

Pediatric inflammatory bowel disease clinical trials: is there a role for placebo?

Athos Bousvaros MD MPH

European Medicines Agency Meeting

June 29, 2015

Disclosures

- Consulting
 - Takeda
 - Dyax
 - Cubist
- Data Safety Monitoring Board
 - Shire
- Medicolegal
 - Peabody Arnold
 - HMDR and S
- Research support
 - Prometheus
- The opinions expressed within this talk are my own. Evidence is provided where evidence exists.

Questions about placebo controlled trials in pediatric IBD

- What is the “placebo response” and “placebo relapse” rate in pediatric IBD?
 - Induction vs. maintenance
- Are placebo controlled trials ethical in pediatric IBD?
 - Are children under 18 “small adults”?
 - Is there still equipoise after a drug is approved in adults over age 18?
- Are placebo controlled trials feasible in pediatric IBD?
 - What do physicians, parents, and patients think?
- Are placebo controlled trials valuable in pediatric IBD?
 - Will trials be adequately powered to allow clinicians, researchers, and to detect meaningful differences?

USA drug development - then

- 1972 – Dr. Charles Edwards (FDA commissioner) – “majority of medications used in children lacked sufficient evidence of safety and effectiveness”
- 1977 – AAP Guidelines on Ethical Conduct
 - Emphasis on safety and unexpected toxicities
 - “Reasonable” evidence for efficacy should exist prior to studying children
 - Sick children should be enrolled in studies
 - Active or historical controls preferred over placebo
- 1979 – “Safety and effectiveness in pediatric patients have not been established”
 - 90% or more of pediatric drug use off label

USA drug development - Now

- Legislation to encourage and facilitate pediatric trials
 - Pediatric Research Equity Act
 - Best Pharmaceuticals for Children Act - 2007
 - Requirement of pediatric plan
- Increasing number of pediatric FDA labels (averaging about 30 per year)
- Increasing international collaboration (with EMA)
- Large lag time (5-10 years) between pediatric approval and adult approval
- Increasing number of insurance company denials simply based on pediatric age, even though medication has proven evidence of efficacy in adults. (aka “label” now is becoming the exclusive indication for payment)

Most drug trials in pediatric IBD have not included placebo

Comparison of 2 active drugs

- Budesonide vs. prednisone*

Open-label induction, followed by randomization of responders to different maintenance intervals

- Infliximab REACH trial (Crohn's) - 2 vs. 3 month infusions**
- Infliximab UC trial – 2 vs. 3 month infusions

Open-label induction, followed by randomization of responders to different maintenance doses***

- Adalimumab IMaGINE for Crohn's
- High vs. low dose for maintenance

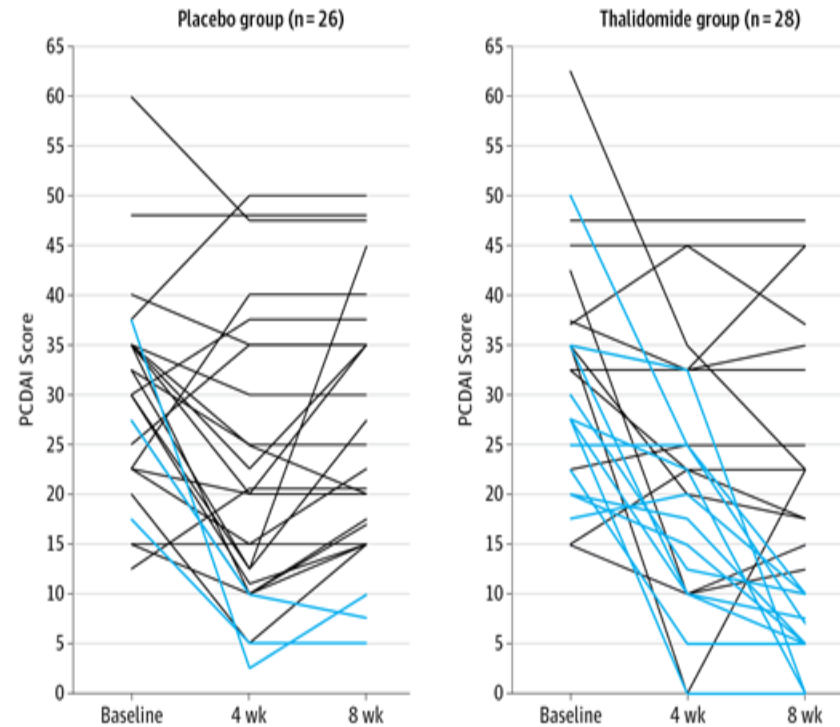
*Escher JC; Eur J Gastroenterol Hepatol. 2004;16(1):47-54

