CAG Symposium: Management of IBD in 2018

Waqqas Afif, MD, M. Sc., FRCPC, Associate Professor, Department of Medicine
Division of Gastroenterology
McGill University Health Center
<table>
<thead>
<tr>
<th>CanMEDS Roles Covered</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medical Expert</strong> (as <em>Medical Experts</em>, physicians integrate all of the CanMEDS Roles, applying medical knowledge, clinical skills, and professional values in their provision of high-quality and safe patient-centered care. <em>Medical Expert</em> is the central physician Role in the CanMEDS Framework and defines the physician’s clinical scope of practice.)</td>
</tr>
<tr>
<td><strong>Communicator</strong> (as <em>Communicators</em>, physicians form relationships with patients and their families that facilitate the gathering and sharing of essential information for effective health care.)</td>
</tr>
<tr>
<td><strong>Collaborator</strong> (as <em>Collaborators</em>, physicians work effectively with other health care professionals to provide safe, high-quality, patient-centered care.)</td>
</tr>
<tr>
<td><strong>Leader</strong> (as <em>Leaders</em>, physicians engage with others to contribute to a vision of a high-quality health care system and take responsibility for the delivery of excellent patient care through their activities as clinicians, administrators, scholars, or teachers.)</td>
</tr>
<tr>
<td><strong>Health Advocate</strong> (as <em>Health Advocates</em>, physicians contribute their expertise and influence as they work with communities or patient populations to improve health. They work with those they serve to determine and understand needs, speak on behalf of others when required, and support the mobilization of resources to effect change.)</td>
</tr>
<tr>
<td><strong>Scholar</strong> (as <em>Scholars</em>, physicians demonstrate a lifelong commitment to excellence in practice through continuous learning and by teaching others, evaluating evidence, and contributing to scholarship.)</td>
</tr>
<tr>
<td><strong>Professional</strong> (as <em>Professionals</em>, physicians are committed to the health and well-being of individual patients and society through ethical practice, high personal standards of behaviour, accountability to the profession and society, physician-led regulation, and maintenance of personal health.)</td>
</tr>
</tbody>
</table>
Dr. Waqqas Afif

**Financial Interest Disclosure**
(over the past 24 months)

<table>
<thead>
<tr>
<th>Commercial Interest</th>
<th>Relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>Janssen/Abbvie/Takeda</td>
<td>Advisory board/consultant/investigator</td>
</tr>
<tr>
<td>Pfizer/Merck/Shire/Ferring/Novartis</td>
<td>Advisory board</td>
</tr>
<tr>
<td>Prometheus/Theradiag</td>
<td>Investigator</td>
</tr>
</tbody>
</table>
Learning objectives

At the end of this session, participants will be able to:

• *Identify targets used to select treatment options in IBD*

• *Incorporate therapeutic drug monitoring into clinical decision making for biologics in management of IBD.*
Treatment targets in IBD
Progressive nature of IBD

- Over median 23 months, bowel damage increased in >1/3 of patients
- Over 5 years, bowel damage increased in 48% of patients
- At 2–10 years post diagnosis, >50% had substantial damage

