Proposal for an international registry for juvenile idiopathic arthritis patients treated with methotrexate

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Overview

- Background
- Proposal
- Feasibility
- Collaboration with existing registries

Background

- Methotrexate (MTX) is the **mainstay of treatment** for children with JIA who do not respond to NSAIDs ± intra-articular steroid injections
  - Giannini for PRCSG NEJM 1992
  - Woo Arthritis Rheum 2000
  - Ruperto for PRINTO Arthritis Rheum 2004

- Little information on long-term safety/efficacy

Hypothesis

- Is MTX ± other drugs able, in the long run, to achieve
  - clinical remission
  - prevent/stop joint erosion development over time
  - maintaining an acceptable safety profile

Primary objectives

- **To evaluate MTX effectiveness**
  - safety,
  - efficacy,
  - erosion,
  - retention on treatment over time

- 5-10 years observation study

Secondary objectives

- to identify **predictors of response**, remission, safety either clinically or laboratory
- to establish a cohort of MTX treated children to be used as **control group** (e.g. biologic agents)
- to collect data to be possibly used by pharma/regulatory authorities to **label MTX** for JIA
- population pharmacokinetics (**PopPK**) and correlation with its pharmacodynamic (PD) effects

Inclusion/exclusion criteria

- **Inclusion criteria**
  - Signed written informed consent by subjects and /or parent or legally acceptable representative
  - JIA (**any subtype**) with age ≤ 18 years at enrolment
  - Indicated for the use of MTX as mono-therapy or in combination with other DMARDs **as per physician discretion**
- **Exclusion criteria**
  - Contraindications to MTX treatment **as per physician discretion**

Choice of the control group

1. JIA treated with MTX alone
2. JIA treated with a combination of MTX ± other DMARDs including biologic agents

3. (JIA treated only with NSAIDs and/or steroid injection with at least 3 years follow-up).

Suggested schedule of assessment

Assessments	Baseline visit	Month 3, 6, and every 6 months thereafter	AE Reporting, any time
Inform consent/assent	X		
Adverse events	**X***	**X**	**X**
JIA core set and clinical assessment	X	X	
(Wrist X-ray assessment)	X	At 12 and 24 months	
(Population PK)		Every 6 months	

The issue of the denominator

- Feasibility
  - Prevalent and incident cases in 2008 (next slide)
- **Meta-analysis of existing national registries and (possibly) data from pharma**
- Census: enrollment log of **all patients** treated with MTX ± other DMARDs in 1-3 months
- After ethics committee approval collection of
  - prevalent cases (retrospective/prospective)
  - incident cases (prospective)

Feasibility as of 19/11/09(refer to 2008)

	Western Europe	Eastern Europe	Latin America	Other	Total
No of centres	83	29	32	28	**172**
Methotrexate					
Prevalent	**9,765**	**3,575**	**3,233**	**3,733**	**20,306**
Incident	**2,010**	**958**	**648**	**775**	**4,391**
Biologic agents					
Prevalent	4,891	814	792	1,329	**7,826**
Incident	1,583	307	284	486	**2,660**

List of approved drugs 1/2

Country	Methotrexate	Etanercept	Infliximab	Adalimumab	Abatacept	Anakinra
Argentina		Yes		Yes	Yes	Yes
Australia		Yes				
Brazil		Yes	Yes	Yes		
Bulgaria	Yes	Yes	Yes	Yes	Yes	Yes
Croatia	Yes	Yes		Yes		
Czech Republic		Yes		Yes		
Denmark	Yes	Yes	Yes	Yes		
Estonia	Yes	Yes	Yes	Yes		
France		Yes				
Georgia	Yes					
Hungary		Yes		Yes	Yes	
India						
Israel	Yes	Yes	Yes	Yes		
Italy	Yes	Yes				
Latvia	Yes	Yes				
Lithuania	Yes	Yes		Yes		
Mexico	Yes	Yes	Yes			

