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Centocor Ortho Biotech Inc.

UCB
Overview

• Introduction: Where are we now
• Pathogenesis and genetics
• Epidemiology and natural history
• Predictors of disease, outcomes, and complications
• Anti-TNF inhibitors
• Other treatments
Pathogenesis and Genetics
Putative Genetic Loci and Confirmation of Association in IBD

• Background
  – >30 distinct loci for CD and >12 loci for UC have been identified

• Objective
  – Confirm genetic loci for IBD in a cohort of IBD patients

• Methods
  – 420 SNPs genotyped in 579 CD patients and 917 ethnically matched healthy Caucasian controls

Pathan S et al. DDW 2010; abstract no. 31.
Putative Genetic Loci and Confirmation of Association in IBD: Results

• Among 30 loci confirmed in a previously published meta-analysis, 17 were replicated in this cohort

• Significant association with UC identified for
  – Tyrosine-protein phosphatase non-receptor type 2 (PTPN2) ($P < .01$)
  – CCDC139
  – ORMDL3

• Significant association with CD identified for
  – Lymphotoxin alpha (LTA) variant (Cys13Arg) ($P = 2.77 \times 10^{-5}$)
  – TRAF-interacting protein (TRAIP) ($P = .002$)

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  – TRAF-interacting protein (TRAIP) ($P=.002$)

Pathan S et al. DDW 2010; abstract no. 31.
New CD Susceptibility Genes Identified by International IBD Genetic Consortium

• Background
  – At least 32 susceptibility loci for CD have been previously been identified using genome-wide association scan (GWAS) data from 3230 cases/4829 controls
  – >80% of genetic variance in CD remains unexplained

• Methods
  – Analysis of GWAS data from an additional 3094 CD patients and 10,225 controls

Parkes M et al. DDW 2010; abstract no. 847v.
The GTPase RAC1 Is Associated With Inflammatory Bowel Disease

• Background
  – RAC1: GTPase that has been shown to coordinate cellular innate immune response

• Objective
  – Identify a role for RAC1 in IBD

• Methods
  – Initial candidate gene approach used with 12 tag SNPs in 2281 Caucasian subjects (754 with CD and 603 with UC)
  – Results confirmed in 2 cohorts (N America and Scotland)

Muise AM et al. DDW 2010; abstract no. 33.
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NEW GENE ASSOCIATED WITH AUTOPHAGY

Muise AM et al. DDW 2010; abstract no. 33.
The GTPase RAC1 Is Associated With Inflammatory Bowel Disease: Results

• RAC1 SNPs were associated with:
  – IBD ($P=4.9 \times 10^{-7}$; OR=0.81)
  – CD ($P=4.3 \times 10^{-3}$; OR=0.86)
  – UC ($P=3.1 \times 10^{-8}$; OR=0.74)

• Cytokine analysis of splenocytes isolated from Rac1-KO mice showed a marked decrease in proinflammatory cytokines in response to lipopolysaccharide

• In vitro, RAC1 was critical for autophagy
  – A cellular degradative pathway known to be important in the development of IBD

Muise AM et al. DDW 2010; abstract no. 33.
Effect of Inflammatory Bowel Diseases Phenotype and NOD2 Genotype on Ileal Associated Microbiota

• Background
  – An association between NOD2 genotype and shift in microbial composition has been previously reported

• Objective
  – To further examine the relationships between microbiota, IBD phenotype, and NOD2 genotype

• Methods
  – Measured relative proportions of predominant *Clostridium* spp. in a set of ileal mucosal samples derived from:
    • Ileal CD patients
    • UC patients
    • Non-IBD control patients
  – Patients were genotyped for the 3 major NOD2 risk alleles
    • NOD2\textsuperscript{R} = \geq 1 risk alleles
    • NOD2\textsuperscript{NR} = no risk alleles

Hamm CM et al. DDW 2010; abstract no. 32.
Effect of Inflammatory Bowel Diseases Phenotype and NOD2 Genotype on Ileal Associated Microbiota: Results

<table>
<thead>
<tr>
<th></th>
<th>Mean –dCT Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ileal CD</td>
</tr>
<tr>
<td>NOD2R</td>
<td>-5.04±2.53</td>
</tr>
<tr>
<td>NOD2NR</td>
<td>-8.09±3.70</td>
</tr>
</tbody>
</table>

- NOD2 genotype (F=4.71; df’s=1, 76; P=.031) and disease phenotype (F=16.34; df’s=2, 76; P<.00001) are associated with shifts in microbial composition.

