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SUBMISSION DATES: AUGUST 17-SEPTEMBER 3, 2020 11:59 PM EDT

IMPORTANT DATES

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SEPTEMBER 3 | 11:59 PM EDT
Submission Site CLOSES (No Exceptions!)

NEW FOR 2020! ACG has added a special category for COVID-19 research to our late breaking call for abstracts. Submit your late breaking COVID-19 research for this new session!

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All attendees will be muted and will remain in Listen Only Mode.

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If you plan to claim MOC Points for this activity, you will be asked to: Please list specific changes you will make in your practice as a result of the information you received from this activity.

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---

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**Week 25:** Management of EoE With Topical Steroids: The When and How of Long Term Management
Gary W. Falk, MD, MS, FACP
*September 10, 2020 at Noon EDT*

**Week 26:** Current and Emerging Concepts in Irritable Bowel Syndrome
Brooks D. Cash, MD, FACP
*September 17, 2020 at Noon EDT*

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Combination Therapies in IBD: Assessing the Evidence for and Against

Stephen B. Hanauer, MD, MACG
Clifford Joseph Barborka Professor of Medicine
Northwestern University Feinberg School of Medicine
Chicago
Outline

• Historical context of combination therapies in IBD
• Efficacy of Combination Biologics with Immunosuppressives
• Efficacy of Combination Biologics with Aminosalicylates
• Other Combinations
• Safety concerns
• Practical applications

Historical Context of Combination Therapies

• Ulcerative colitis
  – Aminosalicylates ➔ Corticosteroids ➔ Thiopurines
  – Cylosporine ➔ Thiopurines

• Crohn’s disease
  – Corticosteroids ➔ Thiopurines/Methotrexate
Concept of Step-Therapy is Flawed

Disease severity at presentation?

- Severe
- Moderate
- Mild

Theoretical Advantages of Combined Therapy

- Prevention of immunogenicity with biologics
- Increased drug concentrations
- Targeting multiple mechanism - greater efficacy

- Disadvantages of combined therapy
  - Increased adverse effects (immunosuppression)
  - Complexity and cost of the regimen
**Immunogenicity of TNF Antagonists in Patients With Detectable Antibodies to a TNF Antagonist**

<table>
<thead>
<tr>
<th>Patients, %</th>
<th>Episodic Maintenance</th>
<th>Scheduled Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IMS-</td>
<td>IMS+</td>
</tr>
<tr>
<td>Infliximab† (CD 5 mg/kg) (CD 10 mg/kg)</td>
<td>38%</td>
<td>16%</td>
</tr>
<tr>
<td>Infliximab‡ (UC 5 mg/kg) (UC 10 mg/kg)</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Certolizumab§ (PRECISE I)</td>
<td>10%</td>
<td>4%</td>
</tr>
<tr>
<td>Certolizumab‡ (PRECISE II)</td>
<td>24%</td>
<td>8%</td>
</tr>
<tr>
<td>Adalimumab§ (RA, all doses)</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Adalimumab‡ (CLASSIC II)</td>
<td>No data</td>
<td>No data</td>
</tr>
</tbody>
</table>


**Factors that Influence PK of TNF Antagonists**

<table>
<thead>
<tr>
<th>Impact on TNF antagonist PK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of ADAs</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Concomitant use of immunosuppressives</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Low serum albumin concentration</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>High baseline CRP concentration</td>
</tr>
<tr>
<td>High baseline TNF concentration</td>
</tr>
<tr>
<td>High body size</td>
</tr>
<tr>
<td>Sex</td>
</tr>
</tbody>
</table>
**TOP DOWN - Remission (CDAI<150) Corticosteroid Therapy**

**Complete Ulcer Disappearance**

**Percent Remission**

- Week 14: P=0.43  
- Week 52: P=0.006  
- Week 78: P=0.03  
- Week 104: P=0.001  
- Week 26: P=0.80  

Top-Down Infliximab Superior to Step-Up in Children With Moderate to Severe CD: A Multicenter Randomized Trial

- International RCT at 12 centers
- 97 children aged 3-17 years with new-onset, untreated CD randomized to Top-Down or Step-Up therapy

Efficacy of Infliximab with/without Immunomodulators in Pivotal Trials

- Patients not randomized to Combination therapy
- Trials not powered to evaluate Combination therapy
Evidence for combination therapy in Crohn’s Disease in immunosuppressive-naive patients: SONIC

