Past, Present and Future Treatment of IBD

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Adam S. Cheifetz, MD

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Research support: Inform Dx
Talk Overview

1. Discuss how we can optimize the treatment of IBD through personalization of care and earlier treatment with effective agents
2. Discuss the goals of care in IBD and how they are evolving
3. Briefly review the medical therapies available for IBD
4. Learn how we choose the first agent in new onset IBD
5. Understand the preventive care that is warranted in the patient with IBD
Clinical pearls (for the non-GI)

When to refer to Gastroenterology
- Rectal bleeding / iron deficiency anemia
- Night time symptoms
- Unintentional weight loss
- Strong family history of IBD or colon cancer

Patient with known IBD with GI symptoms
- Never assume symptoms are a flare of IBD
- Always rule out infection
- Assess for triggers of IBD (nsaids, noncompliance, infection, stress)
Optimizing and Personalizing the Treatment of IBD

• Treat smarter (predict who will have aggressive disease)
• Treat earlier (with effective therapy)
• Treat deeper (mucosal healing)
• Treat to target
• Treat more effectively (proactive TDM)
Why talk about IBD?

- At least 1.6 million cases estimated in US
  - Divided equally between UC and Crohn’s disease
- Approximately 10,000 new cases diagnosed annually
- Onset at any age, but peak incidence is in late adolescence and early adulthood
- Chronic destructive diseases
- Huge impact on QOL

Hanauer S, NEJM 1996;334(13):841-848
Rogers et al, Journal of Chronic Disease 1971;24:743
(Idiopathic) Inflammatory Bowel Disease

Ulcerative Colitis
- Small intestine is NOT involved
- Mucosal disease
- Rectal involvement
- Continuous

Proctitis  Left-sided Colitis

Pancolitis

Crohn’s Disease
- “Mouth to anus”
- Transmural
- Rectal sparing
- Skip lesions

Upper GI 5%
Ileocolic 50%
Perianal 33%
Small bowel 30%
Colon 20%
Crohn’s disease is progressive and destructive

Progression of Digestive Damage and Inflammatory Activity in a Theoretical CD Patient

From controlling disease activity in terms of clinical symptoms and inflammatory markers
To preventing progression of structural bowel damage

Digestive Damage

Disease onset Diagnosis Early disease

Inflammatory Activity (CDAI, CDEIS, CRP)

Surgery Stricture Fistula/abscess

Pre-clinical Clinical

Up to 80% of CD patients will require surgical intervention and there is a high rate of post-operative recurrence.
Personalized Medicine (CD)

Diagnosis →

Risk stratification
- Clinical factors
- Serology/genetics
- Endoscopy

“High risk”

Early biologic / combination therapy
Predict which biologic mechanism is most effective and safest

“Low risk”

Budesonide

www.gastro.org/IBDcarepathway
Optimizing the Treatment of IBD

- Treat smarter (predict who will have aggressive disease)
- Treat earlier (with effective therapy)
- Treat deeper (mucosal healing)
- Treat to target
- Treat more effectively (proactive TDM)
Assessment of Disease Risk in Crohn’s Disease

- Assess current and prior disease burden
- Differentiate between activity and severity

Low Risk
- Age at initial diagnosis > 30 years
- Limited anatomic involvement
- No perianal and/or severe rectal disease
- Superficial ulcers
- No prior surgical resection
- No stricturing and/or penetrating behavior

Moderate/High Risk
- Age at initial diagnosis < 30 years
- Extensive anatomic involvement
- Perianal and/or severe rectal disease
- Deep ulcers
- Prior surgical resection
- Stricturing and/or penetrating behavior

Available at: www.gastro.org/IBDcarepathway. Accessed March 25, 2017
AGA Clinical Pathway for Ulcerative Colitis

Colectomy Risk

Low colectomy risk
• Limited anatomic extent
• Mild endoscopic disease

High colectomy risk
• Extensive colitis
• Deep ulcers
• Age < 40 years
• High CRP and ESR
• Steroid-requiring disease
• History of hospitalization
• C. difficile infection
• CMV infection
Optimizing the Treatment of IBD