List of approved drugs 2/2

Country	Methotrexate	Etanercept	Infliximab	Adalimumab	Abatacept	Anakinra
Netherlands	**Yes**	**Yes**				
Norway	**Yes**	**Yes**		**Yes**	**Yes**	
Oman	**Yes**	**Yes**		**Yes**		
Peru	**Yes**	**Yes**		**Yes**	**Yes**	
Romania	**Yes**	**Yes**				
Russia	**Yes**	**Yes**			**Yes**	
Saudi Arabia		**Yes**		**Yes**		**Yes**
Serbia	**Yes**	**Yes**				
Slovenia		**Yes**		**Yes**		
South Africa	**Yes**	**Yes**		**Yes**		
Spain	**Yes**	**Yes**				
Sweden	**Yes**	**Yes**		**Yes**		
Switzerland	**Yes**	**Yes**				
Turkey	**Yes**	**Yes**				
United Kingdom		**Yes**				
Venezuela	**Yes**	**Yes**				
TOTAL						

The issue of monitoring

- Rely heavily on standardised and validated questionnaire for data collection
  - MEDRA dictionary for AE collected by MDs

- If funding sufficient random local monitoring (e.g. 10% of centres)

- **Question for EMEA:** is GCP compliant monitoring necessary for observational studies?

Strategies for success 1/2

- Meeting with responsible of national registries for meta-analysis (±pharma data)
  - Germany, UK, France, Netherlands, Spain, Czech Republic, Switzerland, USA etc
- **Census** (3 months)
- **Simplified** web CRF
  - e.g. reduced joint count, short parents/children questionnaires

Strategies for success 2/2

- Moderate to severe adverse events (AE)
  - Key expected SAE (e.g. cancer, serious infections) with more detailed info if AE occur
- MD user's friendly web CRF
  - Discarge letter with automatic outcome assessment (ACR pediatric response, flare, JADAS, remission, safety summary)
- Family involvement for AE/outcome reporting
- Regular update to MDs, families

Enrollment target

- Up to 50% of the feasibility sample
- Is this feasible and reasonable?

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	60	7	34	1	2	**94**

Proposal in a nutshell

- One single international JIA registry for **MTX±biologics**
- Combination of existing registries
  - non-profit (Germany, UK, France, Italy, Netherlands, etc)
  - for profit
- Establishment of a **common platform** for an active pharmacovigilance system
  - Update of the current registries
  - Inclusion of remaining countries
  - (ideally) liaison with North America (CARRA/PRCSG)
- Main goals: safety and effectiveness (e.g. retention on treatment)

Caveat…and conclusion!

