Human Hematopoietic Stem Cells with a Defined Immunodeficiency and Enteropathy Transfer Clinical Phenotype to a Novel Humanized Mouse Strain

- Able to transfect human hematopoietic stem cells from patients with specific immunodeficiency syndrome –IPEX which is due to a lack of regulatory T cells –into NOD.Prkdcscid.II2ry-/- (NSG) immunocompromised strain—MHC null
- Expressed human leukocyte antigen-DR1 under the control of the murine MHCII promoter (NSGAboDR1)
- Caused portal inflammation, mild small bowel inflammation, and lung inflammation
- We may be able to engraft CD or UC HSC cells from patients into mice to study the disease
TI1a modulates the differential effect of IL-17 blockade on mucosal inflammation

- A proportion of trial patients who responded to IL-17 blockade were found to carry a risk TL1A IBD polymorphism that predicted elevated expression of TL1A
- Mice that received Il-17a-/- naïve cells had worsened CD45 Rb tsf colitis
- Il-17a deficiency under TI1a driven conditions (TI1a-Tg/Il-17a-/-) ameliorated colitis (reduced DAI and cecal inflammation)
- Highlights why patients failed the clinical trial except for subset with hi TL1a b/c of genetic polymorphism
The Treatment-Naive Microbiome in Early-Onset Crohn’s Disease

Gevers D et al. Abstract no. 850a
Rationale and Methods

• Genetic analysis have linked IBD to an aberrant immune response to intestinal microbiota

• Methods
  – Used samples collected prior to treatment to evaluate the microbiome prior to treatment in a large pediatric CD cohort
  – Included subjects aged 3 to 17 years with CD (n=447) and controls (n=221) with noninflammatory conditions
Results and Author’s Conclusions

<table>
<thead>
<tr>
<th>Increased</th>
<th>Decreased</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterobacteriaceae</td>
<td>Erysipelotrichales</td>
</tr>
<tr>
<td>Pasteurellacae</td>
<td>Bacteroidales</td>
</tr>
<tr>
<td>Veillonellaceae</td>
<td>Clostridiales</td>
</tr>
<tr>
<td>Fusobacteriaceae</td>
<td></td>
</tr>
</tbody>
</table>

- Microbiome comparison between CD patients with and without antibiotic exposure indicated that antibiotic use amplifies the microbial dysbiosis associated with CD

- Microbial signatures at the ileum, rectum, and fecal samples indicated that at early stages of disease, assessing the rectal mucosa-associated, but not fecal, microbiome was a robust disease predictor
Take-home Messages

- Treatment with antibiotic was associated with dysbiosis
- During early stages of disease, samples from rectum or ileum are robust disease predictors
- Fecal samples do not provide robust disease prediction
Trans-Ethnic Association Study of IBD Identifies 14 New Disease Loci and Demonstrates Pervasive Sharing of Genetic Risk Factors and Phenotypic Features Between Europeans and Non-Europeans

Van Sommeren S et al. Abstract no. 784
Rationale and Methods

• **Rationale**
  – Previous studies in IBD patients of European descent identified 163 genetic susceptibility loci
  – Few data are available on the genetic background and phenotypic presentation in IBD patients of non-European descent

• **Methods**
  – East Asian, Indian, Indo-European individuals genotyped
  – Linear mixed model (MMM) used for case-control association tests
  – Data combined with 79,584 individuals of European descent for trans-ethnic meta-analysis
Results and Author’s Conclusions

• 14 novel IBD loci identified
• Data suggest that there is pervasive sharing of genetic risk factors between different ethnicities
• IBD is a highly heterogeneous disease
Take-home Messages

- Across ethnicities, there is a common core of IBD susceptibility genes
- The relative contributions for individual genes differs among ethnicities
A High-fat Diet Containing Coconut Oil Prevents the Onset of Chronic Intestinal Inflammation in Experimental Crohn’s Disease

Cominelli F et al. Abstract no. 787
Rationale and Methods

• Rationale
  – High-fat diets increase the severity of colonic inflammation and alter commensal flora in mouse models of colitis
  – The effects of high fat intake on small intestinal inflammation have not been fully elucidated

• Methods
  – SAMP mice (have CD-like ileitis) and control (AKR) mice fed high-fat diet or standard diet for 24 weeks
  – Ilea were directly examined to calculate percentages of abnormal mucosa
Results and Author’s Conclusions

- SAMP mice fed high-fat diet vs standard diet had:
  - Lower percentages of abnormal gut mucosa (8.7±3.0 vs 40.1±5.2, n=4; $P<.05$)
  - Lower total inflammatory scores (0.8±0.1 vs 6.3±0.3, n=11; $P<.001$)

- 7/11 SAMP H mice showed complete prevention of ileitis ($P<.004$)

- Fecal transplantation from SAMP high-fat donors suppressed colitis in SAMP germ-free mice
Take-home Messages

- A high-fat diet containing coconut oil prevented the onset of ileitis in SAMP mice
- Effects may be mediated, in part, by induction of a “tolerogenic” commensal flora
Therapeutic Monitoring
Higher 6-Thioguanine Nucleotide Concentrations are Associated With Higher Trough Levels of Infliximab in Patients on Combination Therapy

Yarur A et al. Abstract no. 788
Rationale and Methods

• Objective
  – Assess if there is a correlation between 6-thioguanine (6-TGN), IFX trough level, and antibodies to IFX (ATI)

