Highlights of DDW 2015: Crohn’s disease

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## Faculty Disclosure (past 24 months)

<table>
<thead>
<tr>
<th>Commercial Interest</th>
<th>Relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbvie</td>
<td>Advisory Board, Consultant, Research Support, Speaker Fees</td>
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<tr>
<td>Janssen</td>
<td>Advisory Board, Consultant, Research Support, Speaker Fees</td>
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<td>Takeda</td>
<td>Advisory Board, Consultant, Speaker Fees</td>
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<tr>
<td>Prometheus Labs</td>
<td>Advisory Board, Consultant, Research Support, Speaker Fees</td>
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<td>Shire</td>
<td>Advisory Board</td>
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<tr>
<td>Actavis/Allergan</td>
<td>Advisory Board</td>
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</tbody>
</table>
CanMEDS Roles Covered:

<table>
<thead>
<tr>
<th>Role</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical Expert</td>
<td>(as Medical Experts, physicians integrate all of the CanMEDS Roles, applying medical knowledge, clinical skills, and professional attitudes in their provision of patient-centered care. Medical Expert is the central physician Role in the CanMEDS framework.)</td>
</tr>
<tr>
<td>Communicator</td>
<td>(as Communicators, physicians effectively facilitate the doctor-patient relationship and the dynamic exchanges that occur before, during, and after the medical encounter.)</td>
</tr>
<tr>
<td>Collaborator</td>
<td>(as Collaborators, physicians effectively work within a healthcare team to achieve optimal patient care.)</td>
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<tr>
<td>Manager</td>
<td>(as Managers, physicians are integral participants in healthcare organizations, organizing sustainable practices, making decisions about allocating resources, and contributing to the effectiveness of the healthcare system.)</td>
</tr>
<tr>
<td>Health Advocate</td>
<td>(as Health Advocates, physicians responsibly use their expertise and influence to advance the health and well-being of individual patients, communities, and populations.)</td>
</tr>
<tr>
<td>Scholar</td>
<td>(as Scholars, physicians demonstrate a lifelong commitment to reflective learning, as well as the creation, dissemination, application and translation of medical knowledge.)</td>
</tr>
<tr>
<td>Professional</td>
<td>(as Professionals, physicians are committed to the health and well-being of individuals and society through ethical practice, profession-led regulation, and high personal standards of behaviour.)</td>
</tr>
</tbody>
</table>
Objectives

• Discuss the optimal use of anti TNF therapies in specific Crohn’s disease phentotypes
• Review off label use of ustekinumab for CD
• Discuss the outcomes of anti TNF withdrawal in CD
• Review data on biological drug level monitoring with IFX and ADM
Efficacy of adalimumab in patients with Crohn’s disease and symptomatic small bowel stricture: a multicentre, prospective, observational cohort study (CREOLE)

- Subjects not exposed to anti-TNF in prior 12m
- Standard ADM induction
- Primary endpoint: ADM success at week 24 with no steroids after 8w, no other anti-TNF, no dilatation, no surgery, no SAE and no study withdrawal
- 98 patients screened; median of 4m of obstructive symptoms
Efficacy of adalimumab in patients with Crohn’s disease and symptomatic small bowel stricture: a multicentre, prospective, observational cohort study (CREOLE)

- At week 24 - 61% achieved success
- At week 36 ~50% sustained success
- Predictors of success:
  - Immunosuppressant use
  - Obstructive symptoms < 5w
  - Delayed enhancement of TI at MRE
  - No fistula
  - Prox diameter of small bowel 2-3cm or greater
Probability of Success by Prognostic Score

- 0-2 (n=18): 14%
- 3 (n=24): 54%
- 4-7 (n=49): 88%
Message for my Practice?

- Can consider anti-TNF use in selected CD subjects with obstructive symptoms
- Consider pros/cons
- Is surgery acceptable alternative?
Ustekinumab efficacy and safety in Crohn’s disease patients refractory to conventional and anti-TNF therapy: a multicentre, retrospective experience

- UST (Stelara): mAb against p40 subunit of IL12/IL23
- Review of open label experience of consecutive pts receiving UST for disease refractory to conventional/anti-TNF Rx and with > 3m F/U
- Outcome: clinical benefit at 3m defined by “significant improvement” with complete steroid weaning and continued Rx
Ustekinumab efficacy and safety in Crohn’s disease patients refractory to conventional and anti-TNF therapy: a multicentre, retrospective experience

- 122 pts received at least 1 injection
- 100% failed at least 1 anti-TNF and 87% failing 2 anti-TNFs
- 61% prior surgery; med disease duration 12y
- Median F/U 40 weeks
- Mean cumulative induction dose (wk 0-4) was 148mg (range 45 - 396mg)
- Clinical benefit at 3m = 65%
Ustekinumab efficacy and safety in Crohn’s disease patients refractory to conventional and anti-TNF therapy: a multicentre, retrospective experience

- Among 3m responders: 78%/86% experienced clinical benefit at 6/12m
- No SAEs but 15% skin lesions; 7.5% infections
Message for my Practice?