- Treat smarter (predict who will have aggressive disease)
- Treat earlier (with effective therapy)
- Treat deeper (mucosal healing)
- Treat to target
- Treat more effectively (proactive TDM)
Early Treatment with Effective Therapy (Theory)

- Treat disease when inflammatory (before it can be destructive)
- Better able to induce and maintain remission
- Improve function and QOL
- Early mucosal healing to prevent complications and improve long-term outcomes

However,
- Significant number of patients may not require more potent treatments
- Side effects of medications
- Cost
The Window of Opportunity for Early Intervention in IBD

New Treatment Goals - Blocking Disease Progression and Preventing Damage and Disability

Inflammatory activity (CDAI, CDEIS, CRP)

Disease onset, Diagnosis, Early disease

The Importance of Early Intervention – Lessons from Pivotal Anti-TNF Studies – “Time is Gut”

<table>
<thead>
<tr>
<th>Disease duration (years)</th>
<th>CD patients in remission (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>1</td>
<td>SUTD¹</td>
</tr>
<tr>
<td>2</td>
<td>SONIC²</td>
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<tr>
<td>3</td>
<td>GETAID³</td>
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<tr>
<td>4</td>
<td>ACCENT 1⁴</td>
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<tr>
<td>5</td>
<td>CHARM⁵</td>
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<td>10</td>
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Optimizing the Treatment of IBD

- Treat smarter (predict who will have aggressive disease)
- Treat earlier (with effective therapy)
- Treat deeper (mucosal healing)
- Treat to target
- Treat more effectively (proactive TDM)
Evolving goals of therapy for IBD: sustained deep remission

Goal
- Response
- Remission
- Deep remission

Clinical parameters
- Improved symptoms
- No symptoms
- Normal labs
- Normal endoscopy
- Mucosal healing

Outcomes
- Improved QoL
- Decreased hospitalization
- Avoidance of surgery
- Minimal/no disability

SUSTAINED DISEASE CONTROL
Why is endoscopic healing important?

- **In clinical trials**
  - FDA mandated end point
  - More objective end point than clinical remission

- **In clinical practice**, mucosal healing can guide medical therapy
  - Assess disease activity
  - Growing evidence that mucosal healing is an important goal, because it appears to be associated with improved long-term outcomes
    - Decreased likelihood of a flare
    - Decreased progression to disease complications
    - Decreased need for surgery and hospitalization

Treat to Target

1. Initial treatment
2. Assessment of target
3. Adjustment of treatment
4. Assessment of target
5. Target reached: continue monitoring

Treat to Target
What are the options for treating IBD? How do we choose the best medication for new onset IBD?
## Medical Therapy of Ulcerative Colitis

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Induction of Remission</th>
<th>Maintenance of Remission</th>
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<tr>
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<td>+++</td>
<td>+++</td>
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<tr>
<td></td>
<td>(mild to moderate)</td>
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<tr>
<td>Corticosteroids</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>6MP/AZA</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Anti-TNF</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Vedolizumab</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Tofacitinib</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Cyclosporine</td>
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## Medical Therapy of Ulcerative Colitis

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Vedolizumab (Entyvio)

- Selective adhesion molecule inhibitor (SAM-i)
- Monoclonal antibody to $\alpha_4\beta_7$ integrin - intravenous
- FDA approved summer 2014
- Effective for moderate to severe IBD
  - UC > Crohn’s
  - Maintenance > Induction
- Appears safe (safer than anti-TNF)
- 1 case of PML (progressive multifocal leukoencephalopathy) in undiagnosed HIV patient with IBD
Tofacitinib

- Janus Kinase (JAK) inhibitor
- Oral small molecule
- FDA approved 5/30/2018
- Effective for induction and maintenance of remission in moderate to severe UC for both TNF naïve and TNF exposed
- FDA Update 7/2019
  - Inadequate response or are intolerant to anti-TNF
  - Limit 10mg BID dose beyond induction to those with loss of response
    - Based on post-marketing study of RA patients over age 50 with at least 1 cardiovascular risk factor where:
      - “Overall incidence of PE to be 5-fold higher in the tofacitinib 10 mg twice daily arm of the study compared with the TNF inhibitor arm, and approximately 3-fold higher than tofacitinib in other studies across the tofacitinib program. Additionally, all-cause mortality in the 10 mg twice daily arm was higher compared with the tofacitinib 5 mg twice daily and the TNF inhibitor groups.”
- Safety issues
  - Zoster, serious infection, lymphoma (?), non-melanoma skin cancers, lymphopenia, lipid elevation, venous thrombosis