• Methods
  – Cross-sectional study of IBD patients receiving maintenance therapy with IFX with a thiopurine (AZA or 6-MP) for ≥ 4 months
  – Primary outcome: IFX trough level and the presence of ATI
Results

• Significant positive correlation between 6-TGN levels and IFX levels (rho: 0.477 \( P<.0001 \))

• 6-TGN \( \geq 125 \) pmol/8X10^8 RBC best predicted higher anti-TNF levels (ROC: 0.82, \( P=.002 \))

• Only 6-TGN level was predictive of IFX measurements (\( P<.001 \))

• Patients with 6-TGN levels <125 pmol/8X10^8 had a 1.3-fold higher chance of having detectable ATI (OR: 1.3 \( P<.01 \))
Take-home Messages

- 6-TGN metabolite levels rather than weight-based dosing may assist in optimizing treatment when using thiopurines in combination with IFX
- Therapeutic levels of 6-TGN (>232 pmol/8X10^8 RBC) are not necessary to achieve higher trough levels of IFX
- Lower target 6-TGN levels (125 pmol/8X10^8 RBC) may maximize IFX levels while minimizing toxicity
Azathioprine Decreases the Risk of Adalimumab Primary Non-response and Secondary Loss of Response but Only if Adequately Dosed

Kariyawasam V et al. Abstract no. 343
Purpose and Methods

• Purpose
  – Assess the impact of concomitant immunomodulators and drug monitoring to confirm compliance on ADA efficacy

• Methods
  – All patients treated with adalimumab at a single center included (N=118)
  – Treatment periods assessed in 6-month semesters
Results

- Complete clinical response to induction was achieved in 78% (92/118)
  - Thiopurines 3 months prior to starting ADA associated with significantly higher likelihood of response (84.2% vs 66.7%, \( P = .028 \))

- Reclassifying according to TGN levels improved this association (87.3% vs 65.9%, \( P = .011 \))
Results

Figure 1. Time to adalimumab failure according to therapeutic levels of azathioprine for 3 months prior to starting therapy.

Based on TGn levels azathioprine for 3 months:
- Purple line: Yes
- Blue line: No
Results

- 169 semesters in 81 patients were analyzed for the effect of concomitant immunomodulators
- Semesters with concomitant immunomodulators when classified according to TGN showed significantly lower flare (16.4% vs 24.6%) and failed (9.2% vs 2.7%) semesters ($P=0.019$)
- Not seen when TGN levels were not considered ($P=0.074$)
Take-home Message

• Thiopurine use adjusted with drug monitoring may increase rate of successful induction of remission and reduce numbers of flares and failure during maintenance
Elevated Fecal Calprotectin Predicts Relapse in Inflammatory Bowel Disease Patients After Stopping TNFα-Blocking Agents 4:15 | 1054 |

Pauliina Molander¹, ¹³, Martti A. Färkkilä², ¹³, Ari Ristimäki³, Kimmo Salminen⁴, Helena Kemppainen⁴, Timo Blomster⁵, Ritva Koskela⁵, Airi Jussila⁶, Henna Rautiainen⁷, Markku Nissinen⁸, Johanna Haapamäki², Perttu E. Arkkila², Urpo Nieminen², Juha Kuisma⁹, Jari Punkkinen¹⁰, Kaja-Leena Kolho¹¹, Harri Mustonen¹², Taina Sipponen²
Background & Aims

• Few studies have shown that assessment of subclinical inflammation by using surrogate markers such as fecal calprotectin (FC), may indicate the risk of relapse before the actual clinical relapse occurs.

• Aim In this prospective multicenter study: to determinate whether a consecutive elevated FC concentration after stopping TNFα- blocking therapy predicts relapse before the actual clinical or endoscopic relapse occurs.
Methods

- 52 patients with IBD (17 [CD], 30 [UC] and 5 [IBDU]) in clinical, endoscopic and FC-based (<100mcg/g) remission after at minimum one year of TNFα- blocking therapy were recruited.

- They were followed up to one year after discontinuation of TNFα-blocking therapy

- FC was collected monthly for the first six months and every other month thereafter up to one year.

- Colonoscopy was performed at 4 and 12 months after stopping therapy and at the time of clinical relapse.

- In CD, clinical relapse defined by (HBI) and endoscopic relapse by (SES-CD).

- In UC or IBDU, clinical and endoscopic relapse was defined by Mayo score.
Results

• Forty-nine patients (16 CD, 33 UC/IBDU) provided stool samples and comprised the study group.

• Of the 49 patients 15 (31%, 4 CD [25%], 11 UC/IBDU [33%]) relapsed during the one year follow-up and 34 (69%, 12 CD [75%], 22 UC/IBDU [66%]) remained in remission.

• Significant increase in median FC levels was seen two (120 mcg/g, 0-1867, n = 15, p = 0.0014), four (108 mcg/g, 7-650, n = 8, p = 0.0056), and six (120 mcg/g, 0-431, n = 6, p = 0.0029) months before the actual relapse.

• In contrast to those with sustained endoscopic remission, patients relapsing showed constantly elevated FC levels. A cutoff of > 140 mcg/g (ROC analysis) predicted relapse with a 79% specificity and a 53% sensitivity.

• No significant difference was seen in median FC levels in patients having endoscopic remission and those with mild endoscopic activity at follow-up colonoscopies.