- We are seeing more and more anti-TNF failures
- What alternatives are there for out of class therapies in CD
  - Ustekinumab
  - Vedolizumab
Anti-TNF withdrawal in IBD: Relapse and recapture rates and predictive factors from 160 patients in a pan-UK study

- In the UK there is mandatory withdrawal after 12m of therapy where clinical and mucosal remission have been achieved
- Retrospective audit of pts with sustained remission off steroids for at least 6m
- Moderate relapse - oral steroids, IM, anti-TNF
- Severe relapse - hospitalization, IV steroids, surgery
Anti-TNF withdrawal in IBD: Relapse and recapture rates and predictive factors from 160 patients in a pan-UK study

- 80% IFX; 30 ADA with 25m of post DC f/u
- 88% CD
- 100% clinical remission; 62% had normal laboratory tests; 87% complete mucosal healing (102 had pre-withdrawal endoscopy)
- Relapse rates for CD: 36% at 1y; 56% at 2y
- Relapse rates for UC: 44% at 1y; 50% at 2y
- Reintroduction of anti-TNF was successful in 92% (59/81) at induction and 65% at 1 year
Anti-TNF withdrawal in IBD: Relapse and recapture rates and predictive factors from 160 patients in a pan-UK study
Anti-TNF withdrawal in IBD: Relapse and recapture rates and predictive factors from 160 patients in a pan-UK study

- Similar Czech study in CD only with 50% 1 year relapse rate
- In both studies: no good predictors were identified for relapse including “deep” remission, concomitant meds, biomarker normalization, type of anti TNF, disease behaviour, anti TNF trough levels
Message for my Practice

- High relapse rates with withdrawal of anti-TNF therapy even in patients with deep remission (~40%)
- Who can we consider for anti-TNF withdrawal? CD probably not; UC maybe?
- ? Success of reintroduction of prior therapy
Non-trough IFX concentrations reliably predict trough levels and accelerate dose adjustment in Crohn’s disease

- Prospective, observational study
- CD pts in clinical remission on standard IFX maintenance q 8 weeks
- IFX conc measured at week 4 and 6 after last infusion
- Standard ELISA
- 20 subjects with med 63m of IFX treatment
## Results ([IFX])

<table>
<thead>
<tr>
<th></th>
<th>Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 0 (trough) IFX level (µg/ml)</td>
<td>3.7 (2.2-5.2)</td>
</tr>
<tr>
<td>Week 4 IFX level (µg/ml)</td>
<td>15 (9.7-19.3)</td>
</tr>
<tr>
<td>Week 6 IFX level (µg/ml)</td>
<td>7.5 (5.9-10.5)</td>
</tr>
<tr>
<td>Week 8 (trough) IFX level (µg/ml)</td>
<td>4.3 (2.5-6.0)</td>
</tr>
</tbody>
</table>
### Results (ROC)

<table>
<thead>
<tr>
<th>To predict IFX TL ≥3 µg/ml</th>
<th>Cut-off (µg/ml)</th>
<th>Sens. (95% CI)</th>
<th>Spec. (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 4 IFX</td>
<td>15</td>
<td>100% (59-100%)</td>
<td>100% (40-100%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Week 6 IFX</td>
<td>6.5</td>
<td>100% (59-100%)</td>
<td>83% (35-100%)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

NB: sample size was inadequate for reliable ROC-analysis
Early therapeutic drug monitoring for prediction of short term mucosal healing in pts with UC treated with IFX
Adequate Trough Concentrations and Sustained TNF Suppression Early on during Induction Therapy with Adalimumab Predict Remission in Anti-TNF Naïve Crohn’s disease patients

- 23 anti-TNF naïve CD patients
- Standard ADA regimen
- Samples taken at weeks 1, 2, 3, 4 and 12
- Remission assessed at week 12 (HBI)
- Antibodies measured by HMSA (drug tolerant)
Adequate Trough Concentrations and Sustained TNF Suppression Early on during Induction Therapy with Adalimumab Predict Remission in Anti-TNF Naïve Crohn’s disease patients

• 70% achieved clinical remission
• CRP and TNF concentrations were similar in remitters and non-remitters
• ADA levels at week 2 >9.7ug/mL and at week 4 >11.0ug/mL were most associated with clinical remission
• Only 1 patient had early antibodies
Adequate Trough Concentrations and Sustained TNF Suppression Early on during Induction Therapy with Adalimumab Predict Remission in Anti-TNF Naïve Crohn’s disease patients