Avoidance of long-term bowel damage, complications and subsequent disability

CONTROL OF INTESTINAL INFLAMMATION

Treat-to-target concept in IBD

PREDEFINED TIMEFRAME

Assessment (baseline)  Assessment  Assessment

CONTROL OF INTESTINAL INFLAMMATION

Avoidance of long-term bowel damage, complications and subsequent disability

POSSIBLE TREATMENT DE-ESCALATION

Low

Target

Target

Target not reached

Treatment according to risk and target

Continue monitoring to maintain target

Target reached

High

Risk of progression

Assessment

Target

Target not reached
STRIDE: Treat-to-target recommendations in IBD

<table>
<thead>
<tr>
<th>Crohn’s disease</th>
<th>Ulcerative colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Resolution of abdominal pain and normalization of bowel habit should be the target (PRO)</td>
<td>Resolution of rectal bleeding and normalization of bowel habit should be the target (PRO)</td>
</tr>
<tr>
<td>2 Resolution of symptoms alone is not a sufficient target. Objective evidence of inflammation of the bowel is necessary when making clinical decisions</td>
<td>Resolution of symptoms alone is not a sufficient target. Objective evidence of inflammation of the bowel is necessary when making clinical decisions</td>
</tr>
<tr>
<td>3 Absence of ulceration is the target</td>
<td>A Mayo endoscopic subscore of 1 should be a minimum target.</td>
</tr>
<tr>
<td>4 Endoscopic or, where endoscopy cannot be performed, cross-sectional imaging assessment should be performed 6–9 months after the start of therapy</td>
<td>A Mayo endoscopic subscore of 0 is the optimal target.</td>
</tr>
<tr>
<td></td>
<td>Endoscopic assessment should be performed 3–6 months after the start of therapy for a patient with symptoms</td>
</tr>
</tbody>
</table>
Importance of mucosal healing for long-term outcomes in IBD: IBSEN cohort

Mucosal healing status at 1 year and risk of surgery

Ulcerative colitis (n=338)

Proportion of UC patients with no surgery after 1-year visit

Time in years after 1-year visit

0 1 2 3 4 5 6 7 8

Mucosal healing at 1 year

No mucosal healing at 1 year

Crohn’s disease (n=106)

Proportion of CD patients with no surgery after 1-year visit

Time in years after 1-year visit

0 1 2 3 5 7 8 4 6

Mucosal healing at 1 year

No mucosal healing at 1 year

Importance of mucosal healing for long-term outcomes in CD: Meta-analysis

### Association of MH at first endoscopic assessment (MH1) with long-term clinical remission (CR)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>MH 1</th>
<th>No MH 1</th>
<th>Weight</th>
<th>Odds Ratio M–H, Random. 95% CI</th>
<th>Odds Ratio M–H, Random. 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baert 2010</td>
<td>17</td>
<td>24</td>
<td>6</td>
<td>22</td>
<td>8.9%</td>
</tr>
<tr>
<td>Bjorkesten 2013</td>
<td>8</td>
<td>10</td>
<td>20</td>
<td>32</td>
<td>5.0%</td>
</tr>
<tr>
<td>Cohen 2014</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>1.2%</td>
</tr>
<tr>
<td>Czaja-Bulsa 2012</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td>8</td>
<td>1.3%</td>
</tr>
<tr>
<td>Dai 2014</td>
<td>65</td>
<td>78</td>
<td>21</td>
<td>31</td>
<td>15.9%</td>
</tr>
<tr>
<td>Froslie 2007</td>
<td>22</td>
<td>53</td>
<td>22</td>
<td>88</td>
<td>27.6%</td>
</tr>
<tr>
<td>Fukuchi 2014</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>13</td>
<td>1.5%</td>
</tr>
<tr>
<td>Grover 2014</td>
<td>7</td>
<td>15</td>
<td>10</td>
<td>11</td>
<td>1.6%</td>
</tr>
<tr>
<td>Reinisch 2015</td>
<td>54</td>
<td>70</td>
<td>27</td>
<td>53</td>
<td>24.4%</td>
</tr>
<tr>
<td>Rutgeerts 2010</td>
<td>10</td>
<td>20</td>
<td>14</td>
<td>42</td>
<td>12.4%</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>280</td>
<td>308</td>
<td>100.0%</td>
<td>2.80 (1.91, 4.10)</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>193</td>
<td>131</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Heterogeneity.** $\tau^2=0.00$; $\chi^2=4.57$; df=9 ($p=0.87$); $I^2=0\%$; Test for overall effect: $Z=5.26$ ($p<0.00001$)

