



DESIGN OF PAEDIATRIC RHEUMATOLOGY STUDIES: TIME TO MOVE TO ACTIVE COMPARATOR?

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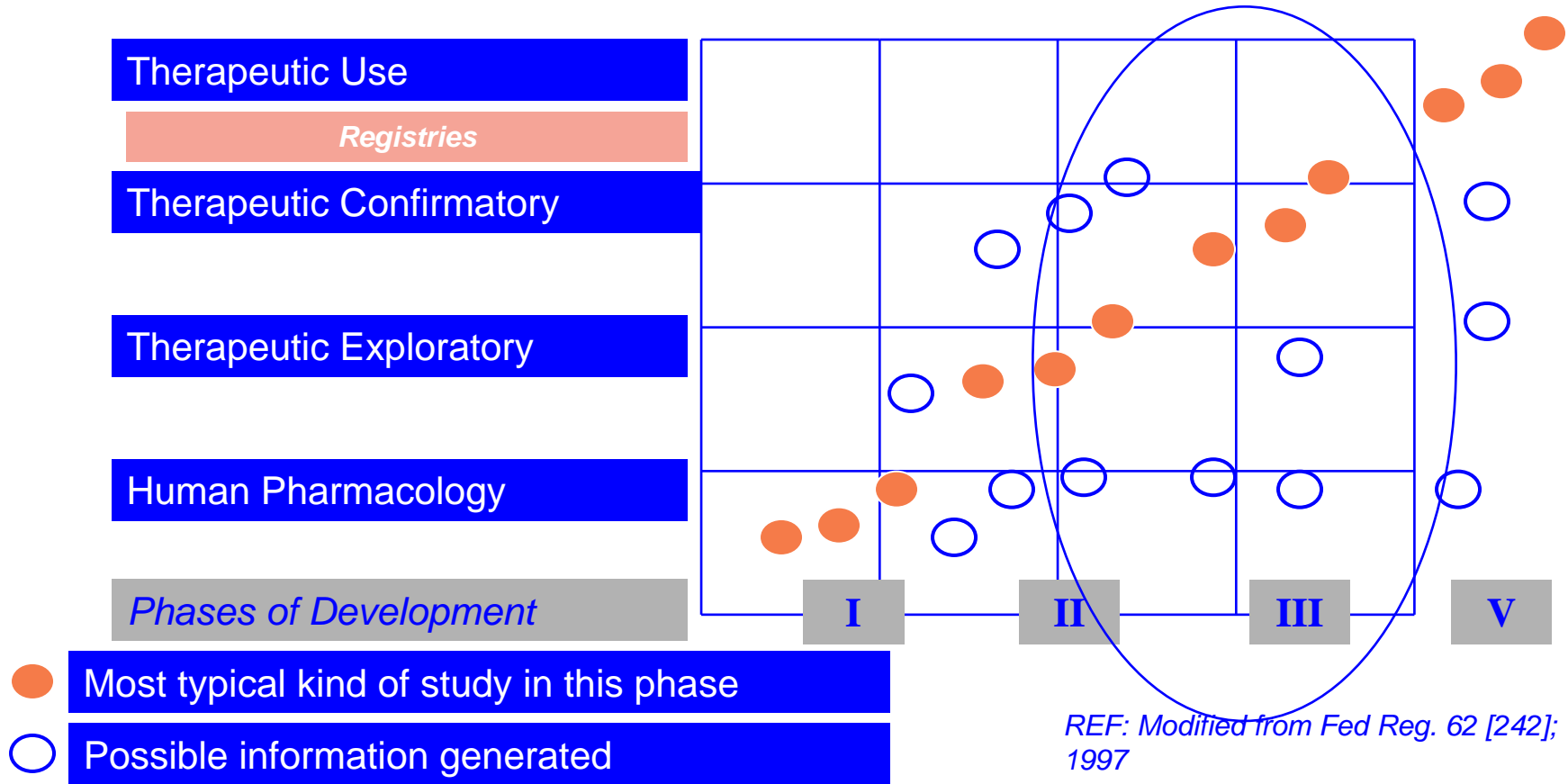
Istituto G. Gaslini Genova (ITALY)

