring and data transfer to companies
  - Analysis and reporting
Feasibility and joint assessor certification

• Feasibility questionnaire with key points agreed with company
• Site feasibility among PRINTO members
• Provision of centre performance
• Final selection by the company among centres suggested by PRINTO
Liaisons with pharma companies

◆ Scientific collaboration:
  - Pediatric rheumatology concerns
  - PIP/Protocol/CRF drafting
    • Study design, inclusion/exclusion criteria
  - feasibility for site selection,
  - Training and investigator certification
    • Joint assessor certificate
  - PRINTO/PRCSG primary outcome evaluation with real time monitoring and data transfer to companies
  - Analysis and reporting
Data Flow

Source document sent in real time

Double Data entry by the centre to PRINTO/PRCSG

Monitoring of source document of the centre
by PRINTO/PRCSG

Monitoring of source document of the centre/PRINTO-PRCSG
by Company

Regular transfer of clean data for data reconciliation
from PRINTO/PRCSG To Company
Independent PRINTO primary outcome real time assessment

**ACR Responder**

<table>
<thead>
<tr>
<th>MODIFIED ACR SCORE Set</th>
<th>Value at Baseline</th>
<th>Value at Week 1</th>
<th>Absolute difference</th>
<th>Percent change</th>
<th>Note</th>
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<tbody>
<tr>
<td>Physician VAS</td>
<td>20</td>
<td>12</td>
<td>-8</td>
<td>-40%</td>
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<tr>
<td>Joints with LOM</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0%</td>
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<tr>
<td>Active joints</td>
<td>4</td>
<td>2</td>
<td>-2</td>
<td>-50%</td>
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</tr>
<tr>
<td>Parent VAS</td>
<td>20</td>
<td>10</td>
<td>-10</td>
<td>-50%</td>
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<td>CHAQ score</td>
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<td>1.25</td>
<td>-0.75</td>
<td>-37.5%</td>
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<tr>
<td>CRP value</td>
<td>30</td>
<td>15</td>
<td>-15</td>
<td>-50%</td>
<td></td>
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<tr>
<td>RESPONDER STATUS</td>
<td>ACR Responder</td>
<td>50</td>
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Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial

Randomized Trial of Tocilizumab in Systemic Juvenile Idiopathic Arthritis
Pharmacovigilance in juvenile idiopathic arthritis patients (Pharmachild) treated with biologic agents and/or methotrexate.

A Pediatric Rheumatology INternational Trials Organisation (PRINTO)/Pediatric Rheumatology European Society (PRES) registry.

PI Nico Wullfraat Co-PI Nicola Ruperto

7,944 patients enrolled in the retrospective part
3,218 patients enrolled in the prospective part

Pharmacovigilance study EU funded

Agreement with one company with data property of PRINTO

No mandatory request to for pediatric safety studies
Liaisons with pharma companies

Scientific collaboration:

- Pediatric rheumatology concerns
- PIP/Protocol/CRF drafting
  - Study design, inclusion/exclusion criteria
- feasibility for site selection,
- Training and investigator certification
  - Joint assessor certificate
- PRINTO/PRCSG primary outcome evaluation with real time monitoring and data transfer to companies
- Analysis and reporting
PRINTO publications: reason for success

- 130 PRINTO manuscripts
- 685 authors
  - 276 (40%) multiple publications
  - H-index 60

- EULAR Centre of Excellence in Rheumatology 2008-2018
- Category 1 ENPrEMA

Early and repeated intervention by academia
- Pre-PIP (attention to pK-dose finding)
- Pre-protocol finalisation
- Prioritization (e.g., anti IL6-IL1 first in children)
- Feasibility for centre identification
- Assistance during the conduct of the trial
  - E.g., PRINTO/PRCSG as primary outcome independent certified assessors (NEJM, Lancet editors added in the methods section)

(??) revision of definitive protocol by PDCO
Open problems

◆ **Paradox:** too many studies too few patients

◆ **Me-too-drugs:** perform «just» pk-dose findings/safety open label trials

◆ **Biosimilars:** missing point in the legislation; perform «at least» pk-dose findings/safety open label trials

◆ **Study prioritisation:** not all studies are scientifically sounded ⇒ greater intervention from academia

Greater use of extrapolation
Juvenile Systemic Lupus erythematosus

- Juvenile SLE is the same disease as adult SLE but with different frequencies of disease manifestations (e.g. renal involvement more frequent and severe)
- Peak around puberty in females
- Very rare in young children or males
- Several PIP in SLE and juvenile SLE
### DRUG TARGETS – PHASE 3 IN ADULTS WITH SLE