Conclusion:
FC seems to rise and remain elevated before the actual clinical or endoscopic relapse, suggesting that FC can be used as a surrogate marker for predicting relapse in patients with IBD, and to identifying patients requiring a close follow-up in clinical practice.
Usefulness of a Rapid Test for Fecal Calprotectin as Predictor of Relapse in Crohn's Disease Patients Under Maintenance Treatment with Adalimumab

Dominguez-Munoz E et al. Abstract no. 345
Purpose and Methods

• Purpose
  – Evaluate predictive value of a rapid test of fecal calprotectin to predict flares in CD patients during ADA maintenance

• Methods
  – Prospective, observational cohort study
  – CD patients in clinical remission for ≥ 6 months with standard dose of 40 mg/every other week adalimumab
  – Calprotectin measured and correlated with relapse over next 4 months
  – “Quantum Blue” rapid 12-15 fecal calprotectin test used for analysis (not available in the US)
Results

- After the four months follow-up, 70.0% patients remained in clinical remission; 30.0% relapsed.
- Fecal calprotectin significantly higher in patients who had a relapse during follow-up.
- Optimal cutoff to predict remission: 204 mcg/g.
Take-home Messages

- In CD patients maintained with adalimumab, fecal calprotectin levels predict relapse with high accuracy
  - Low fecal calprotectin levels exclude relapse within at least the following four months
  - High levels associated with relapse in 3 out of 4 patients
Serum CRP is a Better Early Marker for Response to Infliximab Induction Therapy than Fecal Calprotectin in Patients With Moderate to Severe Ulcerative Colitis

Brandse J et al. Abstract no. 212
Purpose and Methods

• Purpose
  – Aimed to define the optimal timing of serum CRP and fecal calprotectin measurement and compare both markers for response to therapy

• Methods
  – Multicenter prospective observational study
  – Serum CRP, albumin, and fecal calprotectin measured during the first 6 weeks of induction therapy
  – Absence of response defined as need for higher-dose infusion during induction or colectomy within 3 months
  – Endoscopic response defined as improvement at week 6-8 endoscopy
## Results

Markers that significantly discriminate between absence of response and response or endoscopic response or non-response

<table>
<thead>
<tr>
<th></th>
<th>Absence of response (n=3) Median (IQR)</th>
<th>Responders (n=12) Median (IQR)</th>
<th>P value</th>
<th>Predictive value cut-off</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline CRP (mg/l). Cut-off 75mg/l</td>
<td>124 (95-128)</td>
<td>9 (2-41)</td>
<td>P=0.04</td>
<td>OR:54 (95%CI:1.76-1637, P&lt;0.01)</td>
</tr>
<tr>
<td>Day 1 CRP (mg/l). Cut-off 75mg/l</td>
<td>93 (80-123)</td>
<td>7 (2-29)</td>
<td>P=0.04</td>
<td>OR:54 (95%CI:1.76-1637, P&lt;0.01)</td>
</tr>
<tr>
<td>Day 4 CRP (mg/l). Cut-off 25mg/l</td>
<td>59 (30-96)</td>
<td>3.8 (1.3-11.3)</td>
<td>P=0.01</td>
<td>OR:175 (95%CI:2.9-10520, P&lt;0.01)</td>
</tr>
<tr>
<td>Day 4 Albumin (g/l). Cut-off 33mg/l</td>
<td>29 (29-32)</td>
<td>40 (37-46)</td>
<td>P=0.02</td>
<td>OR:54 (95%CI:1.76-1637, P&lt;0.01)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Endoscopic Non-responders (n=8) Median (IQR)</th>
<th>Endoscopic Non-responders (n=7) Median (IQR)</th>
<th>P value</th>
<th>Predictive value cut-off</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 7 CRP (mg/l). Cut-off 5mg/l</td>
<td>15.3 (2-35)</td>
<td>1.6 (0.8-3.4)</td>
<td>P=0.06</td>
<td>OR:23 (95%CI:0.99-556, P&lt;0.02)</td>
</tr>
<tr>
<td>Day 7 Calprotectin (mcg/g). Cut-off 1300ug/g</td>
<td>1800 (1562-1800)</td>
<td>465 (200-1410)</td>
<td>P=0.02</td>
<td>OR:55 (95%CI:1.86.99-1624, P&lt;0.01)</td>
</tr>
<tr>
<td>Day 14 Calprotectin (mcg/g). Cut-off 750ug/g</td>
<td>1800 (1421-1800)</td>
<td>222 (130-837)</td>
<td>P&lt;0.01</td>
<td>OR:55 (95%CI:1.86.99-1624, P&lt;0.01)</td>
</tr>
</tbody>
</table>
Results

Serum CRP during infliximab induction

- Absence of response (n=3)
- Responders (n=12)
- Endoscopic Non-responders (n=8)
- Endoscopic responders (n=7)

Day after first IFX infusion

CRP (mg/L)
Take-home Messages

• Serum CRP is a better early marker for response to IFX vs fecal calprotectin or serum albumin

• Optimal timing for measuring serum CRP to predict absence of clinical or endoscopic response:
  – Day 4 (cut-off value 2.5 mg/dL)
  – Day 7 (cut-off value 0.5 mg/dL)
Development of an Algorithm Incorporating Pharmacokinetics of Adalimumab in Inflammatory Bowel Diseases

