Please note

• Not all slides presented by Dr. Lewis on November 15 are in this handout because of image permissions.
Themes

• IBD statistics, trends and research methods
• Sample of hot topics in IBD today
  – Microbiome
  – Biomarkers
  – Novel therapies

Key Statistics

• Incidence of both CD and UC are increasing in most parts of the world
• 1,400,000 Americans with IBD
  – 80,000 hospitalizations per year
  – 18,000 surgical procedures per year
IBD Care Through the Decades

- Diet
- 5-ASA
- AZA/6MP
- Methotrexate
- Anti-TNF
- Budesonide
- Anti-α4
- Methotrexate
- Anti-???
- Budesonide
- Anti-???

Recent Trends in Pattern of Care for Crohn’s Disease

- Hospitalization rate
- Surgery rate
- Long-term steroids
- Infliximab prevalence

How did we get here?

The Research Methods

- Preclinical research
  - In vitro – test tube, cells culture
  - In vivo – animal models
- Clinical research
  - Observational studies – observations from usual care
  - Interventional studies – randomized controlled trials
What is hot in preclinical research?

Etiologic Theories in Inflammatory Bowel Disease

IBD

Genetic predisposition

Mucosal Immune System (Immuno-regulatory defect)

Environmental Triggers
Gut Bacteria

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Why Do We Think Gut Microbes Are Important for IBD

• Inflammation in both Crohn's disease and ulcerative colitis occur predominantly in the terminal ileum and colon, where the greatest concentrations of bacteria are found
• Antibiotics can be a modestly effective treatment for Crohn’s disease
• Surgical diversion of the fecal stream is an effective treatment for Crohn’s disease where inflammation is known to recur upon restoration of the fecal flow
• Many of the genes associated with IBD are involved in containing normal and disease causing microbes

Genetics + Bacteria Are Necessary to Cause Colitis in Lab Animals

<table>
<thead>
<tr>
<th>Mice</th>
<th>Bacteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-2 -/-</td>
<td>IL-10 -/-</td>
</tr>
<tr>
<td>TCRα -/-</td>
<td>CD4 Eα TG</td>
</tr>
<tr>
<td>SAMPL1 yit</td>
<td>DSS</td>
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<tr>
<td>CD8 RBhi - SCID</td>
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<table>
<thead>
<tr>
<th>Rats</th>
<th>Guinea pigs</th>
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<tbody>
<tr>
<td>B7, B2M TG</td>
<td>Carrageenan</td>
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No bacteria
No immune activation
No Colitis

Bacteria
IL-1β
TNFα
IFNγ
Colitis
How we study bacteria without culturing in the laboratory

- Intestinal microbiota is composed of over 1000 different species, most of which are refractory to cultivation because they cannot live in the presence of oxygen
- Think of CSI
  - Each bacteria has DNA
  - DNA can be used like a fingerprint
  - The more copies of the DNA for a specific bacteria that is present in the sample, the more of the bacteria that is present

Where Might This Take Us?

- Changing the gut microbiome could...
  - prevent the onset of disease in genetically susceptible people
  - change the course of disease
- How to change the human gut microbiome
  - Probiotics – which bugs, how many, how often?
  - Fecal transplantation – experimental evidence strongest for refractory C difficile infection
  - Dietary manipulation – which diet, how long?
What is hot in observational clinical research?

Major Themes
Predicting disease course
Predicting risk of therapy

Bottom Up and Top Down Therapy for Crohn’s Disease

- Surgery
- Anti-α4
- Anti-TNF +/- IM
- AZA/MTX
- Steroids
- 5-ASA

Bottom Up Therapy

Anti-TNF + IM
IM or Anti-TNF mono
Steroids
Anti-α4
Surgery

Top Down Therapy
Predicting Disease Course

What do the findings from colonoscopy tell us about what will happen going forward?

Effect of Deep Ulceration at Diagnostic Colonoscopy on Initial Therapy and One Year Outcome in Children with Crohn’s Disease

Jeffrey Hyams, Mi-Ok Kim, Lee Denson, Michel Stephens, James Markowitz, Anne Griffiths, Wallace Crandall, Jonah Essers, Robert Baldassano, Maris Dubinsky, Joel Rosh, Marian Pfefferkorn, Sandra Kim, Anthony Otley, Richard Kellemayer, Melvin Heyman, Neal LeLeiko, Susan Baker, Stephen Guthery, Jonathan Evans, David Ziring, Subra Kugathasan, Thomas Walters, for the CCFA RISK Study Group

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Deep Ulcers Predict Worse Outcome in Children with CD

• 333 children newly diagnosed with Crohn's disease
• 169 with deep ulcers on initial colonoscopy
  – 2.7x more likely to have active disease at the end of one year than those without deep ulcers
  – If treated with anti-TNF therapy within 3 months of diagnosis, more than 10x less likely to have active disease at one year

DDW 2012

Mucosal Healing One Year After Diagnosis Predicts Time to Surgery

UC – Time to Colectomy
- With Mucosal Healing
- Without Mucosal Healing

CD – Time to Resection
- With Mucosal Healing
- Without Mucosal Healing

Froslie et al. Gastroenterology 2007:133(2):412-422

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Can We Predict As Well Without Colonoscopy?

