Strategies for IBD patients in remission

Salem Khoury MD
Gastroenterology Dpt
Saint George Hospital
university medical centre
University of Balamand
LSGE 2014
Remission rates in IBD
In induction and maintenance therapy

CD

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Induction</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroids</td>
<td>60</td>
<td>0</td>
</tr>
<tr>
<td>AZA</td>
<td>71</td>
<td>0</td>
</tr>
<tr>
<td>MTX</td>
<td>70</td>
<td>39</td>
</tr>
<tr>
<td>Infliximab</td>
<td>45</td>
<td>32</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>43</td>
<td>26</td>
</tr>
</tbody>
</table>

UC

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Induction</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>5ASA</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Steroids</td>
<td>53</td>
<td>54</td>
</tr>
<tr>
<td>IMM</td>
<td>60</td>
<td>0</td>
</tr>
<tr>
<td>Biologics</td>
<td>33</td>
<td>0</td>
</tr>
</tbody>
</table>

Peyrin Biroulet L.  APT  Feb 2011
Managing patients in remission

Outline

• Anemia and Bone loss
• Infections and vaccination
• Skin cancer and lymphoma
• Drugs side effects
• Biomarkers
• Endoscopy and imaging
Anemia and IBD
Prevalence of anemia in IBD patients

ML Holvic  Ecco meeting OP 2013
Causes of Anemia in IBD

- Iron Deficiency
- Chronic Disease
- Bone marrow suppression
- Drug-induced hemolysis
- Vitamin B12 / folic acid deficiency

20% of Out-patients
60% of Hospitalized patients

Guidelines – ECCO 2013

• “Iron supplementation should be initiated when iron deficiency anemia is present, and considered when there is iron deficiency without anemia

• Intravenous iron is more effective and better tolerated than oral iron supplements

• Absolute indications for intravenous iron include severe anemia (hemoglobin < 10.0 g/dL), and intolerance or inadequate response to oral iron

• Intravenous iron should be considered in combination with an erythropoietic agent in selected cases where a rapid response is required”

One proposed algorithm for Iron supplementation
Bone loss in IBD
Osteopenia/Osteoporosis
Bone loss in IBD
Osteopenia/Osteoporosis

General risk factors

- Advancing age
- Female gender
- Family history
- Alcohol use
- White/Asian race
- Smoking
- Physical inactivity
- Low calcium intake
- Small and thin body habitus
Risk of Osteoporosis in IBD

• Low bone mass in 31% to 59% of IBD patients\textsuperscript{1-3}
• IBD-related risk factors\textsuperscript{4}
  – Onset of IBD before reaching age of peak bone mass
  – Inflammatory cytokines
  – Calcium malabsorption
  – Vitamin D deficiency (CD patients)
  – Drugs (corticosteroids)

Prevention and Treatment of Osteoporosis in IBD

• Prevention
  – Baseline and follow-up measurements of bone density (DEXA)
  – Assessment of Vit D levels
  – Lifestyle and nutritional measures (weight-bearing exercise, smoking cessation, vitamin D and calcium supplementation)
  – Possible HRT for high-risk postmenopausal women

• Treatment
  – Biphosphonates, Calcitonin, PTH

Infections

• Opportunistic infection
  – Infection by an organism which has limited pathogenic capacity in ordinary circumstances
  – Immunomodulators favor **viral infections**
  – Biologics favor **bacterial and fungal infections**
  – Risk increases with age, number of drugs and co-morbidities
Mayo Case-Control Study:
Age Associated with Opportunistic Infection

- **Age at first visit:**
  - 0 – 23: 1.0 (reference)
  - 24 – 36: 1.2 (0.5 – 2.8)
  - 37 – 49: 1.1 (0.5 – 2.5)
  - ≥ 50: 3.0 (1.2 – 7.2)

- **Number of drugs**
  - Odds Ratio (95% CI)  
    - 1 medication: 2.65 (1.45-4.82)  
    - ≥2 medications: 14.5 (4.9-43)

Steroids, AZA, MTX, Cys, Biologics.

