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American College of Gastroenterology
Virtual Grand Rounds

ACG 2020 ABSTRACT SUBMISSION DEADLINE EXTENDED 2 WEEKS!

NEW!!

NEW!! DEADLINE: JUNE 15, 2020
11:59pm Eastern
ACG Virtual Grand Rounds

**Week 10: Colorectal Cancer Screening in a Post Covid World**  
Renee L. Williams, MD, MHPE, FACG  
*May 28, 2020 at Noon EDT*

**NEW! Week 11: Non-Alcoholic Steatohepatitis: Disease Burden, Diagnosis, and Treatment**  
Zobair M. Younossi, MD, MPH, FACG  
*June 4, 2020 at Noon EDT*

**Week 12: Gastroparesis: Then, Now, and The Future** – June 11, Noon  
**Week 13: Health Maintenance for the Patient with IBD** – June 18, Noon  
**Week 14: EOE and EGID: Pearls and Pitfalls** – June 25, Noon  
**Week 16: Managing Complications of Cirrhosis** – July 9, Noon

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ABIM Board Certified physicians need to complete their MOC activities by **December 31, 2020** in order for the MOC points to count toward any MOC requirements that are due by the end of the year. No MOC credit may be awarded after **March 1, 2021** for this activity.

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MOC QUESTION

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.

Include specific strategies or changes that you plan to implement. THESE ANSWERS WILL BE REVIEWED.

Disclosures

Dr. Rubin: Consultant and/or Grant Support

- AbbVie
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- Bristol-Myers Squibb
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- Pfizer
- Prometheus Laboratories
- Reistone
- Seres Therapeutics
- Shire
- Takeda
- Target PharmaSolutions, Inc.
- Techlab, Inc

Dr. Shah has indicated no relevant financial relationships.
Positioning of Old and New Therapies in IBD

David T. Rubin, MD, FACG
Joseph B. Kirsner Professor of Medicine
Chief, Section of Gastroenterology, Hepatology and Nutrition
University of Chicago
The Five Phases of Chronic Disease Management

- Pretreatment Assessment
- Initial Titration (Induction)
- Monitor and Re-establish Control
- Maintenance
- Cessation

Prior Treatments for IBD: The “Really Old”

- Intracolonic insufflation of oxygen
- Gentian violet
- Tincture of iodine
- Sodium lauryl sulfate detergent to “destroy” trypsin or lysozyme
- Vaccines
- Azochloramid (“antibacterial” agent)
- Horse serum
- Copper sulfate
- Liver extracts
- Artificial fever therapy
- Hot (120°F) water enemas
- “Extracts” of hog intestine, stomach, and colon to “restore” an “intestinal protective agent”
- Zinc peroxide rectally
- Thiouracil drugs
- Hypnosis
- Neuroanalysis

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Positioning Therapies in IBD c1950-1980s

Prednisone $\rightarrow$ Sulfasalazine

Sulfasalazine $\rightarrow$ Prednisone

Virtual Grand Rounds

Personalized Therapy with Old Drugs!

The New England Journal of Medicine

ADVERSE REACTIONS DURING SALICYLAZOSULFAPYRIDINE THERAPY AND THE RELATION WITH DRUG METABOLISM AND ACETYLATOR PHENOTYPE


AND W. Sercus, M.D., Ph.D., F.R.C.P. (London & Edin.)

GASTROENTEROLOGY 2000;118:859–866

Expression of Glucocorticoid Receptor $\beta$ in Lymphocytes of Patients With Glucocorticoid-Resistant Ulcerative Colitis

Mitsunori Honda, Fumika Orii, Tokiyoshi Ayabe, Shinjiro Imai, Toshifumi Ashida, Takeshi Obara, and Yutaka Kohgo
Virtual Grand Rounds

Theory of Mechanistic Targeting in IBD Management

- Inflammation is a defense reaction to real or perceived threats to preserve self
  - Layered, duplicitous and redundant

- Targeting a dominant pathway (or more than one) may reduce the inflammatory response and “reset” homeostatic control (healing)
  - Persistent drive (antigenic?) may override this approach and result in “mechanistic escape” and loss of response to a specific target


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Modern Treatments for IBD

<table>
<thead>
<tr>
<th>Immune modification/suppression</th>
<th>Microbiota manipulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-ASA (?)</td>
<td>Dietary therapies (exclusion diets)</td>
</tr>
<tr>
<td>Steroids</td>
<td>Antibiotics</td>
</tr>
<tr>
<td>Thiopurines/methotrexate</td>
<td>Prebiotics</td>
</tr>
<tr>
<td>Anti-TNFα therapies</td>
<td>Probiotics</td>
</tr>
<tr>
<td>Anti-integrin therapies</td>
<td>Intestinal microbiota transfer</td>
</tr>
<tr>
<td>Anti-IL12/23</td>
<td>Bacterial derived proteins</td>
</tr>
<tr>
<td>JAK inhibitors</td>
<td></td>
</tr>
</tbody>
</table>