EULAR Centre of Excellence in Rheumatology 2008-2013

Overview

- ◆ Control groups and study design
 - Classic parallel group
 - Withdrawal design
- ◆ Concerns in pediatric rheumatic diseases (PRD)
- ◆ Lessons learned from trials in JIA
- ◆ The issue of feasibility
- ◆ Academic studies

Clinical development program

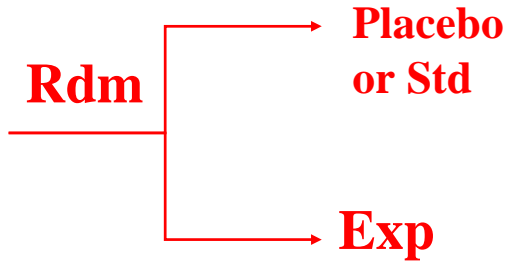




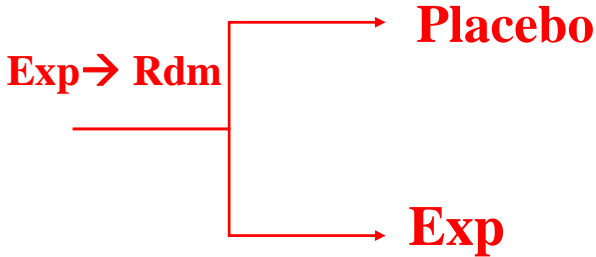
Control groups

1. **No treatment control**
2. **Placebo control**
3. **Active (positive) control**
4. **External control** (e.g. historical)
5. **Multiple control groups.** Several doses active±placebo.
6. **Fixed-dose, dose-response control**
 - *Not all types of control groups are equal in terms of scientific acceptability*
 - *Not all types of control groups are as ethically acceptable*

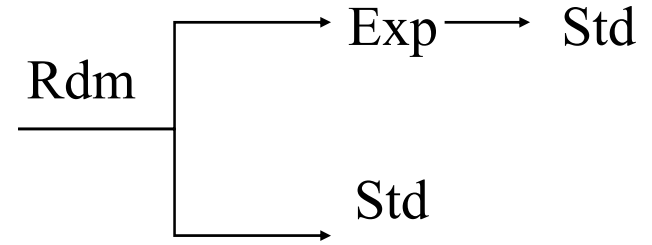
Main trial designs



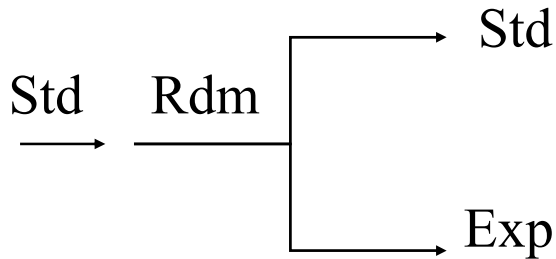
Parallel RCT (placebo, std)



