CAG Symposium: IBD- Managing Biologics “Optimizing Response”

Waqqas Afif, MD, M. Sc., FRCPC, Assistant Professor, Department of Medicine Division of Gastroenterology McGill University Health Center
## CanMEDS Roles Covered

<table>
<thead>
<tr>
<th>Role</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medical Expert</strong></td>
<td>(as Medical Experts, 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. Medical Expert 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></td>
<td>(as Communicators, 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></td>
<td>(as Collaborators, physicians work effectively with other health care professionals to provide safe, high-quality, patient-centred care.)</td>
</tr>
<tr>
<td><strong>Leader</strong></td>
<td>(as Leaders, 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></td>
<td>(as Health Advocates, 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></td>
<td>(as Scholars, 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></td>
<td>(as Professionals, 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</td>
<td>Advisory board/consultant/investigator</td>
</tr>
<tr>
<td>Takeda/Pfizer/Merck/Shire/Ferring</td>
<td>Advisory board</td>
</tr>
<tr>
<td>Prometheus/Theradiag/Buhlmann</td>
<td>Investigator</td>
</tr>
</tbody>
</table>
Learning Objectives

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

- Compare the risks and benefits of combination therapy versus monotherapy in the treatment of patients with IBD
- Assess the utility of premedication in the treatment of patients with IBD on biologic therapy
- Manage the treatment of patients with IBD on biologic therapy using therapeutic drug monitoring
Combination Therapy in IBD

A very long history ...
REACT Trial: Algorithm-based Treatment with Early Combined Immunosuppression Reduced Complications in CD

Inter-level cluster randomisation to early combined immunosuppression algorithm or current best practice

9 patients recruited from 40 centers (n=1982)

Regular clinical review at 4 weeks and then Q12 weeks

Used algorithm to treat to target

Followed for 24 months

Primary endpoint: clinical remission (BI <5 & no steroids) at 12 months

ACT Trial: Algorithm-based Treatment with Early Combined Immunosuppression (ECI) Reduced Complications in CD

Primary endpoint (symptomatic remission) was not met BUT →

Khanna R, et al., Lancet 2018
SONIC: Mucosal Healing at Week 26

Median disease duration 2.4 years

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Proportion of Patients (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZA+PBO</td>
<td>16.5</td>
<td>0.02</td>
</tr>
<tr>
<td>IFX+PBO</td>
<td>30.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IFX+AZA</td>
<td>43.9</td>
<td>0.06</td>
</tr>
</tbody>
</table>

P = .02

P = .06

P = <0.001

Sandborn WJ et al. N
SONIC Study: Serum Infliximab Trough Levels at Week 30

Median IFX Concentration

<table>
<thead>
<tr>
<th>Group</th>
<th>Serum IFX Concentration (ug/ml)</th>
<th>N</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFX</td>
<td>1.6</td>
<td>97</td>
<td>0.1</td>
</tr>
<tr>
<td>IFX+AZA</td>
<td>3.5</td>
<td>109</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Colombel JF et al, N Engl J Med 2010;362
DIAMOND
Combination therapy vs monotherapy with ADAL: Primary Endpoint at week 71.8

DIAMOND
Combination therapy vs monotherapy with ADAL: Primary Endpoint at week

- ADA Trough Level (µg/ml)
  - $p=0.084$

<table>
<thead>
<tr>
<th>ADA</th>
<th>ADA + AZA</th>
</tr>
</thead>
<tbody>
<tr>
<td>13.2</td>
<td>6.5±3.9</td>
</tr>
<tr>
<td>4.0</td>
<td>7.6±3.6</td>
</tr>
</tbody>
</table>

$n=76$ $n=75$

Positive Rate of AAA (%)

Meta-analysis: Anti-TNF mono- or combination therapy:

- Induction of clinical response (between week 4 to 14) and concomitant IMM use

<table>
<thead>
<tr>
<th>Treatment</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>0.88 (0.60-1.27)</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>1.01 (0.66-1.54)</td>
</tr>
<tr>
<td>Tolizumab</td>
<td>2.02 (1.09-3.74)</td>
</tr>
</tbody>
</table>

Systematic review of 11 RCTs in patients with luminal and/or fistulising CD who received anti-TNF therapy with/without concomitant IM therapy; combination therapy was not associated with serious adverse events compared to monotherapy across all anti-TNF therapies

COMMIT: MTX plus IFX in CD

Proportion of patients with treatment success (%)

Weeks since randomization

Patients with treatment success (%)

MTX + IFX
Placebo + IFX

76.2 77.8
55.6 57.1

Week 14
Week 50

p=0.63

COMMIT: MTX for the Prevention of ADA

Methods: 126 MTX-naïve CD pts (63 w/ IFX) – ATI and Trough levels (TL) were measured

