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

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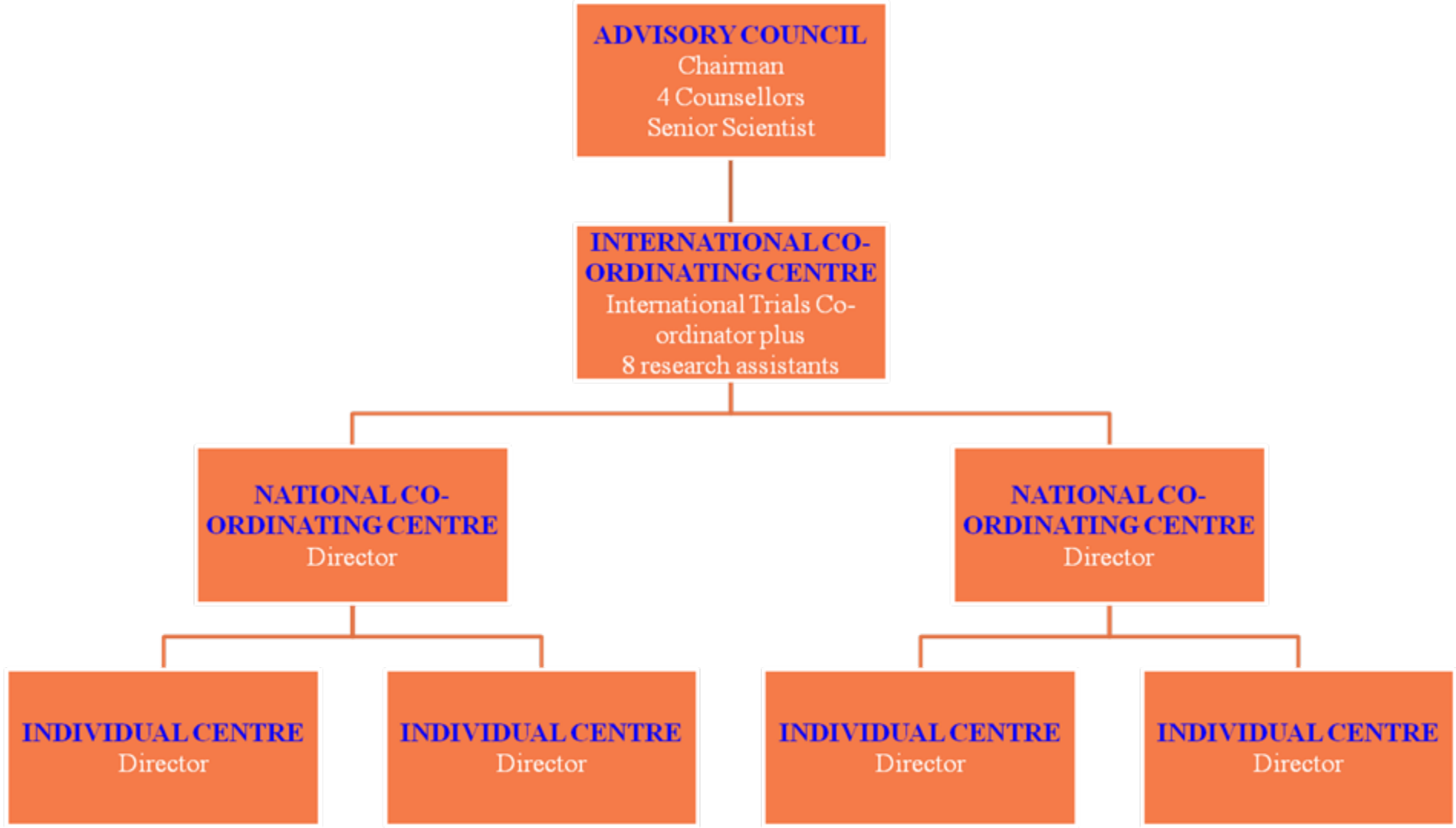
"...to foster, facilitate, and conduct high quality research in the field of paediatric rheumatology..."

PRINTO bylaws

Italy, May 1996

PRINTO: organigramma



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

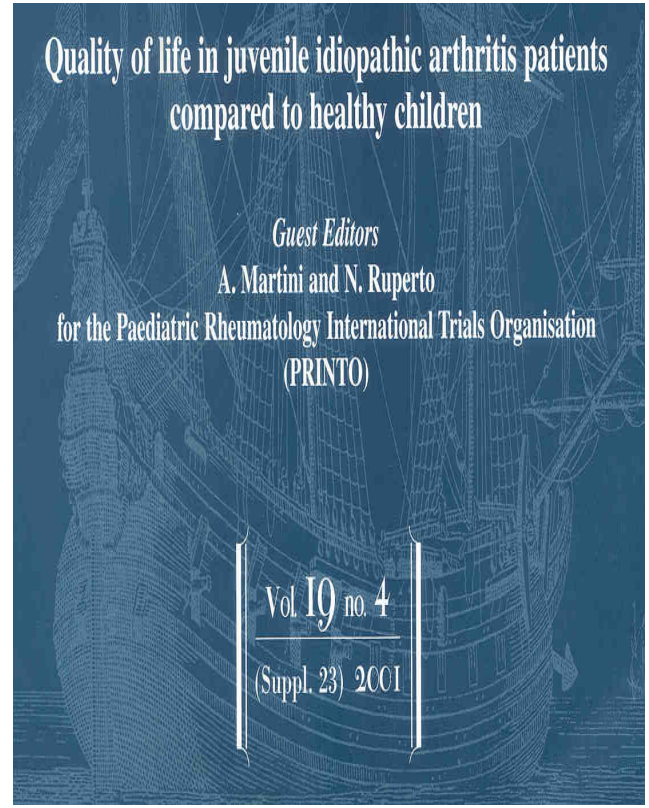
	Western Europe	Eastern Europe	Latin America	North America	Other	Total
MTX	492	55	66	8	12	**633**
QOL	3,988	1,388	903		365	**6,644**
JSLE	243	102	150	37	21	**553**
JDM	162	37	78	18	3	**298**
CSA	203	27	25	85	4	**344**
MTX2	180	80	90		10	**360**
Vascul.	599	353	260	6	181	**1,399**
JDM	53	7	31	1	2	**94**