Sanborn and Feagan, NEJM 2017
EMA and FDA announcements 2019
## Medical Therapy of Crohn’s Disease

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<td>+/-</td>
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<tr>
<td>Antibiotics</td>
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<td>-</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>6MP/AZA</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Anti-TNF</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Anti-integrins (SAM-i)</td>
<td>++</td>
<td>+++</td>
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<tr>
<td>Ustekinumab</td>
<td>+++</td>
<td>+++</td>
</tr>
</tbody>
</table>
New Paradigm: Treating beyond symptoms

Step-up approach

- Biologic therapy
- Immunomodulators
- Corticosteroids
- 5-ASA

Top-down (early aggressive) approach

- Biologic therapy
- Immunomodulators
- Corticosteroids
## Corticosteroid Therapy for CD

<table>
<thead>
<tr>
<th>Immediate Outcome* (n=74)</th>
<th>1-Year Outcome (n=73†)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Remission 58% (n=43)</td>
<td>Prolonged Response 32% (n=24)</td>
</tr>
<tr>
<td>Partial Remission 26% (n=19)</td>
<td>Steroid Dependent 28% (n=21)</td>
</tr>
<tr>
<td>No Response 16% (n=12)</td>
<td>Surgery 38% (n=28)</td>
</tr>
</tbody>
</table>

Steroids are bad

- They are abused by doctors and patients alike
- They do not alter the disease course
- They have bad short term side-effects
- They have very bad long-term side-effects
  - Skin, bones, adrenal axis, cataracts
- Increase risk of mortality in patients with IBD
Anti-TNFs for Crohn’s Disease

Intravenous (IFX); Subcutaneous (ADA, CTP)
Similar efficacy < 40% of responders in remission at 1 year
Safety issues – immunogenicity, infection, melanoma, lymphoma, psoriaform reactions

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo (n=170)</th>
<th>5mg/kg (n=172)</th>
<th>10mg/kg (n=157)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infliximab (Remicade)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remission at 26 weeks, %</td>
<td>17</td>
<td><strong>40&lt;sup&gt;a&lt;/sup&gt;</strong></td>
<td>47&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Remission at 56 weeks, %</td>
<td>12</td>
<td><strong>36&lt;sup&gt;a&lt;/sup&gt;</strong></td>
<td>41&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Adalimumab (Humira)</strong></th>
<th>Placebo (n=170)</th>
<th>Every other week (n=172)</th>
<th>Weekly (n=157)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission at 26 weeks, %</td>
<td>17</td>
<td><strong>40&lt;sup&gt;a&lt;/sup&gt;</strong></td>
<td>47&lt;sup&gt;a,b&lt;/sup&gt;</td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Certolizumab pegol (Cimzia)</strong></th>
<th>Placebo (n=101)</th>
<th>Certolizumab pegol (n=112)</th>
<th>&lt;sup&gt;P&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission at 26 weeks, %</td>
<td>26</td>
<td><strong>42</strong></td>
<td>.01</td>
</tr>
</tbody>
</table>

