Use of biologics as first line therapy in IBD: one size fits all?

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Case 1: New Diagnosis Crohn’s Disease

24-year-old man with new diagnosis Crohn’s disease after 4 months of symptoms

– Diarrhea: 8 loose, urgent stools, including 1 overnight
– Abdominal pain: RLQ starting 30 min after eating, lasting 2 hours
– Weight loss: 10 pounds
– No fever, eye, skin, or joint manifestations
Case 1: New Diagnosis Crohn’s Disease

FH
– Brother diagnosed with ileal CD at age 14 (now 26); severe course, anti-TNF-refractory and 2 resections

SH
– Just married; works for phone company as a lineman; smokes 10 cigarettes a day for the last 5 years

Case 1: New Diagnosis Crohn’s Disease

Exam
– Afebrile
– Abdomen with RLQ fullness and mild tenderness
– Small anal skin tags; no perianal erythema, tenderness or fluctuance; no fissure
Case 1: New Diagnosis Crohn’s Disease

Labs
- WBC 8.9, HGB 10.5, PLT 425K, MCV 72
- CRP 4.5 (ULN=5), ESR 25

Colonoscopy
- Rectum: Edema, erythema, numerous small ulcers
- R colon, cecum: moderately severe inflammation and ulceration
- ICV: entered with difficulty
- TI: numerous large ulcers with marked edema; difficulty advancing more than 5 cm

Case 1: New Diagnosis Crohn’s Disease

MRE
- 35 cm of terminal ileal thickening, mucosal enhancement and “comb sign,” with marked narrowing, no prestenotic dilatation
- sinus tract from distalmost ileum vs. ileocecal fistula
- no abscess
Step-up: Is this what we really do?

Disease Severity at Presentation

Severe

Moderate

Mild

Step-Up according to severity at presentation or failure at prior step

Questions

• Initial medical therapy?
  – Delayed-release mesalamine
  – Budesonide CIR
  – Prednisone
  – Azathioprine or mercaptopurine
  – Methotrexate
  – Infliximab
  – Injectable TNF antagonist: adalimumab or certolizumab pegol
  – Vedolizumab

• What sequence?
• Combination therapy?
Questions

• Which biologic first?

Factors Relevant to Positioning Treatments in IBD

Drug Factors
• Indications
• Efficacy
• Safety
• Cost
• Convenience

Patient Factors
• Current/prior therapies
• Disease activity
• Disease location/extent
• Extraintestinal manifestations
• Complications (stricture, fistula)
• Age
• Other medical conditions
GEMINI II: Vedolizumab in CD
Primary induction endpoints

Placebo (N=148) vs Vedolizumab (N=220)

- Clinical Remission: Placebo 6.8%, Vedolizumab 14.5%, P=0.02
- CDAI-100 Response: Placebo 25.7%, Vedolizumab 31.4%, P=0.23

GEMINI II: Vedolizumab in CD
Through week 52, Maintenance ITT

Placebo (N=153) vs Vedolizumab, every 8 wk (N=154) vs Vedolizumab, every 4 wk (N=154)

- Clinical Remission: Placebo 21.6%, Vedolizumab, every 8 wk 39.0%, Vedolizumab, every 4 wk 36.4%, P<0.001
- CDAI-100 Response: Placebo 15.9%, Vedolizumab, every 8 wk 31.7%, Vedolizumab, every 4 wk 28.8%, P=0.02
- Glucocorticoid-Free Remission: Placebo 14.4%, Vedolizumab, every 8 wk 21.4%, Vedolizumab, every 4 wk 16.2%, P=0.04
Clinical Remission at Weeks 6 and 10 in CD Studies (Gemini 2 & 3)