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)



www.pediatric-rheumatology.printo.it

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

JIA Therapy 1/2

First approach

- Non-steroidal anti inflammatory drugs
- **Intraarticular steroid injections (triamcinolone exacetonide)**

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 : ≤ 4 joints

Polyarthritis: >4 joints

Methotrexate (academic studies)

- 10 mg/m^2/week oral
  - Giannini et al for PRCSG *N Engl J Med 1992*
- 15 mg/m^2/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
  - Giannini NEJM 1992, Woo A&R 2005, Ruperto A&R 2005, Foell JAMA 2010
- 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)

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- What is the standard of care?
- What we are interested in?
  - short-term
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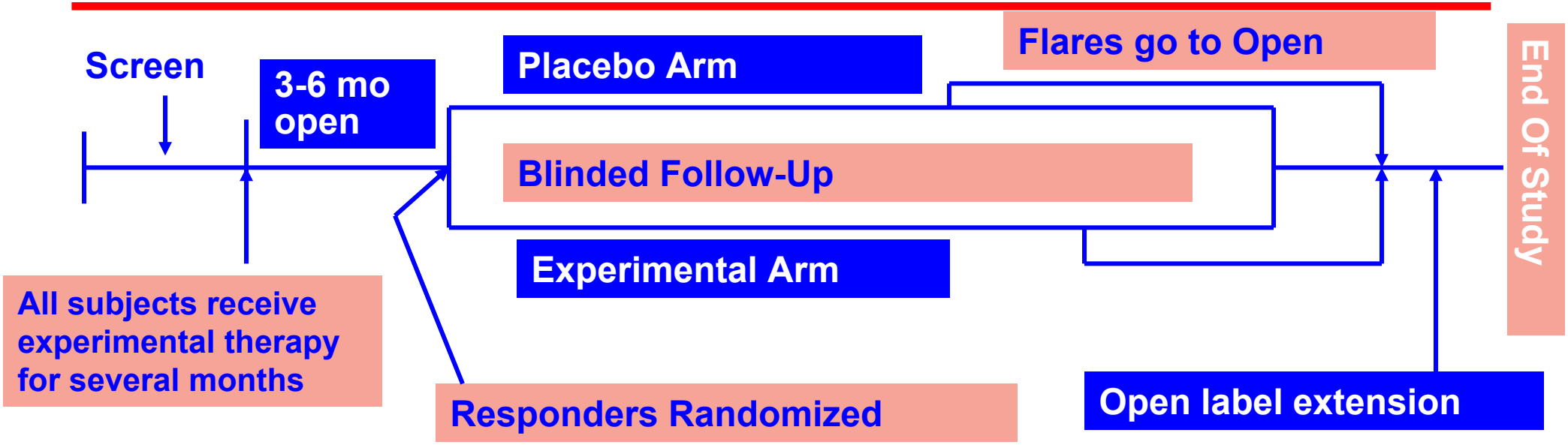
BLINDED WITHDRAWAL STUDIES



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 (eg 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 ≥ 30% (50%, 70%, 90%, 100%) with no more than 1/6 worsened by >30%
- **Flare criteria**: 3/6 core set variables **worsened** ≥ 30% with no more than 1/6 **improved** by ≥ 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**

