Challenges in the management of elderly IBD patients

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• Shire: Grant/Research Support
• Takeda: Grant/Research Support
Case presentation

• 70 yo WM with a history of left sided UC diagnosed in 2011

• Treated initially with combination of oral and topical mesalamine with good results

• Experienced a flare in 2013
  - Responded to prednisone but developed recurrent symptoms after withdrawal
  - Started on azathioprine 100 mg; dose subsequently increased to 125 mg
    • Discontinued secondary to nausea and vomiting
Case presentation (cont.)

- Sigmoidoscopy (see photo)
- Pathology: Chronic active colitis with marked activity and ulceration; no CMV
Case presentation (cont.)

• Started on adalimumab; developed recurrent symptoms after withdrawal of steroids
• Prednisone increased to 40 mg daily and started on vedolizumab
  - After 4 months, unable to taper prednisone below 5 mg
  - Sigmoidoscopy still demonstrates active disease
Case presentation (cont.)

- **PMH**: HTN; Polio; Osteopenia
- **PSH**: Hernia repair 1950
- **Meds**: Amlodipine/valsartan 10-320 mg daily; aspirin 81 mg daily; cholecalciferol 400 units daily; HCTZ 12.5 mg daily; mesalamine 2.25 g daily; mesalamine 1000 mg pr daily; MVI; nebivolol 5 mg daily; prednisone 20 mg daily; vedolizumab 300 mg every 8 weeks
- **Social hx**: Former smoker; 9 glasses of wine per week; no drugs
Goals of therapy

- Induce clinical remission (absence of symptoms)
- Avoid short and long-term toxicity of treatment
- Enhance quality of life
- Maintain steroid-free remission
  - Avoid repeated courses of steroids!
- Induce “deep” remission
  - Biologic remission (normalization of biomarkers)
  - Mucosal healing
- Prevent complications (hospitalizations, surgery, etc)
CIS associated with higher rate of steroid-free remission in CD

Primary Endpoint

![Bar chart showing proportion of patients (%) for AZA + placebo, IFX + placebo, and IFX+ AZA groups.]

- AZA + placebo: 30.6%
- IFX + placebo: 44.4%
- IFX+ AZA: 56.8%

- p<0.001
- p=0.009
- p=0.022

AGA guideline on the use of TP, methotrexate, and anti–TNF-α biologic drugs for induction and maintenance of remission in CD

• We Suggest **Using Anti–TNF-α Drugs in Combination With Thiopurines Over Anti–TNF-α Drug Monotherapy to Induce Remission** in Patients Who Have Moderately Severe CD

  (Weak Recommendation, Moderate-Quality Evidence)

Dassopoulos, T, et al. (2013) Gastroenterology
Challenges in treatment of elderly IBD patients

• Comorbid medical conditions
  – History of prior malignancy
• Polypharmacy
• Increased risk for complications from immune suppressants and biologics
• Does elderly onset IBD have a different disease phenotype?
• Generally underrepresented in clinical trials of pivotal agents
How do you define elderly?

• Elderly (adjective)
  – (of a person) old or age
  – **Synonyms**: aged, old, advanced in years, aging, long in the tooth, past one’s prime, etc.
Most developed countries have accepted the chronological age of 65 years as a definition of 'elderly' or older person...... it is many times associated with the age at which one can begin to receive pension benefits. .....the UN agreed cutoff is 60+ years to refer to the older population.

.........there is no general agreement on the age at which a person becomes old. The common use of a calendar age to mark the threshold of old age assumes equivalence with biological age, yet at the same time, it is generally accepted that these two are not necessarily synonymous.
Contrast in elderly patients
Are there differences in disease phenotypes in older onset IBD?
Older patients with CD more likely to have isolated colonic disease

• Retrospective analysis of 467 adults with CD between 2004 and 2010
• 5% (n=22) diagnosed at age 60 years or greater
• Disease location
  - Ileal 20%
  - Colonic 55%
  - Ileocolonic 20%
  - Upper tract 5%
Less complicated disease phenotypes in elderly IBD patients

Age not independently associated with complicated disease behavior

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis</td>
<td></td>
</tr>
<tr>
<td>≥60 years</td>
<td>0.56 (0.21, 1.65)</td>
</tr>
<tr>
<td>&lt;60 years</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>Disease duration from diagnosis</td>
<td></td>
</tr>
<tr>
<td>&lt;10 years</td>
<td>0.44 (0.28, 0.68)</td>
</tr>
<tr>
<td>≥ 10 years</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>Disease location</td>
<td></td>
</tr>
<tr>
<td>Colonic (isolated)</td>
<td>0.15 (0.09, 0.25)</td>
</tr>
<tr>
<td>Other location</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>Perianal disease</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.70 (1.04, 2.77)</td>
</tr>
<tr>
<td>No</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>Family history</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.69 (0.42, 1.13)</td>
</tr>
<tr>
<td>No</td>
<td>1 (reference)</td>
</tr>
</tbody>
</table>
Disease course in elderly IBD

• French population-based cohort of elderly IBD patients (n=841)
• Inflammatory behavior (78%) and colonic disease location (65%) most common phenotype
• Probability of steroids, IS or anti-TNF at 10 years in CD 47, 27, and 9% respectively
• Probability of surgery at 10 years 32% in CD and 8% in UC respectively

Charpentier, C., et al. (2013). Gut
Are complications increased in elderly patients with IBD?
Characteristics of older hospitalized patients with IBD

