MICHAEL D. KREINES, M.D.

GASTROENTEROLOGY SECTION CHIEF
MEDICAL DIRECTOR, IBD PROGRAM
THE CHRIST HOSPITAL OF CINCINNATI

OHIO GI AND LIVER INSTITUTE
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Today’s Game Plan

• Currently available medications
• Medications undergoing research
• Mechanisms of IBD Meds
• Potpourri of interesting recent IBD topics
IBD – What’s New, Interesting, and Important

NOT

IBD 101
The IBD Pipeline

IL-Inhibitors
- Secukinumab
- Fontolizumab
- Tocilizumab
- Ustekinumab

Cytokines
- Low-dose IL-2
- rhL-11
- IFN-β-1a

Immunomodulators
- Abatacept
- Visilizumab
- Laquinomod
- Rituximab

Anti-adhesion molecules
- Alicaforsen
- PF-00547659
- Etrolizumab

Downstream signaling blockade
- Tofacitinib
- Fingolimod
- Ozanimod
Available Non Biologic Drugs for IBD

Mesalamines:
- Apriso, Asacol, Lialda, Colazal, Pentasa, sulfasalazine
- Rowasa, Canasa

Steroids:
- Prednisone
- Budesonide – Entocort, Uceris

Immunomodulators:
- 6MP (purinithol, mercaptopurine)
- Imuran (azathioprine)
- Methotrexate
Available Biologic Drugs for IBD

Anti-Tumor Necrosis Factor (Anti-TNF):
- Remicade (infliximab)
- Humira (adalimumab)
- Cimzia (certolizumab pegol)
- Simponi (golimumab)

Anti-adhesion molecules:
- Entyvio (vedolizumab)

Anti – interleukin:
- Stelara (ustekimimumab)
What is Inflammation and how do we prevent or neutralize it?
AN ANALOGY

INFLAMMATION = A RIOT

INFLAMMATORY CELLS = “INFLAMMERS”
“Let’s Start a Riot”
Start getting the word out
Recruit many ‘Inflammers’
The message goes ‘viral’
Need to get off of the main transportation ‘artery’ and into the riot zone
Knock down barriers to get from the road into the riot zone
Use something to punch holes in the barriers
Activate the Inflammers
To gather a riot of ‘Inflammers’
PREVENTING AN INFLAMMATORY RIOT
PREVENT THE RIOT

Genetic studies – find the IBD genes and modify or delete them

200 genes identified so far implicated in IBD
Block messaging to inflammatory cells

Mesalamines
Prevent recruiting more ‘Inflammers’ by blocking the message from going ‘viral’
Anti TNF  
Anti-Interleukins
Keep moving on down the road

No exit, no stopping and causing trouble
Anti Adhesion molecules – vedolizumab (Entyvio)
Take away the tools (bacteria?) and keep an intact barrier
No bugs, no inflammation.
Can add good bugs and/or diminish the bad bugs

Antibiotics, probiotics, Fecal transplant
Relax/Prevent activate the Inflammers

Steroids, Mongersen
Redirect the Inflammers
Immune modulators (azathioprine, 6MP, Methotrexate)
No Inflammation, just Happiness
What’s the Best Anti–TNF?

Infliximab (Remicade), Adalimumab (Humira, Certoliumab pegol (Cimzia), Golimumab (Simponi)

UNKNOWN

Comparative Effectiveness and Safety of Anti–Tumor Necrosis Factor Agents in Biologic-Naive Patients With Crohn’s Disease

Siddharth Singh,*,†,§ Herbert C. Heien,‖ Lindsey R. Sangaralingham,‖ Stephanie R. Schilz,‖ Michael D. Kappelman,‖ Nilay D. Shah,‖,⁎,**, and Edward V. Loftus Jr*
NF Antagonist Therapy was a Game Changer– But We Are a Long Way from Perfect......
The Real-World Effectiveness and Safety of Vedolizumab for Moderate–Severe Crohn’s Disease: Results From the US VICTORY Consortium

Parambir S. Dulai, MD1, Siddharth Singh, MD, MS1,2, Xiaoqian Jiang, PhD3, Farhad Peerani, MD3, Neeraj Narula, MD3, Khadija Chaudrey, MD4, Diana Whitehead, MD3, David Hudesman, MD6, Dana Lukin, MD7, Arun Swaminath, MD8, Eugenia Shmidt, MD3, Shuang Wang, PhD5, Brigid S. Boland, MD1, John T. Chang, MD8, Sunanda Kane, MD4, Corey A. Siegel, MD, MS9, Edward V. Loftus, MD3, William J. Sandborn, MD3, Bruce E. Sands, MD3 and Jean-Frederic Colombel, MD3
Ustekinumab (Stelara) Tweet (message) blocker