<table>
<thead>
<tr>
<th>Patients % (95% CI)</th>
<th>Overall Population 100% of Patients</th>
<th>TNFα Failure Population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo C13007 Week 6</td>
<td>C13007* Week 6</td>
</tr>
<tr>
<td></td>
<td>7%</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td>Placebo C13011 Week 6</td>
<td>C13011* Week 6</td>
</tr>
<tr>
<td></td>
<td>12%</td>
<td>11%</td>
</tr>
<tr>
<td></td>
<td>Vedolizumab C13007 Week 10</td>
<td>C13007 Week 6</td>
</tr>
<tr>
<td></td>
<td>19%</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td>Vedolizumab C13011 Week 10</td>
<td>C13011 Week 6</td>
</tr>
<tr>
<td></td>
<td>19%</td>
<td>12%</td>
</tr>
</tbody>
</table>

\[ \Delta = 8\% \quad p = 0.0206 \]
\[ \Delta = 7\% \quad p = 0.0478 \]
\[ \Delta = 16\% \quad p < 0.0001 \]

\[ \Delta = 6\% \quad \text{Not tested} \]
\[ \Delta = 0.4332 \]
\[ \Delta = 14\% \quad p = 0.0012 \]

Vedolizumab
Placebo

Incremental benefit (delta) with prior biologic exposure: Vedolizumab induction therapy

<table>
<thead>
<tr>
<th>Response</th>
<th>Remission</th>
<th>Mucosal Healing</th>
</tr>
</thead>
<tbody>
<tr>
<td>VDZ UC</td>
<td>VDZ UC Biologic exposed</td>
<td>VDZ CD</td>
</tr>
<tr>
<td>22</td>
<td>5.7</td>
<td>1</td>
</tr>
<tr>
<td>19</td>
<td>6</td>
<td>6.7</td>
</tr>
<tr>
<td>12</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>16</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

Feagan BG. NEJM 2013
Sandborn WJ NEJM 2013
Case Scenarios:
Demographics and Concomitant Conditions

Do these features change your approach?
– Woman instead of man
– Age 72 instead of 24
– Marked peripheral arthralgias
– Personal history of renal cell carcinoma diagnosed 3½ years ago
– PSC

Anti-TNF vs Vedolizumab
Distinct Indications?

Anti-TNF
• Acute severe colitis
• Severe EIMs

Vedolizumab
• Patients at risk or with history of opportunistic infections
• Patients at risk or with history of malignancy
• Elderly
• PSC?
Safety Issues With Anti-TNF Therapy

- Infection and malignancy
  - Black-box warning for serious infection and malignancy for all anti-TNF therapies\(^1\)\(^-\)\(^3\)
  - Black-box warning for HSTCL (adalimumab and infliximab)\(^4\)\(^,\)\(^2\)

- Reactivation of hepatitis B\(^4\), tuberculosis

- Skin cancer\(^4\)

- Psoriasis\(^4\)

- Autoimmunity (lupus-like syndrome)\(^4\)

- Immunogenicity – antibodies to anti-TNF\(^4\)

- Demyelinating disorders, CHF, liver toxicity\(^4\)

CHF = congestive heart failure; HSTCL = hepatosplenic T-cell lymphoma.


Vedolizumab: Safety

<table>
<thead>
<tr>
<th>Infusion-related Reactions</th>
<th>Immunogenicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 4 % (vs. 3% placebo)</td>
<td>• 4% anti-vedolizumab antibodies at any time during 52 weeks of study</td>
</tr>
<tr>
<td>• &lt;1% “severe”</td>
<td>- 16% persistently “+”</td>
</tr>
<tr>
<td>• &lt;1% required discontinued therapy</td>
<td>- 59% neutralizing</td>
</tr>
<tr>
<td>• Anaphylaxis:</td>
<td></td>
</tr>
<tr>
<td>- 1 / 1434 (0.07%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PML*</th>
<th>Tuberculosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>• No Cases</td>
<td>• GEMINI 1 - 895 pts: 0 cases</td>
</tr>
<tr>
<td></td>
<td>• GEMINI 2 - 1115 pts: 1 pt</td>
</tr>
</tbody>
</table>