**Hyams Gastroenterology 2007; Mar;132:863

***Hyams Gastroenterology 2012; 143:65

Placebo response/remission rate in children is significant

- Induction trials
 - Thalidomide vs. placebo in CD
 - 54 children randomized, PCDAI primary endpoint
 - Failed multiple treatments, including immunomodulators and biologics
 - PCDAI used as primary endpoint – 8 week trial
 - Remission (PCDAI 10 or less) 46% vs. 12% placebo



Placebo relapse rate in patients on no therapy (after having received induction treatment)

- 6MP vs. placebo
Maintenance trial
 - New onset Crohn's patients all given corticosteroids, then randomized to 1.5 mg/kg/ day 6-MP (n=27) or placebo (n=28) for 18 months.
 - Steroids tapered over 2 months
 - After 18 months, 9% of 6MP patients vs. 47% of controls had relapsed.

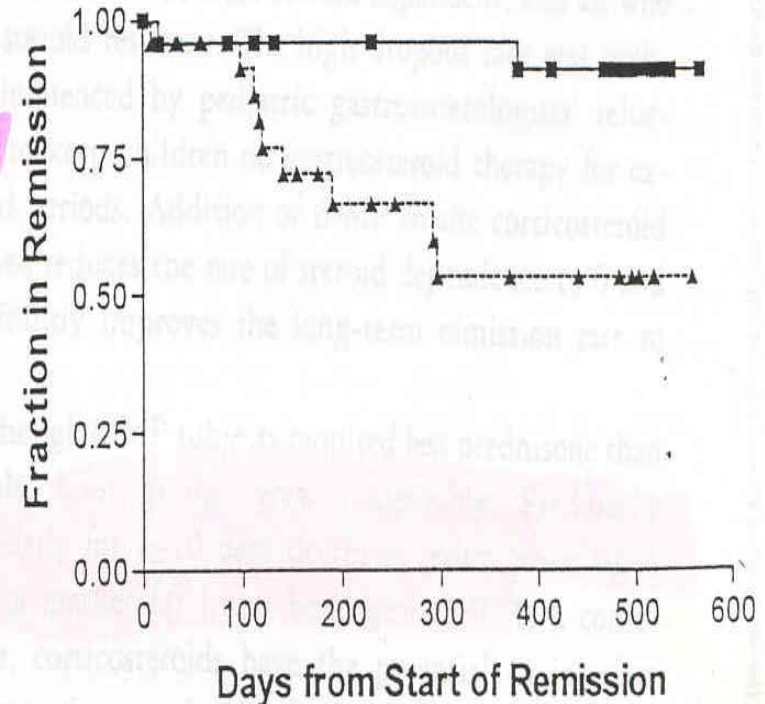
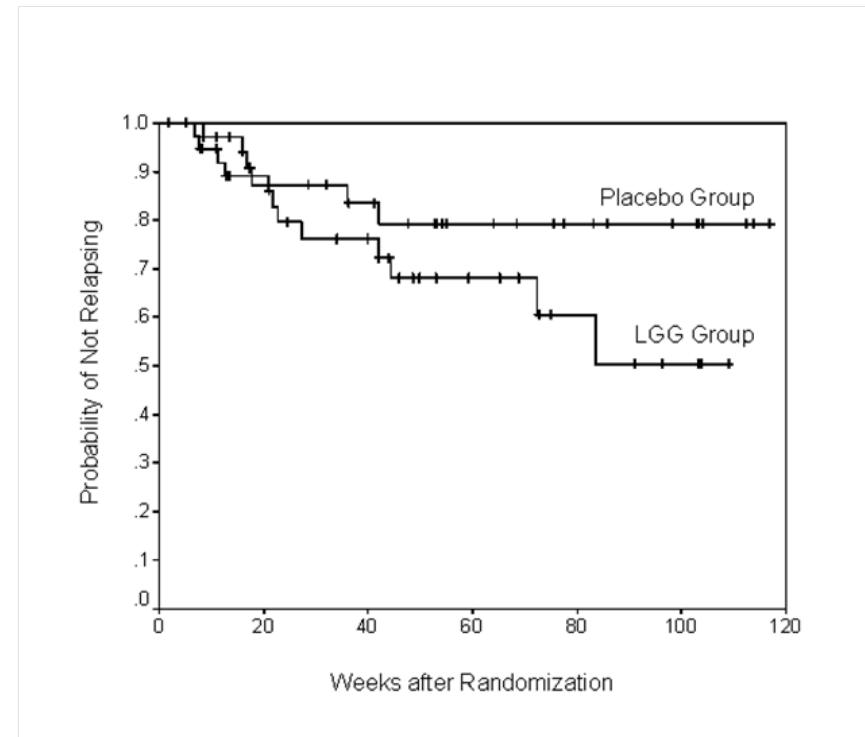


