Clinical Trials
in
Inflammatory Bowel Disease

Gil Y. Melmed, M.D., Cynthia Walsh, R.N.
IBD Clinical Trials Unit, Cedars Sinai Medical Center
April 2013
Outline

• What is a clinical trial?
• Drug development process
• Clinical Trial Design
• What trials are out there now?
• Is this something for me to consider?
Drug Development Takes Time! (and $$$)
FDA Review of New Drugs

- Preclinical (animal) testing.
- Investigational New Drug
  - proposal for human testing in clinical trials.
- Phase 1 studies (SAFETY)
  - 20 to 80 healthy people
- Phase 2 studies (EFFICACY)
  - typically a few dozen to about 300 people
- Phase 3 studies
  - several hundred to about 3,000 people
- New Drug Application
Phase I:

Is it safe???
Phase II:

Does it work?
(i.e. should we invest in a Phase III???)
(and is it safe?)
Phase III:
Does it work???
(and is it safe?)
Phase IV:
Is it safe???
Clinical Trial Design
The Clinical Trial Gold Standard:

- Randomized
- Double-blind
- Placebo-controlled
Schema of a simple trial

Eligible patients → Randomize → RX group 1 → RX group 2
Why Randomize?

- Compare groups at the end of the trial
- Difference is because of the Rx
- For this you need comparable groups
- Purpose of randomization is to make the treatment groups comparable and unpredictable
- Ensures that only difference in groups is due to trial treatments

John Matthews. Why to Randomize a Randomized Controlled Trial? (and how to do it)
www.mas.ncl.ac.uk/~njnsm/talks/vascsurg/vascsurg.ppt
Why Double-Blind/Placebo control?

• Patient-blinding
  – Placebo effect is real (it’s really better)
  – Interpretation effect (it seems better even if it isn’t)
  – Study effect (people in studies are healthier)

• Investigator-blinding
  – Selection bias (pick responders for rx)
  – Observer bias (It seems better even if it isn’t)
  – Regression to the mean
Endpoints

• The outcome measure of interest
• Primary Endpoint
  – Eg. Disease activity
• Secondary Endpoint(s)
  – Other important outcomes
  – May provide preliminary data for future study
Trial Designs in IBD
Types of Clinical Trials in Crohn’s

• New agents with novel mechanisms
• New agents similar mechanism to approved agents
• Approved agents, new indication
• Special populations (e.g., pediatrics)
• Registries
• Diagnostic tests
Types of Clinical Trials in Crohn’s

• Induction (putting out the fire)
  – Mild- to- moderate disease
  – Severe disease
  – Fistulizing disease
  – Steroid-dependent or refractory
  – Refractory to immunosuppressives
• Maintenance (keeping the fire out)

Sandborn Activity Indices: CD. 2005
Commonly Used Endpoints in Clinical Trials

- Disease Activity (clinical, endoscopic)
  - Response
  - Remission
- Biomarkers (CRP, sigmoidoscopy)
- Health-related Quality of Life
# Crohn’s Disease Activity Index

## Description Multiplier

<table>
<thead>
<tr>
<th>Description</th>
<th>Multiplier</th>
</tr>
</thead>
<tbody>
<tr>
<td># liquid/soft stools</td>
<td>X 2</td>
</tr>
<tr>
<td>Abdominal pain (0=no, 1=mild, 2=moderate, 3=severe)</td>
<td>X 5</td>
</tr>
<tr>
<td>General Well-being (0=generally well, 1 = slightly under par, 2=poor 3=very poor 4=terrible)</td>
<td>X 7</td>
</tr>
<tr>
<td># complications (arthritis, iritis, fissure, fistula, fever, etc…)</td>
<td>X 20</td>
</tr>
<tr>
<td>Use of antidiarrheal medication? (0=no, 1=yes)</td>
<td>X 30</td>
</tr>
<tr>
<td>Abdominal mass (0=no, 2=?, 5=definite)</td>
<td>X 10</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>X 6</td>
</tr>
<tr>
<td>Body Weight (1-weight/standard) x 100</td>
<td>X 1</td>
</tr>
</tbody>
</table>