IFX Kinetic Measurements

<table>
<thead>
<tr>
<th></th>
<th>IFX</th>
<th>IFX + MTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATI +* (%)</td>
<td>20.4%</td>
<td>25.9%</td>
</tr>
<tr>
<td>detectable TL (%)#</td>
<td>3.75%</td>
<td>6.35%</td>
</tr>
<tr>
<td>TL (mg/mL)**</td>
<td>4.0%</td>
<td>25.9%</td>
</tr>
</tbody>
</table>

0.01 **P=0.08 #P=0.13

2016 ECCO Guidelines: CD and UC

Safety: Combination Therapy
### EACT: Safety of Early Combined Immunosuppression

No increased risk of infections

<table>
<thead>
<tr>
<th>Types of Complications / SAEs</th>
<th>Conventional Management (n=898)</th>
<th>Early Combined Immunosuppression (n=1084)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worsening Disease</td>
<td>92 (32%)</td>
<td>97 (36%)</td>
</tr>
<tr>
<td>Disease Related Complications</td>
<td>134 (47%)</td>
<td>113 (42%)</td>
</tr>
<tr>
<td>Extra-Intestinal Manifestations</td>
<td>50 (17%)</td>
<td>47 (17%)</td>
</tr>
<tr>
<td>Procedural Complication</td>
<td>2 (0.7%)</td>
<td>2 (0.7%)</td>
</tr>
<tr>
<td>Medication Related</td>
<td>10 (3.5%)</td>
<td>10 (3.7%)</td>
</tr>
</tbody>
</table>

Khanna R, et al., Lancet 2023
CESAME: Risk of Lymphoma with Thiopurines

Figure: Incidence rates of lymphoproliferative disorders according to thiopurine exposure grouped by age at entry in the cohort. LD=lymphoproliferative disorder.

Beaugerie et al. Lancet
CESAME: Risk of NMSC with Thiopurines

Peyrin-Biroulet et al. *Gastroenterology* 2011;141:1
NMSC: Risk with combination therapy likely attributable to immunomodulators

Patients treated with adalimumab combination therapy (either with any IMM or with thiopurine) show a significant 5-fold increased risk of NMSC when compared to the general population.

Osterman et al., Gastroenterology 2014;146(4)
Malignancies excluding NMSC: Risk with combination therapy likely attributable to immunomodulators

Patients treated with adalimumab combination therapy (either with any IMM or with thiopurine) have a significant 3-fold increased risk of malignancies other than NMSC when compared to the general population.

Osterman et al., *Gastroenterology* 2014;146(4)
Do we need to continue immunosuppression long term?
Meta-analysis: Decreased antibody formation with IS Rx

Garces et al. Ann Rheum
Meta-analysis:
Maintenance anti-TNF mono- or combination therapy

6 month remission for infliximab

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Yes IM Events</th>
<th>Total</th>
<th>No IM Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCENT 1</td>
<td>28</td>
<td>53</td>
<td>61</td>
<td>150</td>
<td>83.4%</td>
<td>1.63 [0.87, 3.07]</td>
</tr>
<tr>
<td>RUTGEERTS</td>
<td>12</td>
<td>18</td>
<td>7</td>
<td>15</td>
<td>16.6%</td>
<td>2.29 [0.56, 9.37]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>71</strong></td>
<td><strong>165</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
<td><strong>1.73 [0.97, 3.07]</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td><strong>40</strong></td>
<td><strong>68</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = .00, Chi² = 0.18, df = 1 (P = .67); I² = 0%</td>
<td></td>
<td></td>
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<tr>
<td>Test for overall effect Z = 1.86 (P = .06)</td>
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</tbody>
</table>

6 month remission for adalimumab

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Yes IM Events</th>
<th>Total</th>
<th>No IM Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHARM</td>
<td>64</td>
<td>156</td>
<td>77</td>
<td>173</td>
<td>17.3%</td>
<td>0.87 [0.56, 1.34]</td>
</tr>
<tr>
<td>CLASSIC 2</td>
<td>7</td>
<td>9</td>
<td>21</td>
<td>28</td>
<td>5.6%</td>
<td>1.17 [0.19, 6.98]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>165</strong></td>
<td><strong>201</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
<td><strong>0.88 [0.58, 1.35]</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td><strong>71</strong></td>
<td><strong>98</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = .00, Chi² = 0.10, df = 1 (P = .75); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect Z = 0.58 (P = .56)</td>
<td></td>
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</tr>
</tbody>
</table>

AZA Dose Reduction in Patients on Combination Therapy

- Unfavourable evolution of IFX pharmacokinetics at Week 52
  \[ p = 0.022 \]

