Inflammatory Bowel Disease 2016
What’s In The Pipeline?

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Thank you to Dr. James Lord and Dr. Edward Loftus.

Abbreviations

• IBD = Inflammatory Bowel Disease
• UC or CUC = chronic ulcerative colitis
• CD = Crohn's disease

IBD Drugs in the Pipeline

Aurelien Amiot and Laurent Peyrin-Biroulet,

Why are we here?

• No cure
• Major unmet need—not all respond to current therapies (30-40%)
• Drugs stop working
• Patients and doctors not proactive or aggressive in approach
• Drugs are expensive!
• Drugs have side effects
• No one size fits all solution
• Want to avoid surgery

Close to a cure? It’s complicated...

Causes of IBD

Gut Bacteria

Genetic susceptibility

Environmental triggers (diet)
Multiple Genes/Pathways

Chromosome:

1 2 3 5 10 16 17

INNATE IMMUNITY

ADAPTIVE IMMUNITY

EPITHELIAL

INNATE IMMUNITY

ADAPTIVE IMMUNITY

EPITHELIAL

Courtesy of W.A. Faubion, Mayo Clinic

Patience is a virtue

It takes years for new drugs to come to market

Discovery of the active principles

Preclinical testing

Clinical testing

2-5 years

1-2 years

6-10 years

Identifies candidates that meet the profile of the target site

Safety and efficacy studies in preclinical models

Demonstrates safety and efficacy in patients infected with the disease

• In vitro (test tube or laboratory) studies and trials on animal populations.

• Wide ranging dosages of the compounds are introduced to the animal subjects or to an in vitro substrate.

• Obtain preliminary efficacy and pharmacokinetic information.

• Decisions are made during this phase regarding further development of the test compound, test item, or test article.

Trial Phases

• Preclinical studies

• Phase 0

• Phase I

• Phase II

• Phase III

• Phase IV

Preclinical Phase

• Recent designation for exploratory, first-in-human trials conducted in accordance with the FDA’s 2006 Guidance on Exploratory Investigational New Drug (IND) Studies.

• Designed to expedite the development of promising therapeutic or imaging agents

• Involve the administration of single sub therapeutic doses to a small number of subjects (10-16).

• Gather preliminary data on the pharmacokinetic and pharmacodynamic properties and mechanism of action.
Phase I
- First step in testing in humans.
- Researchers look for safety and potentially harmful side effects.
- Usually include only a limited number of human subjects (20-80).
- This phase of testing usually takes several months.

Phase II
- Once a drug has shown to be safe, then it must be tested for efficacy.
- This phase may last from several months to two years.
- Usually involves several hundred patients
- Most of these trials are randomized trials
- Only about 1/3 of these studies successfully complete both phase I and phase II due to poor patient activity or toxic effects.

Phase III
- Randomized control trials on large patient groups (300-3000).
- Compare the results of the patients on the experimental trial to those patients utilizing standard diagnostic studies or treatment
- Studies move into this phase only after a diagnostic agent, modality, or treatments have shown promise in phase I and II trials.
- These trials are typically multi-center trials.
- Many phase III trials are randomized and blinded.

Phase IV
- Pre-approval, post-launch
- Involve safety surveillance and ongoing technical support of a drug.
- Sometimes mandated by the FDA for additional testing including interactions with other drugs and testing on certain populations.
- Adverse effects detected by Phase IV trials may result in withdrawal or restriction of a drug -recent examples include Vioxx.

Paradigm Shift for Making Treatment Decisions in Patients with Inflammatory Bowel Disease
- OLD: Treat based on symptoms
  - But: symptoms are insensitive and non-specific for bowel inflammation
- NEW: Treat based on objective markers of inflammation
  - Serologic (CRP reduction)
  - Endoscopic (mucosal healing)
  - Radiographic (CTE/MRE improvement)
  - Goal should be “mucosal healing” or absence/reduction in inflammation
  - This will be the only way we can hope to alter the natural history of Crohn’s disease

Implementing “Treat to Target” in IBD: Mucosal Healing as the Target
- Primary target: absence of mucosal ulceration
- Level of target may be influenced by comorbidities and drug-related risks
- Desired target should be maintained indefinitely
- Use both symptoms and objective measures of inflammation (endoscopic or radiologic) to guide treatment decisions
- Assess mucosal healing every 6 months till target is achieved, then every 1-2 years after, adjust according to degree of inflammation