Roblin X et al. Abstract no. 866
Purpose and Methods

• Purpose
  – Determine whether decision algorithms based on measurement of infliximab
trough levels and antibodies can be extrapolated to adalimumab

• Methods
  – Included all consecutive patients with IBD having a disease flare while being on
adalimumab 40 mg every two weeks monotherapy
  – Adalimumab trough levels and antibodies to adalimumab (AAA) were measured
  – All patients were optimized with adalimumab 40 mg weekly
  – Four months later, in the absence of clinical remission, patients were treated with
infliximab
  – Patients were divided into three groups based on ADA trough levels based on
previous studies:
    • Group A: ADA>4.9 mcg/mL
    • Group B: ADA <4.9 mcg/mL and undetectable levels of AAA (<10 ng/mL)
    • Group C: ADA <4.9 mcg/mL and AAA >10 µg/mL
Results

- After optimization of adalimumab treatment, 29.2% of patients achieved clinical remission in the group A*, 67% in the group B, and 12% in the group C (P<.01 between groups A/B and B/C)

- Response to adalimumab optimization was significantly more durable in group B (15 months) than in groups A (4 months) and C (5 months)

- Conclusions
  - Presence of low adalimumab trough levels in serum without AAA is strongly predictive of a favorable clinical response after adalimumab optimization (67%)
  - Low adalimumab levels with detectable AAA are associated with failure of ADA optimization and a switch to infliximab should be considered

*Group A: ADA>4.9 mcg/mL
Group B: ADA< 4.9 mcg/mL and undetectable levels of AAA (< 10 ng/mL)
Group C: ADA<4.9 mcg/mL and AAA > 10 µg/mL
Take-home Messages

• Similar to Afif study with infliximab, adalimumub levels at loss of response predict outcome dose escalation
• Low adalimumub responded
• High adalimumub did not
• Patients with antibodies to infliximab did not respond
Potential Adverse Events of IBD Therapy
The Impact of Age-specific Risks of Lymphoma on the Decision to Use Combination Therapy With Infliximab and Azathioprine Versus Infliximab Alone: A Markov Model

Scott F et al. Abstract no. 4
Rationale and Methods

• Rationale
  – The impact of age-related risk of NHL and HSTCL has not been addressed in prior studies
  – After accounting for age and treatment-specific risks of lymphoma, the preferred treatment strategy in CD may differ by age

• Methods
  – Markov model constructed to assess age-specific risks and benefits of combination therapy vs anti-TNF monotherapy
  – Expected risk and incremental effectiveness calculated for patients initiating therapy across 25 to 75 age range
  – Baseline case: 35-year-old male with severe CD
Results

• Combination therapy was the preferred strategy in the baseline case (0.7714 vs. 0.7611 QALYs)

• Combination therapy resulted in fewer surgeries (94,888 vs. 144,351), deaths (4133 vs. 4155), and patients with active disease (162,524 vs. 198,191)

• Benefit persisted across all ages in the base model, though the margin of benefit decreased with increasing age

Sensitivity Analysis of Impact of Age

![Graph showing the sensitivity analysis of the impact of age on the expected value (in QALYs) for Infliximab Monotherapy and Infliximab and azathioprine.](image)
Results

• When accounting for life years lost due to mortality, monotherapy was preferred if the hazard ratio of NHL with AZA therapy was >11.5 in those age 65 or >6.9 in those age 75

• For 25-year-old males, accounting for the risk of HSTCL, monotherapy resulted in fewer deaths and was the preferred strategy if the incidence of HSTCL was greater than 24 per 100,000
Take-home Messages

• From ages 35 to 65, combination therapy is the preferred strategy

• For those who are >65, and particularly those >75, monotherapy may be a more beneficial strategy due to the increased risk of NHL and NHL-related mortality with combination therapy

• Due HSTCL risk, combination therapy in young males may result in more deaths without providing substantially greater QALYs
Association Between Adherence to Colorectal Cancer Surveillance Guidelines and Cancer Staging at Colectomy in Ulcerative Colitis Patients

Cole E et al. Abstract no. 373
Rationale and Methods

• Rationale
  – There is an increased risk of developing colorectal cancer (CRC) in the setting of UC
  – This study evaluated the relationship between adherence to surveillance colonoscopy guidelines and stage of cancer at diagnosis

• Methods
  – Nationwide data was obtained from the Veterans Affairs (VA) healthcare system database
  – Patients included who had total colectomy for CRC or dysplasia in the setting of UC and a complete surgical pathology report available for review
### Results and Conclusions

<table>
<thead>
<tr>
<th>Patients screened according to guidelines</th>
<th>Stage I or II cancer (n=24)</th>
<th>Stage III or IV cancer (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients screened according to guidelines</td>
<td>19</td>
<td>3</td>
</tr>
<tr>
<td>Patients not screen</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

- Patients who underwent scheduled surveillance having an almost 84% lesser chance of having advanced stage cancer (OR=0.16, 95% CI 0.03-0.90)
Take-home Messages

- Adherence to the screening guidelines results in detection of CRC at an earlier stage
- Those who did not adhere to the guidelines had a greater likelihood of having more advanced cancer
- This study validates the need for screening, but is limited by small N
Risk of Incident Cancer in Patients With Inflammatory Bowel Disease Starting Anti-TNF Therapy While Having Prior Malignancy Within Past 5 Years