• Adequate ADM exposure is associated with response and is a good early predictor of effective disease suppression
Higher adalimumab drug levels are associated with clinical and endoscopic remission in patients with Crohn’s disease

E. Zittan, B. Kabakchiev, JM. Stempak, GC. Nguyen, K. Croitoru, G. Van Assche, AH. Steinhart, MS. Silverberg

Zane Cohen Centre for Digestive Diseases, Mount Sinai Hospital, University of Toronto

1. Background & Aims

The current approach to managing loss of response to anti-TNF agents is based on clinical symptoms and empirically increasing the dose or shortening the treatment interval as opposed to tailoring the drug concentrations in individual patients. We investigated whether adalimumab drug levels (ADL) and antibodies to adalimumab (ATA) were associated with clinical and/or endoscopic remission.

2. Methods

A cohort of patients with Crohn’s disease (CD) treated with adalimumab between 2005-2013 were recruited to the study. Demographic and clinical information was obtained from chart review and patient interview. Disease activity was determined by Harvey-Bradshaw Index (HBI), ileocolonoscopy reports and CRP levels. Clinical remission was defined by HBI \( \leq 4 \). Endoscopic remission was defined by the absence of any ulceration in all ileocolonic segments. ADL and ATA were tested using a liquid phase assay. ATA \( \leq 1 \) U/mL were considered low titer.

3. Results

88 CD patients were included in the analysis. (Table 1). 15 (16%) subjects exhibited elevated ATA titers (>1 U/mL).

ADL levels were significantly higher in patients with low ATA compared to those with elevated ATA titers (median ADL 12.7 and 1.9 µg/mL respectively, \( P<0.000001 \)) and in patients with normal CRP levels (median ADL 13.4 and 7.9 µg/mL respectively, \( P<0.01 \)).

Higher ADL drug levels were significantly associated with the mucosal healing. (17.4 µg/mL vs. 6.6 µg/mL respectively, \( P<0.00001 \)). (Figure 1)

Higher ADL drug levels were significantly associated with the combined outcome of both clinical and endoscopic remission (12.78 µg/mL vs. 7.12 pg/mL respectively, \( P<0.04 \)). (Figure 2)

4. Table 1

<table>
<thead>
<tr>
<th>Mucosal healing</th>
<th>Age [mean(SD)]</th>
<th>Gender (male)</th>
<th>Fistula (yes)</th>
<th>Disease duration years(mean)</th>
<th>Time on ADL years (mean)</th>
<th>Concomitant therapy (yes)</th>
<th>ADL dosage (80mg)</th>
<th>ADL frequency</th>
<th>Age of onset in years [mean(SD)]</th>
<th>IFX exposure (yes)</th>
<th>ATA (bin, &gt; 1 U/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>30.9±10.9</td>
<td>36.0%</td>
<td>20.0%</td>
<td>11.59</td>
<td>2.7</td>
<td>20.8%</td>
<td>12.0%</td>
<td>52.0%</td>
<td>19.2±8.7</td>
<td>64.0%</td>
<td>28.0%</td>
</tr>
<tr>
<td>No</td>
<td>30.6±10.9</td>
<td>57.1%</td>
<td>37.1%</td>
<td>11.4</td>
<td>2.4</td>
<td>37.1%</td>
<td>11.4%</td>
<td>62.9%</td>
<td>18.9±7.8</td>
<td>55.9%</td>
<td>2.9%</td>
</tr>
<tr>
<td>p-value</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>P&lt;0.00007</td>
</tr>
</tbody>
</table>

5. Conclusions

- Higher adalimumab drug levels were significantly associated with mucosal healing.
- Higher levels associated with a lower antibody level and a normal CRP.
- This study suggests that achieving clinical and endoscopic remission is more likely to occur by achieving higher adalimumab levels.