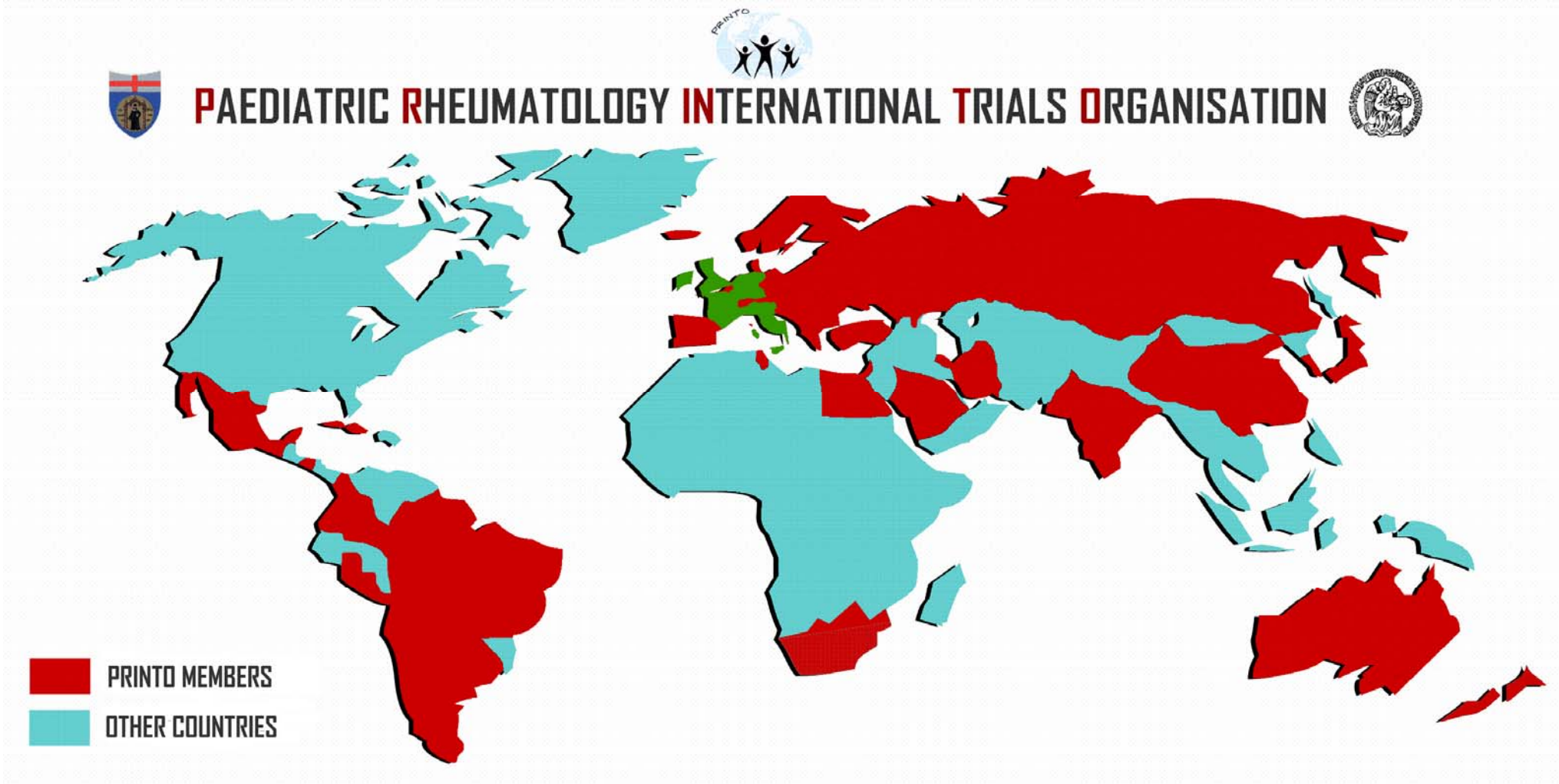
- Adequate financial support!
  - European Union FP7 (HEALTH.2010.4.2-1.: Off-patent medicines for children. FP7-HEALTH-2010-single-stage)
  - In the near future pharma companies

