Beyond Anti-TNFs: positioning of other biologics for Crohn’s disease

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Objectives:

• To define high and low-risk patient and disease features in Crohn’s disease
• To classify Crohn’s disease activity clinically and endoscopically
• To provide guidance for positioning FDA-approved agents for Crohn’s disease
Crohn’s disease treatment options

Level of “aggressiveness”

Most

Surgery

Indicated for moderate to severe Crohn’s disease

Severe

Biologic therapies (Infliximab, Adalimumab, Certolizumab pegol, Natalizumab, Vedolizumab, Ustekinumab)

Mild

Methotrexate, 6-Mercaptopurine/Azathioprine

Corticosteroids

Budesonide

Antibiotics?

Diet – specific carbohydrate

5-ASA/sulfasalazine???

Patient selection is key!!
HIGH RISK vs. low risk

Least

Disease severity
Progression of Digestive Disease Damage and Inflammatory Activity

- **AGGRESSIVE DISEASE**
- **Ideal treatment window**

- Disease onset
- Diagnosis
- Early disease
- Pre-clinical
- Clinical

- Stricture
- Fistula/abscess
- Surgery

CDAI: Crohn’s Disease Activity Index; CDEIS: Crohn’s Disease Endoscopic Index of Severity; CRP: C-Reactive Protein
Step 1: Determine age, location and behavior of Crohn’s disease

**Age at diagnosis**

- **A1:** <16yo
- **A2:** 16-40 yrs
- **A3:** > 40 yrs

**Upper GI and small bowel location** more common among patients diagnosed < 20 years of age
- **AGGRESSIVE DISEASE**
- Proximal disease may be clinically silent

**Colonic disease location** more typical for **older-onset IBD**
- Consider comorbidities
- Adverse effects of therapy

Step 1: Determine age, location and behavior of Crohn’s disease

**Location**

- L1: ileal
- L2: colonic
- L3: ileocolonic
- L4: upper GI

**L1 = isolated ileal AND ileocecal disease**

- L4 → esophageal, gastroduodenal and jejunal locations – greater morbidity with untreated disease
- L4 modifier used if upper GI disease is present in addition to L1-L3

Step 1: Determine age, location and behavior of Crohn’s disease

- **Agglomerative stricture**
  - High likelihood of needing surgery
  - Steroids not helpful to treat chronic stricture

- **“Aggressive” disease behavior**
  - Steroids make penetrating disease worse
  - Surgery often necessary followed by medical therapy

Responds best to medical management

Behavior:

- B1: inflammatory
- B2: stricturing
- B3: penetrating
- p: perianal

Step 1: Determine age, location and behavior of Crohn’s disease

Considered an “aggressive” disease behavior
- Steroids make perianal disease worse
- First control pelvic sepsis, then treat with combo therapy + antibiotics
- MRI pelvis = imaging study of choice

Behavior

- B1: inflammatory
- B2: stricturing
- B3: penetrating
- p: perianal

Step 2: Clinical activity assessment

Are systemic signs of inflammation present?
Are extra-intestinal manifestations present?

Assess inflammatory status

Assess symptoms/signs
- Fever
- Abdominal pain
- GI bleeding
- Localized tenderness
- Weight loss
- Joint pain
- Cutaneous signs