Ustekinumab Has a Favorable Safety Profile Through 44 Weeks: Results from IM-UNITI

Results:
- No notable new safety issues identified
- No deaths or serious opportunistic infections
- 2.3% of patients developed antibodies, but these did not preclude drug efficacy

<table>
<thead>
<tr>
<th>Subjects With (%)</th>
<th>Placebo</th>
<th>90 mg SC Q12w</th>
<th>90 mg SC Q8w</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>AEs</td>
<td>83.5%</td>
<td>80.3%</td>
<td>81.7%</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>15.0%</td>
<td>12.1%</td>
<td>9.9%</td>
</tr>
<tr>
<td>Serious Infections</td>
<td>2.3%</td>
<td>5.3%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Discontinuation due to AE</td>
<td>6.0%</td>
<td>7.6%</td>
<td>3.1%</td>
</tr>
<tr>
<td>Malignancies</td>
<td>0.8%</td>
<td>0%</td>
<td>0.8%</td>
</tr>
</tbody>
</table>

AE, adverse event; Q8w, every 8 weeks; Q12w, every 12 weeks

Many new agents in development for IBD

**Anti-cytokine antibodies**
- Anti-IL-6/Anti-IL-6R
- Anti-p40 antibodies (IL-12/IL-23): ustekinumab
- Anti-p19 antibodies (IL-23): MEDI2070, risankizumab, LY3074828

**Anti-leukocyte trafficking agents**
- Anti-integrin antibodies
- Anti-integrin/anti-adhesion molecule receptor small molecules
- Anti-adhesion molecule receptor antibodies
- Sphingosine 1 phosphate agonists

**Janus kinase (JAK) inhibitors**: tofacitinib, filgotinib

**Anti-SMAD7 antisense oligonucleotide** (mongersen)

**Small molecule inhibitors of phosphodiesterase 4 (PDE4)**: apremilast
Ohio GI (CCR) IBD Studies

- High dose vs standard dose Adalimumab
- SMAD7 Mongersen
- Etrolizumab - Integrin Beta7 inhibitor
- Apremilast – phosphodiesterase inhibitor
- Ustekinumab – Interferon 12/23 inhibitor
- p19 IL-23 subunit antibody
- Clarithromycin, rifabutin, clofazimine antibiotics
- Purified Eubacterial spores with vancomycin
- JAK1 inhibitor
- Interleukin 23 inhibitor
- Adalimumab vs Vedolimumab
Two Concepts about IBD

Chronicity/Progression

Disease Activity vs Disease Severity
• Disease Activity – now, a moment in time
• Disease Severity – summary of disease course over time. Guides long term strategy
• Crohn’s Disease Severity associated with intestinal damage
• UC Disease Severity is more dependent on symptom impact on daily life
Prevention of disease progression through good management of drugs and complications
Early intervention is key to prevention of progression.
Goal of treatment in IBD: Blocking disease progression and damage
Early Intervention: Anti-TNF

Increased Response and Remission Rates in Short-Duration Crohn’s Disease With Subcutaneous Certolizumab Pegol: An Analysis of PRECiSE 2 Randomized Maintenance Trial Data

Stefan Schreiber, MD, Jean-Frédéric Colombel, MD, Ralph Bloomfield, MSc, Susanna Nikolaus, MD, Jürgen Schölmerich, MD, Julian Panés, MD and William J. Sandborn, MD, for the PRECiSE 2 Study Investigators.

- Post Hoc analysis of PRECiSE-2 maintenance trial according to disease duration
- 425 CD patients, randomized, double-blinded, placebo-controlled trial

Increased Response Rates in Earlier CD
Here’s the problem...

- Our most effective drugs (biologics) are indicated only for patients with moderate-severely ACTIVE disease.
- What happens if patient with complex history has low disease ACTIVITY?
  - False sense of security for us as providers
  - Patient doesn’t feel like they “deserve” biologics
  - Payers definitely don’t think they need ‘em
More of what’s Interesting and Important in IBD 2017

• Biosimilars
• Cannabis
• Fecal Transplant
• Naltrexone
• Fish Oil
• Probiotics
• Yoga
• IBD Diet
• Use of the ER
Biosimilars

- Biosimilars are a similar copy of an originator biologic therapy. The originator is also sometimes called "the reference product" or "innovator."