Several biosimilars are FDA approved for adult IBD

<table>
<thead>
<tr>
<th>Product name</th>
<th>Proprietary name</th>
<th>Date licensure</th>
<th>Biosimilar/Interchangeable</th>
</tr>
</thead>
<tbody>
<tr>
<td>adalimumab</td>
<td>Humira</td>
<td>12/31/02</td>
<td>Originator</td>
</tr>
<tr>
<td>- adalimumab-adaz</td>
<td>Hyrimoz</td>
<td>10/30/18</td>
<td>B</td>
</tr>
<tr>
<td>- adalimumab-adbm</td>
<td>Cyltezo</td>
<td>8/25/17</td>
<td>B</td>
</tr>
<tr>
<td>- adalimumab-atto</td>
<td>Amjevita</td>
<td>9/23/16</td>
<td>B</td>
</tr>
<tr>
<td>infliximab</td>
<td>Remicade</td>
<td>8/24/98</td>
<td>Originator</td>
</tr>
<tr>
<td>- infliximab-qbtx</td>
<td>Ixifi</td>
<td>12/13/17</td>
<td>B</td>
</tr>
<tr>
<td>- infliximab-abda</td>
<td>Renflexis</td>
<td>4/21/17</td>
<td>B</td>
</tr>
<tr>
<td>- infliximab-dyyb</td>
<td>Inflectra</td>
<td>4/5/16</td>
<td>B</td>
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Selective adhesion molecule inhibitors (SAM-i)

- Vedolizumab (Entyvio)
  - Monoclonal antibody to α4β7 integrin
  - FDA approved summer 2014 for moderate to severe UC and CD
  - Appears safe
  - 1 case of PML (progressive multifocal leukoencephalopathy) in patient with undiagnosed HIV

- Natalizumab (Tysabri):
  - Monoclonal Ab against α4 integrin
  - Effective and FDA approved for induction and maintenance of remission in moderate-severe Crohn’s who have failed anti-TNF
  - Monotherapy only
  - Risk of Progressive multifocal leukoencephalopathy (PML)
  - JC antibody test available for risk stratification
Ustekinumab (Stelara)

- Monoclonal antibody to IL-12/23 (p40)
- FDA approved October 2016 for moderate to severe CD
- FDA approved 2009 for moderate to severe psoriasis
- Appears safe (most of data in psoriasis)
- Infection
  - Appear lower when compared to anti-TNF
  - Prior to use (rule out latent hepatitis B or tuberculosis)
- Malignancy
  - Similar malignancy rates to general population

JAMA Dermatol. 2015;151(9):961-969. doi:10.1001/jamadermatol.2015.0718
How do we chose the right agent?
Personalized Medicine (CD)

Risk stratification
- Clinical factors
- Serology/genetics
- Endoscopy

"High risk"

"Low risk"

Early biologic / combination therapy

Predict which mechanism is most effective and safest

Budesonide

www.gastro.org/IBDcarepathway
Comparative Effectiveness

- SONIC (Combination of IFX/AZA > IFX > AZA in naïve CD)
- CYSIF (cyclosporine = infliximab in severe steroid refractory UC)
- One head to head trial of different biologics just completed
  - Others are underway
- Can’t compare results across trials
- Anti-TNF, vedolizumab, ustekinumab, and tofacitinib seem to have reasonable efficacy for indications tested
- Systematic review and network meta-analyses
  - Infliximab and vedolizumab appear most effective as first-line agents for UC
  - Infliximab and adalimumab appear most effective as first-line agents for CD
**VARSITY: A Double-Blind, Double-Dummy, Randomised, Controlled Trial of Vedolizumab Versus Adalimumab in Patients With Active Ulcerative Colitis**

Assessed for eligibility, N=1285

Randomised, N=771

**Vedolizumab IV n=385**
- Completed treatment: 287 (74.5%)
- Discontinued study drug:
  - 96 (24.9)
    - 17 (4.4) Pretreatment/AE
    - 41 (10.6) Lack of efficacy
    - 28 (7.3) Voluntary withdrawal
    - 0 Lost to follow-up
    - 4 (1.0) Significant protocol deviation
    - 1 (0.3) Pregnancy
    - 5 (1.3) Other

**Adalimumab SC n=386**
- Completed treatment: 239 (61.9%)
- Discontinued study drug:
  - 147 (38.1)

Excluded, n=514

Schreiber et al, European Crohn’s and Colitis Organization 2019, Abstract OP34
VARSITY: A Double-Blind, Double-Dummy, Randomised, Controlled Trial of Vedolizumab Versus Adalimumab in Patients With Active Ulcerative Colitis

Results:

Clinical remission (Primary endpoint)

Week 52

$\Delta = 8.8\% \ (2.6\%, \ 15.0\%)$

$p=0.0061$

Data from full analysis set, which includes all randomised patients who received at least 1 dose of study drug.