- The effect of NOD2 genotype is independent of disease phenotype as indicated by the insignificant phenotype/genotype interaction term (F=1.80; df’s= 2, 76; P=.172).

Hamm CM et al. DDW 2010; abstract no. 32.
An Algorithm-Based Approach to Effectively Predict Aggressive Disease Behavior in Patients With CD: Results

<table>
<thead>
<tr>
<th>Quartile Sum Score</th>
<th>Count</th>
<th>Complications</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low (6-11)</td>
<td>88 (14%)</td>
<td>23%</td>
<td>10%</td>
</tr>
<tr>
<td>Low (12-14)</td>
<td>130 (21%)</td>
<td>46%</td>
<td>22%</td>
</tr>
<tr>
<td>Medium (15-17)</td>
<td>168 (27%)</td>
<td>55%</td>
<td>35%</td>
</tr>
<tr>
<td>High (18-20)</td>
<td>148 (24%)</td>
<td>79%</td>
<td>49%</td>
</tr>
<tr>
<td>Very high (21-24)</td>
<td>85 (14%)</td>
<td>79%</td>
<td>64%</td>
</tr>
<tr>
<td>Overall (6-24)</td>
<td>619</td>
<td>58%</td>
<td>36%</td>
</tr>
</tbody>
</table>

By combining serologic and genetic markers, and clinical parameters, disease severity can be accurately predicted in patients with CD.

Lichtenstein G et al. DDW 2010; abstract no. 207.
Dynamic Changes in the Expression of MicroRNA-31 During Inflammatory Bowel Disease Associated Neoplastic Transformation

• Background
  – Aberrant microRNA (miR) expression has been linked to tumorigenesis
  – No reports to date document a relationship between IBD-related neoplasia and miR dysregulation

• Objective
  – To evaluate the relationship between miR dysregulation and IBD-associated neoplastic transformation

• Methods
  – Human miR microarrays performed on 8 chronically inflamed and 8 dysplastic specimens from IBD patients

Olaru A et al. DDW 2010; abstract no. 253.
Dynamic Changes in the Expression of MicroRNA-31 During Inflammatory Bowel Disease Associated Neoplastic Transformation

• Several dysregulated miRs were identified between chronically inflamed mucosae and dysplasia arising in IBD
  – MiR-31 was most upregulated miR in dysplasia
    • Stepwise increase in expression from normal to IBD to dysplasia and frank colorectal cancer
    • ROC curve analyses demonstrated that miR-31 accurately discriminated IBD-related neoplasia from normal or chronically inflamed tissues in IBD patients

• Factor inhibiting hypoxia inducible factor 1 (FIH1) was identified as a direct target of miR-31

• Conclusions
  – There is specific miR dysregulation at the transition point from chronic inflammation to dysplasia
  – MiR-31 expression levels increase with disease progression and accurately discriminates between distinct pathological stages that may coexist in IBD patients

Olaru A et al. DDW 2010; abstract no. 253.
The CD Protective SNP Rs11209026 Allele Mediates Alternative Splicing in Human IL23R Transcription

• Background
  – The rs11209026 SNP in the human IL23R gene has been associated with susceptibility to a number of human autoimmune diseases
  – The rarer “A” allele confers strong protection against CD and UC
  – Multiple splice forms of IL23R exist, one of which (∆9) encodes a potent IL-23 inhibitor

• Methods
  – Anti-sense nucleotides used to cause dose-responsive, specific induction of ∆9 in cultured cells

• Results
  – In primary human CD4+ lymphocytes, induction of ∆9 mRNA reduced wt IL-23R expression on the cells’ surface and reduced expression of Th17 cytokines

• Conclusions
  – Elevated expression of ∆9 reduces ability to respond to IL-23 or maintain Th17 activity

Yu RY et al. DDW 2010; abstract no. 282.
The Bacterial Sensor Triggering Receptor Expressed on Myeloid Cells 2 (Trem-2) Is a Crucial Pathogenic Mediator in IBD