Strategies in Bacterial infection

• More common in Biologic users than IMM
• The majority of infections are classic bacterial infections and C diff colitis.
### TABLE 1. Continue, Stop, or Restart Medications for Bacterial Infections

<table>
<thead>
<tr>
<th></th>
<th>Bacterial Mild</th>
<th>Bacterial Severe</th>
<th>Bacterial Opportunistic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Examples:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Escherichia coli</em> UTI</td>
<td>streptococcal pharyngitis</td>
<td>Pneumococcal pneumonia</td>
<td>Mycobacterium</td>
</tr>
<tr>
<td>Note:</td>
<td></td>
<td>Note:</td>
<td>Note:</td>
</tr>
<tr>
<td>Usually antibiotic</td>
<td></td>
<td>Every 5 yr pneumovax in adult patients</td>
<td>Latent TB—INH</td>
</tr>
<tr>
<td>responsive</td>
<td></td>
<td>with IBD</td>
<td>Active TB—3 drugs</td>
</tr>
<tr>
<td><strong>AZA/6MP</strong></td>
<td>Continue</td>
<td>Stop, but may restart once treated</td>
<td>Latent: do not start until 2 to 4 wk INH</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Active: stop, may restart after 1-mo treatment</td>
</tr>
<tr>
<td><strong>Anti-TNFs</strong></td>
<td>Continue</td>
<td>Stop, but may restart once treated</td>
<td>Latent: do not start until 2 to 4 wk INH</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Active: stop, only restart after full treatment, and if IBD is severe</td>
</tr>
</tbody>
</table>

INH, isoniazid; TB, tuberculosis; UTI, urinary tract infection.
Clostridium difficile Infection and IBD

Increasing number of hospitalizations in IBD patients with C. diff

- Prior AB use not necessary
- Pseudomembranes usually not present
- Always check in IBD patients with flares
- No need to stop immunosuppression †

†Swoger j. et al. Inflamm bowel dis May 2014
Fungal

• Candida
• Pneumocystis
• Histoplasma, Coccidiomycosis ...(specific for some geographic areas)
## TABLE 2. Continue, Stop, or Restart Medications for Fungal Infections

<table>
<thead>
<tr>
<th>Fungal Mild</th>
<th>Fungal Severe</th>
<th>Fungal Infection by Geography</th>
</tr>
</thead>
<tbody>
<tr>
<td>Examples:</td>
<td>Example:</td>
<td>Example:</td>
</tr>
<tr>
<td>Oropharyngeal or genital candida</td>
<td>Candida sepsis pneumocystis</td>
<td>Histoplasmosis—Ohio River Valley</td>
</tr>
<tr>
<td>Note:</td>
<td>Note:</td>
<td>Coccidiomycosis—Desert Southwest</td>
</tr>
<tr>
<td>Usually responsive to antifungal therapy</td>
<td>Consider PCP prophylaxis in triple</td>
<td>Note:</td>
</tr>
<tr>
<td></td>
<td>immunosuppression (steroid, 6MP,</td>
<td>Currently no screening recommendations</td>
</tr>
<tr>
<td></td>
<td>anti-TNF, or CYA)</td>
<td></td>
</tr>
<tr>
<td>AZA/6MP</td>
<td>Continue</td>
<td>Stop, restart once treated only if IBD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>severe</td>
</tr>
<tr>
<td>Anti-TNFs</td>
<td>Continue</td>
<td>Stop, restart once treated only if IBD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>severe</td>
</tr>
</tbody>
</table>

CYA, cyclosporine; PCP, pneumocystis jirovecii pneumonia.
Viral

- EBV
- VZV
- CMV
- HSV
- HPV
- HBV
Viral

- EBV: Lymphoma
- VZV: High risk of H.Zoster, Vaccinate prior to TTT
- CMV
- HSV
- HPV: Risk of cervical Ca, vaccinate prior to TTT
- HBV: If seronegative, vaccinate prior to TTT
  If seropositive, Preemptive TTT
  (1-3 weeks before)
EBV and Lymphoma

