Adverse effects of IBD therapies: how medications work and what could happen while taking them

Christina Ha, MD
Center for Inflammatory Bowel Diseases
David Geffen School of Medicine at UCLA
Treatment Goals for IBD

Induction of Remission

Goals:
• Provide relief of GI symptoms
• Promote mucosal healing
• Treat complications
• Improve quality of life

Maintenance of Remission

Goals:
• Maintain remission (absence of symptoms and maintenance of healed mucosa)
• Minimal adverse effects and adherence to therapy
• Maintaining quality of life
• Avoid hospitalizations and surgeries

Most patients will require maintenance therapy to sustain remission
The Traditional IBD “Medicine Cabinet”

- Over-the-Counter
- Antibiotics
- Aminosalicylates
- Corticosteroids
- Immunomodulators
- Biologics

Slide courtesy of the CCFA
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5-ASAs: commonly reported adverse effects

- Headache
- Muscle or joint pain
- Nausea/vomiting
- Heartburn
- Burping/gas/bloating
- Constipation
- Slight hair loss
- Diarrhea.

Consider:
Electrolytes deficiencies:
- Potassium, Magnesium
- Can be associated with muscle cramps, bloating/cramping,
Foods rich in magnesium and potassium

- Leafy greens (Mg, K)
- Nuts and seeds (Mg)
- Fish (Mg, K)
- Beans/lentils (Mg, K)
- Whole grains/Brown rice (Mg)
- Avocados (Mg, K)
- Dark Chocolate (Mg)
- Bananas (Mg, K)
- Low fat dairy – e.g yogurt (Mg, K)
- Dried fruit – e.g figs (Mg, K)
- Squash (K)

Not always compatible with a low-residue diet

Magnesium supplements may have a laxative effect
5-ASAs: common adverse effects

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- Constipation
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Consider:

Vitamin/Minerals - Check iron, B12, folate, Zinc levels

- **Iron deficiency** may be associated with headaches, numbness, restless legs, fatigue, weakness, hair loss
- **Folic acid deficiency** may be associated with loss of appetite, diarrhea, irritability
- **B12 deficiency** may be associated with diarrhea, fatigue, swollen tongue
- **Zinc deficiency** may be associated with hair loss, eczema-like rash
5-ASA hypersensitivity

- Sulfasalazine – up to 30% of patients are sensitive to the sulfa component
  - Symptoms include nausea/vomiting, diarrhea, rashes
- Mesalamines/5-ASAs can also be associated with worsened symptoms of colitis.
  - If continued/worsened symptoms while on these agents, consider discontinuation
Help! There are tablets in my stool!

- Can occur with *delayed-release tablets*
- May be a factor of rapid gut transit
- Pills may not be readily dissolved to absorb in the colon
- If this happens frequently, may need to consider a different formulation of medication

Is this weird? My toilet bowl is stained purple...

- Can occur with mesalamine enemas, occasionally tablets/suppositories
Safety Considerations of 5-ASA Agents: A Focus on Renal Function

- Nephrotoxicity – impacts kidney function
  - UNCOMMON → 0.26% per patient-year
  - Most often reported within the first 12 months of therapy¹
  - Caution recommended when used in patients with known (or history of) renal disease²,³
  - FDA recommends monitoring **blood urea nitrogen (BUN)/serum creatinine**

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How do corticosteroids work?

- Prevent the production of multiple inflammatory proteins by blocking the genes that encode them
- Turn activated inflammatory genes “off”
- May also activate anti-inflammatory genes
- Degrade inflammatory proteins

Potential adverse effects to STEROIDS

- GI upset
- Nausea
- Fatty liver
- Osteoporosis
  - Bone density testing recommended
  - Avascular Necrosis
  - Myopathy
- Glaucoma
- Cataracts
- Adrenal insufficiency
- Diabetes
- Palpitations
- Hypertension
- Swelling
- Moon facies
- Abdominal striae
- Easy bruising
- Adrenal insufficiency
- Sleep disturbances, psychiatric effects
- Hyperactivity, increased appetite

Infection - Impact of vaccinations

Sleep disturbances, psychiatric effects
Hyperactivity, increased appetite
How do thiopurines work?

