Prioritising drug development for children with rhumatologic diseases

The Paediatric Rheumatology InterNational Trials Organization (PRINTO) perspective

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Outline

- PRINTO outline
- Scientific expertise and specialty level needed to design scientifically-sounded paediatric trials and research
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
“...to foster, facilitate, and conduct high quality research in the field of paediatric rheumatology...”

PRINTO bylaws 1996
PRINTO bottom up approach

- Standardized criteria to evaluate response to therapy in JIA, JSLE and JDM
  - ACR pediatric criteria in JIA (FDA, EMA)
- Standardised web information to families
- Non for profit clinical trials (JIA, JDM, JSLE)
- Training to young researchers
- Liaisons with pharmaceutical industries
- Main source of funding European Union, AIFA, pharmaceutical companies
### PRINTO not-for-profit studies (>36,000 pts)

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PRINTO publications

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

- Is there a role for academia for drug approval?
- Which are the problems encountered by academia?
  - The case of the MTX paradox for JIA and Regulation (EC) no 1901/2006 (pediatric legislation)
  - The case of the PRINTO JDM standard of care trial and the Clinical Trial Directive 2001/20/EC
  - The case of the ethical provision of drugs to chronically ill children especially from developing countries
  - The issue of funding for independent research
The paradox of Methotrexate

- Mainstream for treatment, proven efficacy and safety
- Used in combination in several biologic agents trials
  (infliximab, adalimumumab, abatacept, etc)
- No interest from companies (off patent, low cost)
- It was not approved for use in JIA in many countries
- JIA pts treated with biologics required to fail MTX!
- Now MTX finally approved by mutual recognition in many EU countries
Open questions

- Is there a role for academia for drug approval?
- Where are the paediatric centres?
www.pediatric-rheumatology.printo.it

>1,500 people/day from over 130 countries
>1,500 people/day from over 130 countries
Open questions

- Is there a role for academia for drug approval?
- Where are the paediatric centres?
- Do we need standardised clinical trial training?
PRINTO research training

- Fellowships (1-12 months)
  - > 150 physicians from 24 countries
  - Funding: EU, EULAR, Government, self-financing
  - International PhD on-going

- PRINTO joint assessor certificate (required by FDA for clinical trials)
Open questions

- Is there a role for academia for drug approval?
- Where are the paediatric centres?
- Do we need standardised clinical trial training?
- Can we simplify ethics committee rules (at least for academic paediatric studies)?
The “standard of care” PRINTO JDM trial

**Juvenile Dermatomyositis Study Design**

- **Induction Phase**
  - 3 daily iv MPDN pulse
  - PDN
  - Muscle biopsy if indicated

- **Maintenance Phase**
  - PDN + CSA
  - PDN + MTX

- **Long-term Follow-up**

**Drug Treatment According to Clinical Status**

**Suggested Prednisone Use**

- MPDN = methylprednisolone iv (30 mg/kg/day)
- PDN = prednisone or equivalents
- CSA = Cyclosporine A oral or iv (4-5 mg/kg/day)
- MTX = Methotrexate sc or im (15-20 mg/m²/once per week)

Ruperto et al for PRINTO. Lancet 2015
In the new rules no specific provision for pediatric studies especially if run by academia
2000: a radical change

- 1999 FDA “pediatric rule”
- 2007 EMA and EU parliament: pediatric legislation
  - Mandatory to companies Pediatric Investigation Plan (PIP)
- **Pediatric networks**
  - PRCSG: USA
  - PRINTO: Europe and ROW (>60 countries)
- **PRINTO/PRCSG** response to therapy standardisation
- **Introduction of biologic agents**
Open questions

- Is there a role for academia for drug approval?
- Where are the paediatric centres?
- Do we need standardised clinical trial training?
- Can we simplify ethics committee rule (at least for academic paediatric studies)?
- Is there a role for an “academic” CRO?
- Opportunities/weakness of the pediatric legislation
Liaisons with pharma companies

Scientific collaboration:
- PIP/Protocol/CRF drafting, feasibility for site selection, training, PRINTO/PRCSG primary outcome evaluation, monitoring, analysis, reporting

Clinical trials:
- NSAIDs: meloxicam, rofecoxib
- Biologic agents:
  - Approved: etanercept, adalimumab, abatacept, tocilizumab, canakinumab
  - On-going: certolizumab, belimumab, JAK3.
  - Not approved: infliximab, golimuma (??)