- 25% of patients hospitalized in 2004 were ≥65 y
- Older patients less likely to have:
  - Fistulizing disease (4.0 vs. 8.8%, p<0.001)
  - Stricturing disease (4.0 vs. 5.8%, p=0.001)
- After adjustment for comorbidity, higher in-hospital mortality (OR 3.9, 95% CI 1.0-2.2)
- Elderly had increased LOS (1.7 days) after surgery and higher rates of CV complications (OR 2.3, 95% CI 1.1-4.5)
Colectomy associated with decreased mortality compared to medical therapy

- Evaluation of Medicare and Medicaid patients
- Mortality compared between 830 patients undergoing elective colectomy and 7541 matched patients pursuing medical therapy
- Improved survival in colectomy compared to medical therapy patients (HR 0.67, 0.52-0.87)
  - Benefit restricted to those 50 years and older (HR 0.60, 0.45-0.79)
  - Age ≥65 years not an effect modifier

Is medical therapy safe in elderly patients with IBD?
Anti-TNF associated with increased complications in the elderly

- 2475 patients treated with IFX and 604 treated with ADA at 16 referral centers
  - 95 patients 65 years of age or older
  - Two control groups: <65 years treated with anti-TNF and ≥65 not treated with anti-TNF

<table>
<thead>
<tr>
<th>Outcome</th>
<th>&lt;65 anti-TNF</th>
<th>≥65 anti-TNF</th>
<th>≥65 no anti-TNF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious infection</td>
<td>2.6%</td>
<td>11%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Cancer</td>
<td>0%</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Death</td>
<td>1%</td>
<td>10%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Is efficacy of anti-TNF decreased in elderly patient?

- Single center, retrospective study
- Elderly (≥65 years) on anti-TNF vs. younger (<65 years) vs. elderly on steroids/IS
- Response at 10 weeks lower in elderly than controls (68 vs. 89%, p<0.001)
- RR for adverse events 4.7 in elderly on anti-TNF
- Age ≥65 years and CCI >0 risk factors for malignancy and mortality regardless of class of medication

## Lymphoproliferative Disorders in IBD Patients Treated with Thiopurines

<table>
<thead>
<tr>
<th>At cohort entry</th>
<th>N</th>
<th># Lymphomas</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never exposed to thiopurines</td>
<td>10,810</td>
<td>6</td>
<td>Reference</td>
</tr>
<tr>
<td>On therapy with thiopurines</td>
<td>5,867</td>
<td>16</td>
<td>5.3 (2.0 – 13.9)</td>
</tr>
<tr>
<td>Previously discontinued thiopurines</td>
<td>2,809</td>
<td>2</td>
<td>1.0 (0.2 – 5.1)</td>
</tr>
</tbody>
</table>

Lymphoproliferative disorders are increased in the elderly with IBD

Risk of lymphoma is increased in older adults with IBD

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Lymphoma incidence (per 100,000)</th>
<th>NNH if RR =2</th>
<th>NNH if RR =3</th>
<th>NNH if RR =4</th>
<th>NNH if RR =5</th>
<th>NNH if RR =6</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-29</td>
<td>7.3</td>
<td>6897</td>
<td>4598</td>
<td>3448</td>
<td>2759</td>
<td>2299</td>
</tr>
<tr>
<td>30-39</td>
<td>9.5</td>
<td>5291</td>
<td>3527</td>
<td>2646</td>
<td>2116</td>
<td>1764</td>
</tr>
<tr>
<td>40-49</td>
<td>15.6</td>
<td>3205</td>
<td>2137</td>
<td>1603</td>
<td>1282</td>
<td>557</td>
</tr>
<tr>
<td>50-59</td>
<td>29.9</td>
<td>1672</td>
<td>1115</td>
<td>836</td>
<td>669</td>
<td>557</td>
</tr>
<tr>
<td>60-69</td>
<td>59.0</td>
<td>848</td>
<td>565</td>
<td>424</td>
<td>339</td>
<td>283</td>
</tr>
<tr>
<td>70-79</td>
<td>102.5</td>
<td>488</td>
<td>325</td>
<td>244</td>
<td>195</td>
<td>163</td>
</tr>
</tbody>
</table>

IS Associated with an Increased Risk of Incident Cancer

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted HR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age per 1-year increase</td>
<td>1.05</td>
<td>1.04-1.05</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>Ref</td>
<td>0.92-1.44</td>
<td>0.22</td>
</tr>
<tr>
<td>Male</td>
<td>1.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBD Subtype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UC or IBDU</td>
<td>Ref</td>
<td>0.81-1.30</td>
<td>0.82</td>
</tr>
<tr>
<td>CD</td>
<td>1.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Personal Hx of Cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Ref</td>
<td>1.25-2.97</td>
<td>0.003</td>
</tr>
<tr>
<td>Yes</td>
<td>1.92</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exposure to IS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Ref</td>
<td>1.34-2.13</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Yes</td>
<td>1.68</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Primarily TP’s (NMSC, lymphoma, and urinary tract ca)
IS associated with an increased risk of incident cancer in the elderly

Thiopurines and skin cancer

TP associated with an increased risk of NMSC in the elderly with IBD

Summary

• No precise definition of an elderly IBD patient
  – Physiology probably more important than chronology
• Older onset CD may be different (isolated colonic disease, less complications)
• TP and anti-TNF medications associated with increased complications in elderly IBD patients
• Colectomy associated with decreased mortality in older patients with UC compared to medical treatment
Conclusions

• Do not undertreat elderly patients with IBD
  – Poorly controlled disease and repeated courses of steroids are worse than TP and anti-TNF
• Avoid TP if possible in patients ≥60 years old
• Try to utilize monotherapy in elderly patients if possible
• Methotrexate or vedolizumab earlier in treatment course?
• Consider surgery earlier in treatment course?