Corticosteroid-free clinical remission at Week 26

SONIC: Trough Levels at Week 30

Proportion of patients (%)

<table>
<thead>
<tr>
<th>Group</th>
<th>Week 26</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZA+ placebo</td>
<td>30.0</td>
</tr>
<tr>
<td>IFX + placebo</td>
<td>44.4</td>
</tr>
<tr>
<td>IFX + AZA</td>
<td>56.8</td>
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</table>

Proportion of patients (%)

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<tbody>
<tr>
<td>AZA+ placebo</td>
<td>51/170</td>
</tr>
<tr>
<td>IFX + placebo</td>
<td>75/169</td>
</tr>
<tr>
<td>IFX + AZA</td>
<td>96/169</td>
</tr>
</tbody>
</table>

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<td>75/169</td>
</tr>
<tr>
<td>IFX + AZA</td>
<td>96/169</td>
</tr>
</tbody>
</table>
SONIC: Proportions achieving mucosal healing at week 26 by serum trough infliximab concentration at week 30

- SONIC re-analysis
  - Within quartiles, there was no statistically significant difference in proportions of patients achieving CSFR26 between treatment groups
  - No difference in ROC was observed between IFX monotherapy and IFX+Aza treatment groups

![Graph showing proportions achieving mucosal healing](image)

IFX+Aza is Superior to IFX Alone in Ambulatory UC (SUCCESS Trial)

Mucosal Healing

![Bar chart showing mucosal healing](image)
No Effects of Concomitant Immunomodulators on Efficacy and Safety of Adalimumab in Crohn's disease or Ulcerative Colitis Who had Failed Conventional Therapy


Adalimumab in Combination with AZA: Remission and Endoscopic Improvement at 26 wks CD (Diamond Study)

- Randomized (open-label)
- Active CD naïve to biologics and thiopurines
- Efficacy of adalimumab +/- AZA
- Primary endpoint: clinical remission at Wk 26
Adalimumab Monotherapy and a Combination with Azathioprine for Crohn’s Disease: Diamond

- Anti-ADA Ab positive:
  - 13.2% monotherapy group
  - 4.0% combination group \( p = 0.078 \)
- ADA trough level
  - 6.5±3.9 \( \mu \)g/ml monotherapy group
  - 7.6±3.6 \( \mu \)g/ml combination group \( p = 0.084 \).
- Not statistically significant with trends towards a higher ADA trough level and a lower positive rate of Anti-ADA Ab in combination group compared with monotherapy.

Effects of Concomitant Immunomodulator on Efficacy & Safety of TNFi for CD: Meta-analysis of Placebo-controlled Trials

Pooled summary estimate for adverse events:
  - infusion/injection reactions
  - Malignancy
  - Serious infections
  - Death

Mono vs combo therapy not significantly different (OR, 0.71; 95% CI, 0.41–1.25). Odds of infusion reaction with infliximab significantly reduced in subjects taking IM (OR, 0.46; 95% CI, 0.26–0.79).
Methotrexate in Combination With Infliximab in Patients With Crohn's Disease*: COMMIT

50-week, d-b, p-c trial
Compared mtx and ifx with ifx alone
126 patients initiated prednisone within prior 6 weeks
MTX initial 10 mg/wk, escalating to 25 mg/week
IFX (5 mg/kg) at wks 1, 3, 7, and 14, and q 8 wks
Prednisone tapered beginning week 1 and d/c'd no later than week 14

REACT: Time to First Hospitalization, Surgery or Complication

- Cluster randomized controlled trial
- Gastroenterology practices randomized to either implement a treatment algorithm or to continue with their usual care for the management of CD
- 40 practices randomized in a 1:1 ratio using a minimization procedure to balance treatment allocation for country and number of CD patients seen annually at the practice (<100 or ≥100)

HR (95% CI) = 0.73 (0.62, 0.86), p<0.001

- Conventional management
- Early combined immunosuppression

34.7%
27.4%
**Early Combined Immunosuppression (ECI) Reduces Complications in Isolated Colonic- vs Ileal-Dominant Crohn Disease**

Rates of complications stratified by treatment algorithm and disease location

**Post-hoc analysis of REACT**

ECI

Conventional

---

**Benefit of TNFi + IS combination therapy depends on disease phenotype and duration in Crohn's disease**

multicenter prospective cohort

707 CD pts (45% combo therapy)
164 UC pts (38% combo therapy).
Combination therapy not associated with reduction in composite outcome in CD (OR: 0.87, 95% CI: 0.63-1.22) or UC (OR: 1.45, 95% CI: 0.63-3.38).