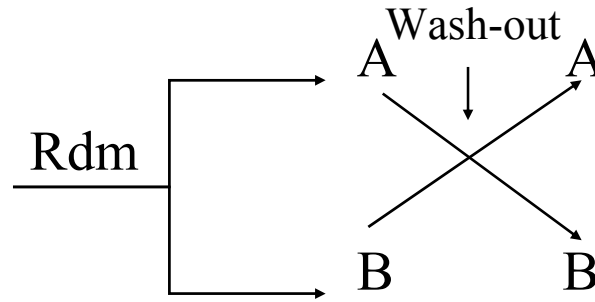
withdrawal



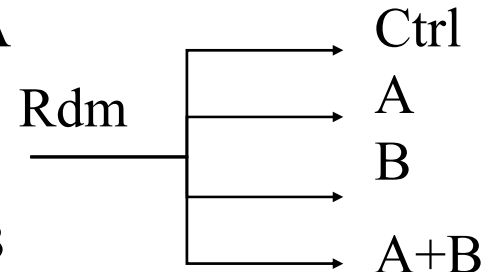
Trial post-event



Therapy exchange



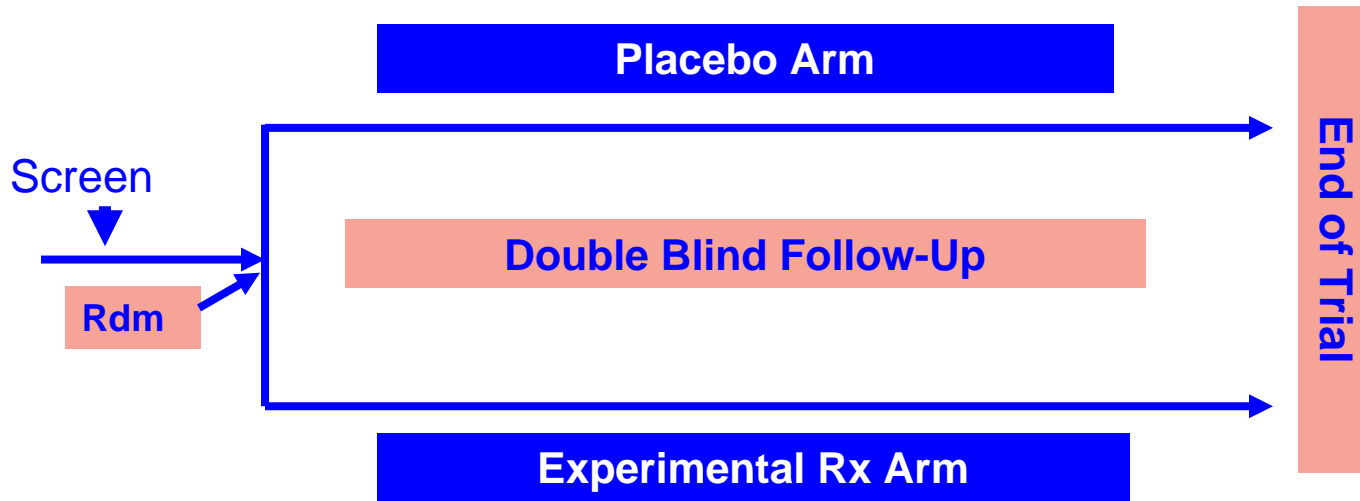
Cross-over (+- wash out)



Factorial trial 2x2

Rdm: randomization; Ctrl: control (no therapy or placebo); Exp: experimental; A+B: combination

Classic parallel RCT (gold standard)



