Future Directions in IBD: Treatments & Approaches

JASON HARPER, MD
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Outline

- Introduction
- Clinical trials: Logistics & Expectations
- Novel Pharmacotherapies
- Novel Approaches
  - Dietary therapy
  - FMT
  - Personalized medicine
Introduction

methotrexate
6-MP
1953

Sulfasalazine (UC)
1977

Azathioprine
1968

Mesalamine (UC)
1992

adalimumab/Humira (CD)
2002

vedolizumab/Entyvio (UC/CD)
2008

certolizumab pegol/Cimzia(CD)
2014

infliximab/Remicade (CD)
1998

Ustekinumab/Stelara (CD)
2016

Golimumab/Simponi (UC)
2013

Ustekinumab/Stelara (CD)
2016

infliximab/Remicade (UC)
2005
Clinical Trials: Nomenclature (New Agents)

**Phase I**
- Very small #
- How is drug metabolized?
- Safe dose ranges

**Phase II**
- Still small # of people
- Does drug work?
- Many drugs stop here

**Phase III**
(>=2 of these before regulatory approval)
- Larger # of people
- Does drug really work?
- Side effects
- Comparison to other treatments
Understanding Clinical Trials

- Placebo-controlled
  - Blinding (single versus double)
- Cross-over
- Randomization
- Active treatment comparison
  - No placebo arm
- Second generation therapy versus novel mechanism of action
Inclusion/Exclusion Criteria

- Common inclusion criteria for IBD trials
  - Moderate to severe disease
  - Endoscopic evidence of disease
  - Failure of first-line IBD therapies

- Common exclusion criteria for IBD trials
  - Multiple prior IBD-related surgeries
  - Having an ostomy
  - Pregnancy (or plan for such)
  - Active infection
  - History of cancer
  - Recent exposure to certain biologic therapies (planned wash-out)
    - Exposure of any kind to similar drug class
Study Protocol: CHARM

854 patients enrolled
778 assessed for response at week 4 and randomized
76 patients withdrew prior to Week 4
45 adverse events
13 lack of efficacy
10 protocol violations
5 withdrawal of consent
1 lost to follow-up
1 death
1 administrative reasons

261 assigned to placebo
170 randomized responders
32 completed 56 weeks on double-blind therapy

91 randomized non-responders
11 completed 56 weeks on double-blind therapy

260 assigned to adalimumab 40 mg eow
172 randomized responders
77 completed 56 weeks on double-blind therapy

88 randomized non-responders
25 completed 56 weeks on double-blind therapy

257 assigned to adalimumab 40 mg weekly
157 randomized responders
82 completed 56 weeks on double-blind therapy

100 randomized non-responders
24 completed 56 weeks on double-blind therapy
Informed Consent: Questions to Ask

- How long is treatment provided? Can I continue to receive study drug after the trial is completed?
- How many visits are required? Am I reimbursed for time/travel?
- How likely am I to get a placebo?
- What happens if I get sicker during the trial? What happens if I don’t respond to my treatment?
- Am I (my insurance) responsible for any costs during this trial?
- Who is supervising my care during the trial?
- What are my alternative treatment options?
Clinical Trials: Pros

- Early access to novel therapies
  - Safer? More effective?
- Close clinical attention
- Help others/advance scientific understanding
- Access to expensive medications without cost (including presently available medications)
Clinical Trials: Cons

- Unproven efficacy/safety
- Significant time expenditure
- Possibility of not receiving therapy after completion of trial
- Uncertain treatment allocation
Novel Pharmacotherapy

- Anti-adhesion therapy
  - Etrolizumab (anti-β7)
  - Anti-MadCAM Ab
- Oral therapy
- Trafficking inhibitors
  - Ozanimod
- Janus kinase inhibitors
  - Tofacitinib
- Anti-SMAD therapy
  - Mongersen
Anti-Adhesion Therapy

Peyrin-Biroulet et al. Lancet 2008
Etrolizumab

- Subcutaneous agent against β7 subunit of integrin complex
- Currently in phase III development for both UC/CD

Vermeire et al. Lancet 2014
Anti-MadCAM Therapy (PF-00547659)

- Completed phase II results for both Crohn’s and ulcerative colitis (OPERA/TURANDOT)
- Subcutaneous agent
- Efficacy noted in UC
  - CD data noted signals for response in people with elevated inflammatory markers
- Phase III trials will be starting up shortly
Oral Anti-Adhesion Therapy

- AJM300: oral α4-integrin inhibitor
- Phase IIA data presented out of Japan suggesting efficacy in UC
- Concern given mechanism of action for risk of PML
- No active trials ongoing
Trafficking Inhibitors

Trafficking Inhibitors, cont.