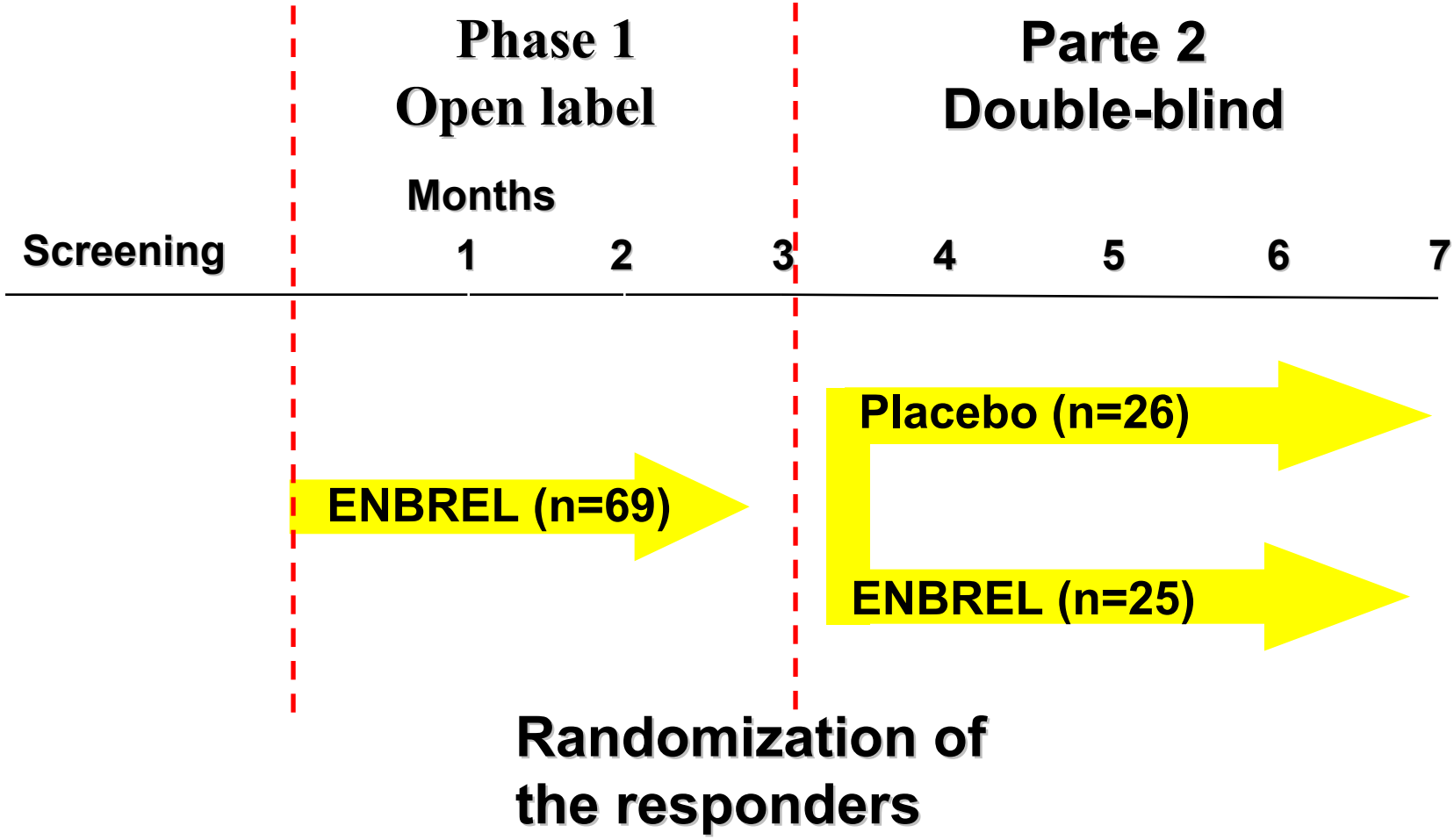
Registrative trials

	Western Europe	Eastern Europe	Latin America	North America	Total
Meloxicam	130	94			**224**
Infliximab	61	10	28	11	**110**
Adalimumab	57	26		88	**171**
CTL4-Ig	75		108	31	**214**
Systemic JIA	54	5	22	24	**112**

Biologic agents

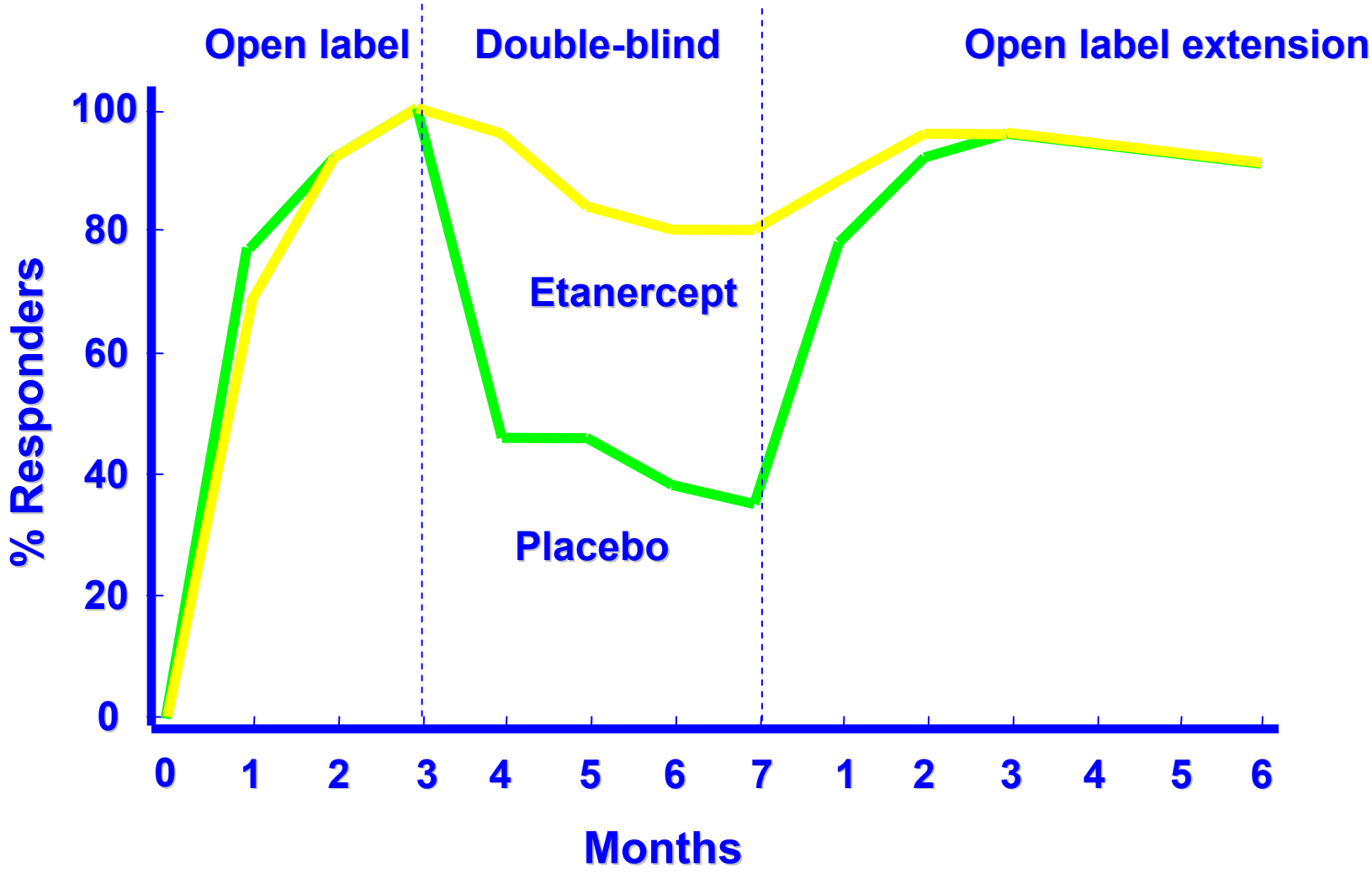
Category	Active principle
TNF-α inhibitors	**Etanercept, Infliximab, Adalimumab**
CTLA4-Ig: inhibitor activation T lymphocytes	**Abatacept**
Anti IL-1	Anakinra, canakinumab, rilonacept
Anti IL-6	Tocilizumab