Treat to Target in Clinical Practice – Crohn’s
• Retrospective analysis of UCSD practice 2011-12 – mostly WJS’ practice
• 110 CD patients had at least 2 endoscopies, and 67 patients had ulcers/erosions at baseline
• Median follow-up, 62 weeks
• Median interval between procedures, 24 weeks
• General plan was to use endoscopy to make decision about whether or therapy should be adjusted (e.g., add anti-TNF, optimize it, combo rx, etc)

Bouguen G et al, Clin Gastroenterol Hepatol 2014 online early

Predictors of Mucosal Healing
Factor | Hazard Ratio (95% CI)
--- | ---
Duration < 2yrs | 2.3 (1.1-4.7)
Female gender | 2.1 (1.1-4.4)
Previous IMM | 0.4 (0.2-0.9)
Previous Surgery | 0.3 (0.1-0.7)
Repeat scope within 26 wks | 2.2 (1.2-4.3)
Med rx adjustment due to ulcers on scope | 2.3 (1.2-4.9)

Bouguen G et al, Clin Gastroenterol Hepatol 2014 online early

Immunopathogenesis of IBD

Cyclosporine vs. Infliximab for Acute Severe UC
• 110 patients steroid refractory UC
• Treatment failure
  - No response day 7
  - No steroid-free remission day 98
  - Relapse between days 7 and 98
  - Colectomy
  - Death
• Conclusion: CyA was not superior to IFX in acute severe UC

Two Major Types of New Drugs

- **Conventional** = “small molecules”
  - Synthesized by organic chemistry
  - Potentially cheaper
  - Usually can be oral (pills)
  - Usually short half life (take daily)
  - Can someday be generic

- **Biologics** = Biologicals = Biopharmaceuticals
  - Synthesized in a cultured cell line, in a “Bioreactor”
  - Very expensive to make
  - Cannot be oral: must be IV or shots
  - Long half life (wks to mos)
  - Can someday be “biosimilar”, not generic

Small Molecules in the Pipeline

Mongersen

- An oral pill consisting of:
  - A delivery capsule that only releases in the last part of the small intestine/first part of the colon
  - Specially designed inhibitory RNA that is easily taken up by the intestinal mucosa, targeting the SMAD7 gene
  - “an inhibitor of an inhibitor of an inhibitor”
  - Mongersen blocks SMAD7 expression
  - SMAD7 blocks TGF-B signaling
  - TGF-B inhibits the immune system

How Mongersen Works:

**How Mongersen Works: “an inhibitor of an inhibitor of an inhibitor”**

Mongersen, an Oral SMAD7 Antisense Oligonucleotide, and Crohn’s Disease

Giovanni Monteleone, M.D., Ph.D., Markus F. Neurath, M.D., Ph.D., Sandro Ardizzzone, M.D., Antonio Di Sabatino, M.D., Massimo C. Fantini, M.D., Ph.D., Fabiana Castiglione, M.D., Maria L. Scribano, M.D., Alessandro Arruzzu, M.D., Ph.D., Flavio Caprioli, M.D., Ph.D., Giacomo C. Stiumolo, M.D., Francesca Rogai, M.D., Ph.D., Maurizio Vecchi, M.D., Raja Atreya, M.D., Ph.D., Fabrizio Bossa, M.D., Sara Onali, M.D., Ph.D., Mana Fichera, M.D., Gino R. Corazza, M.D., Livia Biancone, M.D., Ph.D., Vincenzo Savarino, M.D., Roberta Pica, M.D., Ambrogio Orlando, M.D., and Francesco Pallone, M.D.
Mongersen, an Oral SMAD7 Antisense Oligonucleotide, and Crohn’s Disease

- Phase II, placebo controlled, double-blinded trial
- N=166 patients with moderate Crohn’s disease
- Daily doses of placebo or 10, 40, or 160 mg Mongersen for two weeks, then stopped
- Patients followed out to 12 weeks to evaluate response

Mongersen (GED-0301) safe and effective in steroid dependent or resistant Crohn’s disease

- Mongersen is an oral locally active antisense oligonucleotide that targets Smad7
- Phase 2 RCT, week 12 remission: not affected by hsCRP, disease duration; lower remission with higher baseline CDAI

Remission was maintained out to 12 weeks

- 10 weeks after last dose of Mongersen!!!

How might Mongersen have such a durable effect?