Cl, confidence interval.

*Mucosal healing: Mayo endoscopic subscore of ≤1 point.

Schreiber et al, European Crohn’s and Colitis Organization 2019, Abstract OP34
VARSITY: A Double-Blind, Double-Dummy, Randomised, Controlled Trial of Vedolizumab Versus Adalimumab in Patients With Active Ulcerative Colitis

Results:

Mucosal Healing*
Δ = 12.0% (5.3%, 18.6%)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab SC 160/80/40 mg</td>
<td>27.7 (22.0%, 33.8%)</td>
</tr>
<tr>
<td>Vedolizumab IV 300 mg</td>
<td>39.7 (34.0%, 45.5%)</td>
</tr>
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p=0.0005

*Mucosal healing: Mayo endoscopic subscore of ≤1 point.
Data from full analysis set, which includes all randomised patients who received at least 1 dose of study drug.

Schreiber et al, European Crohn’s and Colitis Organization 2019, Abstract OP34

Ci, confidence interval.
How to Chose the First Agent?

Disease specific factors
- Severity of disease
- EIM
- Perianal disease
- Associated conditions (psoriasis, RA)

Patient specific factors
- Age
- Co-morbidities (CHF, renal disease, recent cancer); pregnancy
- Patient preference

Medication specific factors
- Efficacy (clinical remission, endoscopic healing, perianal, EIM)
  - Safety
  - Rapidity of onset
  - Durability of remission
  - Immunogenicity
  - Availability and data on TDM
  - How it is administered
  - Time on market (devil you know)
  - Cost?

Insurers / Payers

Physician comfort
Some specific situations

- Fistulae
  - Only infliximab has RCTs with fistula as 1° endpoint
  - Some data for other anti-TNF
  - Limited data for vedolizumab and ustekinumab

- Rescue therapy for severe hospitalized UC failing iv steroids
  - Good data for infliximab and cyclosporine
  - Not studied for other anti-TNF, vedolizumab, tofacitinib
Associated Conditions
- Rheumatoid Arthritis
  - Anti-TNF / Tofacitinib
- IBD-associated arthritis
  - Anti-TNF
- Ankylosing spondylitis
  - Anti-TNF
- Psoriasis
  - Ustekinumab / Anti-TNF
- Pyoderma gangrenosum and erythema nodosum
  - Anti-TNF
Optimizing the Treatment of IBD

- Treat smarter (predict who will have aggressive disease)
- Treat earlier (with effective therapy)
- Treat deeper (mucosal healing)
- Treat to target
- Treat more effectively (proactive TDM)
Optimize whatever drug you chose

- First agent works best
- TNF-exposed patients do not respond as well as TNF-naïve patients
- High rate of secondary loss of response
- Risk of developing anti-drug antibodies is not insignificant
  - Highest with anti-TNF
- TDM (particularly proactive TDM) is underutilized
- If you are not doing proactive TDM, combination therapy with infliximab (and likely other anti-TNF) should be used
SONIC: Combination (IFX+AZA) outperforms infliximab which is better than azathioprine

Primary Endpoint: Corticosteroid-free clinical remission at week 26

51/170
44
96/169

Columbel JF, et al NEJM. 2010
Post-hoc analysis of SONIC suggests it is drug concentration, not combination therapy, that is associated with clinical outcomes.

Combo therapy contributes greater number of patients to higher IFX concentration quartiles.

Q1: <0.84 μg/mL; Q2: 0.84 μg/mL to <2.36 μg/mL; Q3: 2.36 μg/mL to <5.02 μg/mL; Q4: ≥5.02 μg/mL

Proactive Therapeutic Drug Monitoring (TDM)

Measurement of trough concentration and antibody levels with the goal of optimizing drug concentrations to achieve a threshold drug concentration at specific time-points (e.g. during induction, at end of induction or during maintenance).