*Range 0 – 600, higher is worse; traditional remission = <150*
Adalimumab (Humira)
GAIN: Induction of Clinical Remission in Patients Who Lost Response or Were Intolerant to Infliximab
(Gauging Adalimumab Efficacy in Infliximab Nonresponders)

<table>
<thead>
<tr>
<th>Screening period</th>
<th>Randomized, double-blind, placebo-controlled period</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 days</td>
<td>Week 0</td>
</tr>
<tr>
<td></td>
<td>n=166</td>
</tr>
<tr>
<td>325 patients</td>
<td>n=159</td>
</tr>
</tbody>
</table>

Primary endpoint: Proportion of patients achieving clinical remission (CDAI <150) at Week 4


Please see Abbott representative for full prescribing information. 64E-175921
### CLASSIC I: Induction of Clinical Remission

*(Clinical assessment of Adalimumab Safety and efficacy Studied as Induction therapy in Crohn’s disease)*

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<tr>
<td>14 days</td>
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<tr>
<td></td>
<td><strong>Week 0</strong></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
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<tr>
<td></td>
<td><strong>Week 2</strong></td>
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<tr>
<td></td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td><strong>Week 4</strong></td>
</tr>
<tr>
<td></td>
<td>40 mg → 20 mg</td>
</tr>
<tr>
<td></td>
<td>80 mg → 40 mg</td>
</tr>
<tr>
<td></td>
<td>160 mg → 80 mg</td>
</tr>
</tbody>
</table>

**299 patients**

*Primary endpoint was induction of clinical remission (CDAI <150) in the 2 higher dose groups vs placebo at Week 4. Secondary endpoint included decrease in CDAI by ≥70 points from baseline.*


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CHARM: Maintenance of Clinical Remission
(Crohn’s trial of the fully Human antibody Adalimumab for Remission Maintenance)

Screening period
14 days

Baseline / Week 0
N=854*
80 mg

Week 2
40 mg

Week 4
n=778

Week 4 stratified by CR-70 response†

Randomized, double-blind, placebo-controlled

Week 26†

Placebo (n=170)
40 mg ew (n=157)
40 mg eow (n=172)

Placebo
40 mg ew
40 mg eow

Week 56†

Randomized Responders

Flare / Nonresponse

40 mg eow Open-label

Flare / Nonresponse

40 mg ew Open-label

*Previous anti-TNF exposure: 49.6%.
†CDAI decrease ≥70 points from baseline.
‡Two coprimary endpoints: Clinical remission (CDAI <150) at Weeks 26 and 56 in Week 4 CR-70 responders vs placebo.


Please see Abbott representative for full prescribing information. 64E-175921
Lots of rules to follow in a trial!

- **Informed consent** process and documents
- **Eligibility** criteria must be met
  - Inclusion
  - Exclusion
- Required and optional tests and procedures
- **Schedule** of visits
Reasons one might think about participation in a trial

• Limited standard of care options available
  – I’ve tried them all and they don’t work
  – I’ve tried them all and I can’t tolerate them
• I don’t feel comfortable with the risks of what’s available
• Want to participate in research for IBD
• Access to care
Reasons one should *not* participate in a clinical trial

- I want to please my doctor
- I want to please my family
- I want to get paid
- I won’t be able to follow all the rules
What Trials are Currently Actively Recruiting for IBD in SoCal?

www.clinicaltrials.gov

www.ccfa.org

• Phase I
  – Placenta cells (CD)
  – Vitamin D (pediatric CD)

• Phase II
  – MEDI2070 anti IL23 (CD)
  – Anti-trafficking (UC)
  – Whipworm eggs for UC

• Phase III
  – Stelara (anti IL12/23) (CD)
  – Entocort (children with CD)
  – Tofacitinib (Xeljanz) (UC)