Purines: framework for two of the four bases that occur in DNA

Thiopurines: Block production of purines
  • Blocks production of immune cells
  • Deactivate processes that lead to more inflammation
  • Increased lymphocyte apoptosis: “programmed cell death”
    – Excess # of activated lymphocytes in IBD
Potential adverse effects to THIOPURINES

- **Drug reaction:** Fever, rash, arthralgias, myalgias
- **GI disturbances**
- **Hepatotoxicity**
  - Usually presents as abnormal liver tests
  - Routine lab monitoring required
- **Infection**
  - Impact of vaccinations
- **Pancreatitis**
- **Bone marrow Suppression**
  - Usually the White blood count
  - Routine lab monitoring required
- **Skin cancers, Lymphoma**
  - Sun protection
  - Dermatology exams
  - Routine follow-up

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Hair loss

Overall incidence rates among current thiopurine users = 9 per 10,000
• Hazard ratio thiopurine exposed vs naïve = 5.3 (2.0-13.9)

Adapted from Cosnes et al. Lancet. 2010.
Thiopurines & Lymphoma

Overall incidence rates among current thiopurine users = 9 per 10,000

• Hazard ratio thiopurine exposed vs naïve = 5.3 (2.0-13.9)

- 18/23 (78%) diagnosed with lymphoma were over 50 yrs old
- 10/18 (65%) current thiopurine use (range 1-10 yrs)

Risk factors for LPD:

• **OLDER AGE** (OR 1.06 per 1-year increase)
• **DURATION OF IBD** (OR 1.04 per 1-year increase)
• **CONTINUED THIOPURINE THERAPY** (OR 5.28)
Hepatosplenic T-cell lymphoma: 36 cases reported as of 2010

- Low **ABSOLUTE** risk (best estimates $<1: \approx 22,000$)
- Majority young males $<35$ years old
- Most patients on combination therapy but more likely to be related to duration of thiopurine exposure

\[\text{A} \quad \text{Thiopurine exposure in combination therapy} \]

\[\text{B} \quad \text{Thiopurine exposure in thiopurine monotherapy} \]

Kotlyar et al. CGH, 2011.
Skin cancer risk and IBD therapies

Non-melanoma skin cancer

Melanoma

<table>
<thead>
<tr>
<th></th>
<th>IBD overall</th>
<th>Crohn’s disease</th>
<th>Ulcerative colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-ASA</td>
<td>1.1 (0.8-1.5)</td>
<td>0.98 (0.6-1.5)</td>
<td>1.2 (0.8-2.0)</td>
</tr>
<tr>
<td>Thiopurines</td>
<td>1.1 (0.7-1.7)</td>
<td>0.9 (0.5-1.6)</td>
<td>1.3 (0.7-2.6)</td>
</tr>
<tr>
<td><strong>Biologics</strong></td>
<td><strong>1.9 (1.1-3.3)</strong></td>
<td><strong>1.9 (1.0-3.7)</strong></td>
<td>1.7 (0.5-5.6)</td>
</tr>
</tbody>
</table>

How do anti-TNF medications work?

- TNF – tumor necrosis factor is an activator/regulator of inflammation
  - Important for cell to cell communication
  - Directs the production of pro-inflammatory molecules
- Anti-TNF therapies bind tightly to TNF molecules, blocking communication pathways that stimulate the production of destructive molecules by immune cells
How does Vedolizumab work?

- Blocks the interaction between $\alpha_4 \beta_7$ and MAdCAM-1
  - This interaction allows for lymphocyte adhesion and trafficking through the blood vessel to the target sites

Potential adverse effects of BIOLOGICS

- Autoimmunity (lupus, psoriasis)
- Immunogenicity
- Congestive heart failure
- Hepatotoxicity
- Hair loss
- Demyelinating disease (e.g. multiple sclerosis)
- Infusion reactions, injection-site reactions
- Bone marrow suppression
- Infection - Impact of vaccinations
- Skin cancers, Lymphoma
  - Sun protection
  - Dermatology exams
  - Routine follow-up

PML, progressive multifocal leukoencephalopathy

Dermatologic side effects of biologic therapy

- **Psoriasis**
  - Female predominance
  - Estimated incidence of 1:1000 patient-years
  - 50% of patients are able to continue TNF therapy with the use of treatment for psoriasis
Drug-induced lupus due to anti-TNF therapies

