Crohn’s Disease

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Chicago Fun Facts

- Chicago....
  - Hosts the world’s largest gum manufacturer (William Wrigley Jr Company), producing 20 million packages per day
  - Has the world’s longest street (Western Avenue)
  - Offers the only post office in the world through which you can drive a car (433 W. Van Buren)
  - Was where the term “jazz” was coined in 1914
  - Is the favourite road city for major league baseball players
  - Reversed the flow of the Chicago River in 1900!
Early Combined Immunosuppression for the Management of Crohn’s Disease: A Community-Based Cluster-Randomized Trial

- Randomized Evaluation of an Algorithm to Treat Crohn’s (REACT-1)
- 29 centres in Canada/Belgium randomized 1:1 to conventional management (CM) vs. early combined immunosuppression (ECI)
- Up to 60 patients with CD age ≥18 followed for 2 years
- Primary outcome: Proportion of patients in steroid-free remission (HBI ≤4) at 12 months
Early Combined Immunosuppression for the Management of Crohn’s Disease: A Community-Based Cluster-Randomized Trial

Khanna R. DDW 2014 [5485] - Tuesday 1600h-1730h
Early Combined Immunosuppression for the Management of Crohn’s Disease: A Community-Based Cluster-Randomized Trial

• N=39 centres (1982 patients)
• Rates of combination anti-TNF+IS therapy
  – 15.1% vs. 6.5% at 12 months (p<0.001)
  – 19.7% vs. 9.6% at 24 months (p<0.001)
• Mean remission rates:
  – 66% vs. 62% at 12 months (p=0.65)
  – 73% vs. 65% at 24 months (p=0.35)
• “Highly significant and clinically important” differences in rates of complications, surgeries and combined outcome of hospitalizations/complications/surgeries at 24 months (27.7% vs. 35.%, HR 0.74, p<0.001)
Early Combined Immunosuppression for the Management of Crohn’s Disease: A Community-Based Cluster-Randomized Trial

Graphs showing:
- Hospitalizations
- Complications (abscess, EIM, new fistula, SAE)
- Surgery
- Combined Outcome

Khanna R. DDW 2014 [5485] - Tuesday 1600h-1730h
Exposure to Anti-TNFα Therapy in Third Trimester is Not Associated with Increased Adverse Outcomes: Results from the PIANO Registry

• Prospective cohort at 30 US IBD centres followed through pregnancy + 4 years
  – 1289 enrolled → 1097 completed pregnancy → 1039 live births
  – 501 exposed to biologics (422 in T3) and 597 unexposed in T3

• Power to detect RR 1.6 at 4 months PP (baseline 11%)

• No significant differences:
  – Disease activity, preterm birth, infant infection

<table>
<thead>
<tr>
<th></th>
<th># observations</th>
<th>OR</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm birth</td>
<td>1019</td>
<td>1.3</td>
<td>0.8-1.9</td>
</tr>
<tr>
<td>Disease Activity T3</td>
<td>977</td>
<td>0.7</td>
<td>0.5-1.0</td>
</tr>
<tr>
<td>Disease Activity PP</td>
<td>767</td>
<td>1.2</td>
<td>0.8-1.8</td>
</tr>
<tr>
<td>Infection Month 4</td>
<td>1009</td>
<td>0.9</td>
<td>0.6-1.3</td>
</tr>
<tr>
<td>Infection Month 9</td>
<td>747</td>
<td>1.1</td>
<td>0.8-1.5</td>
</tr>
<tr>
<td>Infection Month 12</td>
<td>678</td>
<td>1.1</td>
<td>0.5-1.6</td>
</tr>
</tbody>
</table>

Mahadevan U. DDW 2014 [5250] – Tuesday 1000h-1130h
Pregnancy Outcomes Among Mothers with IBD Exposed to Systemic Steroids: Results from the PIANO Registry

• N=969 mothers recorded steroid exposure at preconception, T1, T2, T3

• Exposure (controlled for disease activity, concomitant immunosuppression, breastfeeding) associated with:
  – Increased gestational diabetes (OR 2.8; 95% CI 1.3-6.0)
  – Low birth weight (OR 2.8; 95% CI 1.3-6.1)
  – Trend to pre-term birth (OR 1.8; 95% CI 1.0-3.1)
  – Trend to increased infection at 4 months (OR 1.5; 95% CI 0.9-2.7) but not at 12 months PP (OR 0.8; 95% CI 0.5-1.3)
  – But **NOT** developmental delay or congenital anomaly (OR 1.2; 95% CI 0.6-2.5)
Vaccination Outcomes in IBD

- Retrospective analysis of *Explorys* database (open private cloud-based platform that integrates non-identified patient data from 14 healthcare systems comprising 40 million patients)
- 107,750 adults with IBD
  - 20.7% vaccinated for influenza
  - 3.6% vaccinated for pneumococcus
- Vaccination associated with reduced respiratory infection
  - 9-fold reduction in influenza/common cold
  - 8-fold reduction in pneumonia
- **Conclusion:** Need “renewed vigor” to educate patients and physicians about importance of vaccination