- By differentiating T cells from pro-inflammatory “effector” T cells to anti-inflammatory “regulatory” T cells (Tregs) to promote immune tolerance?

Drawbacks to study

- Outcomes were subjective (symptoms)
- Enrolled patients had moderate (not severe) IBD
- No “hard” (objective) endpoints
  - Colonoscopy/biopsies?
  - Stool tests for inflammation (calprotectin)?
  - Unclear what happens beyond 12 weeks

Mongersen: significance

- If 2 wks of therapy ⇒ 12 wks of remission...
  - Back to intermittent (instead of maintenance) therapy?
  - FOXP3+ Treg induction ⇒ cure?
- First antisense RNA-based therapy to work in IBD...
  - Could be applied to ANY gene target
    - TNF: replace infliximab, adalimumab, etc.?
    - Integrin: replace vedolizumab, natalizumab, etc.?
  - Much cheaper to manufacture than biologics

FOXP3+ Tregs in human colon

*P < 0.0001 vs. placebo
Mongersen: current status

• Small study (16 patients) to directly evaluate the effects of Mongersen on intestinal tissue in Crohn's
• Small (40 patients) phase II study in UC
• Two large (>1000 patients) phase III studies in Crohn’s proposed

Ozanimod

• Oral pills
• Activates the S1P1 Receptor, used by lymphocytes to “smell” their way out of a lymph node

Ozanimod: TOUCHSTONE (phase II trial)

• Induction:
  • N=197 patients with moderate-severe UC
• Maintenance:
  • N=103 responding UC patients from above
  • Continue assigned treatment another 24 wks
• Outcome: Remission at 32 wks

Ozanimod: TOUCHSTONE (phase II trial)

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Ozanimod: Current status
• UC: phase III trial underway
• Crohn’s: phase II trial underway
• Similar drugs:
  • Fingolimod: approved for multiple sclerosis, not IBD
  • Less specific/more toxic than Ozanimod
  • APD334: Undergoing Phase II trial in UC
  • Currently recruiting at Virginia Mason, Seattle

Tofacitinib (Xeljanz™)
• Inhibits Janus Kinases (Jak’s) used by many cytokine receptors to deliver signals inside immune system cells

Phase II trials: Tofacitinib for UC

Tofacitinib: Phase III trials in UC
• OCTAVE 1: N=598 patients
• OCTAVE 2: N=541 patients
• Moderate to severe UC
• Placebo vs. 10 mg tofacitinib twice a day
• Outcome: Remission at wk 8
  • “Both studies met their primary endpoints as measured by the proportion of patients receiving tofacitinib in remission at Week 8 compared to patients receiving placebo” - Pfizer

Tofacitinib: Current status
• FDA-approved for Rheumatoid Arthritis in 2012
• UC: Two phase III trials completed, data not yet public, long-term follow up underway
• Crohn’s: Two phase II trials completed, long-term (48 wk) follow-up underway
• Similar drugs in development:
  • ABT-494: Phase II trial for Crohn’s

Biologics in the Pipeline
**Ustekinumab (Stelara™)**

- Humanized antibody, blocking a p40 subunit common to both IL-12 and IL-23

**Phase III trials of Ustekinumab in Crohn’s disease**

- **UNITI-1**
  - N=741 Biologic-refractory/intolerant Crohn’s patients
- **UNITI-2**
  - N=628 Crohn’s patients:
    - 70% failed immunomodulators (azathioprine, 6-MP, MTX)
    - 80% failed steroid
    - 70% biologic-naive (never used a biologic before)
- **IM-UNITI**
  - N=1316 Crohn’s patients from UNITI-1&2
  - 44 wk maintenance trial

**UNITI -1 & 2:**

- 1:1:1 randomization to a single IV dose of
  - Placebo
  - 130 mg ustekinumab
  - 6 mg/kg ustekinumab
    - 260 mg (weight <= 55 kg)
    - 390 mg (weight > 55 kg and <= 85 kg)
    - 520 mg (weight > 85 kg)
- Primary endpoint: Response (improvement) at wk 6
- Secondary endpoints: Response & remission at wk 8

**Primary endpoint:**

- Response at wk 6

**Secondary endpoint:**

- Remission at wk 8
Ustekinumab: Current Status

- FDA approved for:
  - Moderate-severe psoriasis Sept 2009
  - Psoriatic arthritis Sept 2013
- Crohn’s:
  - Currently under review for FDA approval in 2016
  - Maintenance: IM-UNITI: enrollment closed 2015, results anticipated 2019
- UC: Currently in phase III trials