ADVANTAGES

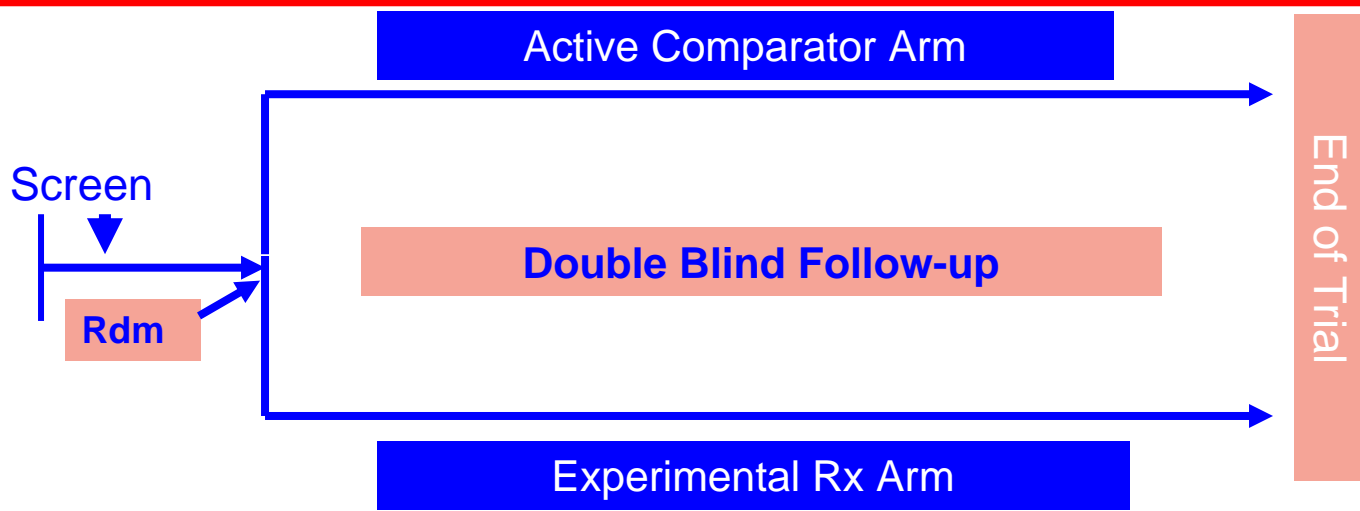
- Arms with clinical equipoise
- Trial has “assay sensitivity”**
- Analysis straight forward (**effect size**)
- Typical of Phase II/III trials

DISADVANTAGES

- Placebo may be ethically unacceptable**
- Doesn't necessarily allow for max info to be derived from every subject
- What to do with subjects who complete before end of trial?



ACTIVE CONTROL equivalency/non-inferiority



ADVANTAGES

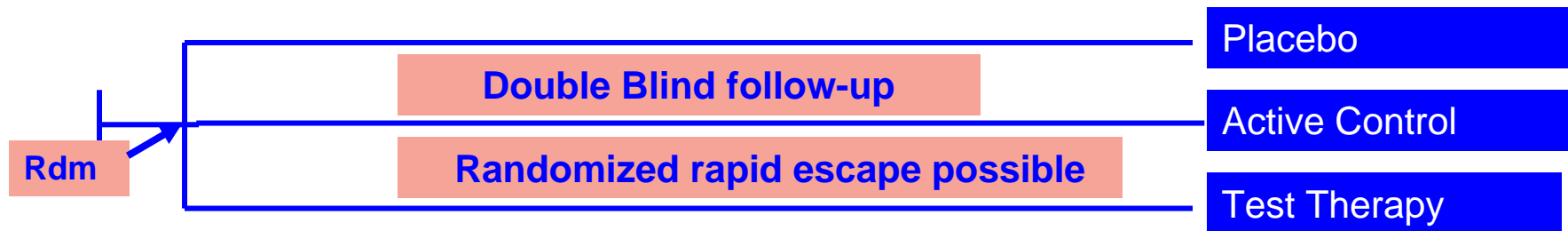
- Allow for comparison with standard therapy
- **User friendly** and simple design
- Arms with clinical equipoise
- Analysis (**confidence intervals**)
- Phase III trials

DISADVANTAGES

- **“Assay sensitivity” difficult**
- If the comparator data good, the approach resembles a historical control.
- Double-dummy design if different dosing
- **Typically require very large N’s**