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**Table 1**

<table>
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<tr>
<th>Mucosal healing</th>
<th>No</th>
<th>Yes</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [mean(SD)]</td>
<td>30.9±10.9</td>
<td>30.6±10.9</td>
<td>NS</td>
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<td>Fistula (yes)</td>
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</tr>
<tr>
<td>Disease duration years(mean)</td>
<td>11.59</td>
<td>11.4</td>
<td>NS</td>
</tr>
<tr>
<td>Time on ADL years (mean)</td>
<td>2.7</td>
<td>2.4</td>
<td>NS</td>
</tr>
<tr>
<td>Concomitant therapy (yes)</td>
<td>20.8%</td>
<td>37.1%</td>
<td>NS</td>
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<td>ADL dosage (80mg)</td>
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<td>ADL frequency</td>
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<td>62.9%</td>
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<tr>
<td>Age of onset in years [mean(SD)]</td>
<td>19.2±8.7</td>
<td>18.9±7.8</td>
<td>NS</td>
</tr>
<tr>
<td>IFX exposure (yes)</td>
<td>64.0%</td>
<td>55.9%</td>
<td>NS</td>
</tr>
<tr>
<td>ATA (bin, &gt; 1 U/mL)</td>
<td>40.0%</td>
<td>82.9%</td>
<td>P&lt;0.0007</td>
</tr>
<tr>
<td>HBI (%) Clinical remission&lt;5</td>
<td>16.0%</td>
<td>5.7%</td>
<td>P&lt;0.0023</td>
</tr>
<tr>
<td>HBI (%) mild Clinical activity5-7</td>
<td>44.0%</td>
<td>11.4%</td>
<td>P&lt;0.00001</td>
</tr>
<tr>
<td>HBI (%) Moderate to severe Clinical &gt;7</td>
<td>41.5%</td>
<td>2.4%</td>
<td>P&lt;0.00001</td>
</tr>
<tr>
<td>CRP (%) (cut off 5 mg/dL)</td>
<td>6.6</td>
<td>17.4</td>
<td>P&lt;0.00001</td>
</tr>
<tr>
<td>ADL median(µg/mL)</td>
<td>6.6</td>
<td>17.4</td>
<td>P&lt;0.00001</td>
</tr>
</tbody>
</table>
Impact of TDM on Outcomes with Dose Optimization with IFX: Mount Sinai Experience

Primary responders to IFX who had dose optimization n=312

- Incomplete data re. decision making n=8
  - TDM based decision n=136
  - Clinical decision n=155
- Lost to follow-up n=13

Kelly et al. DDW 2015
## Better Clinical Outcomes in TDM Group

<table>
<thead>
<tr>
<th>Outcome measure at median 6 months post D.O.</th>
<th>TDM decision group</th>
<th>Clinical decision group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical response (%)</td>
<td>69</td>
<td>57</td>
<td>0.007</td>
</tr>
<tr>
<td>Clinical remission (%)</td>
<td>70</td>
<td>61.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Endoscopic remission (%) (Mayo score 0-1; SES CD &lt;3)</td>
<td>64</td>
<td>51</td>
<td>0.03</td>
</tr>
<tr>
<td>Hospitalizations (mean)</td>
<td>0.3</td>
<td>0.7</td>
<td>0.03</td>
</tr>
<tr>
<td>Flares requiring intervention/ treatment</td>
<td>0.5</td>
<td>0.95</td>
<td>0.02</td>
</tr>
<tr>
<td>Surgery (%)</td>
<td>6</td>
<td>11</td>
<td>0.2</td>
</tr>
</tbody>
</table>

*Kelly et al. DDW 2015*
Dose optimization guided by TDM is more effective in increasing drug levels

A) Dose change results in significant increase in trough in TDM group

B) Post-change troughs are higher in TDM versus clinical group

Kelly et al. DDW 2015
Message for my Practice?

- TDM is growing in relevance and importance in managing anti-TNF patients optimally
- Consider pro-active measurements for optimal results early in induction and/or maintenance
- Keep some notes on studies showing what optimal levels are at various time points until data becomes more mature
Effects of early concomitant IM exposure on outcomes among anti-TNF users: a population-based analysis
New Dispensation of Anti-TNF

- IM Use starting >1 month prior to time of anti-TNF Dispensation
  - YES
  - IM Use continuing after anti-TNF with no gap
    - YES: Combo Tx Prior IM Use
    - NO: Anti-TNF Monotherapy
  - NO: New IM dispensation between 30d prior to 14 days following new anti-TNF
    - YES: Combo Tx IM Naïve
717 anti-TNF starts

285 Combo Tx Prior IM Use
- 227 CD
  - 193 IFX
  - 34 ADA
- 58 UC
  - 55 IFX

407 Anti-TNF monotherapy
- 301 CD
  - 229 IFX
  - 72 ADA
- 106 UC
  - 100 IFX

25 Combo Tx IM Naïve
- 19 CD
  - 19 IFX
  - 0 ADA
- 6 UC
  - 6 IFX
Discontinuation of Anti-TNF Following Full Induction

Crohn’s Disease

Ulcerative Colitis

P>0.20

Proportions with ongoing exposure to IFX/ADA

0%  10%  20%  30%  40%  50%  60%  70%  80%  90%  100%

Years Following 1st Maintenance Dose of Anti-TNF

Mono (n=152)  Combo (n=102)

Mono (n=63)  Combo (n=48)

Proportions with ongoing exposure to IFX/ADA

P>0.20

0%  10%  20%  30%  40%  50%  60%  70%  80%  90%  100%

Years Following 1st Maintenance Dose of Anti-TNF
Message for my Practice?

• In patients with CD and prior IM use when starting anti-TNF therapy there appears to not be a significant benefit with combo therapy as compared to IM naïve patients

• When should I use combo therapy?