• Mainly with IMM
• 2 types
• Young males < 30 years, seronegative for EBV, after acute infection.
• Older patients >30 years, seropositive, after reactivation
• High index of suspicion, FUO, blood count, test for EBV IgM, IgG
Thiopurines, Lymphoma and EBV

Lymphoma Occurrence in IBD Patients Increased in the 8-year Period After Introduction of AZA and 6-MP

### TABLE 3. Continue, Stop, or Restart Medications for Viral Infections

<table>
<thead>
<tr>
<th>Viral Mild</th>
<th>Viral Moderate</th>
<th>EBV</th>
<th>CMV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Examples:</td>
<td>Examples:</td>
<td>2 scenarios:</td>
<td>3 scenarios:</td>
</tr>
<tr>
<td>&quot;Common cold&quot; viruses, for example, rhinovirus</td>
<td>Human papilloma, Varicella zoster, Influenza</td>
<td>-Acute infection, Mononucleosis and hemophagocytic lymphohistiocytosis</td>
<td>1. Colon bx +, but mild colitis (should receive anti-viral rx)</td>
</tr>
<tr>
<td>Note:</td>
<td>Note:</td>
<td>-Reactivation</td>
<td>2. Colon bx +, but severe ulcers</td>
</tr>
<tr>
<td>Supportive care</td>
<td>Vaccinate, avoid live zovirax in immunosupp</td>
<td>Note: Males more susceptible to severe infections and lymphoma</td>
<td>3. Colon bx and blood + for CMV (should receive anti-viral rx)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AZA/6MP</th>
<th>Continue</th>
<th>Stop</th>
<th>Stop, do not restart in male patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-TNFs</td>
<td>Continue</td>
<td>Continue, unless severe sequelae</td>
<td>Continue, unless severe sequelae or viremia</td>
</tr>
</tbody>
</table>

bx, biopsy; rx, treatment; immunosupp, immunosuppressant.
HPV and cervical cancer

- Women with IBD under IMM,
- higher prevalence of abnormal Pap smear (42.5% vs 7% controls)
- Vaccination before or under TTT
- Annual Pap smear surveillance
Strategy for vaccination

• Check for childhood vaccination
• 5 important vaccines

• VZV/Varicella vaccine : Prior to therapy

• HPV, HBV
• Influenza vaccine (non live) yearly
• Pneumococcal vaccine once and booster 3-5y

During therapy
Cancer

• Non melanoma skin cancer (NMSC)

• Lymphoma
Past and current Thiopurine exposure increases the risk for NMSC

Peyrin-Biroulet. Gastroenterology 2011
Risk of NMSC in IBD patients exposed to biologics

<table>
<thead>
<tr>
<th>Biologic</th>
<th>Risk estimate</th>
<th>Biologics increase the risk of NMSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long et al, <em>CGH 2010</em></td>
<td>IFX/ ADA in CD</td>
<td>Recent use (≤90 days): (1\text{OR} 2.07) (95%CI 1.28-3.33)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Persistent use (&gt;365 days): (1\text{OR} 2.18) (95%CI 1.07-4.46)</td>
</tr>
<tr>
<td>Long et al, <em>Gastroenterology 2012</em></td>
<td>IFX/ ADA/ CZP in IBD</td>
<td>Any use (1\text{OR} 1.14) (95%CI 0.95-1.36)</td>
</tr>
<tr>
<td>Burmester et al, <em>Ann Rheum Dis 2013</em></td>
<td>ADA in CD</td>
<td>SIR 2.29 (95%CI 1.44-3.47)</td>
</tr>
</tbody>
</table>

1 – adjusted OR
What about combination therapy?