Laharie D et al. Abstract no. 341
Purpose and Methods

• Purpose
  – Assess survival without incident cancer in a cohort of patients with IBD exposed to anti-TNF therapy while having prior malignancy within past 5 years

• Methods
  – Survey conducted that collected all IBD patients with malignancy diagnosed within 5 years prior to starting an anti-TNF
  – Primary objective: Evaluate the cumulative incidence of incident (new or recurrent) cancer
Results

- 79 cases of IBD patients with prior malignancy identified
- Most frequent: breast (n=17), skin (n=15), urinary tract (n=12), and those attributed to chronic inflammation (n=8)
- After median follow up of 21 [1-119] months, 15 (19%) patients developed an incident cancer: 8 recurrent cancers and 7 new cancers, including 5 BCCs
- Survival without incident cancer was 96%, 86% and 72% at 1, 2 and 5 years, respectively
- Two recurrences possibly related to anti-TNF administration
Take-home Messages

• Risk of recurrent cancer appears about the same as it is for patients with cancer in general
Infliximab Trough Levels are Correlated With Infliximab-associated Adverse Events

Huang V et al. Abstract no. 3
Rationale and Methods

• **Rationale**
  – To determine the prevalence of infliximab-associated adverse events in IBD patients and evaluate their relationship to infliximab trough levels

• **Methods**
  – Cross-sectional study of consecutive patients from a single center (N=75)
  – Infliximab levels obtained before infusion
  – Records reviewed for infliximab-associated adverse events
Results

• Median trough levels were **significantly higher** in patients who reported dermatologic AEs (9.9 μg/mL vs 0.1 μg/mL, \( P = .020 \)),

• Median trough levels were **significantly lower** in patients who reported infusion AEs (0.4 (0-6.3) μg/mL vs 9.9 (0-19.5) μg/mL, \( P = .048 \))

• Median trough levels were **not significantly different** between patients with and without arthralgias or neuropathy AEs (4.1 μg/mL vs. 7.3 μg/mL, \( P = .091 \))
Take-home Messages

• High trough levels of infliximab correlated with dermatologic adverse reactions
• Low trough levels correlate with infusion reactions
• Patients with high levels and with dermatologic reactions may need dose deescalation
Vaccination Outcomes in Inflammatory Bowel Disease

Abdallah J et al. Abstract no. 959
Purpose and Methods

• Purpose
  – Determine pneumococcal and influenza vaccination outcomes in patients with IBD

• Methods
  – Retrospective study utilizing electronic database (~40 million patients)
  – IBD patients (using ICD-9 code criteria) between the years 1999 and 2012 were included
  – Vaccination defined as receiving a single dose of each vaccine at any point of time during the study period
Take-home Messages

• First study performed to evaluate outcomes of vaccination in IBD patients
• Significant reduction in overall infections in patients receiving the pneumococcal and influenza vaccine demonstrated
• Vaccination of patients with IBD has significant value
Pregnancy and IBD
Achievement of Developmental Milestones Among Offspring of Women with Inflammatory Bowel Disease: The PIANO Registry

- Followed patients through pregnancy and the first 4 years of life
- 6-MP/azathioprine (Group A), infliximab, adalimumab, certolizumab (Group B), combination therapy (Group AB)
- When compared to the unexposed infants, infants in Group A, B and AB always had equivalent or better achievement of milestones
- Infants with in-utero exposure to immunomodulator and biologic therapy did not exhibit developmental delay compared to infants not exposed to these agents, controlling for preterm birth
Exposure to Anti-TNFα Therapy in the Third Trimester of Pregnancy is Not Associated with Increased Adverse Outcomes: Results from the PIANO Registry

- Outcomes of women exposed to biologics during the third trimester (T3) were compared to those not exposed during T3 and to those exposed during T1, T2 but not T3.
- 501 women were exposed to biologics during pregnancy
- 422 women were exposed to a biologic in T3 compared to 597 unexposed in T3 (of whom 70 had T1, T2 exposure but stopped prior to T3)
- 247 women had biologic exposure within the last 10 weeks of pregnancy; 369 did not
- Exposure to biologic therapy in the third trimester of pregnancy was not associated with increased infant infection rates even when controlled for biologic of exposure
- Rates of preterm birth and disease activity were also unaffected
Established Therapies
Randomized Controlled Trial of Mesalamine Dose Escalation for Ulcerative Colitis in Remission

Lewis J et al. Abstract no. 862
Purpose and Methods

- **Purpose**
  - In quiescent UC, lower fecal calprotectin concentration is associated with lower relapse rates
  - Examined whether higher-dose mesalamine can reduce FC concentration among patients with quiescent UC

- **Methods**
  - Randomized controlled trial
  - Patients: UC in remission (N=52) taking no more than 3 g/day mesalamine
  - Patients not taking MMX mesalamine switched to 2.4 g/d for 6 weeks prior to randomization
  - Treatments
    - Continue current mesalamine dose
    - Increase dose by 2.4 g/day for 6 weeks
  - Primary outcome: continued remission with FC concentration <50mcg/g at 6 weeks
Results and Conclusions

- Primary outcome achieved by 3.8% of control patients and 26.9% of patients randomized to dose escalation ($P=.0496$).
- More patients in the dose escalation group achieved reduction in FC concentration below 100 mcg/g (52.6% vs 15.8%, $P=.04$) and 200 mcg/g (76.9% vs. 16.7%, $P=.005$)
Mesalamine dose escalation is associated with reductions in FC concentrations to levels associated with lower relapse rates.
Accelerated Infliximab Rescue Reduces Early Colectomy Rate in Acute Severe Colitis