- **Continuous willingness to participate to collaborative projects**

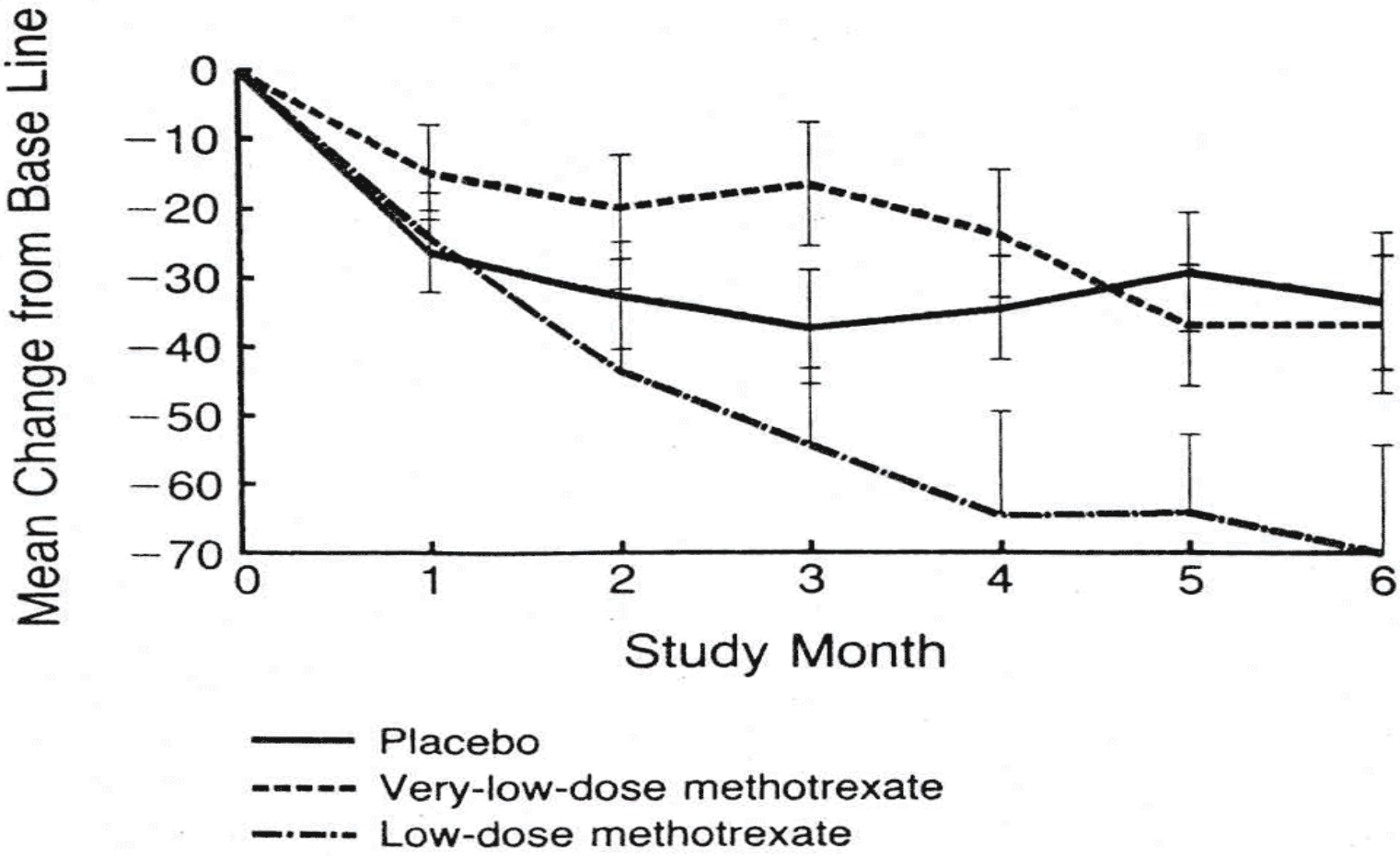
- Back up slides

PRINTO members (51 countries)

Etanercept registries in Europe



Methotrexate in JIA (USA/USSR DBPC)



Placebo 41 patients

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

MTX in extended and systemic arthritis

- Study design: randomized placebo-controlled crossover trail of low-dose oral methotrexate in systemic (45 pts) and extended oligoarthritis JIA (43 pts)
- Results: Oral MTX 15-20 mg/m2 effective for both subtypes

Woo et al . A&R 2000

What about the 27% non-responders?