• Background
  – TREM-2 is a surface receptor on macrophages, dendritic cells, and microglia
  – Binds repeated anionic motifs present on bacteria and yeast
  – In murine models, TREM-2 mediates immune response and inhibits inflammation

• Objective
  – To evaluate the role of TREM-2 in IBD pathogenesis

• Methods
  – TREM-2 expression analyzed in normal, CD, and UC surgical specimens by confocal microscopy and in mouse models of colitis by quantitative PCR

• Results
  – TREM-2 is upregulated in the inflamed mucosa of IBD patients
  – Upregulation of TREM-2 paralleled colitis establishment in mouse models
  – TREM-2 KO mice were significantly protected from experimental colitis

Martinoli C et al. DDW 2010; abstract no. 847u.
### New CD Susceptibility Genes Identified by International IBD Genetic Consortium: Results

<table>
<thead>
<tr>
<th></th>
<th>$P$</th>
<th>Chromosome</th>
<th># Genes</th>
<th>Candidates</th>
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<tbody>
<tr>
<td>rs4077515</td>
<td>4.4x10^{-19}</td>
<td>9</td>
<td>12</td>
<td>CARD9, NOTCH1</td>
</tr>
<tr>
<td>rs17293632</td>
<td>4.5x10^{-15}</td>
<td>7</td>
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<td></td>
</tr>
<tr>
<td>rs181359</td>
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<td>15</td>
<td>1</td>
<td>SMAD3</td>
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<tr>
<td>rs2549794</td>
<td>6.3x10^{-13}</td>
<td>22</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>rs2413583</td>
<td>4.5x10^{-11}</td>
<td>5</td>
<td>4</td>
<td>ARTS1</td>
</tr>
<tr>
<td>rs1250550</td>
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<td>22</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>rs2797685</td>
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<td>1</td>
<td>ZMIZ1</td>
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<td>rs281379</td>
<td>2.7x10^{-10}</td>
<td>1</td>
<td>4</td>
<td></td>
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<tr>
<td>rs12720356</td>
<td>8.6x10^{-10}</td>
<td>19</td>
<td>13</td>
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</tr>
<tr>
<td>rs11167764</td>
<td>9.2x10^{-10}</td>
<td>19</td>
<td>9</td>
<td>ICAM3, ICAM5</td>
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<td>rs3180018</td>
<td>1.1x10^{-9}</td>
<td>5</td>
<td>1</td>
<td>NDFIP1</td>
</tr>
</tbody>
</table>

Parkes M et al. DDW 2010; abstract no. 847v.
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<table>
<thead>
<tr>
<th></th>
<th>$P$</th>
<th>Chromosome</th>
<th># Genes</th>
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<td>3</td>
<td></td>
</tr>
<tr>
<td>rs1998598</td>
<td>4.9x10^{-9}</td>
<td>1</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>rs713875</td>
<td>5.7x10^{-9}</td>
<td>22</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>rs3024505</td>
<td>8.3x10^{-9}</td>
<td>1</td>
<td>5</td>
<td>IL10</td>
</tr>
<tr>
<td>rs8005161</td>
<td>1.3x10^{-8}</td>
<td>14</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>rs13428812</td>
<td>1.4x10^{-8}</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

Parkes M et al. DDW 2010; abstract no. 847v.
Pathogenesis and Genetics

- GWAS continue to identify new genes and genetic associations
- NOD2 is predictive of complicated disease course and is associated with different microbiota
- Novel Genes associated with:
  - TNF pathway
  - Autophagy
  - IL-23
Maria T. Abreu, MD
University of Miami Miller
School of Medicine
Miami, Florida

Jointly sponsored by Purdue University School of Pharmacy and the Gi Health Foundation.
This activity is supported Abbott Laboratories, Centocor Ortho Biotech, Inc., and UCB, Inc.
Epidemiology and Natural History
Environmental Risks for IBD

- Radford-Smith et al (abstract no. 35)
  - GWAS smokers carrying $\geq 1$ minor allele of a novel SNP (rs1923380) had a median time to surgery of 2 years vs 8 years in patients homozygous for the major allele.

