Critical reading
or the lesson how meta-research started

Next slides are taken from the instruction for the assignment quoted in Bad Pharma

Users' guides to the medical literature

- Series published in JAMA, 1993 – 2000
- Critical appraisal of clinical research papers

- Three questions you can always ask:
  1. Are the results valid? - validity
  2. What are the results? - results
  3. Can I apply these results to my patient? - applicability

- Specific questions depending on kind of study

Users' Guides for an Article About Therapy

I. Are the results of the study valid?

- Primary Guides:
  - Was the assignment of patients to treatments randomized?
  - Were all patients who entered the trial properly accounted for and attributed at its conclusion?
  - Was follow-up complete?
  - Were patients analyzed in the groups to which they were randomized?
- Secondary Guides:
  - Were patients, health workers, and study personnel "blind" to treatment?
  - Were the groups similar at the start of the trial?
  - Aside from the experimental intervention, were the groups treated equally?

II. What were the results?

- How large was the treatment effect?
- How precise was the estimate of the treatment effect?

III. Will the results help me in caring for my patients?

- Can the results be applied to my patient care?
- Were all clinically important outcomes considered?
- Are the likely treatment benefits worth the potential harms and costs?

Checklist Clinical Trials

1. What was the research question?
2. Was a method of randomisation performed?
   Yes / No / Don't know
3. If yes, how was randomisation performed?
4. Was the treatment allocation concealed?
   Yes / No / Don't know
5. If yes, how was concealment of treatment allocation implemented?

Checklist Clinical Trials

6. Were the groups similar at baseline regarding the most important prognostic indicators?
   Yes / No / Don't know

7. What was the largest difference between groups?

8. Were eligibility criteria specified?
   Yes / No / Don't know

9. Name two eligibility criteria for patients from this trial

Checklist Clinical Trials

10. Was the outcome assessor blinded?
    Yes / No / Don't know

11. If yes, how was blinding performed

12. Was the care provider blinded?
    Yes / No / Don't know

13. If yes, how was blinding performed

14. Was the patient blinded?
    Yes / No / Don't know

15. If yes, how was blinding performed

Checklist Clinical Trials

14. Were point estimates and measures of variability presented for the primary outcome measures?
    Yes / No / Don't know

15. State the outcome for the primary endpoint, including 95% confidence interval, standard error, standard deviation, or p-value

16. Did the analysis include an intention-to-treat analysis?
    Yes / No / Don't know

17. What was the percentage of drop-out during the trial?

Checklist Clinical Trials

20. Was the study population comparably described in the advertisement and the article?
    Yes / No
21. Was the control group comparably described in the advertisement and the article?
    Yes / No
22. Was the intervention comparably described in the advertisement and the article?
    Yes / No
23. Was the primary endpoint comparably described in the advertisement and the article?
    Yes / No
24. Did the article mention that the pharmaceutical company (that placed the advertisement) sponsored the trial?
    Yes / No
25. Are there other reasons why the claim in the advertisement might not be justified?
    Yes (why?) / No
26. Is the claim in the advertisement justified by the trial?
    Yes / No

Validity, Results and Applicability

Topic	Answer	VRA
research question	PICO	
randomisation performed?	How?	
treatment allocation concealed?	Yes, No, Don't know	
Groups similar at baseline?	Yes, No, Don't know	
In and exclusion ciriteria given?	Yes, No, Don't know	
Blinding (outcome assessor, caregiver)?	Yes, No, Don't know	
Point estimate AND variability provided?	Yes, No, Don't know	
Intention to treat perfomed?	Yes, No, Don't know	
Drop out?	Yes, No, Don't know	
Comparison with advertisement	Yes, No	

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Randomized Trial of Tocilizumab in Systemic Juvenile Idiopathic Arthritis

