Update in IBD

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Potential Role of Serologic and Genetic Markers

1. Diagnosing Disease
2. Predicting Development of Disease
3. Predicting Course of Disease
4. General Health Considerations
Genetics

- >160 genes associated with IBD
- Risk associated with any one gene is small
- Most people will not get CD
ABCs of IBD’s Genetics

- NOD2
- ATG16L1 Autophagy gene CD
- ECM1 UC susceptibility gene
- STAT 3 Proinflammatory Mediator BD
- NKX23 Transcription Factor IBD
- VEGF Angiogenesis
- ICAM-1, VCAM-1 Adhesion Molecules
Prognostic Markers

- Prometheus 7: ASCA, Anti–OmpC, Anti–CBir1, PANCA
- Predictors of Aggressive CD at diagnosis
  - Young age, fistulae, need for steroids, deep ulcerations, high serologic titers, smoking

Lichtenstein G et al, Inflammatory Bowel Disease, Dec 2011
Lab Tests

- CRP
- SAA
- Fecal calprotectin
Treatment

- Step Up vs. Top Down
- Mesalamine Products
- Immunomodulators
- Biologics
The initial metabolism of 6-mercaptopurine occurs along the competing routes catalyzed by thiopurine methyltransferase (TPMT), xanthine oxidase (XO), and hypoxanthine phosphoribosyltransferase (HPRT). Further metabolism of the thionucleotide is catalyzed by inosine monophosphate dehydrogenase (IMPDH) and guanosine monophosphate synthetase (GMPS). The diphosphates and triphosphates are formed by their respective monophosphate (MPK) and diphosphate (DPK) kinases.
A suggested approach for the initiation of therapy with azathioprine or 6-mercaptopurine in patients with inflammatory bowel disease

Assess TPMT enzyme activity

- Homozygous mutant allele with low enzyme activity
  - Avoid use of azathioprine/6-MP
  - Begin AZA (2.0-3.0 mg/kg) 6-MP (1.0-1.5 mg/kg); Monitor WBC count every 1-2 weeks x 6-8 wks; initially, then less frequently
  - No myelosuppression: Continue therapy

- Wild type or normal enzyme activity; Heterozygote mutant allele with intermediate enzyme activity
  - Begin use of azathioprine/6-MP
  - Begin AZA or 6-MP at 50 mg daily and increase 25 mg every 2-4 weeks to
    - AZA (2.0-3.0 mg/kg) 6-MP (1.0-1.5 mg/kg);
    - Monitor WBC count every 1-2 weeks during dose escalation, then less frequently
  - Stop or lower dose by 50 percent if WBC drops below 4.0/mm3
  - No myelosuppression: Continue therapy

TPMT: thiopurine methyltransferase; AZA: azathioprine; 6-MP: 6-mercaptopurine.
Adapted with permission from: Lichtenstein, GR. Use of laboratory testing to guide 6-mercaptopurine azathioprine therapy. Gastroenterology 2004; 127:1558. Copyright © 2004 Elsevier.
Treatment

- DDW 2012 focused on how to best optimize therapeutic response to anti-TNF therapy
- Patient selection is critical—biologics are not for everyone
- Prevent attenuation of response—consider adding immunosuppressant
# When to Introduce Anti-TNF Therapy

<table>
<thead>
<tr>
<th>CD</th>
<th>UC</th>
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<tr>
<td>Steroid Dependent</td>
<td>Steroid Dependent</td>
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<tr>
<td>Steroid Refractory</td>
<td>Steroid Refractory</td>
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<tr>
<td>Immunomodulator Refractory or Intolerant</td>
<td>Immunomodulator Refractory or Intolerant</td>
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<td>Complex fistulizing disease</td>
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<td>Prevention of Post Op Recurrence?</td>
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<td>Clinical Predictors of A Poor Outcome at</td>
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Treatment

• ACT I and II: Infliximab in UC
  – Although not studied in a controlled manner, patients with initial benefit with 5mg/kg who develop attenuated response may benefit from:
    • Dose Escalation
    • Shorten dose interval
    • BOTH

One Drug or Two?

- Combination therapy vs. Monotherapy
  - SONIC: Dual therapy group (AZA+IFX) with highest steroid free remission at Week 26 for CD patients
  - SUCCESS: Steroid free remission at week 16 higher in combination group for UC patients

Panaccione R et al, Gastroenterology, 2011;140(5) Supp 1:Abs 835
Treatment

• How do we predict sustained remission?
  – ATI– and IFX <3mcg/mL --> incr dose
  – ATI+ and IFX <3 --> new anti−TNF
  – ATI+ and IFX <3 with clinical response --> consider adding immunomodulator
  – ATI – and IFX >3 but no response --> confirm diagnosis and switch drug class

Indications for IFX/HACA Testing

- LOR
- Partial Response on Initiation
- Delayed Hypersens Reaction
- Primary Nonresponder
- Reintroduction of Drug after Drug Holiday
- Recurrence of Disease while on Drug
- Acute Infusion Reaction