Abdallah J. DDW 2014 [5250] – Tuesday 1000h-1130h
IFX Trough Levels are Correlated with IFX-Associated Adverse Events

- Cross-sectional study of 75 IFX patients at U of A
- IFX trough level measured using in-house assay
- IFX-associated AE in 36/75 (48.0%)
  - 66.7% of females vs. 33.3% of males (p=0.015)
- Dermatologic AE associated with higher trough level:
  - 9.9 (95% CI 0.2-19.5) vs. 0.1 (95% CI 0-6.3) mcg/ml
- Infusion-related AE associated with lower trough level:
  - 0.4 (95% CI 0-6.3) vs. 9.9 (95% CI 0-19.5) mcg/ml
- No difference in trough level with arthralgia/neuropathy
Higher 6TG Concentration Associated with Higher IFX Levels in Patients on Combination Therapy

- Cross-sectional study of 72 pts on IFX plus thiopurine for ≥4 months, with 6TG and IFX measured within 2 weeks
  - Significant correlation between [IFX] and [6TG] \((r=0.477, p<0.0001)\)
  - No correlation between [IFX] and thiopurine dose or lymphocytes
  - Negative correlation between [6TG] and lymphocytes
- In multiple regression only [6TG] predicted [IFX] \((p<0.001)\)
- \([6TG] < 125 \text{ pmol/8x10}^8 \text{ RBC}\) predicted ATI \((N=8)\) with OR 1.3 (95% CI 2.3-72.5, \(p<0.01\))
- **Conclusion**: 6TG levels may help to optimize combination therapy and target 6TG level may be lower (125 vs. 232)
Development of an Algorithm Incorporating ADA PK in IBD

- Prospective study of IBD patients with disease flare despite ADA 40mg q2weeks as monotherapy
  - All ADA primary responders and previously anti-TNF naïve
  - AAA and ADA levels measured by ELISA
  - ADA optimized to 40mg weekly
- Reassessed after 4 months for remission (HBI/Mayo)
  - Switched to IFX if indicated
- 82 subjects with IBD (55% CD)
  - Mean age 43
  - Mean duration of disease 7.4 years
  - Mean duration of ADA therapy 17 months
Development of an Algorithm Incorporating ADA PK in IBD

• Outcomes:
  – Group A (N=41): ADA > 4.9 mcg/ml
  – Group B (N=24): ADA < 4.9 mcg/ml and undetectable AAA
  – Group C (N=17): ADA < 4.9 mcg/ml and AAA > 10 mcg/ml

• After optimization remission achieved in:
  – 29% in A vs. 67% in B vs. 12% in C
  – Mean duration 4 vs. 16 vs. 5 months

• 57 patients failed optimization and received IFX
  – Remission in 31.6%
  – 12% in A vs. 25% in B vs. 80% in C
  – Mean duration 3 vs. 5 vs. 15 months
Development of an Algorithm Incorporating ADA PK in IBD

**Conclusion:** When patient on ADA loses response….

- Low ADA with no AAA predicts favourable response to ADA dose optimization
- Low ADA with AAA predicts favourable failure of ADA dose optimization and switch to IFX should be considered
- Therapeutic ADA predicts poor response to both ADA dose optimization and switch to IFX, and alternative therapies should be considered
VDZ Exposure Response Relationship During Induction Therapy in Adults with Crohn’s Disease

- Exploratory analyses from week 6 outcomes of GEMINI 2
- Individual predicted average VDZ concentrations derived from VDZ population PK model ($C_{\text{average}}$)
- Increased $C_{\text{average}}$ associated with better outcomes
  - Stronger exposure relationship with response vs. remission
  - Exposure relationship plateaus at higher levels
- Moving from 5th to 95th percentile $C_{\text{average}}$ increased likelihood of clinical response/remission by 15%/10%
- Exposure-response relationship not dependent on any of the covariates tested
**VDZ Efficacy in Crohn’s Disease with Anti-TNF Failure vs. Anti-TNF Naïve**

- Pooled analysis of GEMINI 2 and GEMINI 3
  - VDZ 300mg at W0/W2/W6 vs. Placebo
  - GEMINI 2 W10 data from W6 responders randomized to placebo

- No baseline differences on VDZ vs. Placebo:
  - Disease duration (9.4 vs. 9.2 years)
  - Concomitant immunosuppression (“approximately one third”)
  - Baseline CDAI (321.7 vs. 311.0)

- More TNF failures in GEMINI 3 than in GEMINI 2
  - 76% VDZ / 76% Placebo vs. 48% VDZ / 47% Placebo

Sands BE. DDW 2014 [5110] – Tuesday 0800h-0930h]
VDZ Efficacy in Crohn’s Disease with Anti-TNF Failure vs. Anti-TNF Naïve

