What I do when anti-TNFs fail

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What has failed?

• Are there new symptoms?- sorting out if active disease is present
• If there is active disease- is there adequate drug on board?
• If there is active disease and there is adequate drug on board- what is the next step
• Is the failure a side effect of the drug
ACTIVE SYMPTOMS  \(\equiv\)  ACTIVE DISEASE
A Prospective Population Based Study of Triggers of Flares of IBD

- Prospective
- Recruited from population-based research registry (UMIBDRR)
- completed mailed surveys q3 months for 1 yr (=5 surveys)

- Surveys assessed:
  - Personal characteristics
  - over past 3 months:
    - Disease activity
    - NSAID use
    - Antibiotic use
    - Infections
    - Stressful life events and rating of impact
    - Perceived stress (PSS)
    - Positive / Negative affect (PANAS)
Assessment of risk factors

• Longitudinal assessment – repeated 5X

Period to assess risk factors
- 3 months look back

Period to assess disease activity
0 month assess risk and disease

Assess: Inactive / Inactive vs Inactive / Active

Bernstein Am J Gastroenterol 2010
### Risk of IBD flare

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>Adjusted OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs</td>
<td>1.07</td>
<td>.97</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>1.21</td>
<td>1.08</td>
</tr>
<tr>
<td>Infections</td>
<td>1.00</td>
<td>.86</td>
</tr>
<tr>
<td>Perceived stress</td>
<td>2.63</td>
<td>2.38</td>
</tr>
<tr>
<td>Major life events</td>
<td>1.69</td>
<td>1.30</td>
</tr>
</tbody>
</table>

Bernstein Am J Gastroenterol 2010
Correlation Between Symptom Scores/MIBDI & Fecal Calprotectin
N=487; followed 3 x over 6 months

• High perceived stress highly correlated with symptoms

• High perceived stress did not correlate with FCAL

• Stress \rightarrow \text{Symptoms} \rightarrow \text{modest for UC; no for CD}

\text{FCAL (inflammation)}

Targownik AJGI 2015
What is a Flare?

Manitoba Living with IBD Study
Flare (Case)

Score of $\geq 6$ on 7 point indicator

Compared to 2 weeks ago my IBD symptoms are:

- 1 = much improved
- 2 = moderately improved
- 3 = minimally improved
- 4 = no change
- 5 = minimally worse
- 6 = moderately worse
- 7 = much worse

Data Time Points

**Time #1**: Two weeks before the recorded flare

**Time #2**: At the recorded flare

40 Flares  sex, disease type, time of enrolment  40 Controls

Witges DDW 2017
60% of flares had a Fcal score ≥ 250 compared to 30% of controls
If symptoms not generated by active inflammation; or thought to be functional;

Other possibilities:
1. strictures in Crohn’s
2. previous bowel resection especially IC valve
3. myofascial abdominal pain
4. sleep disorder
Anti TNF Dose Augmentation-based on...

• Medical records of all IBD patients prescribed anti-TNF therapy from 2007-2016 by 8/23 Manitoba gastroenterologists were reviewed.

• Patients who underwent anti-TNF dose augmentation were further reviewed for the presence of any objective assessment of inflammatory activity, including laboratory investigations (CRP, ESR, albumin, ferritin, hemoglobin, fecal calprotectin), cross-sectional abdominal imaging, and endoscopy.

*Elias ACG 2018*
Anti TNF Dose Augmentation-based on...RESULTS

- 151/529 receiving anti-TNF therapy had anti-TNF doses increased on 195 occasions (117 CD, 34 UC).
- 68.7% were assessed for biochemical evidence of disease activity in the 90 days preceding dose augmentation (134/195 occasions).
- The results of these investigations were abnormal in only 23 cases (11.8%).
- Cross-sectional imaging was performed in 11 cases (5.6%) and revealed active disease in 8 (4.1%).
- Endoscopy was performed on 28 occasions (14.4%) with 24 (12.3%) revealing active disease.
• Overall, objective evidence of inflammatory activity was present in only 48/195 dose augmentation events (24.6%)

• No objective evidence of inflammation was present in 95 (48.7%), and in 52 (26.7%), anti-TNF dose was increased without any investigation being performed.
CONCLUSION