Surgery

- Resection of fibrostenosis
- Resection in medically resistant disease
**Treatment Options for Moderate-to-Severe IBD**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Induction</th>
<th>Maintenance</th>
<th>Other Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroids</td>
<td>CD, UC</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Thiopurines</td>
<td>X</td>
<td>CD, UC</td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>CD</td>
<td>CD</td>
<td></td>
</tr>
<tr>
<td>Anti-integrin (natalizumab, vedolizumab)</td>
<td>Natalizumab CD Vedolizumab CD, UC</td>
<td>Natalizumab CD Vedolizumab CD, UC</td>
<td>Natalizumab MS</td>
</tr>
<tr>
<td>Anti-p40 (ustekinumab)</td>
<td>CD, UC</td>
<td>CD, UC</td>
<td>Psoriasis, PsA</td>
</tr>
<tr>
<td>Anti-TNF (adalimumab(^1), certolizumab pego(^2), golimumab(^3), infliximab(^4))</td>
<td>CD, UC</td>
<td>CD, UC</td>
<td>PsA, SpA, RA, uveitis, etc</td>
</tr>
<tr>
<td>JAK inhibitor (tofacitinib)</td>
<td>UC</td>
<td>UC</td>
<td>RA, PsA</td>
</tr>
</tbody>
</table>

---

**Traditional Treatment Sequence in IBD**

- New therapies positioned agnostic to existing ones
- Anti-TNF
- Natailizumab
- Cyclosporine/Tacrolimus
- Mycophenolate
- Azathioprine
- Methylprednisolone
- Infliximab
- Gastroenteritis
- Uveitis

*Doesn’t suggest that de-escalation is possible

**No predictive therapeutic biomarkers**

**Assumption that induction dictates maintenance in all patients**

**Fail first before stepping up**
1. Understand the Multiple Dimensions of Disease Control

- Patient Factors
  - BMI
  - Gender
  - Nutritional status
  - Pharmacogenomics
  - Adherence
  - Smoking

- Therapy Factors
  - Resections
  - Prior failed therapy
  - Steroids
  - Dose-Response
  - Half-life
  - Delivery
  - Antibody complexes

- Disease Control
  - Lag time before dx
  - Phenotype
  - Genotype
  - Microbiome
  - Immunology
  - CRP
  - Disability Index

And know how this changes OVER TIME!


2. Employ Treat to Target

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

2. Choose a Target that Is Individualized for Your Patient (and reliable)

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

Treating to Target


3. Match Treatment Intensity to Inflammatory Burden

Induction therapy continues at same dose as maintenance

Time

Therapy intensity

Inflammatory burden
4. Choose Induction Therapies Wisely

- Based on disease activity and risk for bad outcomes
- Would surgery be best? (LIRIC)\(^1\)
- Based on likelihood of rapid clearance or absorption issues (BMI, gender, CRP, albumin, prior immunogenicity)\(^2\)
- Use organ-selective therapies before systemic therapies\(^3\)
- Based on prior treatment history that worked or did not (Cycle vs. Swap)\(^4\)
- Based on co-morbid illnesses (RA? Psoriasis? SpA? PsA? DM?)

---

\(^4\)Yarur AJ and Rubin DT. Inflamm Bowel Dis. 2015;21(7):1709-18.

---

**Specific Scenarios for Choice of First IBD Therapy**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Modifier</th>
<th>First drug consideration</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD</td>
<td>Perianal</td>
<td>Anti-TNF</td>
<td>Best studied, on label (IFX)</td>
</tr>
<tr>
<td>IBD</td>
<td>Psoriasis</td>
<td>Ustekinumab</td>
<td>On label</td>
</tr>
<tr>
<td>IBD</td>
<td>&gt;60 yo</td>
<td>Vedolizumab, Ustekinumab</td>
<td>Older patients have higher risk of infections</td>
</tr>
<tr>
<td>UC</td>
<td>Synovitis, Arthritis</td>
<td>Anti-TNF or Tofacitinib</td>
<td>On label</td>
</tr>
<tr>
<td>UC</td>
<td>Low albumin</td>
<td>Cyclosporine, Tacrolimus, Tofacitinib</td>
<td>Non-protein-based therapies</td>
</tr>
</tbody>
</table>
5. Optimize Treatment

- Combine therapies:
  - Anti-TNF with IMM
  - Anti-TNF with antibiotics in perianal disease
- Judicious use of proactive therapeutic drug monitoring:
  - Post-loading drug levels in high-risk patients (infliximab week 8, adalimumab week 4)
  - Pediatrics: proactive monitoring of adalimumab beneficial (PAILOT)\(^1\)
  - 6-thioguanine metabolites to assess thiopurines
- Match therapy to disease activity!