Sands BE. DDW 2014 [5110] – Tuesday 0800h-0930h
### Crohn’s Disease Endoscopic Index of Severity (CDEIS)

<table>
<thead>
<tr>
<th>Ileum</th>
<th>Sigmoid and left colon</th>
<th>Transverse</th>
<th>Right colon</th>
<th>Rectum</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 +</td>
</tr>
<tr>
<td>Deep ulcerations</td>
<td>(0 if non; 12 points if present)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Superficial ulcerations</td>
<td>(0 if non; 12 points if present)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Surface involved by disease (cm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 +</td>
</tr>
<tr>
<td>Surface involved by ulcerations (cm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4 +</td>
</tr>
<tr>
<td>TOTAL A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20</td>
</tr>
<tr>
<td>Number of segments explored (1-5)</td>
<td>n</td>
<td></td>
<td></td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Total A/n</td>
<td>TOTAL B</td>
<td></td>
<td></td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>If ulcerated stenosis is present anywhere add 3</td>
<td>C</td>
<td></td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>If non-ulcerated stenosis is present anywhere add 3</td>
<td>D</td>
<td></td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>TOTAL B + C + D = CDEIS score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4</td>
</tr>
</tbody>
</table>

Mary JY Modigliani R. Gut 1989;30:983-9
## Simple Endoscopic Score for Crohn’s Disease (SES-CD)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score</th>
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<tbody>
<tr>
<td></td>
<td>0</td>
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<tr>
<td>Size of ulcers (cm)</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>(diameter 0.1–0.5)</td>
</tr>
<tr>
<td>Ulcerated surface (%)</td>
<td>None</td>
</tr>
<tr>
<td>Affected surface (%)</td>
<td>Unaffected segment</td>
</tr>
<tr>
<td>Presence of narrowings</td>
<td>None</td>
</tr>
</tbody>
</table>

*Total SES-CD: sum of the values of the 4 variables for the 5 bowel segments. Values are given to each variable and for every examined bowel segment (for example, rectum, left colon, transverse colon, right colon and ileum).*
Agreements Among Central Readers in the Evaluation of Endoscopic Disease Activity in Crohn’s Disease

- CDEIS and SES are used to measure endoscopic activity of Crohn’s disease but have not been validated.
- Endoscopy videos from 50 patients participating in a BMS clinical trial were reviewed by 4 central readers.
  - CDEIS, SES and Global Assessment of Lesion Severity (GELS)

<table>
<thead>
<tr>
<th></th>
<th>Intra-rater</th>
<th>Inter-rater</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Original</td>
<td>Modified †</td>
</tr>
<tr>
<td>CDEIS</td>
<td>0.89 (0.86 to 0.93)</td>
<td>0.90 (0.87 to 0.93)</td>
</tr>
<tr>
<td>SES-CD</td>
<td>0.91 (0.87 to 0.94)</td>
<td>0.92 (0.88 to 0.95)</td>
</tr>
<tr>
<td>GELS</td>
<td>0.81 (0.75 to 0.86)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Original versions</th>
<th>Modified † versions</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDEIS-GELS</td>
<td>0.75 (0.63 to 0.85)</td>
<td>0.74 (0.61 to 0.83)</td>
</tr>
<tr>
<td>SES-CD-GELS</td>
<td>0.74 (0.62 to 0.84)</td>
<td>0.75 (0.63 to 0.85)</td>
</tr>
<tr>
<td>CDEIS-SES-CD</td>
<td>0.92 (0.87 to 0.96)</td>
<td>0.75 (0.63 to 0.85) 0.90 (0.84 to 0.94)</td>
</tr>
</tbody>
</table>
Agreements Among Central Readers in the Evaluation of Endoscopic Disease Activity in Crohn’s Disease

• 10 of 50 videos responsible for greatest disagreement

• Delphi panel identified areas requiring greater clarity:
  – Defining of stenosis
  – Scoring after balloon dilation
  – Localizing of ulcers spanning two contiguous segments
  – Differentiating anal vs. rectal lesions

• Conclusions:
  – Expert reading of CDEIS and SES-CD has “substantial” to “almost perfect” intra and inter-rater agreement
  – Further effort is needed to standardize some definitions
  – Removal of stenosis from both scores should be considered

Khanna R. DDW 2014 [5410] – Tuesday 1400h-1530h
SUMMARY:

- Early combined immunosuppression in an accelerated step-up algorithm reduces CD complications.
- Both steroids and anti-TNF therapies appear to be well tolerated during pregnancy.
- Vaccination of IBD patients is effective.
- TDM of both anti-TNF agents and 6TG can improve both safety and efficacy of biologic therapy.
- TDM may also be important for vedolizumab therapy.
- Both CDEIS and SES-CD perform well, but better endoscopic scoring systems can be developed.
Thank you!

Enjoy Chicago and DDW 2014