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<tr>
<th>No longer</th>
<th>Currently under study for Registration</th>
<th>Currently under study but not for Registration</th>
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<tbody>
<tr>
<td>• Abetimus/toleragen</td>
<td>• Atacicept, Blisbimod, belimumumab (LN) / <strong>BCR</strong></td>
<td>• Etanercept, infliximab</td>
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<td>• Ocrelizumab/ CD20</td>
<td>• Sifalumumab, anifrolumab / <strong>Interferon alpha</strong></td>
<td>• Rituximab</td>
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<td>• Epratuzumab/CD22</td>
<td>• Abatacept/ <strong>CTLA4</strong></td>
<td>• Cyclophosphamide</td>
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<td>• Rontiluzumab/ <strong>INFα</strong></td>
<td>• Edratide (IPP-201101, Lupuzor / <strong>toleragen</strong></td>
<td>• Steroid (stopping)</td>
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<td>• Tabalumab/ BCR</td>
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<td>• Mycophenolate</td>
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<td>• Tocilizumab, Sirukumab/ IL6</td>
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<td>• Tacrolimus</td>
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</table>

**FDA approved for adults with SLE:**
Hydroxychloroquine, aspirin, steroids, belimumab

<table>
<thead>
<tr>
<th>Target</th>
<th>Cell types / pathways</th>
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<tr>
<td>CD19</td>
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<tr>
<td>CD28</td>
<td>T cells (costim)</td>
<td>TAB08, lulizumab</td>
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<tr>
<td>CD30</td>
<td>Activated T and B cells</td>
<td>Brentuximab vedotin</td>
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<td>CD40</td>
<td>APC</td>
<td>BI 655064</td>
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<td>CD40L (CD154)</td>
<td>T Helper cells</td>
<td>Dapirolizumab pegol (DZP0)</td>
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<td>CD74</td>
<td>HLA-DR invariant chain</td>
<td>Milatuzumab</td>
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<td>Effects TLR signaling</td>
<td>INV103</td>
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<td>IL 6</td>
<td>Pro-inflammatory cytokine</td>
<td>ALX-0061, PF-04236921, sirukumab</td>
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<td>IL10</td>
<td>STAT 3 signaling</td>
<td>BT063</td>
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<td>P40 unit of IL12/23</td>
<td>Block TH17 pathway</td>
<td>Ustekinumab</td>
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<tr>
<td>Sphingosine 1-phosphate 1 receptor</td>
<td>Anti-inflammatory via T cells and APC</td>
<td>ACT-334441, Amiselimod, Fingolimod</td>
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<td>Ubiquitin ligase modulator</td>
<td>Down regulate NF-kappa beta</td>
<td>CC-220</td>
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<td>Type 1 interferons</td>
<td>Interferon production</td>
<td>INF alpha kinoid (INF-K), RSVL-132</td>
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<td>Janus Kinase</td>
<td>STAT 1,3,5 signaling</td>
<td>Fostamatinib, tofacitinib</td>
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<tr>
<td>Protease inhibition</td>
<td>APC function, T cell function</td>
<td>Nelfinavir</td>
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<tr>
<td>Estrogen receptor alpha</td>
<td>ERK-phosphorylation</td>
<td>ICI 182,780 (Faslodex)</td>
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</table>
The case: belimumab and juvenile SLE

- Pk phase II/III dedicated study dosing
- Double-blind-placebo controlled 1 year study on top of current treatment(s)
- Trials just finished but with great difficulties in recruitment (5 years)
  - EULAR 2016 abstract
  - ClinicalTrials.gov Identifier: NCT01649765
Lessons and proposal for juvenile SLE

- Given the overlapping clinical features of juvenile SLE and adult SLE and the greater incidence around puberty we proposed to companies and regulators:
  - To perform **pk dose finding study** (starting from adult efficaceous and safe dose)
  - To evaluate **long term safety** in registry
Legislation appraisal

The “ethical” case

- **The case:** 35/190 children enrolled in a EMA/FDA approved clinical trial with biologic in JIA in Latin American countries.
- Drug provision stopped once drug approved for JIA.
- Most of the patients could not afford the drug (no insurance) and the disease relapsed

- **PRINTO/PRCSG ethical mandatory request:**
  - Provision of drug to patients until beneficial to child
  - Family reimbursement for travel related expenses
The "broken» triangle

Regulatory authorities

- FDA «moral suasion» versus companies
- EMA link between PIP and pharmacovigilance

Pharmaceutical companies

Academia
Possible proposals for directive’s/regulations’ revision

- Strengthen the role of academia and independent research through regulation
- Demand the provision of drugs to patients (especially children) until beneficial
- Self-maintaining mechanism for academic independent research through large scale patient’s registries
- Provision for pharmacovigilance, «me-too», biosimilar, similar disease (JSLE) ➔ extrapolation