• Anti-TNF dose augmentation routinely occurs in the absence of objective evidence of active inflammatory disease. This represents a target for ongoing quality improvement to optimize care of persons with IBD requiring anti-TNF based therapies, given the significant economic burden of unjustified and potentially unnecessary dose augmentation.
Factors Affecting Biologic Exposure

- Immunosuppressant Usage
  - Antibody formation
  - Drug concentration
  - Drug clearance

- Anti-drug antibodies
  - Drug concentration
  - Drug clearance

- Male Gender
  - Drug clearance

- Low serum albumin
  - Drug clearance

- High BMI
  - Drug clearance

- High inflammatory burden
  - Drug clearance

- High baseline TNF concentration
  - Drug clearance

Ordás Clin Gastroenterol Hepatol 2012
Exposure-response Relationship of Golimumab: Phase 2/3 PURSUIT Induction and Maintenance Studies in Active UC

1. Positive exposure-response relationship in induction and maintenance

2. Different [drug] thresholds for exposure-response in induction vs. maintenance
Exposure-Response Relationship of Adalimumab

Roblin Clin Gastroenterol Hepatol 2014
Exposure-Response Relationship of Ustekinumab

Induction (3.3 ug/ml)

Maintenance (0.8-1.4 ug/ml)
Association of Serum Ustekinumab Concentrations with Clinical, Biochemical and Endoscopic Outcomes

- N = 59 aTNF refractory pts received UST

- UST >4.5 μg/mL predicts endoscopic response, AUC 0.78, p=0.0006

*Prometheus UST Assay; Endoscopic Response: SES-CD decreased by 50% or SES-CD ≤2

Battat et al. ECCO/DDW 2016, Abstract DOP072
Exposure-Response Relationship of Vedolizumab

GEMINI-1 (UC)

GEMINI-2 (CD)
Drug Levels in Peri-Anal Fistulizing Disease

Multicentre
117 patients
IFX ≥ 24 weeks

Mean IFX level – 15.8 μg/mL fistula healing vs. 4.4 μg/mL active fistulas [p<0.0001]

3-10 ug/ml 10-20 ug/ml

Yarur AP&T 2017
Applying Reactive TDM to Clinical Practice
Prospective Controlled Trial of Trough Level Adapted Infliximab Treatment (TAXIT): Study Outline

Primary end point = rate of clinical (Harvey-Bradshaw or Partial Mayo score) and biological (C-reactive protein ≤5 mg/l) remission one year after randomization in each group

CB Group = Clinically Based Group; LB Group = Level Based Group

TAXIT – Dose Optimization Phase

TAXIT – Post-Randomization

ICER - €15,525/QALY for clinically-based dosing

TAILORIX = Pilot RCT of IFX dose adaptation based on drug levels vs. symptoms in biologic-naïve patients

Increasing Infliximab Dose Based on Symptoms, Biomarkers, and Serum Drug Concentrations Does Not Increase Clinical, Endoscopic, or Corticosteroid-Free Remission in Patients With Active Luminal Crohn’s Disease

Article in Press: Accepted Manuscript

Geert D’Haens, Severine Vermeire, Guy Lambrecht, Filip Baert, Peter Bossuyt, Benjamin Parienté, Anthony Buisson, Yoram Bouhnik, Jérôme Filippi, Janneke van der Woude, Philippe Van Hootegem, Jacques Moreau, Edouard Louis, Denis Franchimont, Martine De Vos, Fazia Maria, Laurent Peyrin-Biroulet, Hedia Brixi, Matthieu Allez, Philip Caenepeel, Alexandre Aubourg, Bas Oldenburg, Marieke Pierik, Ann Gils, Sylvie Chevret and David Laharie

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D’Haens et al., Gastroenterology. 2018 Apr;154(5):1343-1351
Clinical relapse in TDM groups based on CDAI (>220 at 1 visit or between 150-220 for 2 consecutive weeks) and elevated CRP and/or fCal

*Infusions

†Decreased trough level (≥1 to <3 μg/mL or ≥3 to <10 μg/mL and >50% decrease compared with week 14. <1μg/mL resulted in dose increases and additional infusion at the 4-week interval.)