Figure 4. Kaplan-Meier survival curve of relapse-free duration of remission. ■, 6-MP; ▲, controls. $P < 0.007$.

Placebo relapse rate in patients on additional active therapy

- Over 70 patients enrolled
- Approximately 60% in each group were receiving 6-mercaptopurine
- No significant differences in the relapse rate of each group
 - 26% relapsed in LGG group
 - 19% relapsed in placebo group
- Time to relapse similar in both groups.
- Conclusion – Lactobacillus GG offers no benefit when added to standard therapy in the treatment of children with Crohn's disease



What is the placebo response in pediatric IBD?

- **Placebo response rate** for an induction study is probably around 10-15% for sick patients
- **Placebo relapse rate** (aka relapse rate after one withdraws medication) ranges from 20-50% over 1-2 years, depending on concomitant medications.
- Conclusions are limited, because of:
 - Limited number of trials
 - Imprecise assessments of remission (aka PCDAI instead of labs, calprotectin, endoscopic appearance).
 - Variable study designs
 - Concomitant therapies are a major confounder
- Placebo response and remission rates do need to be factored into study design (either through a placebo arm or through a “historical control placebo response rate”)
 - Effect of PROs and assessment of mucosal inflammation on placebo response rates needs to be investigated

Are placebo controlled trials ethical in children with IBD?

- Giving a pediatric label to a drug that does not work in children, or harms children, is unethical.
- Using a drug dose that is ineffective or toxic in children, simply based on adult data, is also unethical.
- Most children with IBD have a serious chronic illness, that is life-long. However, most life-threatening IBD can be successfully treated surgically (e.g. colectomy)
 - Patients who need imminent surgery are generally excluded from clinical trials in IBD.

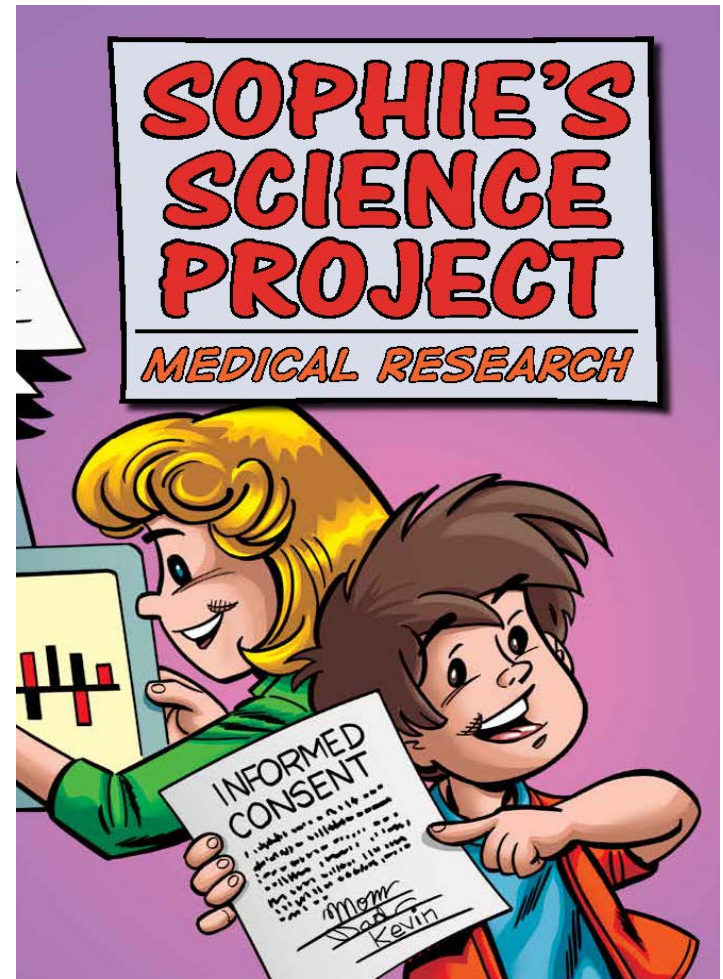
Precedent for placebo-controlled trials in juvenile idiopathic arthritis