No difference with non-stricturing, nonpenetrating CD

Significant reduction in stricturing or penetrating CD (30% vs 39%, OR: 0.58, 95% CI: 0.37-0.90)

Stronger effect disease duration <5 years (OR: 0.35, 95% CI: 0.14-0.87) vs longer duration (OR: 0.75, 95% CI: 0.45-1.27)
Higher Mucosal Healing Rates with TNFı’s in Combination with Thiopurines Compared to Methotrexate in Crohn’s Disease

Retrospective observational study at 2 tertiary centers (2010-2016)

Concomitant Steroids Do Not Improve Crohn’s Remission Rates with TNFı’s

<table>
<thead>
<tr>
<th>Study</th>
<th>SteroidYes</th>
<th>SteroidNo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N.Remission</td>
<td>N.Total</td>
</tr>
<tr>
<td>Schreiber et al.²³</td>
<td>17</td>
<td>76</td>
</tr>
<tr>
<td>Sandborn et al. (PRECISE 1)²⁴</td>
<td>110</td>
<td>251</td>
</tr>
<tr>
<td>Schreiber et al. (PRECISE 2)²⁵</td>
<td>86</td>
<td>235</td>
</tr>
<tr>
<td>Sandborn et al. (WELCOME)²⁶</td>
<td>35</td>
<td>98</td>
</tr>
<tr>
<td>Hamauer et al. (CLASSIC 1)²⁷</td>
<td>26</td>
<td>58</td>
</tr>
<tr>
<td>Colombel et al. (CHAiRA)²⁸</td>
<td>65</td>
<td>279</td>
</tr>
<tr>
<td>Sandborn et al. (Gain)²⁹</td>
<td>18</td>
<td>54</td>
</tr>
<tr>
<td>Watteau et al.³⁰</td>
<td>2</td>
<td>14</td>
</tr>
<tr>
<td>Rutgeerts et al. (EXTEND)³¹</td>
<td>8</td>
<td>31</td>
</tr>
<tr>
<td>Present et al.³²</td>
<td>6</td>
<td>21</td>
</tr>
<tr>
<td>Hamauer et al. (ACCENT 1)³³</td>
<td>27</td>
<td>201</td>
</tr>
<tr>
<td>Sands et al. (ACCENT 2)³⁴</td>
<td>36</td>
<td>78</td>
</tr>
<tr>
<td>Colombel et al. (SonC)³⁵</td>
<td>65</td>
<td>125</td>
</tr>
</tbody>
</table>

**Fixed effect model**

1663 | 2701 | 0.91 [0.80; 1.04] | 100.0% | —

**Random effects model**

9.3 [0.74; 1.17] | 100.0%

P < 0.01

Favor no steroid | Favor steroid
No Benefit of Concomitant Aminosalicylates in Patients with Ulcerative Colitis Escalated to TNFi Therapy

Individual patient data from 5 trials of infliximab and golimumab in moderate-severe UC

Vedolizumab in combination with stable corticosteroids

(Post Hoc Analysis of GEMINI 2/3)

May improve induction of clinical response or remission in moderately-severely Crohn's disease
Percentage of Vedolizumab-Treated Patients in Clinical Remission*

Week 6  * Vs Placebo  Week 52

<table>
<thead>
<tr>
<th>Group</th>
<th>Week 6</th>
<th>Week 52</th>
</tr>
</thead>
<tbody>
<tr>
<td>VDZ (n=71)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CS only and VDZ (n=79)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMM only and VDZ (n=28)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CS and IMM and VDZ (n=47)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VDZ QBW (n=31)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VDZ Q4W (n=32)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CS only and VDZ QBW (n=48)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CS only and VDZ Q4W (n=48)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMM only and VDZ QBW (n=21)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMM only and VDZ Q4W (n=20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CS and IMM and VDZ QBW (n=22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CS and IMM and VDZ Q4W (n=11)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Gemini Trials in UC and CD
  - Immunosuppressives disallowed after 6 weeks in US, allowed in Europe
  - No difference in clinical response/remission in ~20% of patients with/without concomitant IS

Observational Studies Assessing Concomitant Immunomodulators & vedolizumab in UC & CD