- Chan (abstract no. 96)
  - Regular intake of aspirin was positively associated with the risk for developing CD (OR=6.8).
Dietary Oleic Acid Protects Against the Development of UC

• Background
  – Dietary factors, including fatty acids, may be involved in the aetiology of UC
  – Oleic acid is found in high amounts in olive and grapeseed oils and inhibits the formation of the proinflammatory metabolites found in high concentrations UC mucosa

• Objective
  – Prospectively evaluate the effect of dietary oleic acid on risk for UC

• Methods
  – Data derived from EPIC-Norfolk (N=25,639)
  – Participants completed detailed 7-day food diaries
  – ORs calculated for relationship between oleic acid intake and subsequent UC

De Silva PS et al. DDW 2010; abstract no. 100.
Dietary Oleic Acid Protects Against the Development of UC: Results

• **Results**
  – In the total cohort, 22 participants developed incident UC after a median follow-up of 3.9 years
  – The highest tertile of dietary oleic acid intake was associated with an odds ratio for UC of 0.11 (95% CI=0.01-0.87)
  – A statistically significant protective trend was observed across tertiles (OR=0.33 (95% CI=0.12-0.93, P=.04)

• **Conclusions**
  – Dietary intake of oleic acid was negatively associated with the development of UC

De Silva PS et al. DDW 2010; abstract no. 100.
Antibiotics in the First Year of Life Increase Risk for Pediatric IBD: a Population-Based Analysis

• Background
  – Imbalances in normal gut flora may underlie some forms of IBD
  – Use of antibiotics has been linked to changes in commensal gut flora, as well as development of IBD

• Objective
  – Evaluate the relationship between pediatric IBD and antibiotic use

• Methods
  – Case-control study using data from University of Manitoba IBD Epidemiological Database
  – Pediatric cases of IBD with drug dispensation data from first year of life included in analysis (N=264; 79% with CD and 21% with UC)

• Results
  – Children receiving ≥1 dispensation for antibiotics were 5.8-fold more likely to be diagnosed with IBD before the age of 10 (compared with no dispensations)

De Silva PS et al. DDW 2010; abstract no. 100.
• Stone et al (abstract no. 1006)
  – Prevalence of community-acquired *Clostridium difficile* infection was 2-fold greater than hospital-acquired CDI
  – Patients taking immunosuppressive drugs were at increased risk for community-acquired infection
  – Lowest risk was seen among patients who received only 5-ASA compounds
• Minh et al (abstract no. 1004)
  – Heavy CMV infection is associated with higher colectomy rates
    • Peripheral CMV PCR levels do not correlate with histological CMV infection or colectomy rate
    • Antiviral treatment may be more effective in IBD patients with heavy CMV infection
    • Suggests that “heavy” virus burden may contribute more to active inflammatory process and symptom presentation than lower CMV burden where bulk of symptoms due to underlying severe IBD
Sauer et al (abstract no. 153)

- Radiation from imaging is high in the subset of children with CD (mostly due to CT and SBFT)
- Estimation of exposure at age 35 suggests a significant portion will have high radiation exposure in their lifetime
- Nonionizing imaging (such as MRI and ultrasound) should be offered as an alternative
IBD Predictors of disease, outcomes, and complications
An Algorithm-Based Approach to Effectively Predict Aggressive Disease Behavior in Patients With CD

• Background
  – Early treatment with biologic therapy may alter progression of disease and may lead to fewer complications

• Objective
  – To identify a set of biomarkers to detect patients at risk for more severe disease

• Methods
  – Blood from 619 patients with CD analyzed for 6 serologic biomarkers
    • ASCA-IgA, ASCA-IgG, Anti-OmpC, anti-CBir1, pANCA, Anti-I2
  – Complications and surgeries recorded

Lichtenstein G et al. DDW 2010; abstract no. 207.
An Algorithm-Based Approach to Effectively Predict Aggressive Disease Behavior in Patients With CD: Results

Patients with Complications by Quartile (%)

All trends $P < .001$

$P = .03$

Lichtenstein G et al. DDW 2010; abstract no. 207.
Observations Regarding Neoplasia in UC

• Von Schaik et al (abstract no. 250)
  – Flat low-grade dysplasia confirmed by expert pathologist panel
  – Rate of progression to advanced neoplasia 37% in 5 years
  – Confirmed IND associated with low rate progression to advanced neoplasia.