Perform clinical lab testing:
- CBC
- CRP
- CMP
- Fecal calprotectin
- ESR

ALBUMIN
# Harvey-Bradshaw Index

<table>
<thead>
<tr>
<th>General well-being (previous day)</th>
<th>Score</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 = Very Well</td>
<td>3 = Very poor</td>
<td></td>
</tr>
<tr>
<td>1 = Slightly below average</td>
<td>4 = Terrible</td>
<td></td>
</tr>
<tr>
<td>2 = Poor</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Abdominal pain (previous day)</th>
<th>Score</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 = None</td>
<td></td>
<td>Clinical remission</td>
</tr>
<tr>
<td>1 = Mild</td>
<td></td>
<td>Mildly active</td>
</tr>
<tr>
<td>2 = Moderate</td>
<td></td>
<td>Moderately active</td>
</tr>
<tr>
<td>3 = Severe</td>
<td></td>
<td>Severe</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Abdominal mass</th>
<th>Score</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 = None</td>
<td></td>
<td>Clinical remission</td>
</tr>
<tr>
<td>1 = Dubious</td>
<td></td>
<td>Mildly active</td>
</tr>
<tr>
<td>2 = Moderate</td>
<td></td>
<td>Moderately active</td>
</tr>
<tr>
<td>3 = Definite</td>
<td></td>
<td>Severe</td>
</tr>
<tr>
<td>4 = Definite and tender</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of liquid stools per day</th>
<th>Score</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Complications (1 point each)</th>
<th>Score</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthralgias</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uveitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythema nodosum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aphthous ulcers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyoderma gangrenosum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anal fissure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>New fistula</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Harvey RF, Bradshaw JM. Lancet. 1980;1:514.
Clinical activity assessment

Are features of stricturing/penetrating disease present?
Are there other explanations for symptoms?
Step 3: Diagnostic evaluation

Is endoscopy always the first choice in the evaluation or should imaging be the first choice?

- Selection depends on local expertise and experience with imaging modalities. Magnetic resonance enterography is preferred due to the reduction in ionizing radiation, particularly for younger patients. If patient is less than 50 years of age, we suggest using magnetic resonance enterography.

- Consideration could be given as to whether to make treatment decisions based on inflammatory markers versus confirming with colonoscopy. This may depend on whether there was historically good correlation between the biomarker selected and colonoscopy in the specific patient.

If suspect small bowel etiology → obstructive or fistulizing symptoms, then imaging first
If suspect colonic etiology or inflammatory ileal etiology, then colonoscopy first

www.gastro.org/IBDcarepathway.
Step 4: Identify low or high-risk features

Assess current and prior disease burden

Identify patient as low risk:
- Age at initial diagnosis > 30 years
- Limited anatomic involvement
- No perianal and/or severe rectal disease
- Superficial ulcers
- No prior surgical resection
- No stricturing and/or penetrating behavior

Identify patient as moderate/high risk:
- Age at initial diagnosis < 30 years
- Extensive anatomic involvement
- Perianal and/or severe rectal disease
- Deep ulcers
- Prior surgical resection
- Strictureing and/or penetrating behavior

Should you recommend combination or monotherapy?
Proactive therapeutic drug monitoring?
** Assess for response to therapy within 6 months after starting treatment **
Step 5: IBD Pre-treatment evaluation

| Baseline laboratory assessments: | • Complete blood counts  
|• Comprehensive metabolic profile  
|• Fecal calprotectin  
|• Inflammatory markers – CRP, sedimentation rate |
| Disease activity assessments: | • Clinical assessments  
|• Cross-sectional imaging  
|• Endoscopic evaluation  
|• Perianal disease |
| Medication activity: | • Thiopurine methyltransferase activity (TPMT): enzyme activity or genetics |
| Infectious workup: | • Clostridium difficile  
|• Cytomegalovirus infection |
| Exposure workup: | • Hepatitis B testing  
|• TB testing: Quantiferon IGRA or PPD |
| Vaccinations: | • MMR, Varicella exposure/vaccination status  
|• Influenza/Pneumonia (Prevnar-13 and PPSV-23) |
| Prior IBD medication history: | • Responder/non-responder?  
|• Adherence?  
|• Adverse effects of therapy? |

**Step 6: Look for factors that Influence the pharmacokinetics of biologics**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Impact on TNF antagonist PK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of ADAs</td>
<td>Decreases drug concentration</td>
</tr>
<tr>
<td></td>
<td>Increases clearance</td>
</tr>
<tr>
<td></td>
<td>Worse clinical outcomes</td>
</tr>
<tr>
<td>Concomitant use of immunosuppressives</td>
<td>Reduces ADA formation</td>
</tr>
<tr>
<td></td>
<td>Increases drug concentration</td>
</tr>
<tr>
<td></td>
<td>Decreases drug clearance</td>
</tr>
<tr>
<td></td>
<td>Better clinical outcomes</td>
</tr>
<tr>
<td>Low serum albumin concentration</td>
<td>Increases drug clearance</td>
</tr>
<tr>
<td></td>
<td>Worse clinical outcome</td>
</tr>
<tr>
<td>High baseline CRP concentration</td>
<td>Increase drug clearance</td>
</tr>
<tr>
<td>High baseline TNF concentration</td>
<td>May decrease drug concentration by increasing clearance</td>
</tr>
<tr>
<td>High body size</td>
<td>May increase drug clearance</td>
</tr>
<tr>
<td>Sex</td>
<td>Males have higher clearance</td>
</tr>
</tbody>
</table>