Fabrizio De Benedetti, M.D., Ph.D., Hermine I. Brunner, M.D., Nicolino Ruperto, M.D., M.P.H., Andrew Kenwright, B.Sc., Stephen Wright, M.D., Inmaculada Calvo, M.D., Ruben Cuttica, M.D., Angelo Ravelli, M.D., Rayfel Schneider, M.D., Patricia Woo, M.D., Ph.D., Carine Wouters, M.D., Ricardo Xavier, M.D., Lawrence Zemel, M.D., Eileen Baildam, M.D., Ruben Burgos-Vargas, M.D., Pavla Dolezalova, M.D., Stella M. Garay, M.D., Rosa Merino, M.D., Rik Joos, M.D., Alexei Grom, M.D., Ph.D., Nico Wulffraat, M.D., Zbigniew Zuber, M.D., Francesco Zulian, M.D., Daniel Lovell, M.D., M.P.H., and Alberto Martini, M.D., for the PRINTO and PRCSG*

N Engl J Med 2012;367:2385-95.

- Summary of the authors
- Maximum of 200-300 words

ABSTRACT

BACKGROUND

Systemic juvenile idiopathic arthritis (JIA) is the most severe subtype of JIA; treatment options are limited. Interleukin-6 plays a pathogenic role in systemic JIA.

METHODS

We randomly assigned 112 children, 2 to 17 years of age, with active systemic JIA (duration of ≥6 months and inadequate responses to nonsteroidal antiinflammatory drugs and glucocorticoids) to the anti–interleukin-6 receptor antibody tocilizumab (at a dose of 8 mg per kilogram of body weight if the weight was ≥30 kg or 12 mg per kilogram if the weight was <30 kg) or placebo given intravenously every 2 weeks during the 12-week, double-blind phase. Patients meeting the predefined criteria for nonresponse were offered open-label tocilizumab. All patients could enter an open-label extension.

RESULTS

At week 12, the primary end point (an absence of fever and an improvement of 30% or more on at least three of the six variables in the American College of Rheumatology [ACR] core set for JIA, with no more than one variable worsening by more than 30%) was met in significantly more patients in the tocilizumab group than in the placebo group (64 of 75 [85%] vs. 9 of 37 [24%], P<0.001). At week 52, 80% of the patients who received tocilizumab had at least 70% improvement with no fever, including 59% who had 90% improvement; in addition, 48% of the patients had no joints with active arthritis, and 52% had discontinued oral glucocorticoids. In the double-blind phase, 159 adverse events, including 60 infections (2 serious), occurred in the tocilizumab group, as compared with 38, including 15 infections, in the placebo group. In the double-blind and extension periods combined, 39 serious adverse events (0.25 per patient-year), including 18 serious infections (0.11 per patient-year), occurred in patients who received tocilizumab. Neutropenia developed in 19 patients (17 patients with grade 3 and 2 patients with grade 4), and 21 had aminotransferase levels that were more than 2.5 times the upper limit of the normal range.

CONCLUSIONS

Tocilizumab was efficacious in severe, persistent systemic JIA. Adverse events were common and included infection, neutropenia, and increased aminotransferase levels. (Funded by Hoffmann–La Roche; ClinicalTrials.gov number, NCT00642460.)

N Engl J Med 2012;367:2385-95.

- Patient recruitment
  - P I C O
- Study design / defintions
  - P I C O
- Analyses

METHODS

STUDY DESIGN

This ongoing, 5-year study was conducted at 43 centers — members of the Paediatric Rheumatology International Trials Organisation[17] (PRINTO) and the Pediatric Rheumatology Collaborative Study Group (PRCSG) — and has two parts: a randomized, double-blind, placebo-controlled, parallel, two-group, 12-week phase and a single-group, open-label extension (up to 5 years). The institutional review board or independent ethics committee at each center approved the study. Par-

Table 1. Baseline Demographic and Clinical Characteristics of the Patients in the Intention-to-Treat Population.*

Characteristic	Placebo (N=37)	Tocilizumab (N=75)
Female sex — no. (%)	17 (46)	39 (52)
White race — no. (%)†	32 (86)	67 (89)
Age — yr	9.1±4.4	10.0±4.6
Weight — kg	31.7±16.8	34.7±20.9
Duration of disease — yr	5.1±4.4	5.2±4.0
Prior use of DMARDs		
Mean no. of DMARDs	1.4±1.4	1.3±1.1
≥1 DMARD — no. (%)	25 (68)	55 (73)
Methotrexate	20 (54)	45 (60)
Cyclosporine	12 (32)	21 (28)
Sulfasalazine	4 (11)	6 (8)
Thalidomide	3 (8)	7 (9)
Other‡	11 (30)	16 (21)
Prior use of a biologic agent — no. (%)	29 (78)	63 (84)

- Describes patient population aka study domain
- Are there large differences in baseline risk?