ACTIVE CONTROL superiority trial



ADVANTAGES

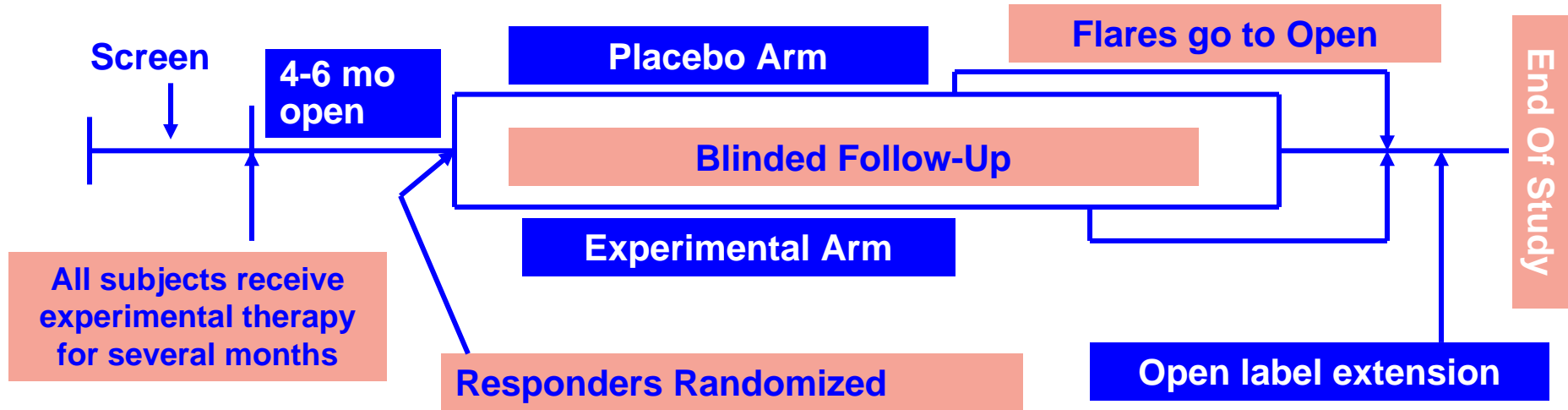
- **“Assay sensitivity” can be assessed**
- Measurement of the effect of the new drug to placebo is possible
- **Comparison of the two active agents** is possible using data totally within the trial

DISADVANTAGES

- **Sample sizes may be larger than 2 arm (but likely smaller than non-inferiority)**
- More complex designs harder to manage (particularly in multi-cent trials)
- **Placebo might be ethically unacceptable**
- Double-dummy design if different dosing



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)



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)*



JIA ACR pediatric core set and definition

- 1) Physician global assessment of overall disease activity
- 2) Parent or patient global assess. 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) ESR or CRP

ACR pediatric definition (FDA, EMEA accepted)

3/6 set variables improved $\geq 30\%$ (50%-70%-90%-100%) from baseline, with no more than one of the remaining variables worsened by $>30\%$

Response to therapy JSLE/JDM

◆ JSLE PRINTO/ACR pediatric criteria

- 2 of any 5 variables **IMPROVED** over baseline by at least 50%, no more than 1 of the remaining variables **WORSENERD** by more than 30%

◆ JDM PRINTO/ACR/EULAR pedc criteria

- 3/6 variable **IMPROVED** over baseline by at least 20%, no more than 1 of the remaining variables **WORSENERD** by more than 30% which cannot be muscle strenght.

