Can I Stop My IBD Therapy?

Or, **Should** I Stop My IBD Therapy?

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Disclosures

• None
Outline

• Goals of IBD therapy
  • Short-term
  • Long-term

• Rationale for maintenance of therapy

• Stopping IBD therapy
Definitions

• IBD therapy to be discussed:
  • Azathioprine (immunomodulatory therapy)
  • Anti-TNF therapy (infliximab [Remicade], adalimumab [Humira], certolizumab [Cimzia], golimumab [Simponi])

• Discussion → people whose disease has been severe enough to require initiation of one or more of the above therapies

• More data for Crohn’s than UC but similar concepts
The Perfect Therapy

• No side effects
• Universally effective
• Easy to administer
• Cheap
• Readily available
Goals of Therapy

• **Short-term goals**
  • Alleviate symptoms (achieve remission)
  • Taper off of more harmful medications (i.e. steroids)

• **Long-term goals**
  • Prevent disease complications
    • Surgery
    • Hospitalizations
    • Cancer (?)
Remission: Types

• Clinical

• Endoscopic

• Histologic
Clinical Remission

• In research, clinical remission is strictly defined

• In practice, means:
  • Little to no symptoms
  • Good quality of life
  • Off steroids

• In people (irrespective of therapy) with CD, 1 year of clinical remission → 80% chance of remission the following year

• On anti-TNF therapy, approx. 60% of people in remission at 1 year sustain remission the following year

Panaccione et al., APT 2013
Munkholm et al., Scand J Gastro 1995
Endoscopic Healing

• “Deep” remission

• Absence of visible endoscopic inflammation

• Clinical remission ↑ 4x at 4 years (CD)

• Also 4x ↑ chance of continued remission at 1 year in UC

Baert et al., Gastroenterology 2010
Meucci et al., IBD 2012
De Chambrun et al., Nat Rev Gastro 2010
Histologic Remission

- “Normal” appearing under the microscope
- Poorly defined
- May predict better outcomes in UC beyond endoscopic healing alone (less colon cancer, e.g.)
- Very little data/difficult to define in Crohn’s

Bryant et al., J Crohn’s Colitis 2014
Long-Term Goals: Disease Behavior

Baumgart et al., Lancet 2012
Long-Term Goals: Change Disease Behavior

Magro et al., AJG 2014
Rationale for Maintenance Therapy

• The “party-line” when starting therapy for Crohn’s or UC beyond steroids is that treatment needs to continue indefinitely

• Why?
  • Treat to resolution of symptoms then observe?
  • Treat intermittently?
Episodic Dosing: Problems

• ACCENT I (pivotal trial of infliximab for Crohn’s)
• 3 groups: episodic treatment and two maintenance treatment arms
• In all domains, maintenance treatment arm did better
• Why?
  • Much higher rate of resistance (antibody formation) with episodic dosing (3-5x higher)
  • Antibody formation associated with loss of response and increased likelihood of adverse reactions to treatment

Hanauer et al., Lancet 2002
Episodic Dosing: Problems

• Another early Remicade study looked at risk of developing anti-infliximab antibodies
• Treatment involved giving a single dose and repeating when symptoms recurred
  • Current standard is doses at 0, 2 and 6 weeks → less likely to form antibodies
• Rate of antibody formation was about 60% after 5 doses
  • Giving azathioprine at the same time lowered antibody formation

Baert et al., NEJM 2003
Episodic Dosing: Problems

• **Mesalamine for UC**
  - Non-adherence to dosing → 5-fold increased risk of disease flare compared to maintenance users with >80% adherence
  - Risk of flare about 40% at 1 year with mesalamine non-adherence

• **Azathioprine**
  - Efficacy correlates with by-product levels in the bloodstream, which can be measured
  - Poor adherence → lower levels → less effective overall

Kane et al., Am J Med 2003
Maintenance Therapy: Conclusions

In general, maintenance therapy is indicated to:

- Prevent disease from recurring
- Prevent resistance to treatment from emerging
- Prevent long-term consequences of persistent or recurrent disease activity
  - Increased steroid use
  - Hospitalization
  - Surgery
So, Can I Stop Therapy?

• **Any discussion about stopping ongoing IBD therapy should be undertaken with careful discussion with your gastroenterologist!**

• The following discussion assumes that the person who wishes to discuss cessation of therapy is in clinical remission

• Will not cover people who have absolute indications to stop therapy
  • Severe or rare infections
  • Cancer
Why Stop Therapy?

- Concern regarding long-term side effects
- Cost of medications
- Inconvenience of medications
- Desire to try alternative therapies
- Development of side effects or contraindications to therapy
- Pregnancy
- Post-surgery (Crohn’s: special circumstances)
Scenarios

1. On both azathioprine and biologic therapy → stop azathioprine
2. On both azathioprine and biologic therapy → stop biologic
3. On azathioprine alone → stop therapy
4. On biologic alone → stop therapy
5. Pregnant → temporarily stop therapy
6. Crohn’s with small bowel resection → ? stop therapy
Scenario 1: Biologic + AZA, stop AZA

- In one small study, no difference in the rate of resistance to Remicade (infliximab) after azathioprine stopped, over 2 years
  - **BUT** this was after, on average, 2 years of combination therapy

- Factors that may predict better outcome if stopping azathioprine:
  - Combination therapy for > 2 years
  - C-reactive protein (marker of inflammation) normal
  - Normal platelet count (another marker of inflammation)

- Azathioprine can be added back if resistance to infliximab (Remicade) develops to restore response

Van Assche et al., Gastroenterology 2008
Oussalah et al., AJG 2010
Ben-Horin et al., CGH 2013
Why Stop Azathioprine?