- Everything that happend after the start of the trial;
  - follow up, effect, safety

RESULTS

STUDY POPULATION

Of the 112 patients enrolled, 37 were randomly assigned to placebo and 75 to tocilizumab. Baseline demographic and disease characteristics were balanced between the groups (Tables 1 and 2). Patients had persistent disease (mean duration, 5 years) and polyarthritis (high counts of active joints), and approximately half had systemic features (fever or rash) at the time of enrollment.

A total of 20 patients who received placebo (54%) met the criteria for nonresponse (including 13 patients within the first 2 weeks), as well as 1 patient who received tocilizumab (1%); these patients did not complete the double-blind phase and made the transition to open-label tocilizumab. A total of 14 patients (2 patients during the double-blind phase and 12 during the open-label extension) withdrew from the study (Fig. S1 in the Supplementary Appendix).

Table 2. Change from Baseline in ACR Core Set of Variables and in Systemic and Laboratory Features of Juvenile Idiopathic Arthritis (JIA) during the Double-Blind Phase.*

Variable	Placebo (N=37)		Tocilizumab (N=75)		Difference (95% CI)
	Baseline	Week 12	Baseline	Week 12	
JIA ACR 30 response and no fever — no. (%)	—	9 (24)	—	64 (85)	61 (45 to 78)
ACR core set of variables†					
No. of joints with active arthritis‡	16.9	15.3	21.3	7.6	−70.4 (−92.3 to −48.5)§
No. of joints with limited range of motion¶	17.9	17.2	20.7	10.4	−86.9 (−128.9 to −44.8)§
Score for physician's global assessment of disease activity‖	61.4	53.8	69.6	22.1	−53.5 (−66.1 to −40.8)
Score for patient's global assessment of overall well-being**	56.3	54.4	60.3	21.8	−71.0 (−88.1 to −53.9)§
CHAQ-DI score††	1.7	1.5	1.7	1.0	−55.7 (−82.1 to −29.2)§

- Primairy Endpoint: point estimate and confidence interval ($p<0.05$?)

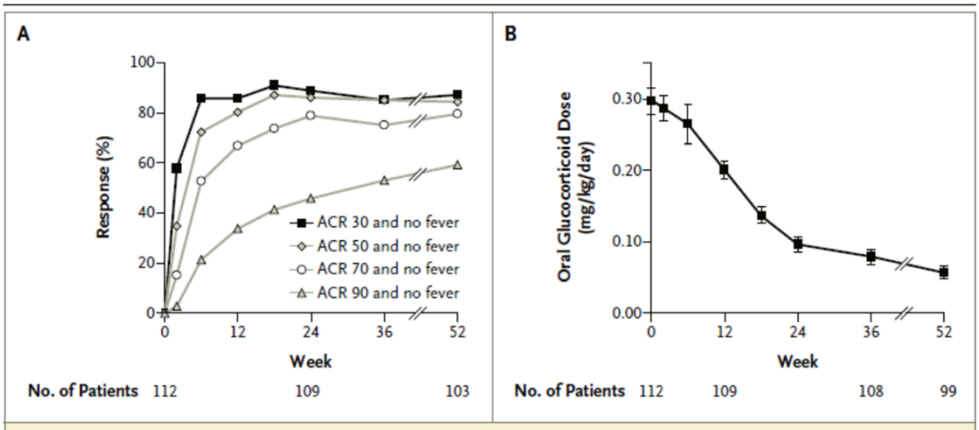


Figure 1. Clinical Improvement after 52 Weeks of Tocilizumab Treatment.