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Country of origin</th>
<th>Number of patients</th>
<th>Comparison</th>
<th>Statistical estimate</th>
<th>Additional effect of combination therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skelton [17]</td>
<td>2015</td>
<td>US</td>
<td>UC, n = 65</td>
<td></td>
<td>OR 0.56; 95% CI 0.19–1.66</td>
<td>No</td>
</tr>
<tr>
<td>Willett [15]</td>
<td>2016</td>
<td>France</td>
<td>UC, n = 16</td>
<td></td>
<td>7/17 (41.2%) vs. 13/30 (43.3%)</td>
<td>No</td>
</tr>
<tr>
<td>Aminie [10]</td>
<td>2016</td>
<td>France</td>
<td>UC, n = 121</td>
<td></td>
<td>p = NS</td>
<td>No</td>
</tr>
<tr>
<td>Stalmarck [14]</td>
<td>2016</td>
<td>Germany</td>
<td>UC, n = 60</td>
<td></td>
<td>OR 0.20; 95% CI 0.02–1.66</td>
<td>No</td>
</tr>
<tr>
<td>Baumgart [11]</td>
<td>2016</td>
<td>Germany</td>
<td>UC, n = 115</td>
<td></td>
<td>OR 0.50; 95% CI 0.24–1.13</td>
<td>No</td>
</tr>
<tr>
<td>Kopcsik [12]</td>
<td>2016</td>
<td>Israel</td>
<td>UC, n = 74</td>
<td></td>
<td>OR 0.77; 95% CI 0.52–1.14</td>
<td>No</td>
</tr>
<tr>
<td>Samaan [13]</td>
<td>2016</td>
<td>UK</td>
<td>UC, n = 20 CD, n = 27 IBD-U, n = 3</td>
<td>Concomitant use of immunomodulators and clinical response/remission at week 14</td>
<td>OR 0.60; 95% CI 0.39–1.66</td>
<td>No</td>
</tr>
<tr>
<td>Eriksson [16]</td>
<td>2017</td>
<td>Sweden</td>
<td>UC, n = 92 CD, n = 147 IBD-U, n = 7</td>
<td>Concomitant use of immunomodulators and clinical response/remission at week 14</td>
<td>OR 0.40; 95% CI 0.19–0.85</td>
<td>No</td>
</tr>
<tr>
<td>Allegretti [18]</td>
<td>2017</td>
<td>UK</td>
<td>UC, n = 40 CD, n = 96</td>
<td>Concomitant use of immunomodulators and drug discontinuation, because of lack of or loss of response, at the last follow-up</td>
<td>OR 0.43; 95% CI 0.05–2.00</td>
<td>No</td>
</tr>
<tr>
<td>Adjunctive therapy after initiation of VDZ and response or remission at week 54</td>
<td>No</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No Effect: No significant difference in clinical response/remission.
Impact of Concomitant Immunomodulator Use on Vedolizumab Effectiveness
Multicentre Consortium Propensity Score-matched Analysis

Hazard Rate
95% CI.

Crohn’s Disease

Ulcerative colitis

Clinical Remission
Steroid-Free Remission
Endoscopic Healing

Clinical Remission
Steroid-Free Remission
Endoscopic Healing

Vedo + IM
Vedo-IM

Hodesman, D et al ECCO DOP 053 (s067) 2018

Combination Therapy Does Not Improve Clinical and Endoscopic Remission Rates with Vedolizumab or Ustekinumab in CD and UC

- Retrospective Study 3 academic sites in US, Canada, France
- Ustekinumab initiated in CD patients (n=291)
  - 44% on combination therapy with thiopurine/MTX
- Vedolizumab initiated in 381 patients (203 CD, 178 UC)
  - 25% on combination therapy with thiopurine/MTX
- Patients followed with DAIIs (HBI, SCCAI, or pMayo Score)
- Primary outcomes were clinical remission or response at 14, 30, and 54 weeks

Kaplan-Meier survival curve comparing monotherapy vs combination therapy
Concomitant Aminosalicylates Not Associated With Improved Outcomes in UC Patients Escalated to Vedolizumab

Retrospective observational cohort 109 UC pts receiving vedolizumab w (n=46) or w/o (n=63) concomitant aminosalicylates

Calcineurin Inhibitors in Combination with Vedolizumab in Refractory UC

Retrospective study of induction therapy with cyclosporine or tacrolimus in combination with vedolizumab 39 pts with refractory UC (most of whom failed TNFi’s)
Efficacy Summary

• Combination therapy more effective than monotherapy for infliximab & adalimumab (?) in both CD and UC
  – Decreased sensitization \ better PK \ targeting multiple mechanisms (?)