<table>
<thead>
<tr>
<th>Medication</th>
<th>NMSC cases (n = 1895) n (%)</th>
<th>Controls (n = 8914) n (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No immunosuppressant</td>
<td>1587 (83.8)</td>
<td>8290 (93.0)</td>
<td>Referent</td>
</tr>
<tr>
<td>Any thiopurine alone</td>
<td>265 (14.0)</td>
<td>484 (5.4)</td>
<td>2.72 (2.27-3.26)</td>
</tr>
<tr>
<td>Any biologic alone</td>
<td>74 (3.9)</td>
<td>181 (2.0)</td>
<td>1.63 (-2.36)</td>
</tr>
<tr>
<td>Combined thiopurine and biologic</td>
<td>31 (1.6)</td>
<td>40 (0.5)</td>
<td>3.89 (2.33-6.46)</td>
</tr>
</tbody>
</table>

“In a sub-analysis, combined use of thiopurines and biologics >1 year was associated with the greatest increased NMSC risk”

Long et al, Gastroenterology 2012
Lymphoma

2 types:

• EBV related lymphoma
• Hepatosplenic T cell lymphoma
LYMPHOPROLIFERATIVE DISORDERS, THIOPURINES USE AND IBD

Beaugerie and Cesame group Lancet 2009
Biologics and Lymphoma

0.61 per 1000 p-y of exposure

Siegel C. Clin Gastroenterol Hepatol 2009;7:874-81
Hepatosplenic T cell Lymphoma

- 5% of peripheral T-cell lymphoma
  - Rare, males<20y, fatal
  - Thiopurine alone 17
  - Anti-TNF alone 1
  - Combination therapy 23
- Median time since initiation of thiopurines ~6 years

Lymphoma in IBD

There is an increased risk of lymphoma in IBD

The lymphoma risk is increased by IMM therapy

Less with Biologicals

Concomitant immunosuppressive therapy ( IMM + BIO) seems to enhance the risk

Lymphoma risk related to EBV status

When justified, the benefit of IS therapy outweighs the risk of malignancies in IBD
Decreasing the malignancy risk

- Cervical ca: gynecological screening, HPV status, HPV vaccination, Pap-smear 1x/year
- Skin: Life long risk. Sun protection, self-monitoring, skin exam every 2 years
- EBV-screening, EBV DNA status if suspicion of lymphoma (FUO)
Monitoring drug side effects

- AZA/6MP
- Methotrexate
Monitoring drug side effects

- AZA and bone marrow suppression
- Leucopenia, Thrombocytopenia and anemia

Table 2. Frequency of leucopenia in IBD patients treated with thiopurine drugs

<table>
<thead>
<tr>
<th>Author</th>
<th>No patients</th>
<th>Number of leucopenia requiring drug withdrawal (%)</th>
<th>Definition of leucopenia</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ansari5</td>
<td>106</td>
<td>2 (1.9)</td>
<td>N&lt;2.0</td>
<td>0</td>
</tr>
<tr>
<td>Schwab9</td>
<td>93</td>
<td>4 (4.3)</td>
<td>WCC&lt;3.0</td>
<td>0</td>
</tr>
<tr>
<td>Connell10</td>
<td>739</td>
<td>28 (3.8)</td>
<td>WCC&lt;3.0</td>
<td>2</td>
</tr>
<tr>
<td>Fraser11</td>
<td>622</td>
<td>21 (3.4)</td>
<td>WCC&lt;3.0</td>
<td>0</td>
</tr>
<tr>
<td>Present12</td>
<td>396</td>
<td>8 (2)</td>
<td>WCC&lt;2.5</td>
<td>0</td>
</tr>
<tr>
<td>Bouhrin13</td>
<td>157</td>
<td>3 (1.9)</td>
<td>WCC&lt;3.0</td>
<td>0</td>
</tr>
<tr>
<td>Qasim14</td>
<td>110</td>
<td>5 (5.5)</td>
<td>WCC&lt;3.0</td>
<td>0</td>
</tr>
<tr>
<td>Katsanos15</td>
<td>740</td>
<td>14 (6.1)</td>
<td>WCC&lt;3.9</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>2223</td>
<td>71 (3.2)</td>
<td></td>
<td>2</td>
</tr>
</tbody>
</table>
Blood surveillance in patients receiving thiopurines