*Deep ulcerations on endoscopy*

Step 7: Identify treatment options - anti-TNF agents for higher-risk patients

- Vedolizumab? Ustekinumab?

START ANTI-TNF agent

- Right dose
- Right interval
- Right timing
- Right indication
- Evaluate for response to treatment
  - Clinical response
  - Laboratory response
  - Endoscopic/histologic response
Start the most appropriate regimen early: Earlier initiation of anti-TNF therapy is associated with an increased likelihood of remission for patients with **INFLAMMATORY** Crohn’s disease.

**Figure 1:**
- **PRECiSE 2 (certolizumab pegol):**
  - **Placebo vs. Adalimumab**
  - Remission rates are significantly higher in the Adalimumab group compared to Placebo across different duration categories.

**Figure 2:**
- **SONIC trial:** Anti-TNF and IMM naïve patients
- Median duration of disease: 2 years

**Table 1:**
- Response and Remission rates at week 26

**References:**
- Colombel et al. NEJM. 2010;362:1383-95.
Proposed Approach to Mono or Combo Therapy in IBD

What is the prognosis?

High Risk

Moderate to high risk features:
- Age at initial diagnosis < 30 years
- Extensive anatomic involvement
- Perianal and/or severe rectal disease
- Deep ulcers
- Prior surgical resection
- Strictureing or penetrating behavior
- Current smoker

Low Risk

Low risk features
- Age at initial diagnosis > 30 years
- Limited anatomic involvement
- No perianal and/or severe rectal disease
- Superficial ulcers
- No prior surgical resection
- No stricturing or penetrating behavior

*** Are risk factors for ADA (anti-drug antibody) formation present? ***

LOW ALBUMIN
**Proposed Approach to Mono or Combo Therapy in IBD**

**What is the prognosis?**

- **High Risk**
  - Combo IMM/anti-TNF
  - Male? MTX instead of Thiopurine?
    - If achieve deep remission
      - Possible de-escalation of Therapy
      - OR
      - Dose reduction of Thiopurine?
    - 12 months

- **Low Risk**
  - Step Care*
    - If deep remission
    - If no deep remission

*Consider immunomodulators, vedolizumab or subcutaneous anti-TNF for moderate disease responsive to budesonide or prednisone
  * Extra-intestinal manifestations present?
  * Optimized biologic monotherapy for moderate to severe disease if contraindications for combo therapy
Proposed Approach to Mono or Combo Therapy in IBD

Anti-TNF therapy

Proactive monitoring:
- Perianal Crohn’s
- Upper GI tract/proximal small bowel Crohn’s
- Smoking history
- Surgical resections with rapid endoscopic recurrence

• Aim for higher levels
• If therapeutic levels but persistent activity → consider ustekinumab or vedolizumab with proactive monitoring
  • Ustekinumab if extra-intestinal manifestations
  • Vedolizumab may take longer to work
• Smoking cessation
• Efficacy of combination therapy to be determined, but immunogenicity still possible
Proposed Approach to Mono or Combo Therapy in IBD

Anti-TNF therapy

Losing Response?