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

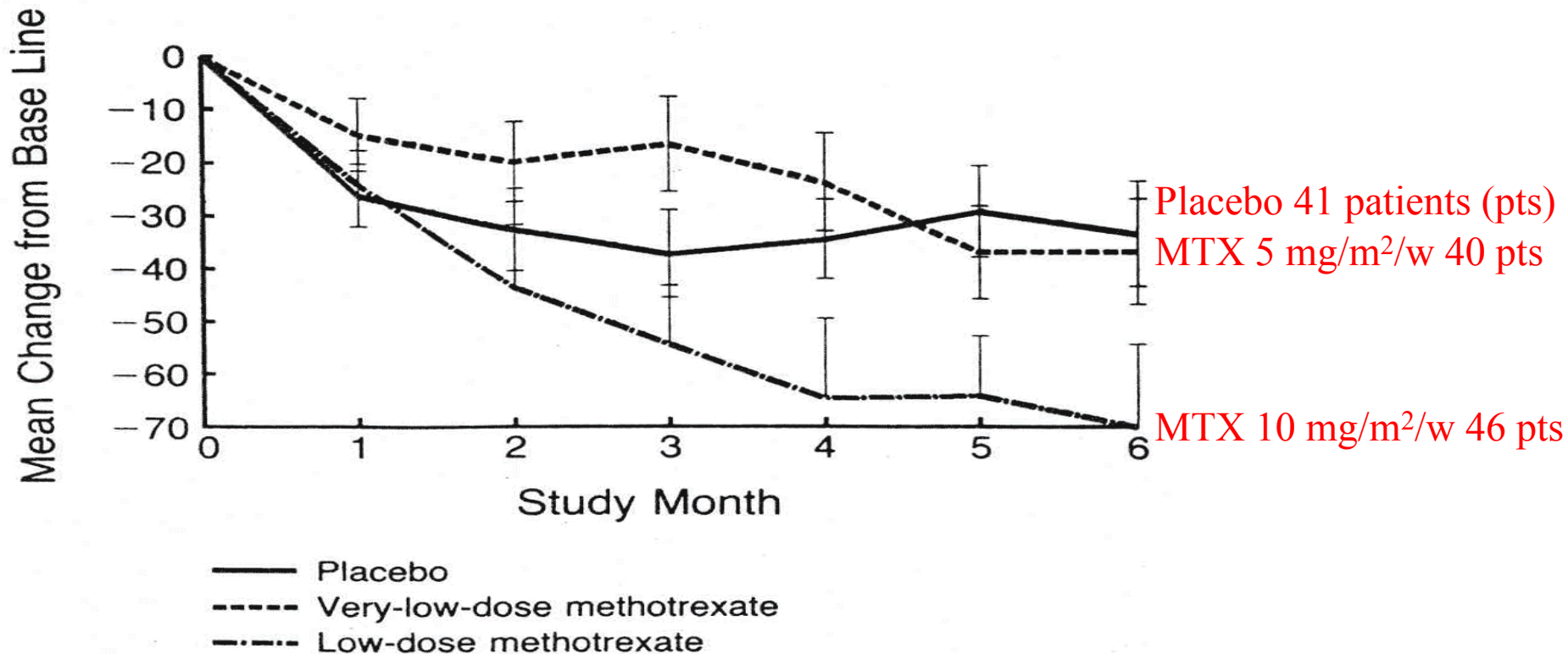
- **Etanercept** (Lovell for PRCSG NEJM 2000)
- **Adalimumab** (Lovell, Ruperto for PRINTO/PRCSG NEJM 2008)
- **Abatacept** (Ruperto, Lovell for PRINTO/PRCSG Lancet 2008)
- **Canakinumab** in sJIA (on going for PRINTO/PRCSG)
- **Tocilizumab in poly JIA** (on going for PRINTO/PRCSG)
- **Other to come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