Etanercept in JIA: study design



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

Etanercept and JIA



Several safety registries

- France: Quartier P. et al. (Arthritis and R 2003)
- Germany: Horneff et al. (Ann Rheum Dis 2004)
- 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)

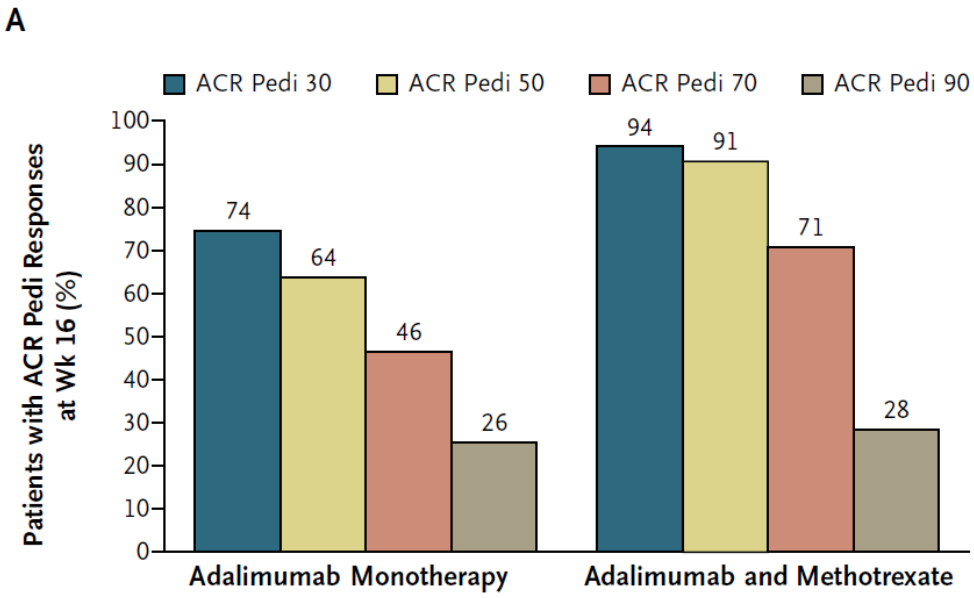
Infliximab safety

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

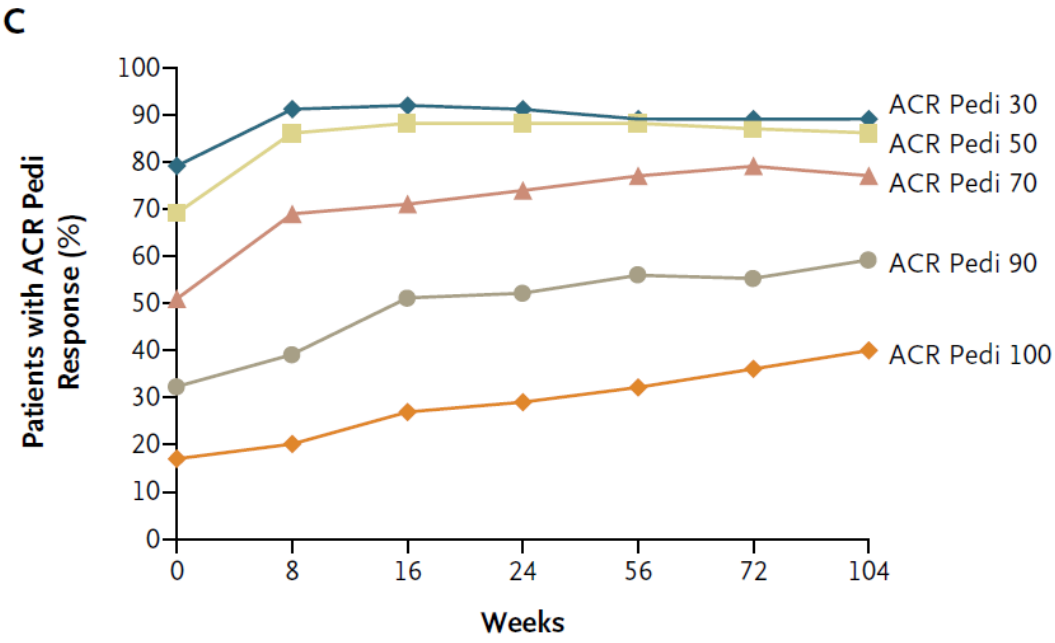
* death

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

Adalimumab



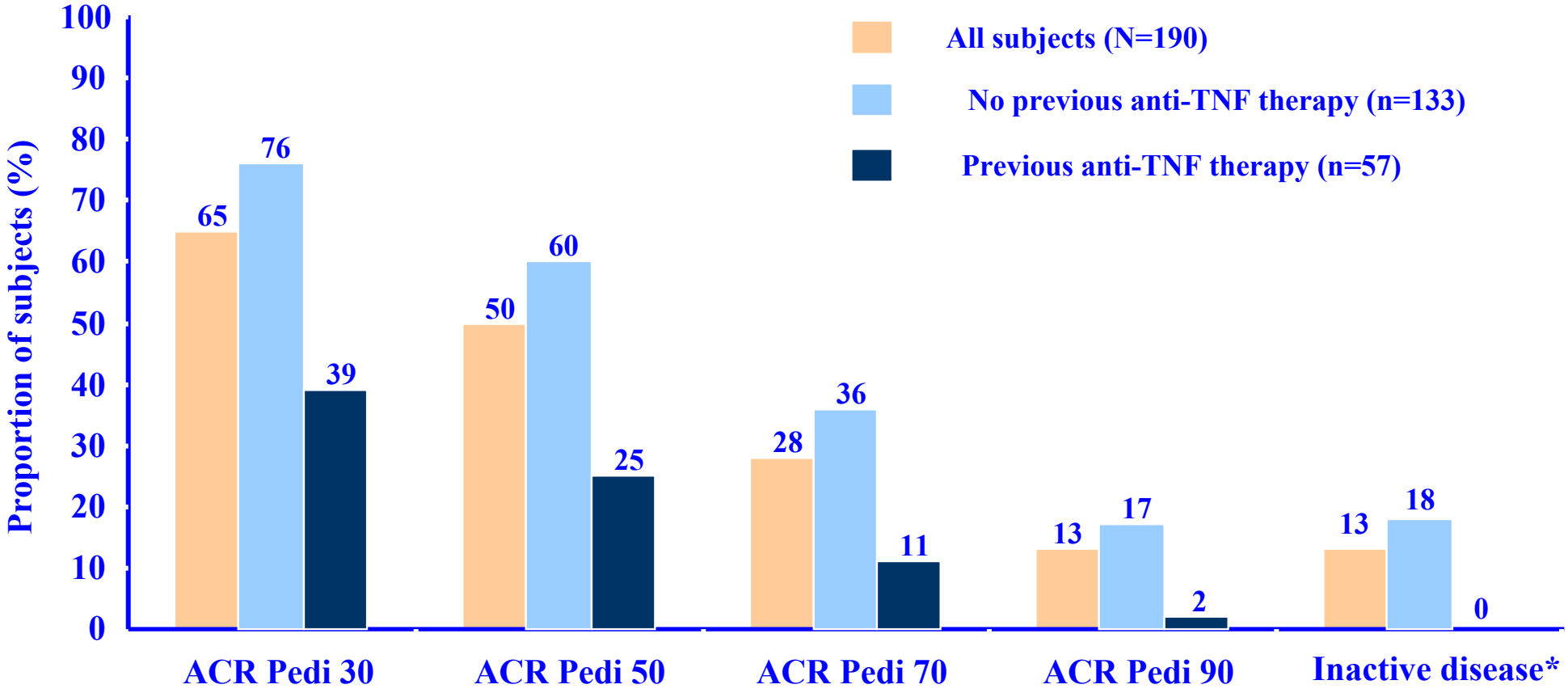
Open label



Extension phase

Lovell, Ruperto for PRINTO/PRCSG NEJM 2009

Abatacept



Ruperto N, et al for PRINTO/PRCSG. *Lancet* 2008.

Trial design in JIA

- Parallel design
  - MTX (Giannini for PRCSG NEJM 1992, Woo A&R 2000, Ruperto for PRINTO A&R 2004)
  - Meloxicam (Ruperto for PRINTO A&R 2004)
  - Infliximab (Ruperto for PRINTO A&R 2007)
  - Tocilizumab and canakinumab in sJIA (on going 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 (on going for PRINTO/PRCSG)
  - Tocilizumab in poly JIA (on going 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:*
  - Giannini for PRCSG NEJM 1990; Ruperto et al for PRINTO *Arthritis Rheum 2004, Foell et al JAMA 2010*
- Anti-TNF
  - Etanercept: Lovell et al for PRCSG *N Engl J Med 2000*
  - Infliximab Ruperto, Lovell for PRINTO/PRCSG AR 2007, ARD 2010
  - Adalimumab Lovell Ruperto for PRINTO/PRCSG *NEJM 2008*
- Anti CTL4-Ig
  - Abatacept Ruperto, Lovell for PRINTO/PRCSG *Lancet 2008, AR 2010*
- *Anti IL6, IL1 Yokota et al Lancet 2008, EULAR and ACR abs 2009*