• Co-administration of immunosuppressives is not necessary for vedolizumab/ustekinumab, if the intent is solely to prevent sensitization*

• Combination therapy may be the only way forward if we are to achieve high (>80%) rates of corticosteroid–free remission

• *Most KOLs recommend combination therapy for subsequent biologics for patients who have demonstrated prior immunogenicity

Mono or Combo: Why is the pendulum swinging?

- COMBO
  - Reduced Immunogenicity and higher troughs
  - Combined clinical trials and cohorts with mAbs

- MONO
  - Lymphomas/ Hepatosplenic T-cell lymphomas

Efficacy

Safety
Risk factors for opportunistic infections
The Mayo experience

Biologic + Azathioprine is Least Risky for Opportunistic Infection

<table>
<thead>
<tr>
<th>Medication</th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.7 (1.5-4.8)</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>2</td>
<td>9.7 (3.3-28.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>3</td>
<td>infinite</td>
<td></td>
</tr>
<tr>
<td>Steroids</td>
<td>2.2 (1.1-4.8)</td>
<td>0.037</td>
</tr>
<tr>
<td>AZA/6-MP</td>
<td>2.5 (1.2-5.1)</td>
<td>0.015</td>
</tr>
<tr>
<td>IFX</td>
<td>11.2 (0.8-153.3)</td>
<td>0.07</td>
</tr>
<tr>
<td>6-MP/aza + ster.</td>
<td>15.7 (4.1-59.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>6-MP+IFX</td>
<td>1.6 (0.1-18.7)</td>
<td>0.71</td>
</tr>
<tr>
<td>6-MP/Aza+IFX+ster.</td>
<td>infinite</td>
<td></td>
</tr>
</tbody>
</table>

Biologic + Azathioprine is Least Risky for Opportunistic Infection

TREAT Registry: Serious Infections Logistic Regression Data (Multivariate)

Steroids are the biggest risk for infections

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>1.01</td>
<td>0.99-1.03</td>
</tr>
<tr>
<td>Female</td>
<td>1.24</td>
<td>0.81-1.90</td>
</tr>
<tr>
<td>Moderate or severe CD</td>
<td>2.11</td>
<td>1.10-4.05*</td>
</tr>
<tr>
<td>Current use of infliximab</td>
<td>1.40</td>
<td>0.95-2.07</td>
</tr>
<tr>
<td>Current use of 6MP/AZA/MTX</td>
<td>0.88</td>
<td>0.61-1.27</td>
</tr>
<tr>
<td><strong>Current use of corticosteroids</strong></td>
<td><strong>2.21</strong></td>
<td><strong>1.46-3.34</strong>*</td>
</tr>
<tr>
<td>Current use of narcotic analgesics</td>
<td>2.38</td>
<td>1.56-3.63*</td>
</tr>
</tbody>
</table>
SONIC Summary of Adverse Events Through Week 50 – All Randomized Patients

<table>
<thead>
<tr>
<th></th>
<th>AZA + placebo (n=161)</th>
<th>IFX + placebo (n=163)</th>
<th>IFX + AZA (n=179)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts with ≥ 1 AE, n (%)</td>
<td>144 (89.4%)</td>
<td>145 (89.0%)</td>
<td>161 (89.9%)</td>
</tr>
<tr>
<td>Pts with ≥ 1 SAE, n (%)</td>
<td>43 (26.7%)</td>
<td>39 (23.9%)</td>
<td>27 (15.1%)</td>
</tr>
<tr>
<td>Serious infections</td>
<td>9 (5.6%)</td>
<td>8 (4.9%)</td>
<td>7 (3.9%)</td>
</tr>
</tbody>
</table>

Combination Therapy had Lowest Risk Of Infections

REACT: Safety-Deaths

<table>
<thead>
<tr>
<th></th>
<th>Conventional Management n</th>
<th>Early Combined Immunosuppression n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Thromboembolic</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Cancer</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Infection</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Other**</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>1 (1.1%)</td>
<td>7 (0.9%)</td>
</tr>
</tbody>
</table>

***exhaustion* (age 96)

**unknown**


Crohn’s Disease Activity and Concomitant Immunosuppressants Affect Risk of Serious and Opportunistic Infections in Patients Treated With Adalimumab

• 2,266 patients treated with adalimumab in placebo-controlled trials
• Each 100-point increase in CDAI associated with >30% increased risk of serious or opportunistic infection.
• Concomitant immunomodulators associated with >3-fold decreased risk of serious infection by 1 year
• Concomitant corticosteroids associated with increased risk of serious infection (HR 2.40 (1.33–4.35), P=0.004)
• Concomitant use of either category of immunosuppressant associated with numerically higher rates of opportunistic infection, 40% due to herpes zoster, compared with adalimumab monotherapy.