<table>
<thead>
<tr>
<th>What should be the same?</th>
<th>What is different?</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ Strength</td>
<td>✓ They are <strong>NOT</strong> an identical copy in every way (glycosylation may differ)</td>
</tr>
<tr>
<td>✓ Route of administration</td>
<td></td>
</tr>
<tr>
<td>✓ Effectiveness</td>
<td></td>
</tr>
<tr>
<td>✓ Safety profile</td>
<td></td>
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Biosimilars for IBD

Inflectra™ is the first FDA approved biosimilar for inflammatory bowel disease
- Has biosimilarity to Infliximab
- Not interchangeable (per regulatory)
- Studied in:
  - Ankylosing Spondilitis
  - Rheumatoid Arthritis
- Extrapolated to:
  - Crohn’s disease (in adults and children)
  - Ulcerative colitis (in adults)
- Not available yet, projected 2018

Amjevita™ is the second FDA approved biosimilar (adalimumab) for inflammatory bowel disease
Interchangeable Biosimilars???

- “Interchangeable” designation of biosimilars may allow for free exchange with originator biologics with no greater risk of adverse effects or diminished efficacy
- Could allow pharmacy substitution without prescriber intervention
- Subject to each state’s laws and regulations governing drug
- FDA determines whether a biosimilar is interchangeable or not
  - Requires studies of switching between originator and biosimilar
Wholesale price for one year

- Infliximab $33,396
- Inflectra $28,388
Therapeutic Use of Cannabis in Inflammatory Bowel Disease

Waseem Ahmed, MD, and Seymour Katz, MD
Cannabis: “symptom relief but worse disease prognosis in patients with Crohn's disease”


- Anonymous survey

- 17.6% used cannabis

- Improved:
  - Abdominal pain (83.9%)
  - Abdominal cramping (76.8%)
  - Pain (48.2%)
  - Diarrhea (28.6%)

Cannabis: “symptom relief but worse disease prognosis in patients with Crohn's disease”

- Use >6 months at any time for IBD symptoms strong predictor for:
  - Surgery for Crohn’s Disease (OR = 5.03; 95% CI. 1.45-17.46)
  - Controlled for smoking, time since IBD dx, biologic used, demographics

- Recommended caution until clinical trials can evaluate efficacy and safety.
Multi Donor FMT is Effective for Resistant UC: A Randomized Placebo-Controlled Trial

Methods:

- Double-blind study of pooled donor FMT therapy for UC patients with active disease (n=81)
- FMT or placebo on day 1, then FMT or placebo 5 times weekly x 8 weeks
- Primary endpoint: steroid-free clinical remission + endoscopic remission or response based on Mayo score at week 8
- Secondary endpoint: steroid free clinical remission (based on Mayo score); endoscopic remission (UCEIS ≤1), endoscopic response, and QoL

Results:

- Compared to placebo, FMT led to higher rates of:
  - Clinical remission (44% vs 20%, p=0.02)
  - Clinical response (54% vs 23%, p<0.01)
  - Endoscopic remission (17% vs 8%, p=0.19)
  - Endoscopic response (37% vs 10%, p<0.01)

Conclusions:

- Even though UC patients with FMT had higher rates of clinical/endoscopic response, this did not achieve steroid-sparing benefits

QoL; quality of life; UCEIS, Ulcerative Colitis Endoscopic Index of Severity

Multi Donor Intense Faecal Microbiota Transplantation is an Effective Treatment for Resistant Ulcerative Colitis: A Randomised Placebo-Controlled Trial

**Safety:**
3 SAE’s: worsening of colitis
- 2 active FMT treatment (1 required colectomy
- 1 placebo.

Primary Endpoint: Steroid-free clinical remission and endoscopic remission or response.
* = corticosteroid free

Paramsothy S et al. (Australia). DDW 2016: Presentation 600
Naltrexone

- What is it?
  - Naltrexone is a drug that blocks the body’s opioid receptor
    - That’s the receptor for morphine, heroin, and other narcotics

- What is it used for?
  Treatment (prevention) of slowing down / stopping up the bowels after surgery (ie. blocks the constipating side effect of narcotics.
  - Alcohol dependence

- Anti-inflammatory effect?
Low Dose Naltrexone “LDN” in Crohn’s Disease

**Adult Study**

- N= 40
- 4.5mg/d vs. placebo x 12 weeks
- Primary endpoint:
  - Clinical Remission:
    - 5pts LDN vs. 3 placebo.
    - (p=NS)
- No SAE’s