• Pekow et al (abstract no. 251)
  – Gene expression changes as "field effects" in UC patients with dysplasia

• Bernstein et al (abstract no. 254)
  – Manitoba IBD database
  – 5-ASA is not chemoprophylactic against CRC
Ulcerative Colitis Gene Signature Distinguishes Patients Harboring Remote Dysplasia

• Background
  – Patients with UC are at increased risk for colorectal cancer
  – Current standard for premalignant surveillance is invasive and samples only a small fraction of colonic mucosa
  – Genetic changes in non-dysplastic tissue may help indicate remote lesions (“field effects”)

• Objective
  – To identify genes associated with dysplasia in UC patients

• Methods
  – Colonic biopsies obtained from healthy controls (n=5); UC patients without dysplasia (n=4); UC patients with dysplasia (n=11)
  – Gene expression assessed using microarrays

Pekow J et al. DDW 2010; abstract no. 251.
Ulcerative Colitis Gene Signature Distinguishes Patients Harboring Remote Dysplasia: Results

• 132 genes were significantly upregulated and 205 downregulated >2-fold in UC patients with dysplasia

• Thirteen genes progressively and significantly upregulated from controls to quiescent non-dysplastic UC to UC with dysplasia
  – CLC, S100A9, CCL4, THBD, ACSL1, CREM, BIRC3, ELTD1, CLU, ANXA3, v-MAF, TPD52L1, and FGG

• Genes belonged to pathways regulating inflammation, proliferation, apoptosis, and angiogenesis

Pekow J et al. DDW 2010; abstract no. 251.
Aminosalicylates, Thiopurines and the Risk of Colorectal Cancer in Inflammatory Bowel Diseases: a Case-Control Study Nested in the CESAME Cohort

• Background
  – ASAS have been suggested as chemopreventive agents in ulcerative colitis
  – Few data are available about the potential chemoprotective effect of thiopurines

• Objective
  – Assess the impact of ASA and thiopurines on risk for colorectal cancer in patients with IBD

• Methods
  – Case-control study nested in CESAME cohort
  – 19,486 patients with IBD, of whom 74 developed CRC before the study period and 79 developed CRC within the study observational period
  – Each case was matched to 2 controls

Carrat F et al. DDW 2010; abstract no. 255.
Aminosalicylates, Thiopurines and the Risk of Colorectal Cancer in Inflammatory Bowel Diseases: a Case-Control Study Nested in the CESAME Cohort

<table>
<thead>
<tr>
<th>Group (number of cancers)</th>
<th>5-ASA</th>
<th>Thiopurines</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (n=153)</td>
<td>0.55 [0.34-0.89] P=.01</td>
<td>0.71 [0.39-1.27] P=.25</td>
</tr>
<tr>
<td>UC (n=95)</td>
<td>0.52 [0.29-0.95] P=.03</td>
<td>0.44 [0.17-1.17] P=.10</td>
</tr>
<tr>
<td>Crohn’s disease (n=58)</td>
<td>0.62 [0.27-1.40] P=.25</td>
<td>0.80 [0.36-1.79] P=.59</td>
</tr>
<tr>
<td>Patients at high risk* (n=94)</td>
<td>0.46 [0.24-0.85] P=.01</td>
<td>0.64 [0.30-1.38] P=.26</td>
</tr>
<tr>
<td>Patients not at high risk (n=59)</td>
<td>0.75 [0.34-1.66] P=.48</td>
<td>0.90 [0.35-2.30] P=.83</td>
</tr>
</tbody>
</table>

*Duration of IBD >10 years and cumulative estimated surface of colonic mucosa involved by IBD >50%

Carrat F et al. DDW 2010; abstract no. 255.
Summary of Epidemiology and Outcomes

- Risk factors for IBD include oleic acid (protective); aspirin and antibiotic use
- Avoid radiation in children with IBD
- CMV burden is important for evaluating its role in flares
- 5-ASA and thiopurines protect against UC-associated cancer
Stephen B. Hanauer, MD
Professor of Medicine
Chief, Section of Gastroenterology
Hepatology & Nutrition
University of Chicago
Chicago, IL