- Syndrome of characteristic lupus symptoms (arthralgias, myalgias, fevers, serositis) temporally associated with the anti-TNF therapy
- Uncommon – 0.5-1% of treated patients

# Recommended vaccinations for IBD patients on immunosuppression

<table>
<thead>
<tr>
<th>Vaccination</th>
<th>Recommended schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetanus</td>
<td>Initial dose with booster every 10 years</td>
</tr>
<tr>
<td><strong>Influenza trivalent (inactivated) vaccine</strong></td>
<td>Annually</td>
</tr>
<tr>
<td><strong>Pneumonia vaccine (PPSV23 &amp; PCV13):</strong></td>
<td></td>
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<tr>
<td>PCV13 (Prevnar), PPSV23 (Pneumovax) →</td>
<td>superior efficacy than PVX alone</td>
</tr>
<tr>
<td>PPSV23: Initial vaccine at age 2+ years with</td>
<td></td>
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<tr>
<td>revaccination 5 years later</td>
<td></td>
</tr>
<tr>
<td>PCV13: 8 weeks before or 1 year after PPSV23</td>
<td></td>
</tr>
<tr>
<td>HPV vaccination series</td>
<td></td>
</tr>
<tr>
<td>• Women and men aged 9-26 years</td>
<td></td>
</tr>
<tr>
<td>• Men who have sex with men</td>
<td></td>
</tr>
<tr>
<td>• Immunocompromised</td>
<td></td>
</tr>
<tr>
<td>Hepatitis A and B</td>
<td>Check titers if prior vaccination history</td>
</tr>
<tr>
<td>Meningococcal vaccine</td>
<td>College age, military, asplenic, travel to endemic country</td>
</tr>
<tr>
<td>Varicella (live vaccine)</td>
<td>• If no evidence of immunity</td>
</tr>
<tr>
<td></td>
<td>• no or low-level immunosuppression only</td>
</tr>
</tbody>
</table>

Hair loss with IBD

- Vitamin/mineral deficiencies: Iron, B6, B12, Zinc
- Medication effect
  - 5-ASAs, thiopurines, anti-TNF therapies, steroids
  - Psoriasis associated alopecia
  - Drug-induced lupus
Hair loss with IBD

- Telogen effluvium – due to change in the number of hair follicles of growing hair
  - Decreased # of hair follicles producing hair results in an increased # of dormant/resting hair follicles
  - Results in shedding
  - Seen in chronic disease states, usually transient

- Autoimmune conditions associated with IBD
  - Alopecia areata
The Traditional IBD “Medicine Cabinet”

- **Over-the-Counter**
- **Antibiotics**
- **Aminosalicylates**
- **Includes CAM therapies, Anti-diarrheals, NSAIDs (ibuprofen, naproxen)**
- **Biologics**
Up to 60% of patients with IBD use CAM\(^1\)

Two most common reasons IBD patients use CAM\(^2\)

- Wanted greater sense of control of self and their IBD
- Lack of efficacy or side effects from conventional therapy

- Not regulated by the Food and Drug Administration
- Only a handful have been studied in a controlled clinical trial setting
- Efficacy based on mostly anecdotal evidence
- No adverse event reporting system, no registries for safety
- Uncertain potential for interactions with other medications

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Weigh the Risks and Benefits of CAM

**Pros:** Can provide benefit when used as *adjunctive* therapy, restores some sense of control.

**Cons:** *Adverse effects not known*, expense (most not covered by insurance), optimal dosing may not be known, *not FDA-regulated*.

**Takeaways**
- Important to seek out good data to minimize potential risk
  - Choose well-researched options
  - Consider the qualifications of the information resource

Alternative therapies should complement, not replace, traditional therapies.

*Tell your doctor everything you are taking!!*
Questions to ask your healthcare team about IBD & medications...

- Where is my IBD located, how severe is it?
- What are my treatment options?
- Why do you recommend this medication(s)?
- What is the likelihood I will respond to this medication(s) given my level of disease activity?
- When and how will I know if it’s working or not?
- How should this medication be stored and taken?
- Are there potential side effects? What should I look out for? When should I contact you?
- Are there any medication interactions?
- How do we monitor for adverse effects?