Panel A shows the American College of Rheumatology (ACR) responses for the core set of variables for juvenile idiopathic arthritis (JIA) and absence of fever. The JIA ACR 30, JIA ACR 50, JIA ACR 70, and JIA ACR 90 responses were defined as improvements of at least 30%, 50%, 70%, and 90%, respectively, in at least three of the six response variables, with worsening of more than 30% in no more than one of the six variables. In patients who were continuing treatment, the last-observation-carried-forward rule was applied to missing data on the JIA ACR response at visits. Panel B shows the mean oral glucocorticoid dose, with I bars indicating standard deviations. For each glucocorticoid used, the prednisone equivalent was calculated. Data at week 52 from three patients were not included because they had not yet reached that time point at the time of the data cutoff.

Table 3. Adverse Events.*

Variable	Double-Blind Phase†		Cumulative Data‡
	Placebo (N=37)	Tocilizumab (N=75)	Tocilizumab (N=112)
Exposure to tocilizumab — patient-yr	5.2	17.4	157.5
Adverse events including fever and JIA			
No. of events	49	161	1315
No. of events per patient-yr	9.4	9.3	8.4
Adverse events excluding fever and JIA			
No. of events	38	159	1266
No. of events per patient-yr	7.3	9.1	8.0
Most frequently reported events — no. of patients (%)§			
Upper respiratory tract infection	4 (11)	10 (13)	35 (31)
Pharyngitis or nasopharyngitis	3 (8)	10 (13)	37 (33)
Diarrhea	1 (3)	5 (7)	19 (17)
Headache	3 (8)	7 (9)	17 (15)
Serious adverse events			
Total — no. of events	0	4	39

- Short summary 'main results'
- Strengths and weaknesses
- Interpretaton by authors

DISCUSSION

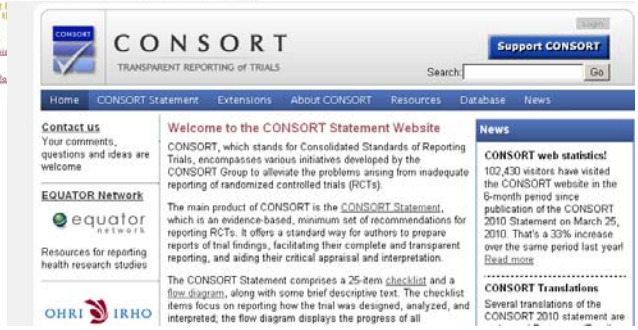
Persistently active systemic JIA represents a major therapeutic challenge. Traditional disease-modifying antirheumatic drugs and tumor necrosis factor inhibitors have limited benefit. The long-term use of glucocorticoids exposes patients to substantial toxicity with little, if any, effect on the outcome. Ample evidence points to excessive production of interleukin-6 as a key pathogenic factor in systemic JIA.[3,12] Our placebo-controlled trial showed that inhibition of interleukin-6 with tocilizumab is efficacious in patients with established disease and widespread chronic arthritis.

In the randomized, double-blind phase, JIA ACR response rates were higher among patients who received tocilizumab than among those who received placebo. The primary outcome (JIA ACR 30 response and absence of fever) occurred in

STROBE-statement.org

STREGA-statement.org

CONSORT-statement.org



STROBE	*Observational studies*
CONSORT	*Clinical trials*
STREGA	*Genetic association studies*
SQUIRE	*Quality improvement studies*
STARD	*Diagnosis accuracy studies*
MIAME	*'-omics' studies*

Twenty tips for interpreting scientific claims

21 NOVEMBER 2013 | VOL 503 | NATURE | 335

- Differences and chance cause variation
- Significance is significant
- Separate no effect from non-significance
- Effect size matters
- Bigger is usually better for sample size
- No measurement is exact
- Extreme measurements may mislead
- Controls are important
- Bias is rife
- Randomization avoids bias
- Regression to the mean can mislead
- Extrapolating beyond the data is risky
- Beware the base-rate fallacy
- Seek replication, not pseudoreplication
- Study relevance limits generalizations
- Correlation does not imply causation
- Dependencies change the risks
- Feelings influence risk perception
- Scientists are human
- Data can be dredged or cherry picked

Can the results be attributed to chance?