• Infection risk unchanged on combo therapy
• Lymphoma (blood cancer) risk does increase with long term use of azathioprine
  • **BUT** absolute risk is low → 1 extra case of lymphoma per every 4,500 people per year under age 30
• Risk of hepato-splenic T cell lymphoma associated with azathioprine use over time
  • **BUT** only 36 reported cases with Crohn’s and 9 with UC as of 2013 AND almost all cases >2 years of azathioprine use

Kotylar et al., CGH 2014
Deepak et al., AJG 2013
Kotylar et al., CGH 2011
Lichtenstein et al., AJG 2012
Scenario 2: Combo therapy, stop biologic

- Based on one trial of Crohn’s patients in clinical remission for at least 6 months, after 1 year of combo therapy, stopping Remicade (infliximab) and continuing azathioprine:
  - 44% relapsed within 1 year
  - 52% relapsed within 2 years
  - Factors predictive of relapse:
    - Male sex
    - No prior history of surgery
    - Elevated white blood cell count or low red blood cell count
    - Elevated C reactive protein or fecal calprotectin (both markers of inflammation)
    - People with <2 of these factors had a relapse rate of 15%
  - Nearly everyone who relapsed successfully re-started Remicade

Louis et al., Gastroenterology 2012
Scenario 2: Combo therapy, stop biologic

- Another study showed that when biologic therapy is stopped after 1 year of clinical remission (in a group mostly also on azathioprine), 45% will relapse within another year (average 6 months)
  - Of those who re-started, only about 50% achieved remission again, and 10% needed surgery
- Factors predictive of relapse:
  - Previous biologic dose adjustment
  - Having been on >1 biologic
  - Smoking

Molnar et al., APT 2010
Scenario 3: Stopping AZA alone

- About 20% chance of relapse when stopping AZA with Crohn’s in remission at 1 year
  - Elevated C-reactive protein predicts relapse
- Risk in UC is about 12-36% at 1 year
- Long term rates of relapse off AZA in both CD and UC approaches 50-60% at 5 years
- Re-introduction of AZA successful in about 70%, but steroids required in over half to achieve remission again

Kennedy et al., APT 2014
Lemann et al., Gastroenterology 2005
Cassinotti et al., AJG 2009
Treton et al., CGH 2009
Scenario 4: Stopping biologic alone

• Little to no data to guide this decision

• In most of these studies, people remained on azathioprine or other immunosuppressive medications

• Rate of relapse would be at least as high as that already noted, if not higher
Scenario 5: Pregnancy

• No association between anti-TNF agent exposure and birth defects or adverse delivery outcomes (e.g. pre-term delivery)

• All currently available biologic agents aside from Cimzia (certolizumab) cross the placenta

• Pregnancy → risk of flare for some women with IBD
  • Active IBD → risk of pre-term delivery and low birth weight

• Re-introduction of therapy after pregnancy usually successful if disease in remission before stopping (80% response at 1 year)

Baert et al., CGH 2014
Scenario 6: After surgery

- Unique situation for people with Crohn’s disease

- Scenario: Disease limited to the ileum, undergoing resection of all active areas of disease due to obstruction
  - Do you need to restart therapy after surgery?

- After surgery, initial evidence of recurrent disease seen in 70% of people at 1 year (85% at 3 years)
  - Symptoms will be present in about 20%
  - Severe recurrence seen by colonoscopy $\Rightarrow$ nearly 100% will develop symptoms
  - Risk of second surgery $\Rightarrow$ about 25-30% at 5-10 years

Rutgeerts et al., Gastroenterology 1990
Frolkis et al., AJG 2014
Scenario 6: After surgery, cont.

• Using Remicade (infliximab) after surgery leads to low rate of endoscopic recurrence (10% at 1 year)
  • Larger study ongoing to confirm this

• Risk factors for post-surgery recurrence
  • Smoking
  • Surgery for fistula (as opposed to obstruction)
  • Personal history of multiple surgeries

Regueiro et al., Gastroenterology 2009
The One (or 15) Percenters

• There is a subset of IBD patients who sustain long-term remission off therapy after initially severe disease
  • Why?
  • How do we identify these people?
  • Future direction of active research
Conclusions

- A decision to stop or de-escalate therapy **must** be individualized.

- Must have back-up plan if/when symptoms return:
  - If decision to stop is based on concerns about risks of therapy, **share these concerns with your gastroenterologist**!

- De-escalating combination therapy may be reasonable:
  - Complete cessation of all IBD therapy typically **not** advisable.

- Ideal candidate to consider this:
  - Clinical and endoscopic remission
  - Tolerated therapy well (no dose escalation needed)
  - Non-smoker
  - Normal labs
  - At least 2 years in remission