### Association of MH with CD-related surgery-free rate

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>MH 1</th>
<th>No MH 1</th>
<th>Weight</th>
<th>Odds Ratio M–H, Random. 95% CI</th>
<th>Odds Ratio M–H, Random. 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baert 2010</td>
<td>24</td>
<td>24</td>
<td>22</td>
<td>22</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Bjorkesten 2013</td>
<td>10</td>
<td>10</td>
<td>26</td>
<td>32</td>
<td>10.0%</td>
</tr>
<tr>
<td>Froslie 2007</td>
<td>47</td>
<td>53</td>
<td>70</td>
<td>88</td>
<td>89.9%</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>87</td>
<td>118</td>
<td>142</td>
<td>100.0%</td>
<td>2.22 (0.86, 5.69)</td>
</tr>
<tr>
<td>Total events</td>
<td>81</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Heterogeneity.** $\tau^2=0.00$; $\chi^2=0.35$; df=1 ($p=0.55$); $I^2=0\%$; Test for overall effect: $Z=1.65$ ($p=0.10$)

If mucosal healing is the target, how can we make sure we are going in the right direction?
**Canadian guide on fecal calprotectin monitoring**

*May include additional FC tests, cross sectional imaging, colonoscopy, or videocapsule endoscopy*

Bressler, B *et al.* *Gastroenterology* (2015), 148:1035-1058

<table>
<thead>
<tr>
<th>FC LEVEL</th>
<th>INTERPRETATION</th>
<th>SUGGESTED ACTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50-100 µg/g</td>
<td>Quiescent disease likely</td>
<td>Continue therapy</td>
</tr>
<tr>
<td>100-250 µg/g</td>
<td>Inflammation possible</td>
<td>Further testing* required to confirm presence/absence of inflammation</td>
</tr>
<tr>
<td>&gt;250 µg/g</td>
<td>Active inflammation likely</td>
<td>Optimize therapy to address ongoing inflammation</td>
</tr>
</tbody>
</table>

*Le guide du clinicien sur l’utilisation de la calprotectine fécale afin de déterminer et de surveiller l’activité des maladies inflammatoires de l’intestin*


*ORIGINAL ARTICLE*

**Clinicians’ guide to the use of fecal calprotectin to identify and monitor disease activity in inflammatory bowel disease**

Brian Bressler MD¹, Remo Panaccione MD², Richard N Fedorak MD³, Ernest G Seidman MD³

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*The information provided is for educational purposes only and should not be used as a substitute for professional medical advice.*

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*May include additional FC tests, cross sectional imaging, colonoscopy, or videocapsule endoscopy*
Biomarkers for detection of endoscopic activity in symptomatic IBD Patients: A systematic review and meta-analysis