- Full blood counts
  - Every week for 4 weeks,
  - Then, every 3 months
  - If WBC <3500 reduce dose
  - If WBC <3000 Stop

Avoid drug interaction with Allopurinol
Methotrexate, CD and Liver Toxicity

Rare in CD pts
Risk factors:
  – Diabetes type 2
  – Overweight
  – Alcohol
  – Virus B or C
• Monitor Liver tests every 3 months
• If Transaminases increase, Check every 1 month
• If Transaminases 3 ULN, STOP MTX
• Liver Biopsy:
  - If persistent Transaminases elevation
  - After 1.5 gr or 2 years of TTT if TTT is to be continued

  Remember daily folic acid

Cunliffe, Scott  APT 2002
Biomarkers in remission

• CRP level
• Fecal markers: Calprotectin, Lactoferrin.
• Proposed roles:
  To assess mucosal healing
  To distinguish IBS from IBD flares
  To predict relapse
  Before deescalating or stopping therapy
Biomarkers in remission

CRP level: Better correlation with CD than UC

Jurgens M at Al  Clinical Gastroenterology and Hepatology 2011
### Value of Calprotectin in IBS and IBD

#### Table 3

Sensitivity and specificity at different cut-off ranges to distinguish IBS from IBD and IBD in remission compared with active disease

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBS vs IBD at FC 50 µg/g</td>
<td>87.5</td>
<td>77.7</td>
<td>79.2</td>
<td>86.5</td>
</tr>
<tr>
<td>IBS vs IBD at FC 100 µg/g</td>
<td>97.2</td>
<td>76.3</td>
<td>75.3</td>
<td>97.4</td>
</tr>
<tr>
<td>IBD remission vs active at FC 50 µg/g</td>
<td>55.2</td>
<td>98.9</td>
<td><strong>97.0</strong></td>
<td>77.4</td>
</tr>
<tr>
<td>IBD remission vs active at FC 100 µg/g</td>
<td>72.4</td>
<td>95.6</td>
<td>91.3</td>
<td>84.3</td>
</tr>
<tr>
<td>IBD remission vs active at FC 250 µg/g</td>
<td><strong>89.7</strong></td>
<td>75.6</td>
<td>70.3</td>
<td><strong>91.9</strong></td>
</tr>
</tbody>
</table>

FC, faecal calprotectin; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; NPV, negative predictive value; PPV, positive predictive value.

Dhaliwal A et al. Frontline Gastroentero-2013
Value of Calprotectin for prediction of relapse in CD

Figure 3 Kaplan–Meier (K–M) cumulative event curves of time to relapse in days for the 92 patients, stratified by whether their FC was below or above 240 μg/g.

Biomarkers

• To assess mucosal healing (mainly under Bio)
• Repeat CRP every 4 weeks till normalization than q 3 months
• Repeat fecal biomarkers q 4 weeks till normalization
• No fecal markers follow up except in recurrent symptoms, changing or stopping therapy.
Endoscopy and imaging

• To assess mucosal healing with biologics:
  6 months after starting
• Before stopping or downgrading therapy
• No role for routine tests
In conclusion

• Monitoring IBD patient in remission is crucial
• Correct anemia and treat osteoporosis
• Vaccinate prior to therapy
• Vaccinate on therapy:
  Influenza, Pneumococcus, HBV, HPV
• Be vigilant for infection: EBV, TB ...
• Be vigilant for lymphoma detection
• Prevent cancers: NMSC, Cervical cancer
• Avoid drug toxicities and drug/drug interaction
• Do not overuse biomarkers, endoscopy and imaging
Thank you