Jointly sponsored by Purdue University School of Pharmacy and the Gi Health Foundation.
This activity is supported Abbott Laboratories, Centocor Ortho Biotech, Inc., and UCB, Inc.
Anti-TNF inhibitors
Decreased Activity of DNase-I Predisposes to Immune-Mediated Complications in IBD Patients During Anti-TNF-α Treatment:

• Background
  – DNAse I degrades DNA during apoptosis
    • Deficiency in DNAse I may result in a failure to remove DNA from nuclear antigens
    – Deficiency in DNAse I may promote susceptibility to autoimmune phenomena

• Objective
  – Evaluate relationship between immune-mediated complications and DNAse I deficiency in patients with IBD treated with Anti-TNF-α

• Methods
  – DNAse I activity assessed in 92 patients with IBD treated with infliximab or adalimumab

Malickova K et al. DDW 2010; abstract no. 202.
Decreased Activity of DNase-I Predisposes to Immune-Mediated Complications in IBD Patients During Anti-TNF-α Treatment: Results

• Results
  – DNase I activity in uncomplicated patients was significantly higher than in patients with skin involvement (75.5±11.7% and 47.8±14.2, respectively, \( P<.001 \))
  – DNase I activity in IBD patients was significantly lower compared with healthy blood donors (\( P<.001 \))
  – DNase I activity was significantly lower in female patients (regardless of response or complications (\( P=.0294 \))

• Conclusions
  – Activity of DNAse I was significantly decreased in IBD patients with skin complications during anti-TNF therapy
  – Measurement of DNAse I may be used to identify subjects at increased risk for these events

Malickova K et al. DDW 2010; abstract no. 202.
Infliximab Trough Levels and Mucosal Healing

• Von Moerkercke et al (abstract no. 405)
  – Infliximab trough levels related to degree of mucosal healing.
  – Measurement of trough levels useful in optimizing therapy
  – Patients with low TR and no healing:
    • Increase dose and/or decrease the interval
  – Patients with high TR and no healing:
    • Switching therapy/target is mandatory
  – Patients with high TR and healing can continue treatment.
Controlled Clinical Trials

• Rutgeerts et al (abstract no. 604)
  – Mucosal healing wk 12 predicted 1-yr outcomes (CDAI score and clinical remission) with adalimumab 40-mg eow

• Van Assche et al (abstract no 645)
  – Assessment of tolerability and efficacy of switching to adalimumab in patients responding to infliximab maintenance
    • 77% (28/36) remained in the ADA group
    • More patients crossed over to IFX than vice versa
    • Main indication to return from ADA to IFX was intolerance
    • Electively switching patients to a second anti-TNF is not recommended
Adalimumab for UC

- **Abstract no. 847**
  - Multicenter, double-blind, placebo-controlled study to assess efficacy and safety of adalimumab for induction of clinical remission in anti-TNF naïve patients with moderately to severely active ulcerative colitis

**Clinical Remission at Week 8**

<table>
<thead>
<tr>
<th>Proportion of Patients (%)</th>
<th>Placebo</th>
<th>ADA 80/40</th>
<th>ADA 160/80</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>9.2</td>
<td>10</td>
<td>18.5</td>
</tr>
</tbody>
</table>

*P*=.031 vs. placebo
† *P*=.833 vs. placebo
# Adalimumab in UC: Secondary Endpoints

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=130)</th>
<th>ADA 80/40 (N=130)</th>
<th>ADA 160/80 (N=130)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical response</strong></td>
<td>44.6%</td>
<td>51.5%</td>
<td>54.6%</td>
</tr>
<tr>
<td><strong>Mucosal healing</strong></td>
<td>41.5%</td>
<td>37.7%</td>
<td>46.9%</td>
</tr>
<tr>
<td>Rectal bleeding subscore ≤ 1</td>
<td>66.9%</td>
<td>70.0%</td>
<td>77.7%*</td>
</tr>
<tr>
<td>PGA subscore ≤ 1</td>
<td>46.9%</td>
<td>53.8%</td>
<td>60.0%†</td>
</tr>
<tr>
<td>Stool frequency subscore ≤ 1</td>
<td>37.7%</td>
<td>36.2%</td>
<td>49.2%‡</td>
</tr>
</tbody>
</table>