Del Tedesco E, et al.
Primary Endpoint:
No need for early ‘rescue’ IFX

Log Rank (Cox): 0.735;
Breslow: 0.906

FX trough levels at the time of withdrawal predicts loss of response

223 CD on IFX maintenance trial serum samples for TLs

Drobne D et al., Gastroenterology 2011; 140(5) (Suppl) S-62. (oral pres)
Optimizing Therapy: Combination Therapy

Consider combination therapy during induction

Increased risk of malignancy with thiopurines

After 6-12 months, consider ½ dose thiopurine versus low dose MTX

Consider withdrawal in patients with a durable response and adequate drug concentrations
Optimizing Therapy

Premedication
Premedication with IV corticosteroids in episodic therapy
Decreased antibody formation with regular dosing

Farrell RJ, Alsahli M, Jeen YT et al. Gastroenterology 2003; 124
Pediatric IBD study of 243 pts (Jacobson et al.):
- No decreased risk of infusion reactions with pre-medications
- Non significant trend towards less repeat infusion reactions with pre-medications

Jacobstein DA, Markowitz JE, Kirschner BS et al.. Inflamm Bowel Dis 2005;
Optimizing Therapy

Post-induction
Post Induction TDM

ROC analysis of TLI at week 14 showed that a TLI < 2.2 gave 94% specificity and 79% sensitivity for ATI formation.

An IFX trough level at week 14 < 2.2 μg/ml predicted loss of response due to persistent loss of response (LOR) and hypersensitivity reactions with 74% specificity and 82% sensitivity (likelihood ratio 3.1; P=0.0026).

Vande Casteele et al.
Post Induction TDM

Pediatric IBD prospective cohort

Hypothesis: Trough levels at week 14 predict IFX durability

Results

<table>
<thead>
<tr>
<th>Trough level at week 14</th>
<th>&gt;3mcg/mL</th>
<th>&gt;4mcg/mL</th>
<th>&gt;7mcg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPV for week 54 clinical remission without IFX intensification</td>
<td>64%</td>
<td>76%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Infliximab trough level <3μg/ml: 4 fold increased risk of developing ADA

Figure 3. Distribution of serum infliximab concentrations during induction therapy on the basis of STMH. Gray boxes represent

Papamichael et al.,
Association Between Low VDZ TLs During Induction Predicts Need for Optimization Within 6 months

A retrospective study of 27 CD and 7 UC pts starting VDZ, low TL's at week 6 (<19 μg/mL) are associated with additional doses (given at week 10 and then every 4 weeks) for patients receiving these additional doses achieved a clinical response 4 weeks later.

Optimizing Therapy

Maintenance Treatment
A prospective controlled trial of trough level adapted infliximab treatment (TAIReen). Maintenance phase (52 weeks) with IFX dosing based on IFX TL (3-7 µg/mL). Optimization phase (n weeks) with IFX dosing based on IFX TL (3-7 µg/mL) for n weeks. Randomization: CB Group (IFX dosing based on clinical symptoms & CRP) and LB Group (IFX dosing based on IFX TL (3-7 µg/mL)). 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.

Clinically Based Group; LB Group = Level Based Group

TAXIT Results: Maintenance Phase

Primary end point

*Harvey-Bradshaw index score ≤4 (CD) or Partial MAYO score ≤2 (UC) and C-reactive protein level ≤5 mg/l. Primary end point could not be calculated for 3 Patients (1 CD from CB and 1 UC and 1 CD from LB group).

TAXIT Results: Maintenance Phase

Secondary end point (loss of response and need for an intervention)

17.3% of CB Group of LB Group needed therapy by the end of maintenance phase.

LogRank P=0.0038
Breslow P=0.0058

Vande Casteele N, et al. Gastroenterology 2015;1
TAILORIX: Proactive TDM in Maintenance

Results:
Proactive trough-level–based dose intensification was not superior to dose intensification based on symptoms alone.

A dose increase of 2.5mg/kg as effective as 4mg/kg
detailed pharmacokinetic, immunogenicity, and biomarker analysis pending

Primary endpoint

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

ECCO 2016. OP029 G. D’Haens et al.
Suboptimal IFX concentrations of the TDM group

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>Sustained IFX &gt; 3 µg/ml weeks 14-52</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>

ECCO 2016. OP029 G. D’Haens et al.
Optimizing Therapy
Loss of Response
Progressive LOR to Anti-TNF Therapy in CD

Primary non responder rate ; 20%

Variables Affecting TNF-α Inhibitor Levels

- Immunomodulator Usage
  - Antibody formation
  - Drug concentration
  - Drug clearance