Secondary NonResponders

- **GAIN Trial**: Change from IFX to ADA (CD) vs Placebo --> 21% vs. 7% achieved remission at week 4

- **WELCOME**: Change from IFX to Certolizumab (CD) --> 62% achieved response and 39% remission at week 6, ~40% achieved response and ~30% achieved remission at week 26
Switching to a 3rd Anti-TNF

- Open label study using ADA or Certolizumab after failure and/or intolerance to two different anti-TNF agents
  - Of 67 patients, clinical response in 61% at week 6 and 51% at week 20

Allez M et al, Aliment Pharmacol Ther 31(1)92-101
Long Term Prognosis After Discontinuation of Anti–TNF

- GETAID: 115 patients stopped IFX and continued AZA
- 44% 1 year relapse rate
- Higher risk for males, WBC > 6, HGB <14, CRP >5, calprotectin >300
- 88% of those retreated achieved remission, 98% had response
Factors Associated with Loss of Response

– Serum levels, immunogenicity, loss of mechanism, duration of disease, prior anti–TNF therapy
  • ACCENT, CLASSIC I, CHARM
Refractory IBD

- Establish correct diagnosis, severity of disease, extent of disease
- Eval for disease complications
- Eval for enteric infections
- Optimize medication dosing
- Misc: Nonadherence, NSAIDs, Cigarettes
Post-Op Recurrence of Crohn’s Disease

• Despite IBD medications, 60–75% of CD patients require resection in their lifetimes
• Studies by Regueiro, Sorrentino, Yoshida have shown that early post op IFX decreases likelihood of disease recurrence at one year
• RF assoc with recurrence: early age of surgery, short time to first surgery, ileocolonic disease, cigarette smoking, fistulizing disease, h/o prior resection, progression to surgery despite immunomodulators
Minimizing Side Effects of IBD Medications

- **Immunomodulators**
  - CESAME cohort: France, 5 fold increase in risk of lymphoma in IBD patients receiving thiopurines vs. those never exposed
  - most cases were with combination immunomod + anti-TNF
  - HSTCL in 12 patients on immunomod alone, in 19 with combo therapy
<table>
<thead>
<tr>
<th>Event</th>
<th>Est Annual Frequency</th>
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<tbody>
<tr>
<td>NHL baseline</td>
<td>2/10,000</td>
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<tr>
<td>NHL on IM</td>
<td>4/10,000</td>
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<tr>
<td>NHL on anti-TNF+IM</td>
<td>6/10,000</td>
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<tr>
<td>HSTCL</td>
<td>Unknown</td>
</tr>
<tr>
<td>Death from sepsis</td>
<td>4/1000</td>
</tr>
<tr>
<td>TB</td>
<td>5/10,000</td>
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Minimizing Toxicity from Anti–TNF Therapy

• Update vaccinations and cancer screening
• Monitor for heart failure, skin cancers
Novel Therapies
Natalizumab

- Integrin antagonist
- 99,600 patients have received this drug. 264 cases of JC virus related progressive multifocal leukoencephalopathy.
  - All cases after 8 months of therapy
  - Most at risk patients include those who previously received immunosuppressive therapy
  - Patients who received natalizumab for 1–2 years have 1 in 500 risk for PML
Vedolizumab

- Humanized monoclonal antibody that binds to alpha4beta 7 integrin protein that helps move leukocytes into the gut
- 300mg IV Q4 weeks
- Steroid free remission at one year with a delta over placebo of 30%
- Of 2500 recipients, no cases of PML

Feagan BG et al
Ustekinumab

- Human monoclonal antibody against IL-12 and IL-23 (good early results for mod–severe CD in anti–TNF resistant patients)
- 45mg SQ Q 4 weeks
Tofacitinib

- Oral janus kinase inhibitor (promising early results vs. placebo in UC patients)
- 15mg PO BID

General Health Considerations in Patients with IBD
Health Care Maintenance

• Vaccines– Flu, pneumovaxl, HPV
  – Avoid live viruses if on immunosuppressives
  – Hep B
• Labs– Medication based
  – Annual PPD
Health Care Maintenance

• Cancer Screening– CRC, Anal, Cervical, skin
• Tobacco Cessation
• Osteoporosis
• BP screening
• Ophtho Exam
• Psych/depression screen
Update on Chemoprevention

• 5 ASA: Inconsistent results
• Thiopurines: May reduce risk
• Anti-TNF: Limited data so far

Problem with studies: Confounders not accounted for

NOTE! No agent changes surveillance recommendations!

Nguyen GC et al Am J Gastroenterol 2012 Sept; 107 (9): 1298-1304
Summary

• Serologic diagnostic and biomarker testing provide a molecular snapshot of patients with IBD
• Further trials are required to correlate immunologic, molecular, and clinical patterns of IBD
• Assessing patients’ risk factors for aggressive disease assists in selecting most appropriate therapies
• Early studies on new agents appear promising