- Reassess disease activity
- Assess adherence to maintenance schedule
- Appropriate dosing relative to disease activity/patient factors

Assess drug level/antibodies (if available)

Anti-TNF level (if available)

No or low levels & ADAs (+)

High titers

High Clearance

Switch anti-TNF *

TNF dose escalation or switch *

Low titers

Impact Clearance

Dose escalation

Sub-therapeutic

Therapeutic*

Confirm disease activity, if present, then switch to a different drug mechanism #

(+): levels & ADA (-)

* Consider adding or optimizing immunomodulators

# Consider SURGERY if appropriate including exams under anesthesia for perianal disease
Step 7: Identify treatment options: vedolizumab (anti-TNF failures)

Inclusion criteria – required objective evidence of disease activity and CDAI between 220-400
Step 7: Identify treatment options: vedolizumab (anti-TNF failures)

CDAI 100 Response (≥100-Point Reduction in CDAI Score From Baseline to Week 6)

Anti-TNFα Failure Population
(PBO, n=157; VDZ, n=158)

Placebo (PBO)  Vedolizumab (VDZ)
22.3  39.2

Overall Population
(PBO, n=207; VDZ, n=209)

Placebo (PBO)  Vedolizumab (VDZ)
22.7  39.2

Sands, Gastro 2014

CDAI 100 Response (≥100-Point Reduction in CDAI Score From Baseline to Week 10)

Anti-TNFα Failure Population
(PBO, n=157; VDZ, n=158)

Placebo (PBO)  Vedolizumab (VDZ)
22.0 (95% CI, 11.4, 32.6)

Overall Population
(PBO, n=207; VDZ, n=209)

Placebo (PBO)  Vedolizumab (VDZ)
23.7 (95% CI, 14.5, 32.9)

* P<0.0001.
### Treatment-Emergent Adverse Events: Safety Population

<table>
<thead>
<tr>
<th></th>
<th>Anti-TNFα–Failure Population (N=315)</th>
<th>Overall Population (N=416)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo n=157</td>
<td>VDZ n=158</td>
</tr>
<tr>
<td><strong>Any adverse event (AE), %</strong></td>
<td>102 (65)</td>
<td>94 (59)</td>
</tr>
<tr>
<td><strong>Serious AEs, %</strong></td>
<td>14 (9)</td>
<td>8 (5)</td>
</tr>
<tr>
<td><strong>Discontinued due to AE</strong></td>
<td>2 (1)</td>
<td>6 (4)</td>
</tr>
</tbody>
</table>

Sands, Gastro 2014
Step 7: Identify treatment options: ustekinumab (all anti-TNF exposed)

Inclusion criteria based on CDAI only

Step 7: Identify treatment options: ustekinumab

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo (N=132)</th>
<th>Ustekinumab</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 mg/kg (N=130)</td>
<td>3 mg/kg (N=133)</td>
</tr>
<tr>
<td>Any adverse event</td>
<td>94 (71.2)</td>
<td>89 (68.5)</td>
</tr>
</tbody>
</table>

Sandborn, NEJM, 2012
### Step 8: Look for factors that Influence the safety of prescribing biologics

<table>
<thead>
<tr>
<th>Condition</th>
<th>Action</th>
</tr>
</thead>
</table>
| Abscess on imaging                | Drain first if accessible via IR
Consider surgical resection if appropriate with post-op treatment |
| Recurrent obstructions            | Consider surgical resection first with appropriate post-op treatment  |
| (+) TB testing                    | Consider vedolizumab
Treatment delay by 1-2 months prior to anti-TNF or ustekinumab |
| Melanoma history                  | Consider vedolizumab
Avoid anti-TNFs, ustekinumab |
| Current or recent malignancy      | Hold treatment if current chemotherapy
Consider vedolizumab |
| Drug-induced lupus                | Vedolizumab or ustekinumab |
| TNF-associated psoriasis          | Vedolizumab or ustekinumab |
| Older age                         | Moderate disease – vedolizumab
Severe disease or higher risk features – ustekinumab
Surgery if limited stricturing disease |
Summary

• Risk stratification based on disease and patient factors is key for positioning biologics
• Severe disease – infusion based-anti-TNF as combo therapy, optimized infusion-based anti-TNF monotherapy, ustekinumab
• Moderate disease – subcu or IV anti-TNF (IV if obese), vedolizumab (if no EIM)
• Older patients – moderate: vedolizumab, severe: ustekinumab
• Malignancy history – vedolizumab (including melanoma)
• Surgery first for appropriate indications