- Anedoctal report on higher dose MTX

  Wallace CA et al. J Rheumatol 1992

  Reiff A et al Clin Exp Rheumatol 1995

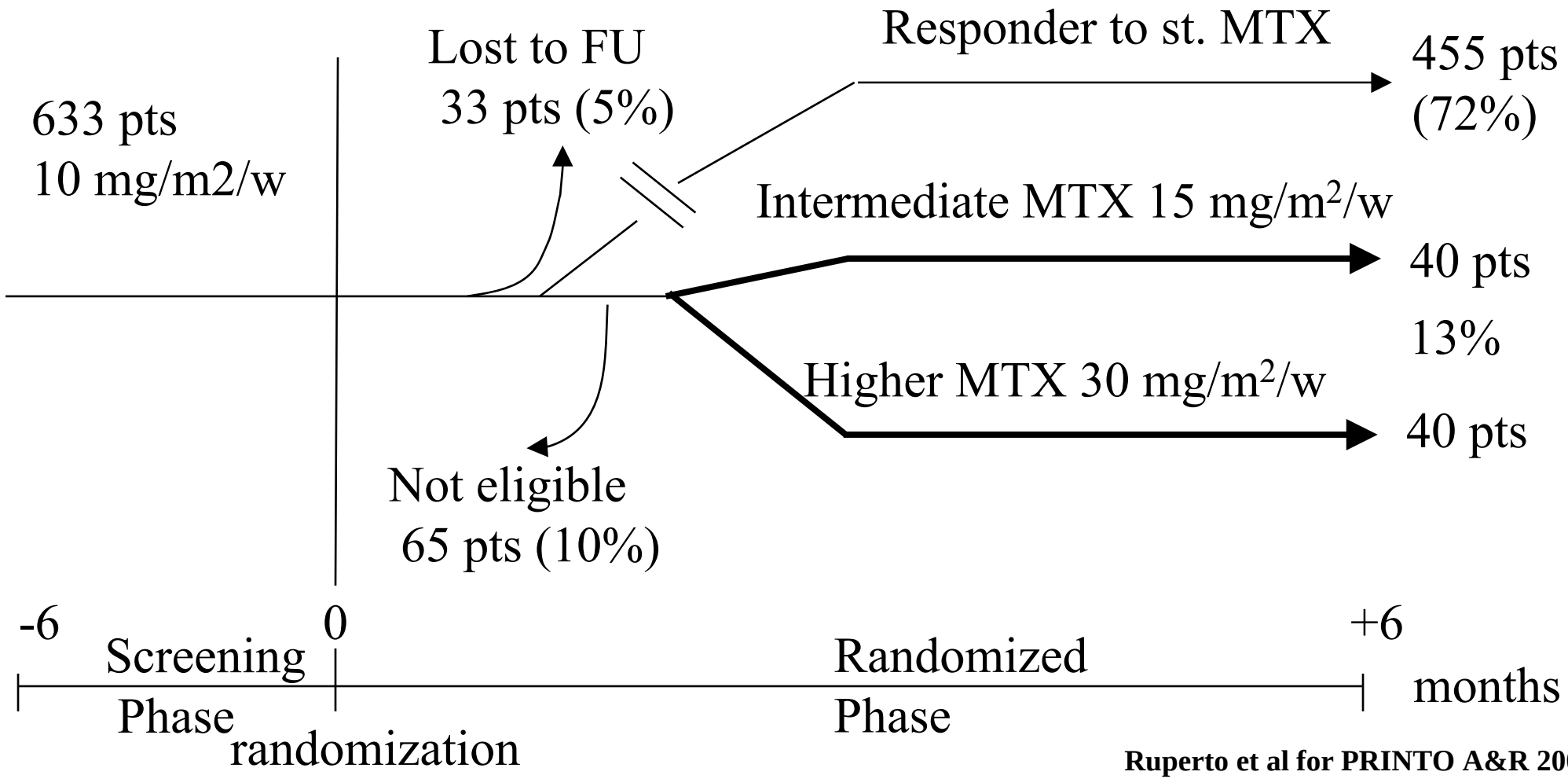
- 1996: International survey to select the most important trial(s) to be performed.