*Progressive multifocal leukoencephalopathy

Entyvio [package insert]. Deerfield, IL: Takeda Pharmaceuticals America, Inc; May 2014.
## Most Common Adverse Events Reported in the Integrated Safety Population

<table>
<thead>
<tr>
<th>AE, Preferred Term</th>
<th>UC (N=1107)</th>
<th>CD (N=1723)</th>
<th>UC and CD (N=2830)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>No. Patients with event/100 Patient-Years</td>
<td>n</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>211</td>
<td>13.2</td>
<td>300</td>
</tr>
<tr>
<td>Headache</td>
<td>168</td>
<td>10.1</td>
<td>289</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>145</td>
<td>8.4</td>
<td>294</td>
</tr>
<tr>
<td>CD*</td>
<td>NA</td>
<td>NA</td>
<td>457</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>85</td>
<td>4.7</td>
<td>263</td>
</tr>
<tr>
<td>UC*</td>
<td>266</td>
<td>15.4</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Exacerbation of disease

Incidence rate per 100 years = (Number of patients experiencing an AE of interest/Total Person Time in Years) x 100.

Most common AEs are defined as those with an exposure-adjusted incidence rate of ≥10 patients/100 person years.

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## Infections of Interest Reported as Serious Adverse Events in the Integrated Safety Population

<table>
<thead>
<tr>
<th>SAE, Preferred Term</th>
<th>PBO (N=504)</th>
<th>UC and CD (N=2830)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>No. Patients with event/100 Patient-Years</td>
</tr>
<tr>
<td>Patients with ≥1 infections (SAE)*</td>
<td>8</td>
<td>3.8</td>
</tr>
<tr>
<td>Anal abscess</td>
<td>1</td>
<td>0.47</td>
</tr>
<tr>
<td>Sepsis and related terms</td>
<td>2</td>
<td>0.94</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><em>Clostridium difficile</em> infection</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cytomegalovirus colitis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Viral meningitis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Salmonella gastroenteritis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Salmonella sepsis</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*As coded to the MedDRA system organ class infections and infestations
Other Risks

<table>
<thead>
<tr>
<th></th>
<th>Vedolizumab</th>
<th>Anti-TNF therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious Infection</td>
<td>-</td>
<td>+/-</td>
</tr>
<tr>
<td>Opportunistic</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Demyelinating</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Autoimmune (SLE, vasculitis)</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Dermatologic (psoriasis)</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Cardiac (CHF)</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Pulmonary (Sarcoidosis, ILD)</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

Caveat: most new drugs have additional toxicities identified during post-marketing surveillance

Questions

• Combination therapy?
• Which patients?
• Which immunomodulator?
Overall Risk of Cancer in IBD with Anti-TNF Agents: Denmark, 1999-2012

Rate Ratios for incident Overall Cancer Among 56,146 Patients With Inflammatory Bowel Disease Exposed and Unexposed to TNF-a Antagonists

<table>
<thead>
<tr>
<th>TNF-a Antagonist Exposure</th>
<th>Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exposed</td>
</tr>
<tr>
<td>Total</td>
<td>Person-years Cases</td>
</tr>
<tr>
<td></td>
<td>18,440</td>
</tr>
<tr>
<td></td>
<td>4,365</td>
</tr>
<tr>
<td>Female</td>
<td>Person-years Cases</td>
</tr>
<tr>
<td></td>
<td>10,665</td>
</tr>
<tr>
<td></td>
<td>1,803</td>
</tr>
<tr>
<td>Male</td>
<td>Person-years Cases</td>
</tr>
<tr>
<td></td>
<td>7,776</td>
</tr>
<tr>
<td></td>
<td>1,622</td>
</tr>
</tbody>
</table>

Adjusted for age, calendar year, disease duration, baseline propensity scores, use of 5-ASAs/sulphasalazine, local/systemic corticosteroids, methotrexate/cyclosporine/cyclophosphamide, and azathioprine.