- Horneff et al (Arthritis Res Therapy 2012) – adalimumab vs. placebo in juvenile onset ankylosing spondylitis
 - 34 patients, 8 week response 53% vs. 33%
- Lovell et al (NEJM 2008) – Patients with NSAID refractory JRA (n=171), randomized to adalimumab or placebo for 16 weeks
 - Concomitant MTX allowed, not mandated
 - No MTX – Disease flares 43% ADA, 71% placebo
 - With MTX – Disease flares 37% ADA, 65% placebo
 - Difference persisted through 104 weeks

Ethical trials in children require:

- **Equipoise**
- Consent from parent
 - Assent from child
- In studies that are greater than minimal risk:
 - “empirical evidence of sufficient direct benefit” from the medication that will be studied in the trial
- Placebo controls are considered “minor increase over minimal risk”
- Is withholding known effective treatment appropriate (depends on the severity of the disease)?

Roth-Cline and Nelson RM, in Mulberg,
“Pediatric Drug Development”



Are children and adults the same?

- If a drug is FDA/EMA approved in adults, and we believe pediatric and adult IBD is the same, then equipoise does not exist
 - (i.e. the drug almost certainly works in children)
- Genetics and response to therapy are similar in older children and adults (Jeffrey Hyams, GREAT 2)
- IBD in a 17 year old is probably the same as IBD in an 18 year old (i.e. legal age has no bearing on biology)
- However, IBD in a 5 year old (or in an 80 year old) may well be different from IBD in an 18 year old
- Differences in IBD and response to drugs exists at:
 - the extremes of life (on either end of the spectrum)
 - in high risk populations

What are the “high risk populations” in pediatric IBD?

- Critically ill children
 - Severe colitis
 - Imminent surgery
- “Very early onset IBD” (under age 5)
 - Some have undiagnosed immune deficiency
- Diagnosed immune deficiency
 - Anti-TNF therapy can be fatal in patients with chronic granulomatous disease*
 - Anti-TNF therapy ineffective in patients with IL10R mutations
- IBD developing in the post-transplant patient already receiving immunosuppressive therapy

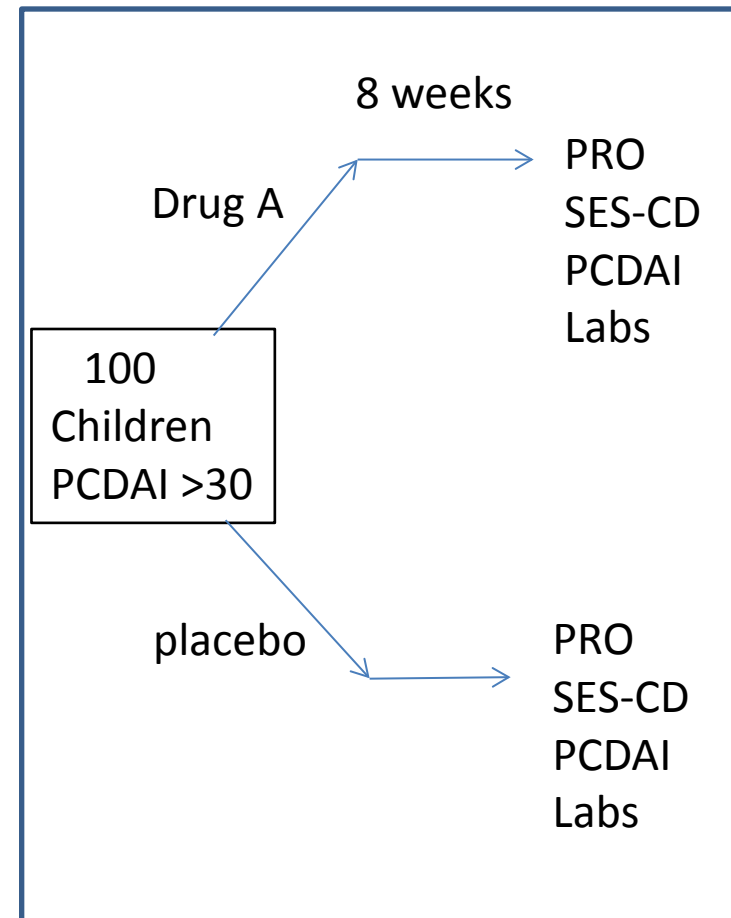
Underlying ethical principle

- “A child’s health or welfare should not be placed at a disadvantage by being enrolled in a clinical investigation”.
- Factors to be considered:
 - Anticipated benefit from the treatment
 - Severity of the disease
 - Alternative treatments available