<table>
<thead>
<tr>
<th>Marker</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive LR</th>
<th>Negative LR</th>
<th>AUC</th>
<th>Diagnostic OR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C-reactive protein</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBD</td>
<td>0.49 (0.34, 0.64)</td>
<td>0.92 (0.72, 0.98)</td>
<td>6.3 (1.9, 21.3)</td>
<td>0.56 (0.44, 0.71)</td>
<td>0.72 (0.68, 0.76)</td>
<td>11 (3, 38)</td>
</tr>
<tr>
<td><strong>Fecal calprotectin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBD</td>
<td>0.88 (0.84, 0.90)</td>
<td>0.73 (0.66, 0.79)</td>
<td>3.2 (2.6, 4.1)</td>
<td>0.17 (0.14, 0.21)</td>
<td>0.89 (0.86, 0.91)</td>
<td>19 (13, 27)</td>
</tr>
<tr>
<td>CD</td>
<td>0.87 (0.82, 0.91)</td>
<td>0.67 (0.58, 0.75)</td>
<td>2.7 (2.1, 3.4)</td>
<td>0.19 (0.14, 0.27)</td>
<td>0.85 (0.82, 0.88)</td>
<td>14 (9, 22)</td>
</tr>
<tr>
<td>UC</td>
<td>0.88 (0.84, 0.92)</td>
<td>0.79 (0.68, 0.87)</td>
<td>4.2 (2.8, 6.4)</td>
<td>0.15 (0.11, 0.20)</td>
<td>0.91 (0.89, 0.94)</td>
<td>28 (18, 46)</td>
</tr>
<tr>
<td>Sensitivity analysis 1a</td>
<td>0.87 (0.82, 0.90)</td>
<td>0.71 (0.62, 0.78)</td>
<td>3.2 (2.3, 3.8)</td>
<td>0.19 (0.14, 0.24)</td>
<td>0.87 (0.84, 0.90)</td>
<td>16 (11, 23)</td>
</tr>
<tr>
<td>Sensitivity analysis 2a</td>
<td>0.87 (0.83, 0.91)</td>
<td>0.71 (0.63, 0.78)</td>
<td>3.2 (2.3, 3.9)</td>
<td>0.18 (0.13, 0.24)</td>
<td>0.88 (0.85, 0.91)</td>
<td>19 (14, 28)</td>
</tr>
<tr>
<td>Sensitivity analysis 3a</td>
<td>0.88 (0.84, 0.91)</td>
<td>0.73 (0.66, 0.79)</td>
<td>3.2 (2.5, 4.1)</td>
<td>0.17 (0.13, 0.21)</td>
<td>0.89 (0.86, 0.92)</td>
<td>19 (14, 28)</td>
</tr>
<tr>
<td>Sensitivity analysis 4a</td>
<td>0.87 (0.83, 0.90)</td>
<td>0.72 (0.65, 0.78)</td>
<td>3.2 (2.5, 3.9)</td>
<td>0.17 (0.14, 0.21)</td>
<td>0.88 (0.85, 0.91)</td>
<td>17 (12, 24)</td>
</tr>
<tr>
<td><strong>Stool lactoferrin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBD</td>
<td>0.82 (0.73, 0.88)</td>
<td>0.79 (0.62, 0.89)</td>
<td>3.8 (2.0, 7.5)</td>
<td>0.23 (0.14, 0.38)</td>
<td>0.87 (0.84, 0.90)</td>
<td>16 (6, 48)</td>
</tr>
</tbody>
</table>

AUC, area under the curve; CD, Crohn’s disease; IBD, inflammatory bowel disease; LR, likelihood ratio; OR, odds ratio; UC, ulcerative colitis.

aSensitivity analysis 1: excluding studies that included healthy controls that did not undergo colonoscopy; sensitivity analysis 2: excluding studies that included any patient not known to have a diagnosis of inflammatory bowel disease; sensitivity analysis 3: excluding one study that examined patients presenting with lower gastrointestinal symptoms; and sensitivity analysis 4: excluding two studies that were published in abstract form.

CALM: Effect of tight control using fecal calprotectin

Study design

* CDAI > 220 AND one of the following: steroid therapy > 4 weeks and best to taper per investigator assessment, intolerant/contraindication for steroid therapy, best interest of the patient per investigator assessment.

** CDAI > 300 for 2 consecutive visits 7 days apart or per investigator discretion (elevated CRP/FC, ulceration taken into consideration); moved to TC group.

CALM Results: Primary endpoint 48 weeks after randomization

CDEIS < 4 AND NO DEEP ULCERATIONS

P=0.010

<table>
<thead>
<tr>
<th>Clinical Management</th>
<th>Tight Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>30.3 (37/122)</td>
<td>45.9 (56/122)</td>
</tr>
</tbody>
</table>
CALM: Post-hoc analyses

- Compared with clinical management, treat to target was associated with significant reductions in:
  - CD-related hospitalizations
  - Time to CD-related flare
- No significant difference:
  - CD-related surgical procedure
  - CD-related hospitalizations or serious complications
- TC had £669 higher total direct medical costs and 0.032 higher QALYs
- ICER was £20,913 per QALY, which is below the UK NICE threshold of £30,000