Aim: To improve response rates and prevent secondary loss of response by targeting drug concentrations which are considered to be in the optimal therapeutic range. Proactive TDM may facilitate longer persistence of drug as well as improving other more objective outcomes.
Therapeutic Drug Monitoring – Proactive Monitoring

- Commonly performed in other situations
  - Cyclosporine, tacrolimus in solid organ transplantation
  - Cyclosporine and tacrolimus use in UC
  - Vancomycin and gentamycin in sepsis
- Therapeutic window
  - High concentrations can result in increased toxicity
  - Low concentrations result in lack of efficacy
  - Biologics – low concentrations result in immunogenicity

Patients who achieved a trough concentration ≥ 5 ug/ml had a longer duration on infliximab

Retrospective, observational study.
126 patients with IBD who responded to infliximab and received maintenance therapy and underwent either proactive TDM or standard of care (reactive TDM or empiric dose escalation)

<table>
<thead>
<tr>
<th>Number at risk</th>
<th>IFX trough ≥ 5</th>
<th>IFX trough &lt; 5</th>
<th>Not tested</th>
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<tr>
<td></td>
<td>37  29  14  9  4  4  2</td>
<td>15  8  5  3  3</td>
<td>74  27  8  4  3  2</td>
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P = 0.6

Similar results seen with cut off of 3ug/ml

Less IBD-Related Surgery, Hospitalization, ATI, and Serious Infusion Reactions with Proactive TDM

Take home points

• Personalize and optimize the treatment of IBD
  • Assess disease severity and predictors of complicated disease
  • Treat earlier in disease course with an effective agent
  • Goal should be at least steroid-free clinical remission, but consider endoscopic healing or, at least, improvement
• Treat to target
• First agent is the most effective agent. Optimize it!
  • Proactive TDM
• Effective disease control is the best strategy to avoid infectious complications
ACG Clinical Guideline: Preventive Care in Inflammatory Bowel Disease

Francis A. Farraye, MD, MSc, FACG1, Gil Y. Melmed, MD, MS, FACG2, Gary R. Lichtenstein, MD, FACG3 and Sunanda V. Kane, MD, MSPH, FACG4

Farraye FA, Melmed G, Lichtenstein GR, Kane S. Am J Gastroenterol. 2017 Feb;112(2):241-258
ACG Vaccination Guidelines for Adults with IBD

• Annual influenza vaccination with non-live trivalent inactivated vaccine

• Pneumococcal vaccination with both Prevnar 13 and Pneumovax 23 if on immunosuppressive therapy

• If over age 50, consider vaccination against herpes zoster

• Before initiating immunosuppressive therapy, assess for prior exposure to varicella and vaccinate if naive, when possible

• Age-appropriate vaccinations before initiating immunosuppressive therapy, when possible

• Vaccination against diphtheria, pertussis, and tetanus; hepatitis A; hepatitis B; and human papilloma virus, per CDC guidelines

Other ACG Recommendations for Adults with IBD

• Annual cervical cancer screening for women who are on immunosuppressive therapy
• Melanoma screening, independent of the use of biologic therapy
• Screening for non-melanoma skin cancer if any history of azathioprine or 6-mercaptopurine
• Screening for depression and anxiety
• Osteoporosis screening for patients with conventional risk factors
• Counseling on smoking cessation, if needed, for patients with CD

Bone Health

• Patients with IBD are at increased risk of osteopenia (~50%), osteoporosis (~15%) and osteoporotic fracture.
• Indications for bone density screening in IBD:
  • History of fracture
  • Corticosteroids (longer than 3 months’ exposure or repeated use)
  • Postmenopausal women
  • Males older than 50 years
  • Hypogonadism
• Additional risk factors for bone loss:
  • Chronic inflammation, smoking, malnutrition

Cancer Prevention

- Cervical cancer
  - Yearly Pap if immunosuppressed

- Skin cancer
  - Yearly dermatology exam (ALL patients)
  - Sun-exposure precautions

- Colon cancer
  - Risk is ≈ 2-3 times higher than general population
  - Occurs at younger age
  - Risk is same for UC and CD
  - Certain factors increase risk of colon cancer
    - Extent of disease (1/3), duration of disease (8-10 years), PSC, inflammation
  - Surveillance colonoscopies for patients with 1/3 colon involved
    - Every 1-3 years after 8-10 years of disease