**Pediatric Study**

- N=14. Mean age 12.3 (8-17)
- LDN 0.1mg/kg/d x 8 weeks vs. placebo
  - Subsequent 8 week open label LDN
  - “the differences ...did not reach statistical significance.”
- No SAE’s

**Cochrane Analysis**

“...insufficient evidence regarding the efficacy and safety of LDN...in) active Crohn's disease.”
Fish Oil

- Not so fishy!
- Redirects arachidonic acid pathway from producing LTB4 to less inflammatory LTB5.
- Potential role in maintaining remission.

Fish Oil

- Crohn’s disease: little / no evidence of efficacy:
  - Induction of remission (no)
  - Maintenance of remission (no)
  - Steroid sparing (no)
- Ulcerative colitis: also little convincing evidence of:
  - Induction of remission (weak data; not statis. signif)
  - Maintenance of remission (no)
  - Steroid sparing (weak data; not statis. signif)
Effect of Yoga in the Therapy of Irritable Bowel Syndrome: A Systematic Review

Dania Schumann,* Dennis Anheyer,* Romy Lauche,*,†† Gustav Dobos,* Jost Langhorst,* and Holger Cramer*,††
Yoga Eases Symptoms, Boosts Mood in UC

• 12 weeks of yoga or not
• IBDQ statistically improved
• Rechecked after 3 months and the benefit persisted
The “Anti-IBD Diet” May Be Useful to Preserve Remission in IBD

**Background:**
- Anti-IBD diet restricts carbohydrates, wheat, most grains, additives, and preservatives

**Methods:**
- Randomized, double-blind, placebo-controlled trial
- 54 patients with quiescent CD randomized to 3 groups:
  - FOS, placebo, and anti-IBD diets
  - Followed until flare or 12 months

**Results:**
- Flares occurred in 6/19 FOS, 4/19 placebo, and 0/16 anti-IBD diet (p=0.035)
- Trend toward longer survival without flare in diet group (p=0.053)

**Conclusions:**
- Flares occurred in 6/19 FOS, 4/19 placebo, an 0/16 anti-IBD diet (p=0.035)
- Trend toward longer survival without flare in diet group (p=0.053)

CD, Crohn’s disease; FOS, fructo-oligosaccharides; IBD, inflammatory bowel disease

Avoidance of Fiber Is Associated With Greater Risk of Crohn’s Disease Flare in a 6-Month Period

Carol S. Brotherton,* Christopher A. Martin,‡§ Millie D. Long,‡§ Michael D. Kappelman,‡‖ and Robert S. Sandler‡§
Alternative Therapies – Strength of Evidence

- Naltrexone – weak
- Fish oil – weak
- Prebiotics and probiotics – weak
- Fecal transplant – possible but needs more study
- Cannabis – weak to none
Fecal Calprotectin Predicts Relapse and Histological Mucosal Healing in Ulcerative Colitis

Klaus Theede, MD,* Susanne Holck, MD, DMSc,† Per Ibsen, MD,† Thomas Kallehave, MSc,‡ Inge Nordgaard-Lassen, MD, DMSc,* and Anette Mertz Nielsen, MD, DMSc*
The HyGleaCare® Prep System

FDA-cleared Class II Medical Device

RX ONLY
IEC 60601-1 3rd edition

Indications for Use:
when medically indicated, such as before radiological or endoscopic examination.
CCFA Initiatives

• Specific Carbohydrate Diet vs Mediterranean Diet
• Microbiome
• IBD Trigger Study
• Nutritional Pathways
• Anxiety/Depression Workshop

CCFA supports patients, family members, medical practitioners – let’s support the CCFA
THE IBD PROGRAM MULTIDISCIPLINARY TEAM

Patient

- Financial Counseling
- Gastroenterology
- Research Consultants for Clinic Research
- Nutrition Counseling
- Pain Specialist
- Rheumatology
- Dermatology
- Education
- Psychology
- Social Work
- Primary Care
- Ostomy Care
- Radiology
- Pathology
- Surgery
- Oncology
What Have We Learned?

- IBD has many mechanisms of inflammation that can be targeted by existing and new drugs. Much work to do.
- UC and CD are chronic and often progressive
- More aggressive therapy early on appears better in the long run for many patients
- Alternative therapies are interesting but most at this time offer little objective improvement