Rates of CD-related hospitalizations after randomization

<table>
<thead>
<tr>
<th></th>
<th>Clinical Management</th>
<th>Tight Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events/100 PY</td>
<td>29</td>
<td>14</td>
</tr>
<tr>
<td>N = 122</td>
<td>PY = 103.6</td>
<td>N = 122</td>
</tr>
<tr>
<td>P = 0.021</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CD: Crohn's Disease

*CD-related hospitalization, other than CD-related major surgery, on or after randomization and ≤ 70 days after last dose.
## Reasons for escalation in tight control arm

<table>
<thead>
<tr>
<th>Lab visit</th>
<th>Escalated Patients, n</th>
<th>Proportion of patients violating each success criterion*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>FC, n (%)</td>
</tr>
<tr>
<td>Week 11</td>
<td>50</td>
<td>31 (62.0)</td>
</tr>
<tr>
<td>Week 23</td>
<td>39</td>
<td>53 (56.4)</td>
</tr>
<tr>
<td>Week 35</td>
<td>20</td>
<td>9 (45.0)</td>
</tr>
</tbody>
</table>

*Patients are counted under each reason

How to take a stool sample: 11 Steps (with pictures)

http://www.wikihow.com/Take-a-Stool-Sample
So how do we get to a normal FC and MH?
AGA Guidelines:

Induction of remission (moderate to severe)

Moderately severe IBD despite standard therapies
(CD: budesonide/corticosteroids & 5-ASA/corticosteroids in UC)

Use anti-TNF monotherapy
or ustekinumab (CD) or
vedolizumab

or

Use anti-TNF + thiopurine
or ustekinumb (CD) +/-

thiopurine or vedolizumab +/-
thiopurine

AGA Guidelines:

Maintenance of Remission

Remission

Steroid induced

IM (thiopurine or MTX for CD) or

Biologic ± thiopurine

Biologic induced ± thiopurine

Biologic + thiopurine induced

Biologic induced ± thiopurine

Mucosal healing

• Significant evidence for mucosal healing with anti-TNF therapy

• UST (CD):
  • Multiple real life cohorts
  • IM-UNITI

• VDZ (UC/CD):
  • Multiple real life cohorts
  • LTE from GEMINI trials

Rutgeerts et al. UEGW 2016, Abstract OP104
Noman et al., J Crohns Colitis. 2017;11(9):1085-1089
## Potential Considerations for Choosing a Biologic?

<table>
<thead>
<tr>
<th>Drug Factors</th>
<th>Patient clinical factors at initiation</th>
<th>Physician factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical efficacy</td>
<td>Active perianal disease</td>
<td>Time on the market/comfort level</td>
</tr>
<tr>
<td>Mucosal healing/fistula healing</td>
<td>Pregnancy</td>
<td>Ease of use</td>
</tr>
<tr>
<td>Favourable safety profile</td>
<td>Presence of EIM’s</td>
<td>Personal experience</td>
</tr>
<tr>
<td>Durability of remission (dose optimization +/- TDM)</td>
<td>Age/co-morbidity</td>
<td></td>
</tr>
<tr>
<td>Immunogenicity (need for combo)</td>
<td>Tolerate IS Rx</td>
<td></td>
</tr>
<tr>
<td>Rapid induction of remission</td>
<td>Steroid refractory</td>
<td></td>
</tr>
</tbody>
</table>

### Patient factors
- Mode of administration
- Ease of use/cost
- Work/travel/time spent on Rx
IBD Therapeutics: 2018 and beyond


Janus kinase inhibitors

Cytokine antagonists

Spingosine-1-phosphate

Lymphocyte trafficking inhibitors

Phosphodiesterase 4 inhibition
Tofacitinib in UC: Induction and maintenance

- Dose-dependent increase in herpes zoster observed
- Changes in lipid and creatine kinase levels
- Oral small molecule → immunogenicity not a concern
Optimizing Therapy