After adjusting for azathioprine use, risk disappears


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Age ≥65 Is a Predictor of Infectious Complications in IBD Patients

Retrospective cohort study of 292 patients, 146 patients ≥ 65 years

<table>
<thead>
<tr>
<th>Incidence Rate Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elderly IBD patients</td>
<td>1.58</td>
</tr>
<tr>
<td>Elderly IBD patients on corticosteroids</td>
<td>3.15</td>
</tr>
<tr>
<td>Elderly IBD patients on corticosteroids and immunomodulator therapy</td>
<td>10.58</td>
</tr>
<tr>
<td>Elderly IBD patients on corticosteroids and anti-TNF therapy</td>
<td>10.64</td>
</tr>
</tbody>
</table>

Conclusions:
- Increasing age is associated with an increased risk for infection in IBD patients on corticosteroids, immunomodulators, and anti-TNF therapies
- Corticosteroids had the highest incidence rate ratio for infection as compared to all other therapies
- Infectious risk is increased when corticosteroids are added to an immunomodulator or to an anti-TNF

Malignancies in Children Receiving IBD Therapies: A Multicenter, Prospective, Pediatric Registry (DEVELOP)

Malignancy event rates from DEVELOP were compared with the expected event rates using the SEER database; adjusted for age, gender, and race

4,343 patients enrolled
2,586 exposed to anti-TNFs (2,503 to IFX); 1,757 received non-biologic therapies

No malignancies in patients without prior immunomodulator exposure

<table>
<thead>
<tr>
<th>Medication use</th>
<th>Observed Rate of Malignancies (per 10,000 patients)</th>
<th>Standardized Incidence Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-TNF + immunomodulator combination</td>
<td>10.7</td>
<td>5.73 (1.56-14.70)</td>
</tr>
<tr>
<td>Immunomodulator monotherapy</td>
<td>12.4</td>
<td>7.12 (1.47-20.80)</td>
</tr>
<tr>
<td>Anti-TNF monotherapy</td>
<td>0</td>
<td>0 (0-21.40)</td>
</tr>
<tr>
<td>Neither Anti-TNF nor immunomodulator</td>
<td>0</td>
<td>0 (0-17.90)</td>
</tr>
</tbody>
</table>


Case Scenarios: Prognosis

Do these features change your approach?

- CRP 25, ESR 55
- ASCA IgG +, ASCA IgA+, OmpC +, cBir1 +, pANCA -
Which prognostic factors to use?

- **Clinical** (age, extent, behaviour, symptoms)
- **Endoscopic** (mucosal healing)
- **Imaging**
- **Genetic** (>100, primarily NOD2/CARD15)
- **Serological and laboratory markers** (CRP, ASCA, ANCA, OmpC)
- **Fecal** (calprotectin)

ANCA: anti-neutrophil cytoplasmic antibodies; ASCA: anti-Saccharomyces cerevisiae antibodies; OmpC: outer membrane protein C precursor

---

Individual predictive markers for severe CD

<table>
<thead>
<tr>
<th>Marker</th>
<th>Predicted outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ileal location</td>
<td>Complications, surgery</td>
</tr>
<tr>
<td>Location proximal to the last third of ileum</td>
<td>Relapses, surgery</td>
</tr>
<tr>
<td>Colonic or rectal disease</td>
<td>Perianal disease</td>
</tr>
<tr>
<td>Anal lesions</td>
<td>Disabling disease</td>
</tr>
<tr>
<td>Stenosing penetrating behaviour at diagnosis</td>
<td>Surgery</td>
</tr>
<tr>
<td>Age &lt;40 years</td>
<td>Disabling disease</td>
</tr>
<tr>
<td>Smoking</td>
<td>Relapses, complications</td>
</tr>
<tr>
<td>Deep colonic ulcers</td>
<td>Surgery</td>
</tr>
<tr>
<td>CARD15 variants</td>
<td>Complications, surgery</td>
</tr>
<tr>
<td>IBD5/JCTIN variants</td>
<td>Perianal disease</td>
</tr>
<tr>
<td>Anti-glycan antibodies</td>
<td>Complications, surgery</td>
</tr>
<tr>
<td>Anti-bacterial antibodies</td>
<td>Complications, surgery</td>
</tr>
</tbody>
</table>