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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 scietntific approach to find the best available treatments for children with rheumatic diseases

PRINTO Address for new members

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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
  - Giannini NEJM 1992, Woo Arthritis Rheum 20005, Ruperto Arthritis Rheum 2005
- Used in combination in several biologic agents trials (infliximab, adalimumab etc)
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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

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)

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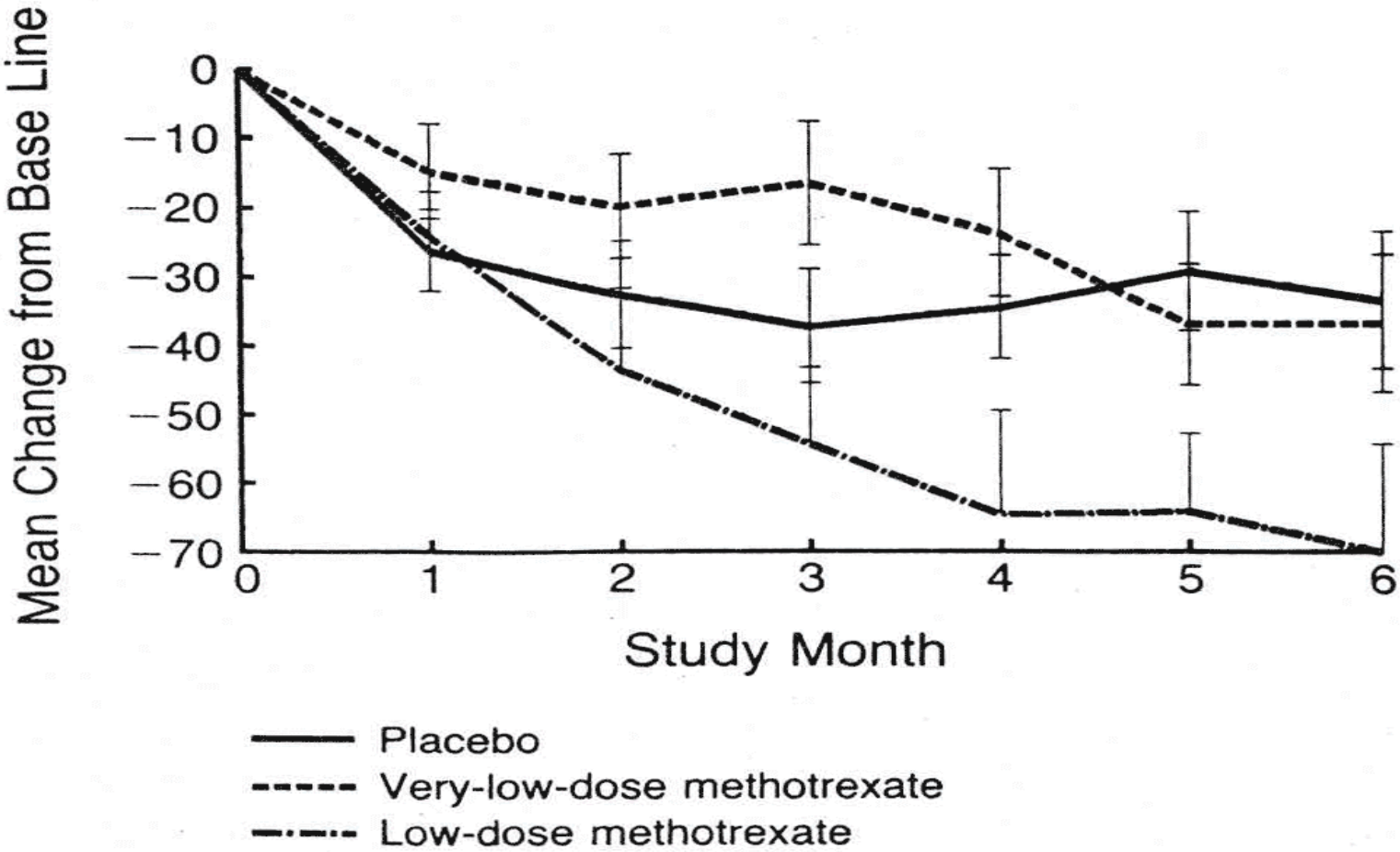
4. **Polyarthritis(FR negative)** **17%**
5. Psoriatic arthritis 5%
6. Arthritis/enthesitis 10%
7. Other

Arthritis in the first 6 months of the disease

Oligoarthritis : ≤ 4 joints

Polyarthritis: >4 joints

Methotrexate in JIA (USA/USSR)



Placebo 41 patients

(pts)