With mucosal healing being only 40% in most biologic studies, can we optimize therapy during induction using TDM?
Serum concentrations of IFX and ADA are associated with mucosal healing in patients with IBD

Mucosal healing therapeutic range revealed by incremental gain analysis of anti-TNF treated IBD patients

TAILORIX: Week 2 and 6 IFX are associated with MH

Figure 1. Receiver operating characteristic (ROC) curves of infliximab trough concentrations at (A) week 2 and (B) week 6 as a predictor of endoscopic remission at week 12. se: sensitivity; sp: specificity; AUROC: area under the ROC curve.

D’Haens et al., ECCO 2018
Trough IFX concentrations during induction associated with UC MH

• **Methods**
  - Retrospective study in 101 UC pts
  - STMH was defined as Mayo endoscopic sub-score ≤1, assessed at weeks 10-14

• **Results**
  - 53.4% of patients achieved STMH
  - IFX concentration ≥15 at week 6 (P = .025; OR, 4.6; 95% confidence interval, 1.2-17.1)
  - IFX concentration of ≥2.1 μg/mL Week 14 (P = .004; OR, 5.6; 95% confidence interval, 1.7-18) as independent factors associated with STMH.

Papamichael et al., CGH, 2016
But drug concentrations could just be a biomarker of MH?

Does dose escalation during induction improve outcomes?
Study cohort randomization and standard ADA induction at week 0 (160mg SC) and week 2 (80mg)

- **Active optimization arm**
  - Week 4 ADA trough concentration \(\geq 15\ \mu g/ml\)
    - **Yes**
      - Continue standard 40mg SC every 2
    - **No**
      - 80mg SC at week 6 Followed by 40mg SC every week

- **Placebo arm**
  - 40mg SC every 2 weeks

---

**Early Optimization Study**

McGill, Montreal  
U of Sherbrooke, Sherbrooke  
U of O, Ottawa  
UWO, London  
U of C, Calgary  
UBC, Vancouver
Therapeutic drug monitoring in IBD AGA guidelines:

Reactive vs proactive testing

<table>
<thead>
<tr>
<th>Statement</th>
<th>Strength of recommendation</th>
<th>Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>In adults with active IBD treated with anti-TNF agents, the AGA suggests reactive therapeutic drug monitoring to guide treatment changes. Conditional recommendation, very low quality of evidence.</td>
<td>Conditional recommendation</td>
<td>Very low quality</td>
</tr>
<tr>
<td>In adult patients with quiescent IBD treated with anti-TNF agents, the AGA makes no recommendation regarding the use of routine proactive therapeutic drug monitoring.</td>
<td>No recommendation</td>
<td>Knowledge gap</td>
</tr>
<tr>
<td>Statement</td>
<td>Acceptance (%)</td>
<td>EL</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------</td>
<td>----------------</td>
<td>----</td>
</tr>
<tr>
<td>1. In patients in clinical remission following anti-TNF therapy induction, TDM should be considered to guide management</td>
<td>100</td>
<td>II</td>
</tr>
<tr>
<td>2. TDM can inform clinical decision-making in patients with primary nonresponse</td>
<td>100</td>
<td>III2</td>
</tr>
<tr>
<td>3. TDM should be performed in patients with secondary loss-of-response to guide clinical decision-making</td>
<td>100</td>
<td>I</td>
</tr>
<tr>
<td>4. TDM should be considered periodically in patients in clinical remission if the results are likely to impact management</td>
<td>90</td>
<td>IV</td>
</tr>
<tr>
<td>5. Patients maintained in clinical remission in whom a drug holiday is contemplated, are suggested to have TDM along with other investigations to help guide this decision</td>
<td>100</td>
<td>III2</td>
</tr>
</tbody>
</table>