Farraye FA et al. Am J Gastroenterol. 2017
Laine L et al. Gastroenterology. 2015
Therapy related monitoring

- Mesalamines
  - Yearly renal function (also CBC, LFTs with sulfasalazine)
- Thiopurines
  - CBC, LFTs (every 3 months; more frequent at initiation)
- Methotrexate
  - CBC, LFTs (every 3 months; more frequent at initiation); periodic renal function
- Anti-TNF and ustekinumab
  - TB and HBV prior to initiation; yearly assessment of risk factors
  - Periodic CBC, LFTs
- Natalizumab
  - JC virus prior to initiation and following on therapy; TOUCH program
  - CBC, LFTs
- Vedolizumab
  - CBC, LFTs
- Tofacitinib
  - CBC, LFTs, lipids
IBD

Key Points:
• Differentiate between UC and Crohn’s
• Rapid advances in medications
• Goals of care and treatment paradigms are changing
  – endoscopic healing, treat to target; early aggressive therapy

Next best steps:
• Vaccinate patients
• Screen and treat for osteopenia / osteoporosis
• Cancer surveillance is important
  • Colon cancer, skin cancer, and cervical cancer (on IMM)
• Monitor for complications of IBD medicines
• GI consult should be considered to treat patients with IBD
### CCFA Health Maintenance Checklist for Adult IBD Patients

**Vaccine-Preventable Illnesses**

<table>
<thead>
<tr>
<th>Vaccine Preventable Illnesses</th>
<th>Which Patients</th>
<th>How Often</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza (inactive)</td>
<td>All</td>
<td>Annually</td>
</tr>
<tr>
<td>Pneumococcal PCV13</td>
<td>If on/planning immunosuppression</td>
<td>Once¹</td>
</tr>
<tr>
<td>Pneumococcal PPSV23</td>
<td>If on/planning immunosuppression</td>
<td>At baseline, repeat in 5 years</td>
</tr>
<tr>
<td>Tdap</td>
<td>All</td>
<td>Every 10 years</td>
</tr>
<tr>
<td>HPV</td>
<td>All aged 18-26</td>
<td>Once (3 doses within 6 mos.)</td>
</tr>
<tr>
<td>Meningococcal meningitis</td>
<td>All adult patients at risk of meningitis</td>
<td>Once</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>If non-immune</td>
<td>Once (2 doses within 6 mos.)</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>If non-immune</td>
<td>Once (3 doses within 6 mos.)</td>
</tr>
<tr>
<td>MMR (live vaccine)</td>
<td>If non-immune²</td>
<td>Once (1-2 doses)</td>
</tr>
<tr>
<td>Varicella (live vaccine)</td>
<td>If non-immune²</td>
<td>Once (1-2 doses within 6 mos.)</td>
</tr>
<tr>
<td>Zoster (live vaccine)</td>
<td>All aged &gt; 50 years²</td>
<td>Once</td>
</tr>
</tbody>
</table>

**Cancer Prevention**

<table>
<thead>
<tr>
<th>Cancer Prevention</th>
<th>Which Patients</th>
<th>How Often</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical PAP smear</td>
<td>All on systemic immunosuppression⁴</td>
<td>Annual</td>
</tr>
<tr>
<td>Skin screen</td>
<td>All on systemic immunosuppression⁴</td>
<td>Annual</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>All with extensive disease for &gt;8 years</td>
<td>Every 1-3 years</td>
</tr>
</tbody>
</table>

**Other Screenings**

<table>
<thead>
<tr>
<th>Other Screenings</th>
<th>Which Patients</th>
<th>How Often</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEXA Scan</td>
<td>High risk; women with low BMI, post-menopausal, chronic steroid exposure</td>
<td>At least 2 years apart</td>
</tr>
<tr>
<td>PPD or IGRA</td>
<td>Prior to anti-TNF or anti-IL-12/23</td>
<td>Once</td>
</tr>
<tr>
<td>Smoking status</td>
<td>All</td>
<td>Annual</td>
</tr>
<tr>
<td>Depression check</td>
<td>All</td>
<td>Annual</td>
</tr>
</tbody>
</table>