- Standard dosing: Infliximab given at 0, 2, and 6 weeks and every 8 weeks thereafter
- Accelerated dosing: patients given accelerated dosing (AD) received all three induction doses of infliximab within 2 weeks and 8 weekly thereafter
- 18/38 (47.3%) required surgery in the standard dosing (SD) group and 4/14 (28.5%) in the AD group during follow-up
- Rate of colectomy at 3 months was significantly lower with accelerated dosing versus standard dosing

Take-home message
- More frequent and higher doses of infliximab may benefit severe UC patients
Early Combined Immunosuppression for the Management of Crohn's Disease: a Community-Based Cluster Randomized Trial 4:00 | 1053

Reena Khanna¹, ², Barrett G. Levesque¹, ³, Brian Bressler⁴, Guangyong Zou¹, ⁵, Larry Stitt¹, Gordon R. Greenberg⁶, Remo Panaccione⁷, Alain Bitton⁸, Pierre Pare⁹, Severine Vermeire¹⁰, Geert R. D'Haens¹, ¹¹, Donald G. MacIntosh¹², William Sandborn¹, ³, Margaret K. Vandervoort¹, Joan C. Morris¹, Brian G. Feagan¹, ²
Background

- Conventional management of CD consists of sequential use of corticosteroids, antimetabolites, and TNF antagonists.
- Recent evidence indicates that early combined immunosuppression with a TNF antagonist and an antimetabolite may be more effective than conventional management.
- Study compared the effectiveness of early combined immunosuppression to conventional management in community gastroenterology practices.
Design

- Patients randomly assigned in a 1:1 ratio to early combined immunosuppression or conventional management
- Up to 60 consecutive adult patients (≥18 years of age) with CD in each practice evaluated for 24 months
- Primary outcome: Proportion of patients in remission at 12 months
- Secondary measures were the rates of complications, hospitalizations, and surgeries over the entire follow-up period, based on patient-level analyses.
• Mean remission rates in the ECI and CM groups were:
  – 66% and 62% at 12 months ($P=.65$)
  – 73% and 65% at 24 months ($P=.35$).

• Highly significant and clinically important differences in the rates of complications, surgeries, and the combined outcome of hospitalizations, complications, and surgeries were observed in favor of ECI over 24 months.

• Community-based data indicate that 1) a symptom based conventional approach to CD management may not be optimal and 2) ECI may be more effective in preventing CD-related complications.
Therapeutic Algorithm for Crohn’s Disease

Active Luminal CD (HBS > 4)

- Without Fistula:
  - GCS (Bud vs Pred depending on disease activity and localization)
    - Evaluate in 4 wks* - remission? (HBS ≤ 4)
      - Yes: Taper GCS
      - No: Add Adalimumab + AZA or MTX
        - Re-evaluate in 12 wks - remission?
          - Yes: Continue Combination Maintenance Therapy
          - No: Increase Adalimumab to weekly dose
            - Re-evaluate in 12 wks - remission?
              - Yes: Continue Combination Maintenance Therapy
              - No: Switch Antimetabolite
                - Re-evaluate in 12 wks - remission?
                  - Yes: Continue Combination Maintenance Therapy
                  - No: Switch TNF Blocker
                    - Re-evaluate in 12 wks - remission?
                      - Yes: Continue Combination Maintenance Therapy
                      - No: Consider Resection

- With Fistula:
  - Complex Fistula
    - With Fistula
      - Yes: MRI, US, EUA to rule out abscess
      - No: Antibiotics/Fistulotomy
        - Abscess present?
          - Yes: Drainage/Seton + Antibiotics
          - No: Surgical Reassessment
            - Re-evaluate in 4 wks - improved?
              - Yes: Follow Algorithm for Active Luminal CD Without Fistula
              - No: Surgery Reassessment

*For patients in Belgium, evaluate in 12 wks
New Medications, New Targets
Efficacy of Vedolizumab Induction Therapy in Patients With Crohn’s Disease Who Have Experienced Tumor Necrosis Factor Antagonist Failure or Are Tumor Necrosis Factor Antagonist Naive

Sands B et al. Abstract no. 864
Background

• Background
  – Vedolizumab is a anti-α4β7 integrin monoclonal antibody
  – Evaluated in 2 phase 3 studies (GEMINI 2 and GEMINI 3)

• Methods
  – Induction data were pooled from the randomized GEMINI 2 and 3 studies of patients with moderately to severely active CD who received placebo or vedolizumab 300 mg by intravenous infusion at weeks 0, 2, and 6
  – Proportions of patients in clinical remission and with a CDAI-100 response (≥ 100-point decrease from baseline in CDAI score) were assessed at weeks 6 and 10 for the TNF antagonist failure and TNF antagonist–naive subgroups
## Results