- First generation: fingolimod → approved for multiple sclerosis
- Non-specific binding to multiple receptors → idiosyncratic side effects
- Ozanimod: 2nd generation therapy, more specific to type 1 receptor → less side effects
- Oral therapy
- Phase II trial completed for UC
- Phase III ongoing
- Phase II trial in progress for CD
JAK inhibitors
JAK inhibitors

- Broad anti-inflammatory mechanism of action
- Oral therapy
- Tofacitinib → approved for rheumatoid arthritis
- Efficacy demonstrated for UC in phase II trial
  - Phase III trial completed (OCTAVE 1/2)
- Phase II trial for CD did not demonstrate clinical efficacy
  - Signals for improved CRP and other markers of inflammation
  - 2nd generation therapy (filgotinib) studied for CD with + phase II trial reported
- Unique side effect profile
  - Increases LDL (bad) cholesterol
  - Increased risk of GI perforation (no reports in IBD)
Anti-SMAD therapy
Anti-SMAD Therapy

- Novel mechanism of action: turns off SMAD, which in turns, shuts off TGF-β production (anti-inflammatory compound)
  - “Enemy of my enemy is my friend”
- Mongersen → oral anti-SMAD therapy
- Phase II study in CD → dramatic and quick improvements
  - Very short trial (2 weeks to primary outcome)
  - Results less impressive with elevated CRP
- Phase III studies ongoing for CD
  - Phase II for UC
Novel Pharmacotherapies: Summary

- Multiple new agents are expected within the next several years for both UC and CD
  - Oral agents
    - Small molecule therapy → no risk of antibody-mediated resistance to therapy
  - Novel mechanisms of action
  - Apparently good safety profile for novel agents
  - Where to position these therapies?
    - Role for biologics? Combination therapy?
- Biosimilars → What is old is new again
  - Akin to “generic” drugs but more complex approval process
  - Infliximab biosimilar currently approved for use
  - Adalimumab biosimilar approved but not presently available
Novel Approaches

- Dietary therapy
  - Specific Carbohydrate Diet (SCD)
- Microbiotic therapy
  - Fecal microbiota transplant (FMT)
- Personalized therapy
Specific Carbohydrate Diet (SCD)

- Eliminates multiple dietary sources of complex carbohydrates (e.g. grains in particular, as well as any disaccharides [lactose, sucrose])
- May change GI bacteria populations → reduced inflammation?
- Limited data suggestive of benefit in pediatric populations
  - Small #’s but some prospective data showing both improved symptoms and improved CRP
  - No comparison arms as yet
- CCFA Partners Trial: patient-originated research protocol to compare SCD versus Mediterranean diet in adults with CD
  - Will start enrollment this year, estimated completion 2019
Fecal Microbiota Transplant (FMT)

- Three RCTs to date publishing results of FMT for UC
  - No standardized protocol (given by nasal tube or enema)
  - No standardized frequency (every 3 weeks, weekly or nightly administration)
  - Unclear which bacteria are the most “helpful”
- Two studies have reported benefit using enema approach
  - In one of these studies, benefit was exclusively seen with one particular donor
  - In the other study, no steroid-sparing effect was seen to this therapy
- Maximal follow-up 6-8 weeks: unclear role as maintenance therapy
- Appears to be safe including in immunocompromised individuals (i.e. on biologics)
Personalized Medicine

• Current and future therapies for IBD appear to be disease-modifying: targeting early use of these therapies appears to decrease future disease complications
  • Better methodologies for predicting severe disease in the future
    • Clinical variables
    • Genetic variables
    • Serologic (blood-test) results
  • Therapeutic drug-level monitoring
• Genetic testing to predict responsiveness to classes of therapy
  • Not clinically applicable or available, but studies have shown that various genes involved in the immune system’s function influence the likelihood of response to anti-TNF biologics