**General approach to patients with symptoms of active disease on anti-TNF therapy**

6. Patients with symptoms of active disease on anti-TNF therapy should have active inflammatory disease confirmed via objective measures (endoscopy, imaging, serum/faecal biomarkers) and investigations to exclude alternative/concomitant causes of symptoms, prior to change in therapy | 100 | III3 | C |
Reactive Testing

1. Presence of symptoms and objective inflammation
   - Check anti-TNF concentrations and anti-drug antibodies

   - Therapeutic anti-TNF levels (>10μg/mL for IFX; >15μg/mL for ADAL)
     - Endoscopy or imaging
       - Active disease: Switch out of class
       - Inactive disease: Explore alternative causes of patient's symptoms

   - Sub-therapeutic anti-TNF levels (<10μg/mL for IFX; <20μg/mL for ADAL)
     - Undetectable levels of anti-drug antibodies
     - Low titre antibodies (<8μg/mL for IFX; <5μg/mL for ADAL)
       - Optimize dose (increase anti-TNF dose or decrease dose interval) +/- Add immunosuppressant

     - High titre antibodies (>8μg/mL for IFX; >5μg/mL for ADAL)
       - Add immunosuppressant +/- Optimize dose

     If no response despite therapeutic concentration, switch out of class; If can not achieve therapeutic concentration, switch to different biologic medication

Heron and Afif, GCNA, 2017
Point of Care TDM in the IBD Clinic

• Use of a POC device for FC and IFX TDM in LOR IBD pts
• Secondary clinical LOR, defined as worsening of symptoms with HBI ≥ 5 for CD and partial Mayo score ≥ 3 for UC
• Optimized according to LOR algorithm and follow-up at 12 weeks

Restellini et al, ECCO 2018 Abstract
In the IBD clinic:

**Anti-TNF Concentrations (ug/ml)**

**Dose escalate:** <3 for IFX & < 5 for ADA & < 3 for GLM

**Consider dose escalation:** 3-10 for IFX & 5-15 for ADA

**Consider switch out of class:** > 10 for IFX & > 15 for ADA & > 3 for GLM

**High Titer Antibodies (switch Rx):** >8 ug/ml (> 130 AU/ml) for IFX/ADA & >56 AU/ML for GLM

(> 500 AU/ml in QC for IFX)

**USE CLINICAL JUDGEMENT !**
**Results:**

- Proactive trough-level–based dose intensification was not superior to dose intensification based on symptoms alone starting at week 14.
- 30% drop-off rate
- Elevated CDAI needed for optimization (elevated CRP/FC not enough)
  - In TDM arm: 53% of dose escalation was avoided, but not clear how many pts had only elevated FC
  - In usual care arm: normal CRP/FC in 60% of patients that were dose escalated

*Steroid-free clinical remission from weeks 22-54 & absence of ulceration at 1 year

D’Haens et al., Gastroenterology, Jan 2018
Suboptimal IFX concentrations in the TDM groups

Additional 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>51</td>
<td>65</td>
<td>40</td>
</tr>
<tr>
<td><strong>Sustained IFX &gt; 3 µg/ml weeks 14-52</strong></td>
<td>47</td>
<td>46</td>
<td>60</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>
</tbody>
</table>

D’Haens et al., Gastroenterology, Jan 2018
Proactive versus reactive testing with IFX

Figure 2. Kaplan-Meier cumulative probability curves of treatment failure in patients undergoing either reactive (dotted line) or proactive therapeutic drug monitoring (TDM) (solid line) based on the first infliximab (IFX) concentration measured (A), stratified also by the type of IBD, Crohn’s disease (B) or ulcerative colitis (C).