JIA population

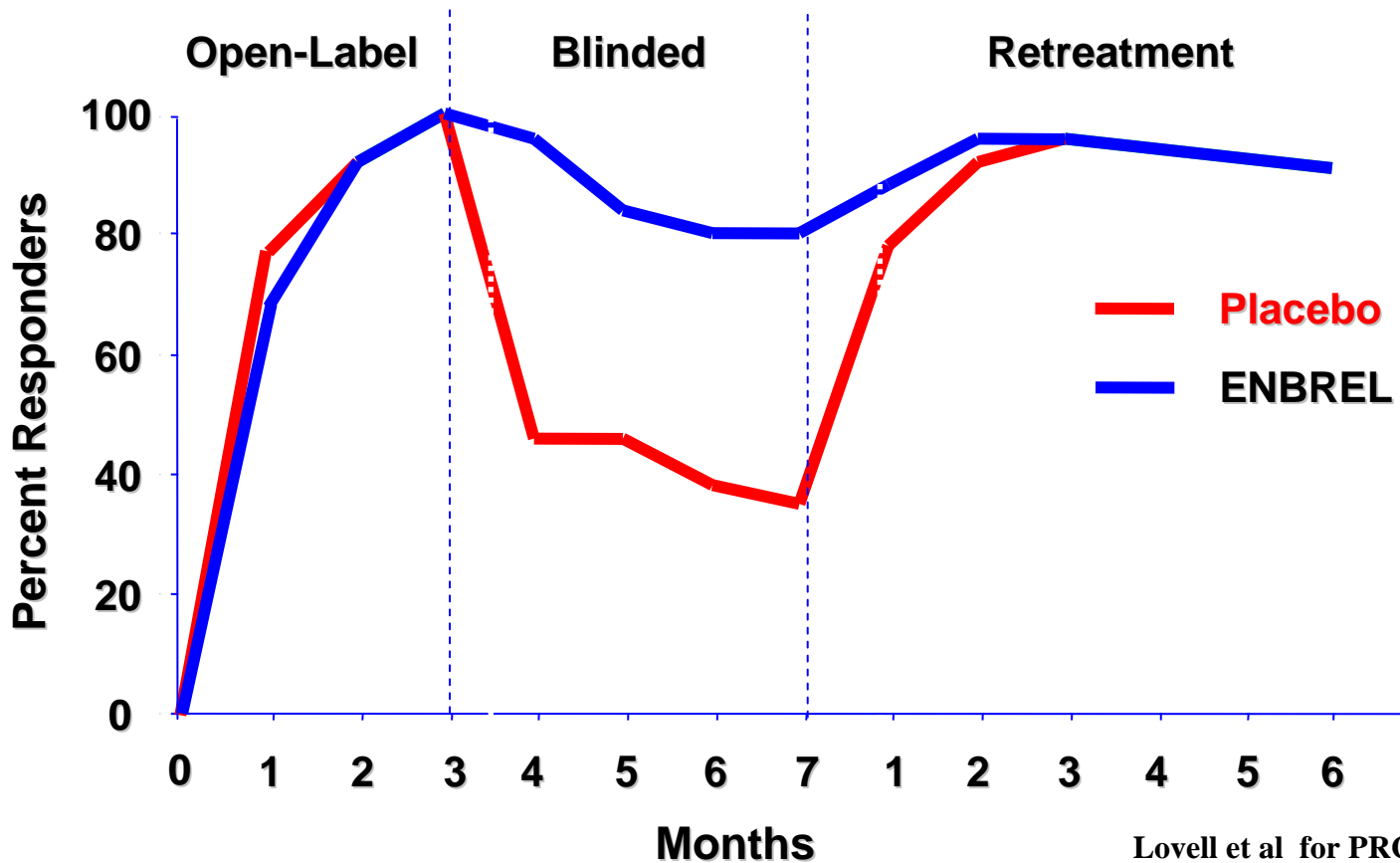
- ◆ Different populations similar efficacy/safety profile
- ◆ Methotrexate: **NSAIDs non responders**
- ◆ Etanercept: **MTX non responders** (NR) (MTX stopped)
- ◆ Adalimumab: (**MTX NR and MTX naive**)
- ◆ Abatacept: (**MTX NR and biologics NR**)
- ◆ Tocilizumab, canakinumab: **systemic JIA**

Methotrexate in JIA (USA/USSR)



Change in the articular severity score

Etanercept in JIA



Placebo effect in JIA

TABLE 4: Key data in the meta-analysis

Number	N responders	N treated	Duration (months)	Weight (%)	Estimated response rate (CI)
1	16	51	12	15.86	31.4 (19.5, 46.0)
2	28	85	6	27.12	32.9 (23.4, 44.1)
3	14	39	6	12.96	35.9 (21.7, 52.6)
4	9	26	4	8.50	34.6 (17.9, 55.6)
5	15	88	4	17.97	17.0 (10.2, 26.9)
6	3	34	3	3.95	8.8 (2.3, 24.6)
TOTAL	85	323			28.9 (24.0, 34.2)