The Incidence of Pneumonia & Impact of Immunosuppressive Medications on Risk of Pneumonia Among Patients with IBD

• Nationwide cohort of IBD patients from VA, 2000 - 2019
  – 56,398 patients with IBD
  – 9 years median follow-up
• 6.4 per 1000 patient-years of follow-up risk of developing pneumonia
• Anti-TNF agents and corticosteroids associated with increased risk of pneumonia

<table>
<thead>
<tr>
<th>Medications (5-ASA reference)</th>
<th>Adjusted HR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charlson comorbidity index</td>
<td>1.16</td>
<td>1.14, 1.18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Influenza vaccination</td>
<td>1.28</td>
<td>1.19, 1.38</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Narcotic within 60 days prior to index date</td>
<td>1.45</td>
<td>1.34, 1.57</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prednisone cumulative (mg/day)</td>
<td>1.02</td>
<td>1.01, 1.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prednisone within 30 days prior to index date</td>
<td>1.99</td>
<td>1.78, 2.22</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IBD flare</td>
<td>2.64</td>
<td>2.38, 2.93</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

- Thiopurines
- Anti-TNF
- Thiopurine/anti-TNF combination
- Vedolizumab
- PPSV23
Exposure to Thiopurines and Lymphomas in IBD

HR thiopurines = 5 [CI 95%: 2-14]  Increases with Age

Beaupre L et al., Lancet 2009 374:1617-25
Risk of Skin Cancer Associated with Thiopurines (CESAME)

- 19,486 IBD patients
- 32 cases of skin cancer (20 basal cell, 12 squamous)

Incidence rate per 1000 pt-years

<50 years: 0.59
50-65 years: 2.59
>65 years: 5.65

Thiopurines continued
Thiopurines discontinued
Never thiopurines

Hepatosplenic T-cell lymphomas

- Main features
  - Rapidly fatal lymphoproliferations
  - Young men <35 yrs
  - Non EBV-related
  - Combo therapy thiopurines/anti-TNF, and less frequently monotherapy with thiopurines
  - Rare within the first two years of treatment
- Rare (<0.1/1000 PY) – 20 cases with Combo and 16 with AZA/6-MP
Systematic review: hepatosplenic T-cell lymphoma on biologic therapy for inflammatory bowel disease

- 62 cases (identified from 2486 abstracts and 181 FDA AERS)
- Median age 28 years (12-81)
- 83% Male
- 84% Crohn’s disease
- 5/62 No thiopurine exposure
- All cases with biologics had TNFi exposure
- 88% Mortality (median survival 5 months)

Risk of Serious/Opportunistic Infections & Lymphoma Associated with Treatment of IBD
French Administrative Databases (n=190,694)

<table>
<thead>
<tr>
<th>Lymphoma</th>
<th>Incidence Rates per 1000 p/ys</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unexposed</td>
<td>0.26</td>
</tr>
<tr>
<td>Thiopurine</td>
<td>0.54</td>
</tr>
<tr>
<td>Anti-TNF</td>
<td>0.41</td>
</tr>
<tr>
<td>Combined</td>
<td>0.95</td>
</tr>
</tbody>
</table>


Kirchgesner, J, et al Gastroenterology 2018 155, 337-346

Lemaitre, M et al JAMA 2017; 318: 1679–1686
Combination therapy

**Positives**

- Pharmacokinetics
  - Higher drug levels
  - Optimizing 2 drugs?