<table>
<thead>
<tr>
<th>End Point</th>
<th>TNF Antagonist Failure</th>
<th>Stage III or IV cancer (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VDZ (n=263)</td>
<td>PBO (n=227)</td>
</tr>
<tr>
<td>Week 6 clinical remission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. patients (%)</td>
<td>35 (13.3)</td>
<td>22 (9.7)</td>
</tr>
<tr>
<td>P-value*</td>
<td>0.157</td>
<td>-</td>
</tr>
<tr>
<td>Week 10 clinical remission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. patients (%)</td>
<td>57 (21.7)</td>
<td>25 (11.0)</td>
</tr>
<tr>
<td>P-valuea</td>
<td>0.0008</td>
<td>-</td>
</tr>
<tr>
<td>Week 6 CDAI-100 response,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. patients (%)</td>
<td>87 (33.1)</td>
<td>51 (22.5)</td>
</tr>
<tr>
<td>P-valuea</td>
<td>0.005</td>
<td>-</td>
</tr>
<tr>
<td>Week 10 CDAI-100 response,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. patients (%)</td>
<td>103 (39.2)</td>
<td>51 (22.5)</td>
</tr>
<tr>
<td>P-valuea</td>
<td>&lt;0.0001</td>
<td>-</td>
</tr>
</tbody>
</table>

Data are from post hoc analyses; aP-value versus PBO and based on the Cochran-Mantel-Haenszel chi-square test.
Take-home Messages

- Vedolimumab is effective in patients who experienced failure of prior TNF antagonist therapy and those who were TNF antagonist naive.
- In clinical practice it may take 10 weeks or more to see a clinical effect in some patients.
AJM300, an Oral α4 Integrin Antagonist, for Active Ulcerative Colitis: a Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase 2A Study

Watanabe M et al. Abstract no. 370.
Background and Methods

• Background
  – AJM300 is an orally active, small molecule α4 integrin antagonist

• Methods
  – Multicenter, randomized, double-blind, placebo-controlled phase 2a study
  – Patients with the Mayo Clinic score of 6-10, an endoscopic subscore ≥ 2 and a rectal bleeding subscore ≥1 were enrolled
  – Patients were also required to have an inadequate response or intolerance to 5-ASA or corticoids
  – Treatments:
    • AJM300 at a dose of 960 mg or placebo TID for 8 weeks
    • The primary endpoint was a clinical response at week 8
Results

• Clinical response at week 8, was 62.7% versus 25.5% in the AJM300 group and placebo group, respectively (OR: 5.35; 95% CI, 2.23 to 12.82; \( P=0.0002 \)).

• Secondary endpoints:
  – Clinical remission at week 8: 23.5% versus 3.9% (OR, 7.81; 95% CI, 1.64 to 37.24; \( P=0.0099 \))
  – Mucosal healing at week 8: 58.8% versus 29.4% (OR, 4.65; 95% CI, 1.81 to 11.90; \( P=0.0014 \))

• Serious adverse events (including PML and serious infections) were not observed
Fecal Biotherapy
A Randomized, Placebo-Controlled Trial of Fecal Microbiota Therapy in Active Ulcerative Colitis

Moayyedi P et al. Abstract no. 929c
Rationale and Methods

• Rationale
  – Fecal microbiota therapy (FMT) has been successful in treated *C difficile* colitis
  – Small case series suggest it may be effective in active UC

• Methods
  – Randomized, placebo-controlled clinical trial
  – Enrolled patients with active UC
  – Patients (n=63) randomized to 6 weeks of once weekly treatment with:
    • FMT (50 mL retention enema)
    • Placebo (50 mL water enema)
  – Primary outcome: Remission of UC (Mayo score ≤2 with endoscopic score = 0) at Week 7
Results and Conclusions

<table>
<thead>
<tr>
<th>Parameter</th>
<th>FMT (n=27)</th>
<th>Placebo (n=26)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-week Mayo score</td>
<td>6.81 ± 3.72</td>
<td>6.19 ± 3.36</td>
<td>0.52</td>
</tr>
<tr>
<td>6 week IBDQ</td>
<td>148.4 ± 41.9</td>
<td>146.4 ± 33.3</td>
<td>0.82</td>
</tr>
<tr>
<td>Primary end point met</td>
<td>4 (15%)</td>
<td>2 (8%)</td>
<td>0.41</td>
</tr>
<tr>
<td>30% improvement in Mayo score</td>
<td>7 (26%)</td>
<td>8 (31%)</td>
<td>0.70</td>
</tr>
</tbody>
</table>

- No statistically significant effect of FMT in active UC
- May require a longer time period/more intensive therapy
Fecal microbial transplant following ileocolic resection reduces post-operative ileitis but restores colonic disease and induces growth of γ-proteobacteria in IL-10−/− mice

Madsen K et al. Abstract no. 151
Rationale and Methods

• Rationale
  – Disease commonly recurs early in neoterminal ileum following ileocolonic resection (ICR)
  – Immune dysregulation and microbial dysbiosis may contribute to disease recurrence
  – Restoring healthy microbiota through fecal transplant following ICR may prevent postoperative ileitis

• Methods
  – ICR performed in adult IL10-/- mice
  – At 14 days, mice gavaged with fecal slurry from healthy wild-type mice
  – Stool samples collected for sequencing
  – Neoterminal ileum and colon scored for histologic injury
Results and Conclusions

• Divergent results were seen in the neoterminal ileum and colon between control and fecal transplant groups that were reflected by differences in immune cell recruitment

• ICR resulted in the depletion of Bacteroidia and Clostridia and suppression of immune responses in the colon

• Fecal transplant following ICR reduced histological disease in the neoterminal ileum