- Anti-drug antibodies
  - Drug concentration
  - Drug clearance

- Male Gender
  - Drug clearance

- Low serum albumin (marker for protein losing colopathy?)
  - Drug clearance

- High BMI
  - Drug clearance

- High baseline TNF concentration
  - Drug clearance

- High baseline C
  - Drug clearance

Managing loss of response: dose intensification

Dose escalation results in ~60-70% short-term response

Ben-Horin S, *Aliment Pharmacol*
in drug (and anti-drug antibodies) concentrations guide which intervention is best for loss of response?
Levels of drug/anti-drug antibodies and outcome of interventions after loss of response to infliximab or adalimumab

Low drug and high titer anti-drug Ab

Low drug and low titer anti-drug Ab

$p=0.03$ (Log rank test)

Dose intensification
Switch anti-TNF

$p=0.02$ (Log rank test)

Yanai H, Clin Gastroenterol Hepatol
Disappearance of Anti-Drug Antibodies to IFX and ADA Following Immunosuppressant in IBD

Rate of Antibody-Positivity

Antibody-positive if levels were ≥ 12 AE/ml

<table>
<thead>
<tr>
<th>Antibodies to IFX</th>
<th>Antibodies to ADA</th>
</tr>
</thead>
<tbody>
<tr>
<td>26/98 (26.5%)</td>
<td>27/61 (44.3%)</td>
</tr>
</tbody>
</table>

Intervention after antibody formation (n = 159)

- Anti-TNF switched/terminated (n = 118/159)
  - + MTX: 86% (n = 7)
  - + AZA: 70% (n = 10)
  - Optimize...: 36% (n = 22)

Rate of Success Following Intervention (reduction of antibodies and/or inc. drug levels)

- 100% (n = 2)

Cross-sectional study of 602 IBD pts receiving aTNF therapy

Antibody levels measured with ELISA and RIA, respectively (Sanquin)

Strik et al. ECCO 2016
The titer of measurable antibodies predicts response to dose-escalation versus switch
Anti-TNF concentrations
Drug concentration is adequate and IBD inflammation: switch out-of-class is better than anti-TNF optimization

\[ p = 0.006 \] (Log rank test)

Adequate:
- IFX >3.8 µg/mL
- ADL >4.5 µg/mL

Yanai H, Clin Gastroenterol Hepatol
Improved outcomes using TDM

Response: Subtherapeutic IFX

Result: Detectable ATI

Single centre, retrospective study, n = 155 pts with TDM test

Afif et al. Am J Gastroenterol 2010;105:
Dose Optimization Using TDM is More Effective Than Dose Optimization Based on Clinical Assessment Alone

IBD pts → IFX dose optimization following secondary LOR (2008-2014)

Clinical-based optimization led to higher rates of clinical response, endoscopic remission, hospitalization and flares (all p < 0.05)

Clinical response

Endoscopic remission

Median IFX TL (ug/mL)

Post Dose Adjustment

TDM-based (n=88)

Clinically-based (n=130)

Hospital admissions Flares

* P < 0.05

Remission: Mayo subscore ≤ 1 or SES-CD < 3 or Rutgeert’s score ≤ i1, Assay: Prometheus HMSA

Kelly et al. DDW 2015, Abstr...
TDM Results and Algorithm
Verify that the patient is taking the drug!

Up to 15%–29% of adalimumab/infliximab-treated patients are not adherent to their injections
(Missed at least one injection/infusion during the last 3 months)

Presence of symptoms and objective inflammation

Check anti-TNF concentrations and anti-drug antibodies

Therapeutic anti-TNF levels
µg/mL for IFX; >15µg/mL for ADAL)

Endoscopy or imaging

- Active disease
- 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

Optimize dose (increase anti-TNF dose or decrease dose interval) +/− Add immunosuppressant

Low titre antibodies
(<8µg/mL for IFX; <5µg/mL for ADAL)

Add immunosuppressant +/− Optimize dose

High titre antibodies
(>8µg/mL for IFX; >5µg/mL for ADAL)

Switch to a different biologic medication

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

Heron and Afif, GCNA, 2017 (ahead)
Optimizing therapy for differing phenotypes
Perianal fistulising disease

117 Crohn’s patients with perianal fistulising disease

Higher concentration for fistula healing vs active fistulas. Median infliximab trough level

- 18.5μg/mL versus 6.5μg/mL, P<0.0001

<table>
<thead>
<tr>
<th>Incremental improvement in perianal fistula healing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trough level (μg/ml)</td>
</tr>
<tr>
<td>Fistula healing rate %</td>
</tr>
</tbody>
</table>

Optimizing treatment using TDM in IBD

Secondary loss of response/partial response: yes
Post induction prior to maintenance therapy likely
Maintenance therapy in patients in remission no
Withdrawal of immunosuppression in combination therapy yes

Dose de-escalation yes
After drug holiday yes
Use for UST and VDZ likely

Heron and Afif, GCNA, 2017 (ahead of
Evaluation and Certificate of Attendance

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