• Calprotectin is one of several proteins from white blood cells found in stool when there is inflammation in the colon
• Multiple studies demonstrate that high levels of calprotectin in stool of patients without symptoms predicts high rate of relapse in near term
• Are we ready to adjust therapy before relapse occurs?

Predicting Risk of Therapy
Natalizumab and Progressive Multifocal Leukoencephalopathy

- PML is an infection of brain by JC virus
- Fatal or debilitating outcomes are common
- Primarily affects immunocompromised individuals
  - Hematologic malignancies
  - HIV
  - Organ transplantation
- Observed in patients treated with natalizumab

Distinguishing Between High Risk and Low Risk Patients

- All natalizumab treated patients who developed PML had antibodies against JC virus prior to developing symptoms
- If antibody positive, risk higher if prior treatment with immunosuppression and with longer duration of treatment (1 in 90 risk with >2 years therapy)

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What is hot in clinical trials?

Fundamentals of New Drug Development

- **Phase 1** – first time drug used in humans
- **Phase 2** – first time estimating efficacy
- **Phase 3** – definitive randomized trials to prove efficacy

- Randomization is what makes clinical trials so special
  - Helps assure that the treatment groups are comparable
Anti-α4 Therapy

- Think of erasing the address on a mailed package
- White blood cells have receptors (integrins) on their surface that bind to markers on the lining of blood vessels to know where to leave the blood and enter organs
  - α4β1 binds to blood vessels of gut and brain
  - α4β7 binds to blood vessels only of gut
- Natalizumab blocks α4β1 and α4β7
- Vedolizumab blocks only α4β7

GEMINI I – Vedolizumab for the Treatment of UC (6 week outcomes)

Response Remission Mucosal healing

Placebo Vedolizumab

Prior TNF No Prior TNF

PURSUIT – Phase 3 Trial of Golimumab Induction Therapy in Moderate-Severe UC

Golimumab: A fully human monoclonal antibody against TNF-α


*T < 0.0001 vs placebo

Tofacitinib For UC

- Oral inhibitor of Janus kinases 1, 2, and 3
- Block signaling of cytokines including interleukins 2, 4, 7, 9, 15, and 21
- Phase 2 placebo controlled trial
  - 4 doses or placebo twice daily for 8 weeks
  - Outcome – clinical response at 8 weeks

High Dose Tofacitinib is Superior to Placebo for UC

Clinical Response at 8 Weeks

Ustekinumab for CD

- IL-12/23 and IL-23 receptor implicated as involved in CD biology based on genetic studies
- Ustekinumab is a human IgG antibody that blocks IL-12 and IL-23 activity
- Effective in treating psoriasis
- Phase 2 placebo controlled trial of ustekinumab for 28 weeks (intravenous induction; subcutaneous maintenance therapy)
  - All patients were previously treated with anti-TNF drug
Ustekinumab is Superior to Placebo for Active CD

Response at Week 6

% of patients

Placebo (n=132)  1mg/kg (n=131)  3mg/kg (n=132)  6mg/kg (n=131)

23.5  36.6  34.1  39.7


Ustekinumab Maintains Response in CD

A Clinical Response

What’s Next?

- Comparative effectiveness comes to IBD
  - Head to head comparison of management strategies
- Renewed interest in diet
  - Observational and interventional studies on the horizon
- Technology will allow us to identify new therapeutic targets
  - Omics revolution—study of genes, proteins, metabolites, etc.

How Can You Get Involved

- Participate in research
  - Clinical trials
  - CCFA Partners
- Support the CCFA research mission
  - Take Steps
  - Team Challenge
  - Lobby for IBD research funding
Resources

• Clinical Trials
  - CCFA listing: www.ccfa.org/research or call 888-MY.GUT.PAIN
  - Clinical Trials.Gov: www.clinicaltrials.gov
  - CCFA Partners: www.ccfapartners.org

Question & Answer Session
We Want Your Feedback!
www.surveymonkey.com/s/IBDresearch

To Register for Next Webcast on Decision Making:
www.ccfa.org/resources/ibd-decisions.html

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