28.9% (95% CI 24-32)



Sample size based on ACR 30

Drug	Alfa	Power	Delta	Sample	Active	Placebo	Delta
Parallel							
Infliximab	5%	79%	55-30=25%	120	65%	48%	18%
Tocilizumab (2:1 tcz:placebo)		80%	70-40=30%	108			
Withdrawal					Flare		
Adalimumab	5%	80%	70-40=30%	171/ 116	43%	71%	28%
Abatacept	5%	95%	65-35=30%	200/ 128	42%	75%	33%
Canakinumab	2.5%*	90%	70-25=50%	214/ 58			



Registrative trials

	Western Europe	Eastern Europe	Latin America	North America	Total
Meloxicam	130	94			224
Etanercept				69	69
Infliximab	61	10	28	11	110
Adalimumab	57	26		88	171
CTL4-Ig	75		108	31	214
Tocilizumab	59	7	22	24	112



Active comparator? Non-inferiority

Drug	ACR response	Active N	Active % (95% CI)	Exp 1 (-5%)	N 1	Exp 2 (-10%)	N 2
Etanercept	30%	51/69	74% (62-84%)	70%	4008	66.5%	1196
	50%	44/69	64% (51-75%)	61%	8210	57%	1548
	70%	25/69	36% (25-49%)	34%	17770	33%	7830
Methotrexate	30%	430/595	72% (68-76%)	69%	7316	65%	1410
	50%	360/595	61% (56-64%)	58%	8430	55%	2138
	70%	225/595	38% (34-42%)	36%	18218	34%	4486



Non inferiority trials

SAMPLES TOO HIGH

**TRIALS IMPOSSIBLE TO BE
IMPLEMENTED**



Active comparator? superiority

Drug	ACR response	Compar. N	Response % (95% CI)	Exp Tot sample (+20%)	Exp Tot sample (+30%)
Etanercept	30%	51/69	74% (62-84%)	190	54
	50%	44/69	64% (51-75%)	376	158
	70%	25/69	36% (25-49%)	1170	624
Methotrexate	30%	430/595	72% (68-76%)	210	68
	50%	360/595	61% (56-64%)	474	194
	70%	225/595	38% (34-42%)	2102	632



Superiority 2 arms

**DO WE CLINICALLY BELIEVE TO
FIND A DRUG THAT WILL BE
20-30% SUPERIOR TO
ETANERCEPT OR
METHOTREXATE?**



Superiority 3 arms

Drug	ACR response	Compar. N	Response % (95% CI)	Sample	Total Sample
• Etanercept	30%	51/69	74% (62-84%)	19	
• Experimental			70%	19	
• Placebo			29% (24-32%)	27	65
• Methotrexate	30%	430/595	72% (68-76%)	39	
• Experimental			69%	39	
• Placebo			29% (24-32%)	55	132



Superiority 3 arms

- ◆ Possible compromise but with following caveats
 - It will confirm superiority of standard therapy (etanercept or methotrexate) toward placebo
 - It might prove superiority of experimental drug toward placebo
 - **It WILL NOT** demonstrate non-inferiority, superiority or equivalence of standard therapy (etanercept or MTX) versus experimental
 - It will remain the ethical problem to treat active patients with placebo when an effective treatment is available



“Me too” drugs? e.g. other anti-TNF

Should we consider

PK-PD trials (dose finding)
followed by a **registry** for
long term safety/efficacy?

Conclusions

- ◆ MTX withdrawal still the “gold standard” for new therapy
- ◆ Consider PK/PD plus registry for me too drugs

◆ **These slides represent the PRINTO/PRCSG point of view**

◆ **Acknowledgments**

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