Starting point: FDA, EU pediatric legislation
Drug development/PIP/PRINTO

PRINTO collaboration with pharmaceutical companies

Phase I

Phase II

Phase III

Phase IV and post-marketing

No specific pediatric requests by the legislation

PRINTO academic pharmacovigilance pharmachild
PRINTO perspective

- Early and repeated intervention by academia
  - Pre-PIP (attention to pK-dose finding)
  - Pre-protocol finalisation
  - Prioritization (eg 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
An appraisal of the legislation

Impact of the European paediatric legislation in paediatric rheumatology: past, present and future

Nicolino Ruperto,¹ Richard Vesely,² Agnes Saint-Raymond,² Alberto Martini,¹,³ for the Paediatric Rheumatology International Trials Organisation (PRINTO)

PRINTO-PRCSG Enrollment (N~3000)

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Primary data outcome evaluation independently performed by PRINTO/PRCSG and directly transferred to companies (database audited).
The issue of the «me-too drugs» (e.g. anti-TNF)

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PRINTO/PRCSG proposal to perform «just» pK-dose finding/safety open label trials

On going
The issue of the biosimilars (e.g. anti-TNF)

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PRINTO/PRCSG proposal to perform «at least» pK-dose finding/safety open label trials

NO PROVISION FOR PAEDIATRICS even for pK-dose finding studies
Are all studies needed or scientifically sounded?

- **Study 1:** strategies to limit/prevent safety events
- **Study 2:** graduated syringes to eliminate/reduce dosing error in children
  - Good questions but… agreed sample size 15-20 patients!
- **Study 3:** a proper formulation for little children
  - US: fixed dose regiment (half of the adult dose)
  - EU: initial marketing just for children > 12 years
- **Study 4:** adult dose to treat children
  - Study negative drug not registered for use in children but legislation requirements fullfilled
Other open questions

- Do we need all these «unsufficient and unsounded studies»?

- Do we have «just» to replicate in children what is useful in adults?

- Could/should academia intervene on the choice of the PDCO approved list of studies for pharmaceutical companies?
Open questions

- Is there a role for academia for drug approval?
- Where are the paediatric centres?
- Do we need standardised clinical trial training?
- Can we simplify ethics committee rule (at least for academic paediatric studies)?
- Is there a role for an “academic” CRO?
- Opportunities/weakness of the pediatric legislation
- Ethics and other provisions?
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 and the disease relapsed

- **PRINTO/PRCSG ethical mandatory request:**
  - Provision of drug to patients until beneficial to child
  - Family reimbursement for travel related expenses
Other provisions

- Feasibilities for centre identifications through recognised networks:
  - European Network of Paediatric Research at the EMA (ENPr-EMA) Ruperto et al. Arch Dis Child 2012

- Central network contract negotiation (e.g. minimum per patient fee for all participating countries)

- Authorship for collaborative publication (122 papers with ~550 co-authors)

- The use of registries and link with pharma companies
The issue of public funding

- 3 millions € in public grants from 1998
  - PRINTO as support for academic research with reinvestment of funding coming from pharmaceutical industries

- CARRA (North American network) 33 millioni $ in 2 years!
Open questions

- Is there a role for academia for drug approval?
- Where are the paediatric centres?
- Do we need standardised clinical trial training?
- Can we simplify ethics committee rule (at least for academic paediatric studies)?
- Is there a role for an “academic” CRO?
- Opportunities/weakness of the pediatric legislation
- Ethics and other provisions?
Possible proposals for directive’s/regulations’ revision

- Strengthen the role of academia and independent research through regulation
- Simplify the ethics approval in **paediatrics** in conjunction with the clinical trial 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
Pharmacovigilance in juvenile idiopathic arthritis patients (Pharmachild) treated with biologic agents and/or methotrexate.

Study 5: pharmacovigilance study funded by EU.
Agreement with one company.
No mandatory request to for pediatric safety studies

9,536 patients enrolled in the retrospective/prospective part
(6171 retro 3365 retro+prosp)
Back up
Patient Registries Workshop questions

- Identify the challenges faced by registries and industry when collaborating;
- Understand the **technical challenges** presented by disparate datasets;
- Identify **concrete solutions** to better facilitate relations to avoid duplication.
Academia and industry challenges

- Identify the challenges faced by registries and industry when collaborating;
  - Public support (e.g. Pharmachild)
  - Private support (e.g. Pharmachild/abatacept but with PRINTO data property as per ENCEPP)
    - Pharmachild platform accepted by industries (and potentially suggested by regulatory bodies)
  - Interaction of academia with regulatory authorities directly or indirectly (via companies)
Long-Term Effectiveness and Safety of Abatacept in JIA: Interim Results From the Abatacept in JIA Registry

N Ruperto, DJ Lovell, N Tzaribachev, A Zeft, R Cimaz, V Stanevica, G Horneff, J Bohnsack, TA Griffin, R Carrasco, M Trachana, JA Dare, I Foeldvari, RK Vehe, TA Simon, A Martini, HI Brunner

PRES 2016

• Data Property of academia (PRINTO as per ENCEPP) with total academic independence
• Pharmachild platform used for regulatory purposes
• Funding
  • directly to centres (central negotiation PRINTO/Company)
  • Funding to PRINTO reinvested for the overall management of the registry (all drugs reported)
The "broken» triangle

Regulatory authorities

Pharmaceutical companies

Academia
The "broken» triangle

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

- Pharmaceutical companies

- Academia
Technical challenges

- Understand the technical challenges presented by disparate datasets;
  - Web platform health professionals/parents userfriendly with return

  - Combine national data (or avoid national data at least in pediatrics)
1996: PRINTO start
1996-2016: collaboration
How to combine data from different sources?