• Fecal transplant following ICR caused a heightened immune response in the colon and resulted in a bloom of potentially pathogenic species of γ-proteobacteria

• Take home message:
  – Immunologically, the ileum and colon are not the same
Faecal Calprotectin is Superior to Faecal Lactoferrin and S100A12 as a Surrogate Marker for Post-Operative Crohn’s Disease Endoscopic Recurrence—Prospective Longitudinal Endoscopic Validation: Results from the POCER Study

Wright E et al. Abstract no. 100
Purpose and Methods

• Purpose
  – Assessed the relative value of the fecal biomarkers lactoferrin (FL) and S100A12 (FS) for detecting recurrent disease

• Methods
  – 318 stool samples from 136 patients were tested for FC, FL and FS pre-operatively and 6, 12, 18 months after resection
  – Colonoscopy was performed at 6 and/or 18 months
  – Endoscopic recurrence was assessed blindly and centrally using the Rutgeerts score
Results and Conclusions

- Fecal calprotectin was the optimal marker for endoscopic postoperative recurrence, with high sensitivity and negative predictive value
  - Superior to CRP and CDAI
  - Identifies which patients require colonoscopy
- Fecal lactoferrin offered only modest sensitivity for detecting recurrent disease
- Fecal S100A12 was sensitive but had low specificity and NPV
Prospective Therapeutic Drug Monitoring to Optimizing Infliximab Maintenance Therapy in Patients With IBD

Vaughn B et al. Abstract no. 209
Background and Methods

• Background
  – Response to IFX diminishes over time
  – Secondary loss of response can result from antibody to IFX (ATI) formation and lead to recurrence of symptoms or antibody-mediated side effects
  – Prospectively optimizing IFX trough concentrations to a target range of 5-10ug/ml may decrease the rate of loss of response and increase the durability of IFX therapy

• Methods
  – Identified patients (N=48) whose IFX trough concentrations were prospectively measured
  – Compared with a control group that did not have IFX optimization
Results

Probability on Infliximab

Weeks

Optimized
Not Optimized

P = .0006
Conclusions

• Prospective dose optimization of infliximab increases the duration of infliximab therapy, presumably due to a reduced rate of secondary loss of response

• Trough concentration monitoring appears to be useful for patients who respond to infliximab
Achievement of Developmental Milestones Among Offspring of Women With Inflammatory Bowel Disease: the PIANO Registry

Mahadevan U et al. Abstract no. 1
Rationale and Methods

• Rationale
  – IBD in the mother is associated with higher rates of adverse pregnancy outcomes.
  – The long-term effects of maternal IBD on childhood growth and development are unknown

• Methods
  – Prospective cohort of pregnant women (n=1289) at 30 US IBD centers to follow patients through pregnancy and first four years of a child’s life
  – Ascertained IBD medications and disease activity during gestation, complications of pregnancy and delivery, and achievement of developmental milestones
  – Classified by exposure to drugs taken between conception and delivery: 6-MP/Azathioprine (Group A), infliximab, adalimumab, certolizumab (Group B), combination therapy (Group AB)
Results and Conclusions

- Infants with in utero exposure to immunomodulator and biologic therapy did not exhibit developmental delay compared to infants not exposed to these agents, controlling for preterm birth.
- Scores of exposed infants were slightly higher in some categories.

**Selected Significant Differences in Developmental Milestones by Drug Exposure**

<table>
<thead>
<tr>
<th>Exposure Group</th>
<th>Outcome</th>
<th>Delta (Exposed-Reference)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-TNFs</td>
<td>Denver Development: Month 12</td>
<td>.02</td>
<td>.0169</td>
</tr>
<tr>
<td>Combo</td>
<td>Denver Development: Month 12</td>
<td>.03</td>
<td>.0307</td>
</tr>
<tr>
<td>Imm</td>
<td>Problem solving: Month 36</td>
<td>3.37</td>
<td>.0472</td>
</tr>
<tr>
<td>Imm</td>
<td>Problem solving: Month 48</td>
<td>2.26</td>
<td>.0194</td>
</tr>
<tr>
<td>Imm</td>
<td>Personal/social development: Month 48</td>
<td>3.41</td>
<td>.0381</td>
</tr>
<tr>
<td>Anti-TNFs</td>
<td>Communication: Month 24</td>
<td>3.31</td>
<td>.0410</td>
</tr>
</tbody>
</table>
Anti-TNF is Safe to Stop in the Second Trimester of Pregnancy in IBD Women in Remission

dele Lima A et al. Abstract no. 340
Purpose and Methods

• Purpose
  – Evaluated maternal safety of discontinuing anti-TNF in the 2nd trimester
  – Compared relapse between females that stopped and continued anti-TNF

• Methods
  – Study and control group were drawn from a population of 210 pregnant IBD patients
Results and Conclusions

- In the study group, 32 patients stopped anti-TNF before week 25 and in the control group 22 patients continued anti TNF until at least week 30.
- In the study group, 2 patients relapsed in week 30 and 36 after anti-TNF cessation in week 22, while in the control group 1 patient relapsed (P=1.000).
- No significant differences in birth weight, gestational term, and congenital abnormalities between the study and the control group.

Conclusions:
- Anti-TNF is safe to stop in the 2nd trimester in IBD women in sustained remission.
- Anti-TNF cessation before gestational week 25 is not associated with a higher risk for relapse compared with women who continue anti-TNF treatment.