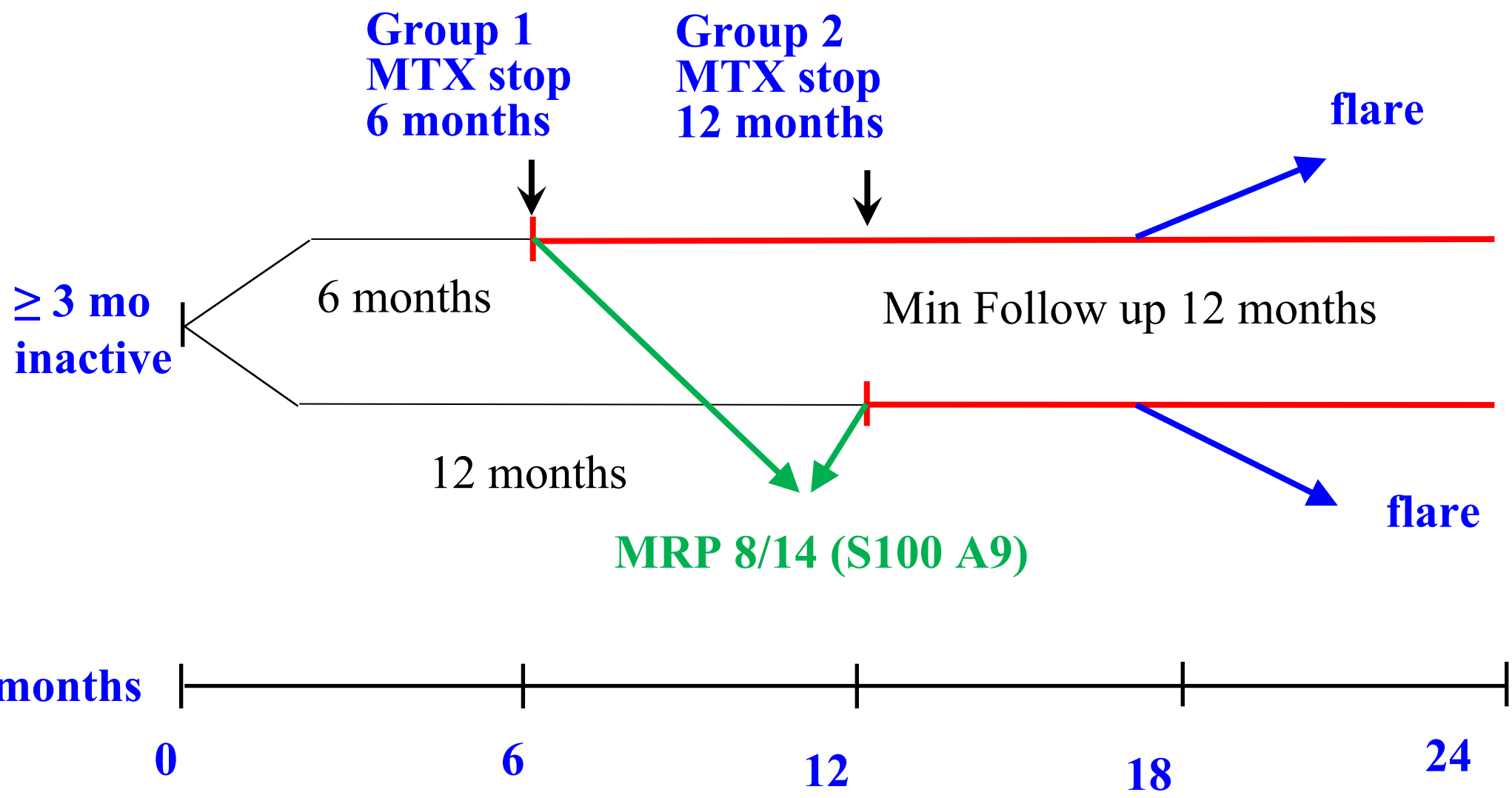
MTX 5 mg/m^2/w 40 pts

MTX 10 mg/m^2/w 46 pts

Change in the articular severity score

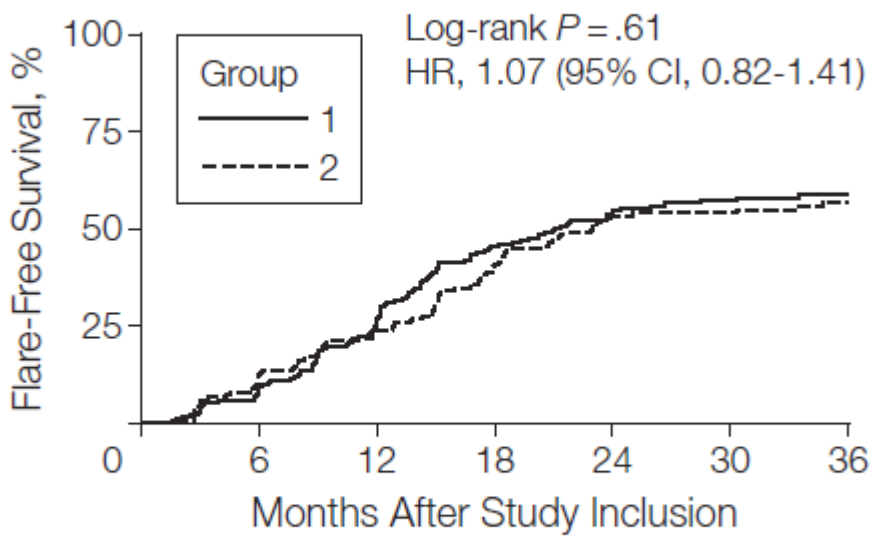
Giannini et al for PRCSG NEJM 1992

Study design



MTX: time to flare and MRP 8/14 (S100 A9)