Roth-Cline and Nelson RM, in Mulberg,
“Pediatric Drug Development”

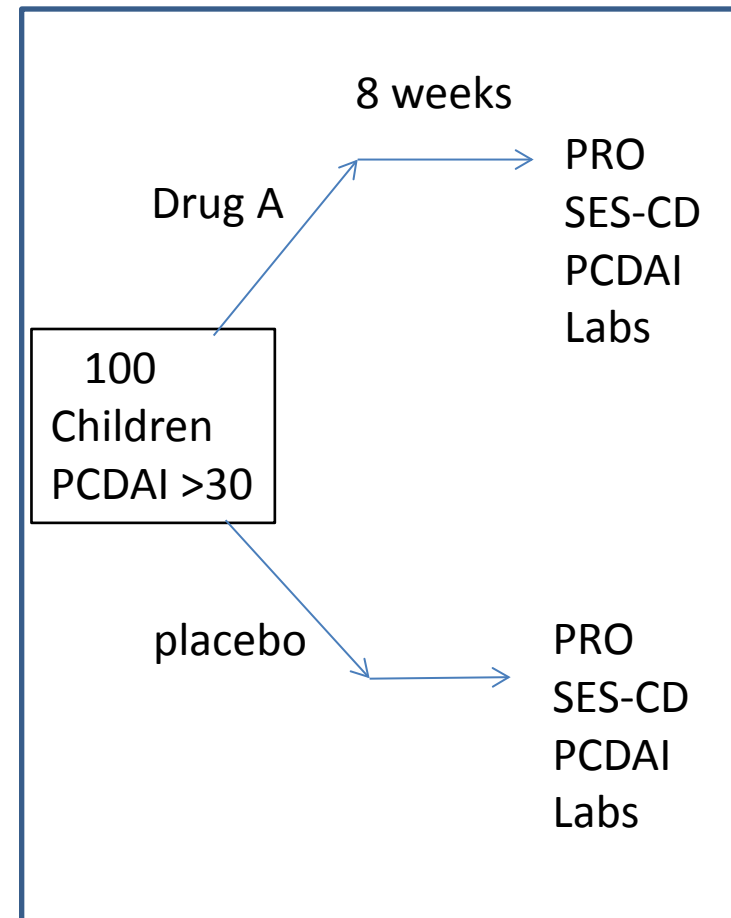
Ethical or not? Trial 1

- Drug A vs. Placebo for induction
 - Effective in active Crohn disease phase 2 studies
 - Not yet approved in adults or children
 - Induction trial in phase 3 wants to enroll both adults and children age 10 or over
 - 8 week trial, simple parallel design
- Ethical? Yes!
 - Equipoise still exists
 - “Reasonable” evidence of efficacy exists
 - Drug not available any other way
 - High risk children (e.g. those with immune deficiencies) not included



Ethical or not? Trial 2

- Drug A vs. Placebo for induction
 - Effective in active Crohn disease phase 3 studies in adults
 - FDA approved in adults, not children
 - Induction trial in phase 3 wants to enroll children age 0-18 years
 - 8 week trial, simple parallel design
- Ethical? Probably not
 - No equipoise in the older children
 - Drug has been approved in adults
 - Lack of access by children = discrimination by insurance
 - High risk children (e.g. very young, those with immune deficiencies) are included



Conclusions

- Testing drugs and getting data on safety and efficacy in children is essential, and requires partnership between academic centers, practitioners, industry, and regulatory agencies.
- Despite limited data, there is a placebo response rate in pediatric IBD which should be factored into trial design.
 - Function of measurements, concomitant medications.
- Ethical placebo controlled trials in children require equipoise
 - Ethical if done prior to drug approval in adults
 - Placebo is our best control for assessing efficacy and AE.
 - After approval, if there is no equipoise, consider other study designs to obtain drug dose and PK/PD data
- Special populations in pediatric IBD (e.g. very young patients, immune deficient patients) require a different approach
 - “rare disease” approach*