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1. Recommended timing of serial pneumococcal vaccination with both PPSV23 and PCV13 available in ACIP recommendation
2. Patients treated with systemic immunosuppressive therapy (steroids, thiopurines, anti-TNFs) should not receive live (attenuated) vaccines e.g. measles, mumps, rubella, varicella, and yellow fever
3. Patients receiving anti-TNFs, anti-IL-12/23, or >20 mg prednisone should NOT be given the live zoster vaccine. Vaccine can be administered if on methotrexate < 0.4 mg/kg/wk, 6-mercaptopurine < 1.5 mg/kg/d or azathioprine < 3 mg/kg/d
4. “Systemic immunosuppression” currently includes azathioprine, mercaptopurine, methotrexate, anti-TNFs, anti-IL-12/23

### ADDITIONAL INFORMATION

- ACG
- ACIP
- ACOG
- AGA
- National Cancer Institute
- National Osteoporosis Foundation
- PHQ-9 Depression Survey
- US Preventive Services Task Force (USPSTF) Osteoporosis
- USPSTF Tobacco

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The evidence base for this checklist varies from “insufficient to assess benefits” to “moderate net benefits.”

Developed by the CCFA Professional Education Committee Sub-Group: Alan Moss MD, Francis Farraye MD, MSc, Glenn Gordon MD, Raluca Vrabie MD • Approved by Committee Chairs: Samir Shah MD, Millie Long MD • V2_January_2017

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start immunosuppressants within 4 weeks. Consider vaccination with PSV23 if immunosuppressed patients and those planning to receive immunosuppressive therapy (e.g., MTX, 6-MP, azathioprine), but not on biologics. Can be considered in patients on “low dose” immunosuppression (prednisone ≤20mg/day, MTX, ≤20mg/day, 6-MP, ≤50mg/day) if patient is ≥65 yrs or with comorbidities. Can administer ≥4 weeks prior to starting biologics.

Zoster (Varicella Zoster Virus IgG) - Administer to patients ≥50 on “low dose” immunosuppression (prednisone ≤20mg/day, MTX, ≤20mg/day, 6-MP, ≤50mg/day) if patient is ≥65 yrs or with comorbidities. Can administer ≥4 weeks prior to starting biologics.

MMR (Live Vaccine) - Contraindicated in immunosuppressed patients and those planning to receive immunosuppression (e.g., MTX, 6-MP, azathioprine), but not on biologics. Can be considered in patients on “low dose” immunosuppression (prednisone ≤20mg/day, MTX, ≤20mg/day, 6-MP, ≤50mg/day) if patient is ≥65 yrs or with comorbidities. Can administer ≥4 weeks prior to starting biologics.

Diphtheria and Pertussis (Non-Live Vaccine) - Vaccinate with Tdap if not given within last ten years, or if Td ≥2 years.

Influenza (Non-Live Vaccine) - 1 dose annually to all patients during flu season (avoid intranasal live vaccine in immunosuppressed patients).

HPV (Non-Live Vaccine) - Related to cervical and anal cancer; 3 doses approved for females and males ages 9-26 (regardless of immunosuppression).

Hepatitis B (Non-Live Vaccine) - Check hepatitis B surface antibody (HBsAb) before initiating anti-TNF therapy. If non-immune consider vaccination series with non-live hepatitis B vaccine, 3 doses of hepatitis B vaccine (HepB) ≥8 weeks later followed by PSV23 booster after 5 years.

Pneumococcal Pneumonia (Non-Live Vaccine) - If not previously vaccinated regardless of immunosuppression.

Bone Health

Vitamin D 25-OH Level - Check at least once in all patients and supplement if deficient or insufficient.

Bone Density Assessment - Assess bone density if the following conditions are present: 1. Steroid use >3 months; 2. Inactive disease but past chronic steroid use of at least 1 year within the past 2 years; 3. Inactive disease but maternal history of osteoporosis; 4. Inactive disease but recent (<4 months) active disease but amenorrheic; 5. Post menopausal women; 6. Any disease regardless of disease status.

Prescription of Calcium & Vitamin D - Prescribe daily supplements for all patients with each course of oral corticosteroids and if vitamin D deficient or insufficient.