  Lovell DJ, Prieur AM, Woo P, Martini A Arthritis Rheum 1996

- 1998: European Union grant no BMH4 983531 CA

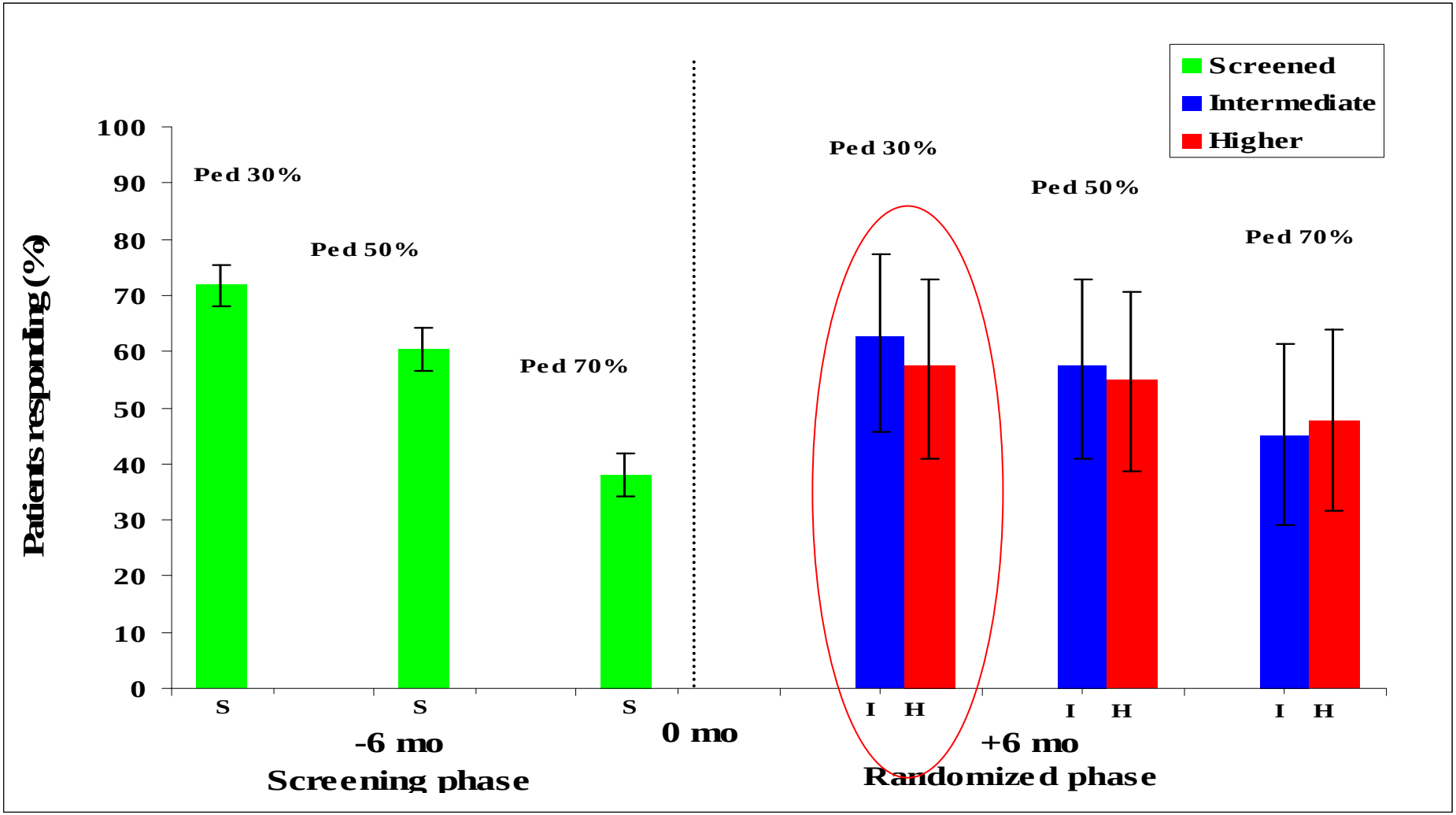
Flow diagram

Ethics Committee approval: 63 centres in 20 countries



Ruperto et al for PRINTO A&R 2004

ACR pediatric definitions (30-50-70%)



Ruperto et al for PRINTO A&R 2004

MTX, ETN, MTX+ETN safety

Table 3. Summary of adverse events with exposure-adjusted rates of ≥0.5 per 100 patient-years*

	MTX (n = 197)	Etanercept (n = 103)	Etanercept plus MTX (n = 294)
Total patient-years of exposure	387.80	224.11	635.17
Total adverse events, no. (rate per 100 patient-years)	71 (18.31)	42 (18.74)	137 (21.57)
Preferred term, no. (rate per 100 patient-years)			
Arthritis flare	4 (1.03)	1 (0.45)	15 (2.36)
Depression	4 (1.03)	3 (1.34)	11 (1.73)
Personality disorder	2 (0.52)	2 (0.89)	8 (1.26)
Emotional lability	2 (0.52)	2 (0.89)	6 (0.94)
Headache	0 (0.0)	1 (0.45)	6 (0.94)
Abnormal thinking	0 (0.0)	1 (0.45)	5 (0.79)
Leukopenia	1 (0.26)	0 (0.0)	4 (0.63)
Asthenia	1 (0.26)	1 (0.45)	5 (0.79)
Anxiety	1 (0.26)	4 (1.78)	3 (0.47)
Anemia	1 (0.26)	2 (0.89)	1 (0.16)
Increased SGOT	3 (0.77)	0 (0.0)	1 (0.16)
Increased SGPT	8 (2.06)	0 (0.0)	1 (0.16)
Asthma	2 (0.52)	0 (0.0)	1 (0.16)
Abnormal liver function (hepatic enzymes increased)	8 (2.06)	0 (0.0)	0 (0.0)
Hydroureter	3 (0.77)	0 (0.0)	0 (0.0)
Hostility	3 (0.77)	0 (0.0)	0 (0.0)
Agitation	3 (0.77)	1 (0.45)	0 (0.0)
Thyroiditis	2 (0.52)	0 (0.0)	0 (0.0)
Viral infection†	0 (0.0)	2 (0.89)	0 (0.0)
Neuropathy	0 (0.0)	3 (1.34)	0 (0.0)