D’Haens et al., Gastroenterology. 2018 Apr;154(5):1343-1351
Results

27 centres in Belgium, France, and the Netherlands from July 2012-July 2014

Primary endpoint = Continuous corticosteroid-free remission weeks 22-54, no ulcers at week 54, no surgery

Secondary outcomes

<table>
<thead>
<tr>
<th>Percent of patients</th>
<th>TDM1</th>
<th>TDM2</th>
<th>Usual care</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFX dose escalation</td>
<td>44</td>
<td>62</td>
<td>40</td>
</tr>
<tr>
<td>Sustained IFX &gt; 3 µg/ml weeks 14-52</td>
<td>47</td>
<td>46</td>
<td>60</td>
</tr>
<tr>
<td>ATI</td>
<td>22</td>
<td>16</td>
<td>12.5</td>
</tr>
<tr>
<td>CD Endoscopic Index of Severity &lt; 3</td>
<td>49</td>
<td>51</td>
<td>45</td>
</tr>
<tr>
<td>Absence of ulcers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 12</td>
<td>36</td>
<td>16</td>
<td>40</td>
</tr>
<tr>
<td>Week 54</td>
<td>36</td>
<td>43</td>
<td>48</td>
</tr>
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</table>

D’Haens et al., Gastroenterology. 2018 Apr;154(5):1343-1351
• There is active disease
• The infliximab level is 15 ug/ml
• Now what?
## Relative efficacy of drug classes

<table>
<thead>
<tr>
<th></th>
<th>Onset of action</th>
<th>Clin remission UC</th>
<th>Clin remission CD</th>
<th>Endosc Healing UC</th>
<th>Endosc Healing CD</th>
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</thead>
<tbody>
<tr>
<td><strong>Anti TNF</strong></td>
<td>&lt;8 wks</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>&gt;8 wks</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Anti adhesion</strong></td>
<td>&lt;8 wks</td>
<td>+</td>
<td>+/-</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td></td>
<td>&gt;8 wks</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td><strong>Anti IL12-23</strong></td>
<td>&lt;8 wks</td>
<td>+</td>
<td>++</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>&gt;8 wks</td>
<td>+</td>
<td>++</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td><strong>JAK inhibitors</strong></td>
<td>&lt;8 wks</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>?</td>
</tr>
<tr>
<td></td>
<td>&gt;8 wks</td>
<td>+</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

*Hindryckx JCC 2018*
### Whats the clinical scenario?

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fistulizing disease</td>
<td>2nd anti TNF</td>
</tr>
<tr>
<td>Active Crohn’s</td>
<td>Ustekinumab/&gt;60 give Vedolizumab</td>
</tr>
<tr>
<td>Active UC</td>
<td>Vedolizumab</td>
</tr>
<tr>
<td>Inpatient with UC (failed inflix)</td>
<td>Cya +Vedo</td>
</tr>
<tr>
<td>Comorbid AS, PG, uveitis</td>
<td>2nd anti-TNF/Ustekinumab</td>
</tr>
<tr>
<td>Comorbid psoriasis/secondary psoriasis</td>
<td>Ustekinumab</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>2nd anti TNF/If UC consider Vedo depends on severity</td>
</tr>
<tr>
<td>Age &gt;60</td>
<td>Vedolizumab</td>
</tr>
<tr>
<td>New malignancy</td>
<td>Vedolizumab</td>
</tr>
<tr>
<td>Serious infection</td>
<td>Vedolizumab</td>
</tr>
<tr>
<td>Other adverse event to anti TNF</td>
<td>Depends............i.e. Withdraw therapy altogether ?UC; wants oral drug</td>
</tr>
</tbody>
</table>
Patient DW

- 63 yr old male
- CD x 15 years; Infliximab and MTX x 10 yrs
- Ileal disease
- No surgeries
- Feb/18 increased diarrhea, fatigue; no new stressors
- Colonoscopy=active ileal disease
- Infliximab level=2.23; no ADA
• Increase in infliximab from 10 mg/kg to 13.3 mg/kg (800 mg in 60 kg male)
• Resolution of symptoms
• Could do FCAL to verify response
• Increased symptoms, no ileal disease, infliximab level=2.23
• Increased symptoms, active ileal disease, infliximab level=16
• Increased symptoms, active ileal disease, infliximab level=0, ADA
• Increased symptoms, no ileal disease, infliximab level = 2.23

No change in inf for now; more investigations
• Increased symptoms, active ileal disease, infliximab level=16

Vedolizumab
• Increased symptoms, active ileal disease, infliximab level=0, ADA++

Vedolizumab or adalimumab