Papamichael et al, CGH 2017;15; 1580-1588
Proactive versus reactive testing with IFX

Figure 4. Kaplan-Meier cumulative probability curves of inflammatory bowel disease (IBD)-related surgery (A), IBD-related hospitalization (B), detectable antibodies to infliximab (IFX) (C), and serious infusion reaction (D) in patients undergoing either reactive (dotted line) or proactive therapeutic drug monitoring (TDM) (solid line) based on the first IFX concentration measured.
TDM with UST and VDZ

Assays for UST and VDZ are already available
UST TL maintenance at week 24: IM-UNITI remission exposure-clinical remission

The highest remission rates were associated with concentrations ~1 µg/mL

Adedokun, O.J., UEGW 2017.
UST TL maintenance at > week 26:
Exposure-endoscopic response

- N = 59 aTNF refractory pts received UST (90 mg SC wk 0,1,2; 90 mg SC q4w)
  - Two cohorts: prospective (n = 24), X-sectional retrospective (n = 35)
  - Concomitant-IS did not effect on UST concentration; **ATU 0%**

<table>
<thead>
<tr>
<th>CRP Normalization</th>
<th>Endoscopic Response</th>
<th>SFR + Endoscopic Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1 (n=15): &lt; 3.12</td>
<td>Q2 (n=16): 3.12-4.61</td>
<td>Q4 (n=13): &gt;5.73</td>
</tr>
<tr>
<td>Fraction of patients (%)</td>
<td>Fraction of patients (%)</td>
<td>Fraction of patients (%)</td>
</tr>
<tr>
<td>53.3%</td>
<td>31.3%</td>
<td>66.7%</td>
</tr>
</tbody>
</table>

**UST Exposure-Efficacy Relationship: Outcomes at Week 26**

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

Battat et al. CGH 2017
VDZ TL at Week 52:
GEMINI I and II exposure-clinical remission

Trough concentrations of UST and VDZ associated with improved outcomes

<table>
<thead>
<tr>
<th>Drug</th>
<th>Time Period</th>
<th>Approximate trough concentrations associated with improved outcome</th>
<th>Outcome Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ustekinumab</td>
<td>Induction (Week 8)</td>
<td>3.2-3.9 ug/ml</td>
<td>Clinical</td>
</tr>
<tr>
<td></td>
<td>Maintenance</td>
<td>1.0-4.5 ug/ml</td>
<td>Clinical/Endoscopic</td>
</tr>
<tr>
<td>Vedolizumab</td>
<td>Induction (Week 6)</td>
<td>33.7-38.3 ug/ml</td>
<td>Clinical/Endoscopic</td>
</tr>
<tr>
<td></td>
<td>Maintenance (Q8 dosing)</td>
<td>5.1-11.0 ug/ml</td>
<td>Clinical/Endoscopic</td>
</tr>
</tbody>
</table>

Restellini, Khanna and Afif et al, IBD 2018 (accepted)
Optimizing treatment using TDM in IBD

- Secondary loss of response/partial response: YES
- Dose de-escalation: YES
- Withdrawal of immunosuppression: YES
- After drug holiday: YES
- During induction prior to maintenance therapy: LIKELY
- Use for UST and VDZ: LIKELY
- Maintenance therapy in patients in remission: MAYBE

Heron and Afif, GCNA, 2017 (ahead of print)
IBD treatment in 2018

• Treat to patient related outcomes AND mucosal healing
  • Can use fecal calprotectin for tight control and to improve patient outcomes
  • Multiple options now available and more in the pipeline
    • Biologic sequencing has not yet been determined
    • Need personalized testing to choose optimal mechanism of action
    • Combination biologic therapy

• Consider early optimization and proactive TDM to improve outcomes in selected patients
  • Further studies need to be completed prior to these strategies becoming standard of care

• Manage partial response and loss of response with FC/TDM
  • Adequate data for anti-TNF’s
  • Emerging data for UST/VDZ
Evaluation and Certificate of Attendance

Please download the CDDW™ app to complete the session evaluation and to receive your certificate of attendance.