Giannini et al for PRCSG. A&R 2009

Medically important infections

Table 4. Summary of medically important infections with exposure-adjusted rates per 100 patient-years

	MTX (n = 197)*	Etanercept (n = 103)	Etanercept plus MTX (n = 294)
Total patient-years of exposure	387.80	224.11	635.17
Total medically important infections, no. (rate per 100 patient-years)	5 (1.29)	4 (1.78)	13 (2.05)
Preferred term, no. (rate per 100 patient-years)			
Body as a whole			
Abscess	1 (0.26)	0 (0.0)	2 (0.31)
Sepsis	0 (0.0)	0 (0.0)	1 (0.16)
Blood culture positive	0 (0.0)	1 (0.45)	0 (0.0)
Infection	0 (0.0)	2 (0.89)	1 (0.16)
Bacterial infection	1 (0.26)	0 (0.0)	0 (0.0)
Viral infection	0 (0.0)	1 (0.45)	0 (0.0)
Digestive system			
Colitis	0 (0.0)	0 (0.0)	1 (0.16)
Gastroenteritis	0 (0.0)	0 (0.0)	1 (0.16)
Respiratory system			
Bronchitis	0 (0.0)	0 (0.0)	1 (0.16)
Pharyngitis	0 (0.0)	0 (0.0)	1 (0.16)
Sinusitis	1 (0.26)	0 (0.0)	0 (0.0)
Skin and appendages			
Herpes zoster	1 (0.26)	0 (0.0)	2 (0.31)
Urogenital system			
Pyelonephritis	1 (0.26)	0 (0.0)	2 (0.31)
Urinary tract infection	0 (0.0)	0 (0.0)	1 (0.16)

* MTX = methotrexate

Giannini et al for PRCSG. A&R 2009

Retention over time

Table 2. Summary of patient retention over time

	MTX only (n = 197)*	Etanercept only (n = 103)	Etanercept plus MTX (n = 294)
Months 0–6			
No. of patients available at the beginning of the period	197	103	294
Patient-years during the period	98.3	50.6	141.8
No. (%) of patients who withdrew during the period	42 (21.3)	12 (11.7)	39 (13.3)
No. (%) of patients who withdrew due to adverse events during the period	2 (1.0)	2 (1.9)	1 (0.3)
No. (%) of patients who withdrew due to insufficient therapeutic effect during the period	14 (7.1)	5 (4.9)	20 (6.8)
Months 6–12			
No. of patients available at the beginning of the period	155	91	255
Patient-years during the period	77.8	45.4	127.8
No. (%) of patients who withdrew during the period	22 (14.2)	15 (16.5)	27 (10.6)
No. (%) of patients who withdrew due to adverse events during the period	0 (0.0)	0 (0.0)	0 (0.0)
No. (%) of patients who withdrew due to insufficient therapeutic effect during the period	8 (5.2)	1 (1.1)	13 (5.1)
Months 12–24			
No. of patients available at the beginning of the period	133	76	228
Patient-years during the period	125.4	70.6	206.3
No. (%) of patients who withdrew during the period	38 (28.6)	19 (25.0)	58 (25.4)
No. (%) of patients who withdrew due to adverse events during the period	1 (0.8)	0 (0.0)	0 (0.0)
No. (%) of patients who withdrew due to insufficient therapeutic effect during the period	9 (6.8)	1 (1.3)	18 (7.9)
Months 24–36			
No. of patients available at the beginning of the period	95	57	170
Patient-years during the period	86.3	57.4	159.4
No. (%) of patients who withdrew during the period	29 (30.5)	10 (17.5)	38 (22.4)
No. (%) of patients who withdrew due to adverse events during the period	0 (0.0)	0 (0.0)	0 (0.0)
No. (%) of patients who withdrew due to insufficient therapeutic effect during the period	5 (5.3)	1 (1.8)	8 (4.7)

Giannini et al for PRCSG. A&R 2009