*P*=.052, †P=.035, ‡P=.061 vs. placebo.
Other Treatments for IBD
Randomized, Controlled Trial of MDX-100 (Anti IP-10) in UC

• Background
  – IP-10 is a CXC chemokine ligand that mediates T cell migration via its receptor CXCR-3
  – IP-10 may also inhibit proliferation and migration of gut epithelial cells

• Objective
  – Evaluate the safety and efficacy of MDX-1100 in patients with moderate to severe UC and inadequate response and/or intolerance to medical therapy

• Patients
  – N=109
  – Mayo score 6-10
  – Endoscopic subscore ≥2

• Treatments
  – MDX-100 10 mg/kg every 2 weeks (4 doses)
  – Placebo

• Primary end point
  – Clinical response* at Day 57
  – Prespecified statistical analyses defined patients as nonresponders if <3 diary entries were present during the 7 days prior to assessment
  – More conventional analyses where any diary entry within a 3-day window prior to assessment contributed to the Mayo score were performed post-hoc

*Clinical response defined as reduction in Mayo score ≥3 points (≥30%) and decrease in rectal bleeding subscore ≥1 point or absolute rectal bleeding subscore ≤1 point

Randomized, Controlled Trial of MDX-100 (Anti IP-10) in UC: Results

Prespecified Statistical Analysis
(Patients defined as nonresponders if <3 diary entries were present during 7 days prior to assessment)

\[ P = 0.083 \]

Randomized, Controlled Trial of MDX-100 (Anti IP-10) in UC: Results

Post-hoc “Conventional” Analysis
(Any diary entry within a 3-day window prior to assessment contributed to Mayo score)

![Graph showing response, remission, and mucosal healing percentages for Placebo and MDX-100 groups.]

\[ P = 0.02 \]

Randomized, Controlled Trial of MDX-100 (Anti IP-10) in UC: Additional Results

- Efficacy was influenced by tertile of MDX trough serum concentration (SSCmin)
  - Response: 53%, 63%, and 88%
  - Remission: 12%, 25%, and 44%
  - Mucosal healing: 29%, 44%, and 69%

- Increase in SSCmin led to increase in:
  - Clinical response (OR 3.77; P<0.017)
  - Remission (OR 2.85; P=.071)
  - Mucosal healing (OR 3.08; P=.03)

- Proportions of patients with adverse events were low and comparable between the 2 groups
  - A higher proportion of patients had infection (12.7% vs 5.8%) and serious infection (5.5% vs 1.9%) in the MDX group vs PBO

Tinidazole to Prevent Pouchitis

- Ha et al (abstract no. 488)
- 38 UC patients randomized in a 2:1 ratio to receive tinidazole 500 mg or placebo within 1 month of final stage of IPAA for 12-months
  - 8.0% of tinidazole group developed pouchitis vs 38.5% patients taking placebo ($P=0.03$)

Kaplan-Meier estimates of cumulative rates of pouchitis per-protocol during 12 months of treatment with placebo or tinidazole ($P=0.026$).
Naltrexone for Crohn’s Disease

- Smith et al (abstract no. 646)
- Randomized double-blind, placebo-controlled study to test efficacy and safety of naltrexone 4.5 mg/d
  - 82% of the naltrexone-treated subjects had 70-point drop in CDAI
  - 45% achieved clinical remission
  - Placebo response??
Herbal Therapy of UC

• Sandborn et al (abstract no. 847x)
  – Double-blind, placebo-controlled phase IIb trial of *Andrographis paniculata* extract in mild-to-moderate UC
  – Herbal mixture used to treat inflammatory diseases in Asia inhibits induction of TNF-α, IL-1β RNA, and IL-6, & inhibits NF-κB activation in vitro.
Summary of Clinical Trials

• Trough levels of anti-TNF antibodies
  – Associated with Loss of Response
  – Mucosal Healing

• Mucosal Healing is associated with long-term outcomes

• Optimal dosing of anti-TNF in UC with sub-q not established

• Antibiotics ~ Pouchitis → Microbiota associated with pathogenesis