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Individual predictive markers for severe UC

<table>
<thead>
<tr>
<th>Marker</th>
<th>Predicted outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extensive colitis</td>
<td>Colectomy, cancer, mortality</td>
</tr>
<tr>
<td>Colitis extension</td>
<td>Colectomy</td>
</tr>
<tr>
<td>Sclerosing cholangitis</td>
<td>Cancer</td>
</tr>
<tr>
<td>Extra-intestinal manifestations</td>
<td>Colectomy</td>
</tr>
<tr>
<td>Young age</td>
<td>Colectomy, cancer</td>
</tr>
<tr>
<td>Non smoking</td>
<td>Relapses, Colectomy</td>
</tr>
<tr>
<td>Systemic inflammation</td>
<td>Colectomy</td>
</tr>
<tr>
<td>No response to first line therapy</td>
<td>Colectomy</td>
</tr>
<tr>
<td>No mucosal healing 1 year after diagnosis</td>
<td>Colectomy</td>
</tr>
<tr>
<td>HLA variants</td>
<td>Colectomy</td>
</tr>
<tr>
<td>ANCA</td>
<td>No response to anti-TNF</td>
</tr>
</tbody>
</table>

Evolving treatment strategies for Crohn’s disease

- Severe
  - TNF antagonist + IMS
  - Corticosteroids + IMS

- Moderate
  - Conventional step-care
  - Accelerated step-care
  - Early top-down

Early disease: Who should get top-down?

Early Crohn’s Disease (Moderate To Severe)
High risk for rapid progression to bowel damage and disability

Potential predictors from literature
- Early onset (<40 yrs)
- Small bowel involvement
- Perianal disease at diagnosis
- Endoscopic severe lesions

potential predictors in clinical practice
- Diagnosis age <40 yrs
- Extensive anatomic involvement
- Perianal or severe rectal disease
- Deep ulcers
- Prior surgical resection
- Restricting and/or penetrating behavior

YES
Early top-down IMM + TNF antagonist

NO
Accelerated step-care IMM + TNF antagonist

Fail to respond
TNF antagonist ± IMM

Management of Crohn’s disease: from the start

Mild Crohn’s disease
Budesonide (terminal ileum) or systemic steroids (colon)

Moderate Crohn’s disease without poor prognostic factors AND without disease complication
Steroids + azathioprine or methotrexate

Severe disease, complicated disease (presence of bowel damage) and/or poor prognostic factors
Anti-TNF therapy

Monitoring objective signs of inflammation at 6-9 months: endoscopy, cross-sectional imaging and/or fecal calprotectin

Vedolizumab First

**Pro**
- Better response in TNF-naïve
- Safety
  - No infection, cancer signals
  - Safe in MS, CHF
- Robust maintenance data
- Faster infusion (vs. IFX)

**Con**
- Lower rates of induction
- Longer time to effect
- IV only
- ?PML

Anti-TNF First

**Pro**
- Also better response in TNF-naïve
- Safety profile well-understood
- Efficacy in severe UC, fistulas, EIMs
- Flexible dosing (interval and dose)
- Possibility to use TDM
- SC available
- Rapid onset
- ?Better induction rates
- ?Biosimilars coming
- Three in class (opportunity for “cycling”)
- Track record in pregnancy

**Con**
- Safety
  - Cancer
  - Infection
  - CHF exacerbation
  - Psoriasiform skin lesions
  - Lupus-like reactions
Conclusion

• Risk stratification should lead to tailored selection of treatment for each patient
  – Careful appraisal of patient’s current and projected status
  – Good knowledge of each agent’s known risks and efficacy