**Negatives**

- Immunosuppression
  - Synergistic efficacy (?)
  - Infections (Steroids)
  - Malignancy (Thiopurines)

---

**Risk-Benefit of Stopping Combination Therapy**

**Benefits**
- Reduced risk of lymphoma (?)

**Risks**
- Disease Flare
- Disease Progression
Can We Stop Biologic and Continue Immunomodulator?

Discontinuation of Infliximab in Patients in Stable Remission on Combination Therapy (Azathioprine Maintained, STORI trial)

- 52 relapses in 115 patients
- Median (±SE) follow-up 21 ± 1 mo

Louis, E. Gastroenterology. 2012 142:63-70
Probability of Crohn’s Relapse on Azathioprine after Discontinuing Infliximab

Long-term response

“Deep Remission”


Pragmatic Approach to Stopping Immunomodulators

• Assure Deep Remission (Symptoms, Endoscopy, Biomarkers)
• Determine Trough Biologic Levels
  – Therapeutic Level → Stop IMM
  – Non-Therapeutic Level → Measure Thiopurine Level
    • Therapeutic Thioguanine → Consider Stopping Biologic (?) or Continue Combo (?)
    • Non-Therapeutic → Continue Combination (?)
Can Biologics be Restarted?

Long-term efficacy of Infliximab re-treatment (GETAID)

Kaplan Meier loss of response over time in the STORI cohort
52 retreated patients after 6.6 months drug holiday; 6/52 only loss of response over a median follow-up of 24 months

- Measuring Anti-Drug Antibodies NOT Likely Helpful
  - ADA's decline over time
  - Negative ADA does NOT Preclude Infusion Reaction
- Steroid-pre-treatment & Combination Therapy for Re-Induction
  - Observe for Inadequate Response
  - Consider TDM

Louis, E. Gastroenterology. 2012 142:63-70
Which Patients Should Receive Combination Biologic and Immunosuppressive Therapy?

- Patients Initiating TNF inhibitor
  - Continue for 6-12 months
  - Assess for Deep Remissions & Therapeutic Drug Levels
- Patients who have developed Immunogenicity with First Biologic starting Second Biologic
  - Continue for 6-12 months
  - Assess for Deep Remissions & Therapeutic Drug Levels
- Patients being treated without TDM

Which Patients Should NOT Receive Combination Biologic and Immunosuppressive Therapy?

- Teenage and young adult males appear to have an increased relative risk of hepatosplenic T-cell lymphoma with combination anti-TNF agents and thiopurines
  - Consider EBV titers for young males
- Patients >65 years have an increased risk of serious infection with anti-TNF therapy and combination therapy
- Patients >65 years have an increased risk of non-Hodgkin’s lymphoma with AZA therapy
Summary

• Higher rates of clinical response and remission demonstrated in IBD patients treated with TNFi combined with immunomodulators:
  – Associated with higher trough serum TNFi concentration, Lower incidence of anti-drug antibodies
• There are significant differences between TNFi anti-TNF drugs and vedolizumab/ustekinumab
  – Different nature of the target molecule, Longer half-life, Not certain strategies that optimize anti-TNF effectiveness are applicable to vedolizumab/ustekinumab
• Higher serum concentrations of vedolizumab and ustekinumab are associated with increased rates of clinical response and remission
• Currently available evidence suggests that concurrent treatment with immunomodulators does not result in higher serum vedolizumab/ustekinumab concentrations
• Anti-vedolizumab/Anti-ustekinumab antibodies are generated, although probably to a lesser extent and with less effect on vedolizumab/ustekinumab clearance compared with anti-TNF drugs
• No currently available studies that specifically assess additional benefit of adding immunomodulators to vedolizumab/Ustekinumab (most data do not suggest effect)

Future Treatment Strategy for Ulcerative Colitis

The AGA suggests early use of biologic agents with or without immunomodulator therapy, [or tofacitinib], rather than gradual step up after failure of 5-aminosalicylates.

High risk for colectomy:
• Extensive colitis
• Deep ulcer
• EIM
• Recurrent steroids

Low risk for colectomy:
• Limited extent
• Mild colitis

AGA UC decision tool 2015

Step-Up according to severity or failure at prior step

American College of Gastroenterology
Looking Backwards

• Be cautious of post-hoc analyses!
  – They are often disproven in prospective studies

Looking Forward

• Prospective studies of ustekinumab & vedolizumab + IMM in bio-/IMM naive
• Comparative effectiveness trial
• Expanding Real-World data
Questions?

Stephen B. Hanauer, MD, MACG

Mark C. Mattar, MD, FACG

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ACG Hepatology Circle
ACG Functional GI Health and Nutrition Circle
ACG GI Circle
ACG Women in GI Circle

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