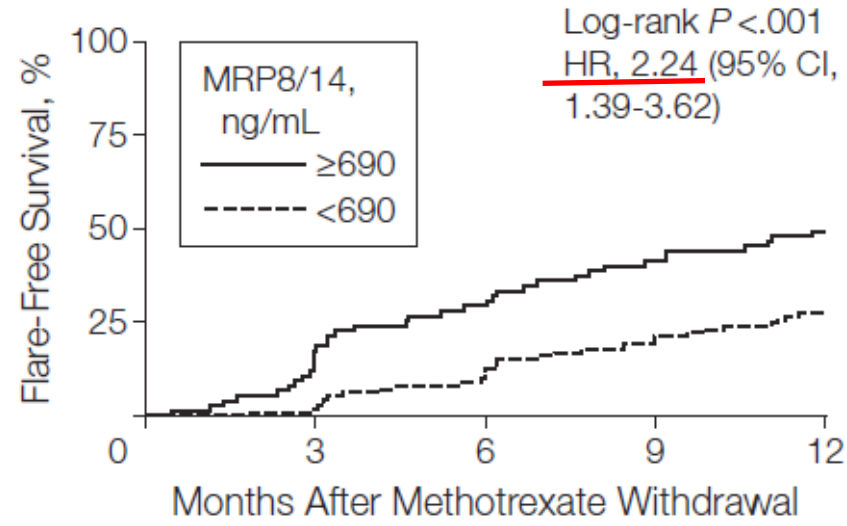
Figure 2. Analysis of Flare-Free Survival



No. at risk

Group 1	183	165	132	96	75	60	35
Group 2	181	157	135	105	75	58	30

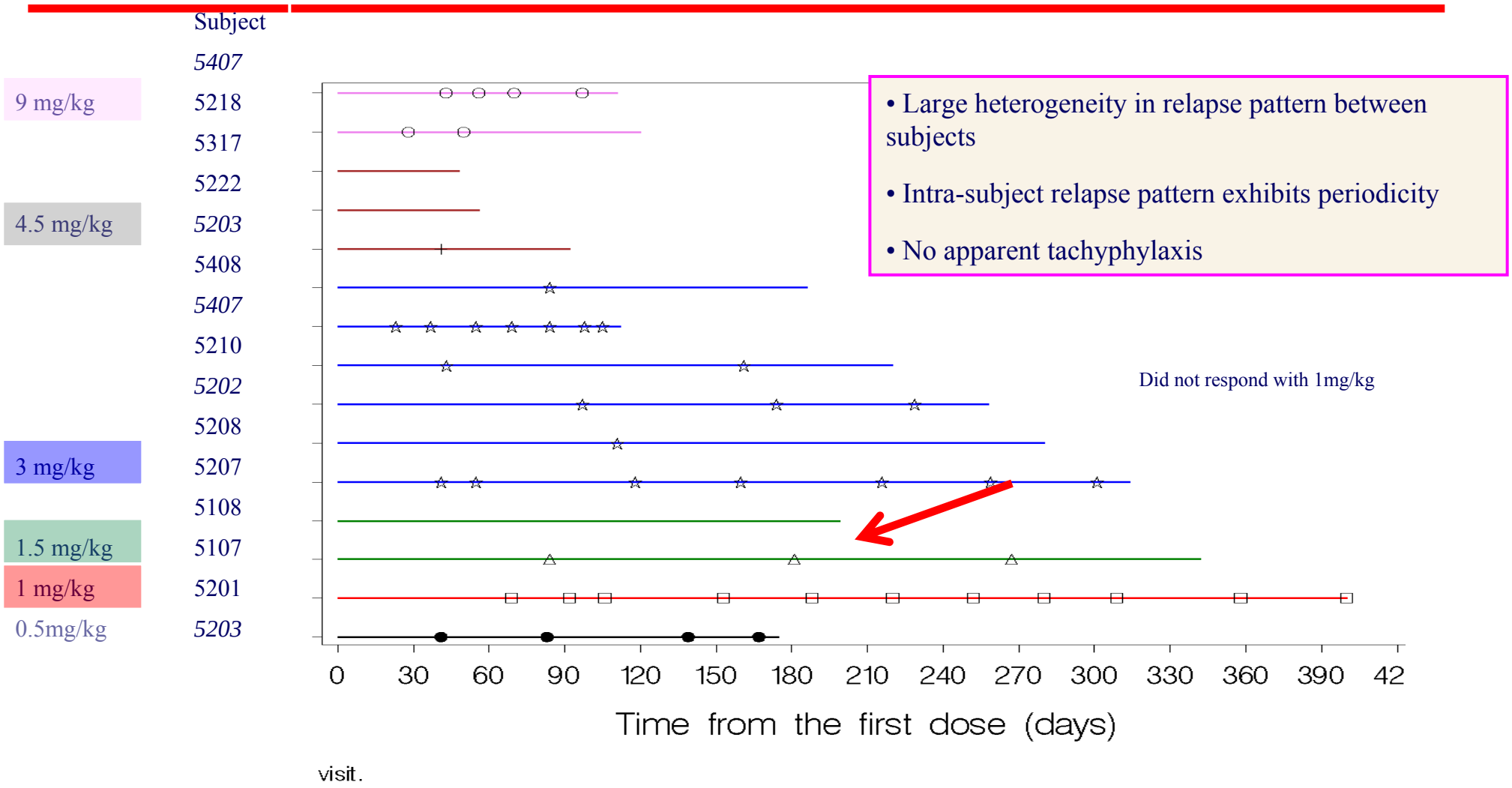
Figure 4. Analysis of Flare-Free Survival Using MRP8/14 as a Molecular Marker of Relapse Risk



No. at risk

MRP8/14, ng/mL					
≥690	75	62	53	44	37
<690	113	111	100	89	81

Canakinumab time to flare



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