- Problems
  - Different data fields
  - Different data dictionaries
  - Missing data

- Possible solution
  - Combine the results for manuscripts, reports etc
## How to combine data from different sources?

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<th>NR Germany N = 3139#</th>
<th>NR Portugal N = 112</th>
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<td>22 (37.5)</td>
<td>170 (33.4)</td>
<td>3370/10376 (33.1)</td>
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</table>

### Diagnosis

- **Systemic**: 604 (12.2) vs 199 (13.2) vs 202 (6.4) vs 14 (12.5) vs 84 (13.3) vs 1103 (10.7)
- **Oligoarticular**: 1792 (36.1) vs 399 (26.4) vs 1011 (32.2) vs 31 (27.7) vs 198 (31.3) vs 3431 (33.1)
- **Polyarticular RF-**: 1342 (27.1) vs 506 (33.5) vs 944 (30.1) vs 26 (23.2) vs 160 (25.3) vs 2978 (28.8)
- **Polyarticular RF+**: 177 (3.6) vs 140 (9.3) vs 199 (6.3) vs 21 (18.8) vs 15 (2.4) vs 552 (5.3)
- **Psoriatic**: 185 (3.7) vs 98 (6.5) vs 244 (7.8) vs 3 (2.7) vs 34 (5.4) vs 564 (5.5)
- **Enthesitis**: 607 (12.2) vs 100 (6.6) vs 438 (14.0) vs 17 (15.2) vs 124 (19.6) vs 1286 (12.4)
- **Undifferentiated**: 252 (5.1) vs 68 (4.5) vs 101 (3.2) vs 0 (0.0) vs 17 (2.7) vs 438 (4.2)

### Age at onset

- 5.4 (2.4-10.0) vs NA vs 7.2 (3.1-11.4) vs NA vs 6.3 (2.5-10.9) vs NA

### Age at JIA Diagnosis

- 6.2 (2.8-11.0) vs 5.5 (2.1-10.2) vs 8.2 (4.0-12.3) vs 7.3 (3.3-12.3) vs NA vs NA

### Disease duration at the last available follow up

- 4.9 (2.5-8.2) vs 5.4 (2.7-8.8) vs 5.2 (3.1-8.4) vs 3.0 (0.5-9.6) vs NA vs NA

### Therapy:

- **MTX only**: 1220 (28.1) vs 503 (32.7) vs 1132 (36.1) vs 0 (0.0) vs 36 (5.7) vs 2891 (29.9)
- **Only one Biologic Drug**: 181 (4.2) vs 307 (20.0) vs 104 (3.3) vs 1 (0.9) vs 127 (20.1) vs 1447 (14.9)
- **Only one Biologic Drug + MTX**: 2109 (48.6) vs 586 (38.1) vs 1545 (49.2) vs 27 (24.1) vs 286 (45.3) vs 3967 (41.0)
- **More than one Biologic**: 29 (0.7) vs 22 (1.4) vs 13 (0.4) vs 6 (5.4) vs 31 (4.9) vs 79 (0.8)
- **More than one Biologic + MTX**: 797 (18.4) vs 116 (7.5) vs 340 (10.8) vs 78 (69.6) vs 87 (13.8) vs 1302 (13.4)

### Nr. patients with ESI or AE

- 942 (19.0) vs 1093 (71.1) vs 1163 (37.1) vs 27 (24.1) vs NA vs 3225 (31.1)
- **Nr. patients with ESI**: 446 (9.0) vs 230 (15.0) vs 249 (7.9) vs 5 (4.5) vs NA vs 930 (9.0)
- **Nr. patients with AE**: 635 (12.8) vs 1075 (69.9) vs 1069 (34.1) vs 24 (21.4) vs NA vs 2803 (27.0)
Possible solutions

- Identify concrete solutions to better facilitate relations to avoid duplication
  - Partnership academia/industries/regulators
  - «Provide advantages» to health professionals/families
  - Combine results from different sources

- Scientific reputation (authorship involvement)
  - 130 manuscripts with 685 authors (40% on multiple publications)
## PRINTO not-for-profit studies (>36,000 pts)

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