The main question with Ustekinumab: $$$

- Current cost for psoriasis:
  - 45 mg syringe: $8,400
  - 90 mg syringe: $16,000
- Dose for Crohn’s:
  - Induction (single dose):
    - 130 mg: c. $23,000
    - c. 6 mg/kg: $46,000-$92,000
  - Maintenance:
    - 90 mg Q8 wks: $104,000/yr
    - 90 mg Q12 wks: $70,000/yr

MEDI2070: anti-IL-23 p19

MEDI2070 Phase II trial in Crohn’s

- N= 121 Crohn’s patients
  - Active disease
  - Elevated blood or stool inflammatory markers
  - Biologic (anti-TNF) failure
- 1:1 randomization
  - Placebo
  - 700 mg IV MEDI2070 @ 0 & 4 wks

Week 12 Outcomes

ECCO 2015, OP025

MEDI2070: Current status

- Crohn’s: a second phase II trial is still recruiting

Anti-Adhesion Biologics: Block immune cell trafficking
**Anti-Integrin therapy blocks lymphocyte migration to tissue**

**Etrolizumab as induction therapy for ulcerative colitis: a randomised, controlled, phase 2 trial**

Etrolizumab significantly induced remission at week 10, not 6 (no dose-response seen)

Etrolizumab did NOT significantly improve response, mucosal healing, or bleeding

**Etrolizumab was much more effective among people who had never used a biologic before (“naïve”)**

**Etrolizumab: Current status**

- UC: 4 phase III trials underway
  - 1 for UC patients who previously failed anti-TNF
  - 3 comparative efficacy trials for anti-TNF-naïve:
    - 1 comparing efficacy of etrolizumab and infliximab
    - 2 comparing efficacy of etrolizumab and adalimumab
- Crohn’s: phase III trial underway

**Anti-MAcAM Antibody PF-00547659**
**TURANDOT: Anti-MAdCAM Antibody PF-00547659 phase II trial**

- N=357 patients with moderate to severe UC randomized to:
  - Placebo
  - 7.5 mg PF-00547659 Q4wks x 3
  - 22.5 mg PF-00547659 Q4wks x 3
  - 75 mg PF-00547659 Q4wks x 3
  - 225 mg PF-00547659 Q4wks x 3

**TURANDOT: Anti-MAdCAM Antibody PF-00547659 trial**

- Week 12 Outcomes

**PF-00547659: Current status**

- No trials currently recruiting
- UC: phase II trials completed
- Crohn’s: phase II trial completed

**GS-5745: anti-MMP9 (matrix metalloproteinase 9)**

- MMP9: enzyme involved in tissue breakdown
  - Up-regulated in the colon in ulcerative colitis
- GS-5745 blocks MMP9 \( \rightarrow \) stops tissue damage?
- Phase I/II trial in ulcerative colitis underway

**GS-5745: anti-MMP9 (matrix metalloproteinase 9)**

- Clinical efficacy of GS-5745
  - Placebo
  - 0.3 mg/kg
  - 1 mg/kg
  - 2.5 mg/kg
  - 5 mg/kg
  - 150 mg

**Summary: Small Molecules**

- Inhibitory RNA
  - Mongersen (SMAD7)
    - UC: phase II
  - Crohn’s: phase II
- S1P1 receptor agonist
  - Ozanimod
    - UC: phase II
    - Crohn’s: phase II
  - APD334
    - UC: phase II
- Janus Kinase (JAK) inhibitor
  - Tofacitinib
    - UC: phase II (x2)
    - Crohn’s: phase II (x2, completed)
  - ABT-494
    - Crohn’s: phase II
Summary: Biologicals

• Anti-cytokine antibodies:
  • Ustekinumab (IL-12/23 p40):
    • Crohn’s: pending FDA approval
    • UC: phase III
  • MEDI2070 (IL-23 p19):
    • Crohn’s: phase IIb

• Anti-adhesion antibodies:
  • Etrolizumab (integrin α7):  
    • UC & Crohn’s: phase III
  • PF-00547659 (MadCAM-1)
    • UC & Crohn’s: phase II (closed)

• Anti-matrix metalloproteinase
  • GS-5745 (MMP9)
    • UC: phase II/III