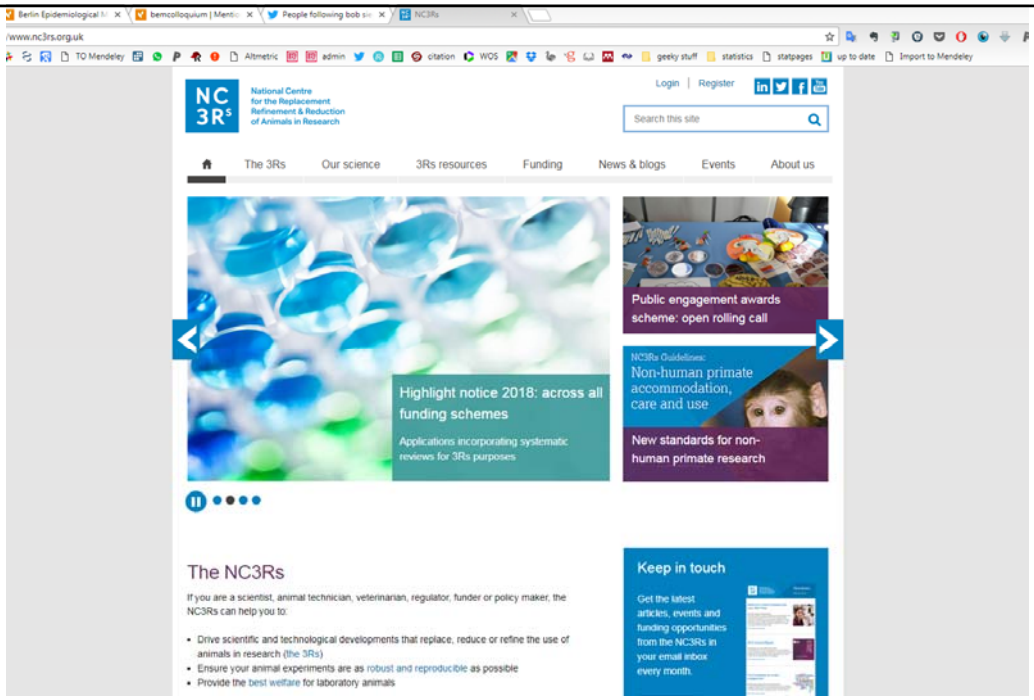
What are the characteristics of the Study design

Are the conclusions applicable to this case?

Interpretation of data: is conclusion justified?

Assignment for today

- Preclinical != preclinical
  - Or is it?
  - 5 groups: do we need a reporting guideline on preclinical sciences?
    - Spoiler: yes
  - What should be in there? Come up with a list of elements that should be in a reporting guideline, which at the end we will discuss and compare.



Arrive guideline

ARRIVE

The ARRIVE Guidelines Checklist

Animal Research: Reporting In Vivo Experiments

Carol Kilkenny[1], William J Browne[2], Innes C Cuthill[3], Michael Emerson[4] and Douglas G Altman[5]

[1]The National Centre for the Replacement, Refinement and Reduction of Animals in Research, London, UK, [2]School of Veterinary Science, University of Bristol, Bristol, UK, [3]School of Biological Sciences, University of Bristol, Bristol, UK, [4]National Heart and Lung Institute, Imperial College London, UK, [5]Centre for Statistics in Medicine, University of Oxford, Oxford, UK.

	ITEM	RECOMMENDATION	Section/ Paragraph
Title	1	Provide as accurate and concise a description of the content of the article as possible.	
Abstract	2	Provide an accurate summary of the background, research objectives, including details of the species or strain of animal used, key methods, principal findings and conclusions of the study.	
INTRODUCTION			
Background	3	a. Include sufficient scientific background (including relevant references to previous work) to understand the motivation and context for the study,	

Conclusion

- Meta research is designed to help us understand how we do research
  - Use and misuse of methods / policies etc
  - Reporting and sharing of results etc
  - Understanding the impact of different methods of science funding
  - Hopefully can be used to inform policies to improve the scientific enterprise
- Clinical research has a head start compared with preclinical research
  - Reporting guidelines is a good example