---

Fecal Calprotectin Predicts Endoscopic Response to Therapy with VDZ and UST

- FC levels decreased as early as week 2 in responders
- FC<250 ug/g at week 8 predicts endoscopic response at week 16

**Optimizing Response to Thiopurines**

Understand TMPT and NUDT15

<table>
<thead>
<tr>
<th>6-TG</th>
<th>6-MMP</th>
<th>Possible cause</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undetectable</td>
<td>Undetectable</td>
<td>Non-adherent or underdosed</td>
<td>Understand why pt not taking med or increase dose</td>
</tr>
<tr>
<td>Low (&lt;230)</td>
<td>Low or undetectable</td>
<td>Non-adherent or underdosed</td>
<td>Discuss adherence, increase dose</td>
</tr>
<tr>
<td>Low (&lt;230)</td>
<td>High (&gt;5700)</td>
<td>6-MMP shunter</td>
<td>1. Consider allopurinol, or 2. Switch agents</td>
</tr>
<tr>
<td>“Therapeutic” (&gt;230-&lt;400) or High (&gt;400)</td>
<td>Normal range or high</td>
<td>Primary non-responder</td>
<td>1. Assess disease 2. Switch agents</td>
</tr>
</tbody>
</table>

Optimizing Response to Biologics

• CD patients with short disease duration treated with anti-TNF:
  - Respond better\(^1\)
  - Lose response less often\(^2\)
  - Have less surgery\(^3\)

• Your first therapy will work better
  - Vedolizumab
  - Ustekinumab
  - Tofacitinib


Comparative Effectiveness Studies in IBD Favor Anti-TNF (mostly infliximab) Combined with IMMস...

...BUT, Infliximab Level is A More Important Predictor of Remission Than Combination Therapy
SONIC Post-hoc Analysis


It is Safe to Stop 5-ASA in Patients Escalated to Biological Therapy

- Analysis of clinical trials of infliximab and golimumab in moderate-severe UC
- Health claims data of UC and CD

5-ASA vs. no concomitant 5-ASA in TNFi-treated patients

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Adjusted OR (95% CI)</th>
<th>p-value</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Remission</td>
<td>0.67 (0.45-1.01)</td>
<td>0.06</td>
<td>Clinical Remission</td>
</tr>
<tr>
<td>Clinical Response</td>
<td>0.89 (0.60-1.33)</td>
<td>0.58</td>
<td>Clinical Response</td>
</tr>
<tr>
<td>Endoscopic Remission</td>
<td>1.12 (0.82-1.51)</td>
<td>0.48</td>
<td>Endoscopic Remission</td>
</tr>
<tr>
<td>Biochemical Remission</td>
<td>0.94 (0.61-1.46)</td>
<td>0.79</td>
<td>Biochemical Remission</td>
</tr>
</tbody>
</table>

Risk of major adverse outcomes according to 5-ASA use

More Anti-TNF is Not Always Better

- Meta-analysis: accelerated dosing of infliximab in acute severe UC does not prevent colectomy\(^1\)

- High-dose adalimumab (160 mg qw x 4) not better than standard dosing (160 mg week 0 then 80 mg week 2) in induction of remission in UC\(^2\)

---


---

6. Choose Maintenance Therapies Wisely

- Based on induction therapy
- Don’t forget adherence issues!
- Don’t forget changes that may occur over time: MONITOR for LOR
  - Are symptoms stable between doses?
  - Objective assessment over time

---

Can You De-intensify Therapy?

Induction therapy continues at same dose as maintenance

Inflammatory burden

Therapy intensity

Time

How long?

Drug

Drug

Examples of “De-Intensification” of Therapy

• Steroid induction → steroid-sparing maintenance therapy

• 5-ASA
  • 4.8 g induction can be reduced to 2.4 g maintenance (IF ENDOSCOPIC IMPROVEMENT)¹

• Concomitant IMM + anti-TNF therapy
  • Possibility of withdrawing IMM (IMM experienced)²
  • Possibility of withdrawing anti-TNF (Crohn’s disease)³ (IF DEEP REMISSION)

7. Planning for De-escalation in IBD

1. Discuss WHY this might be reasonable (Is the patient healthy because of your therapy or in spite of it?)
2. Confirm deep remission (mucosal healing), preferably for >1 year
3. Confirm optimization of drug (make SURE it’s working)
4. De-escalate
5. Have a monitoring strategy (Serial labs, fecal calprotectin, scope)
6. Know your rescue plan (Resume prior therapy or Move on to next strategy)


8. Reasons to Switch Therapies and What to Choose

<table>
<thead>
<tr>
<th>Disease</th>
<th>Modifier</th>
<th>First drug consideration</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>UC/CD</td>
<td>Anti-TNF-induced lupoid reaction</td>
<td>Non-anti-TNF</td>
<td>Not reported with non-anti-TNF drugs</td>
</tr>
<tr>
<td>UC/CD</td>
<td>Joint pain+ vedolizumab</td>
<td>Anti-TNF (UC+CD)</td>
<td>On label</td>
</tr>
<tr>
<td>UC/CD</td>
<td>Anti-TNF-induced psoriasis or palmar plantar pustulosis</td>
<td>Ustekinumab (CD) Tofacitinib (UC) Vedenizumab (UC+CD)</td>
<td>On label Not reported Case Reports¹</td>
</tr>
<tr>
<td>UC/CD</td>
<td>Cancer (solid tumor)</td>
<td>None during Chemo Vedenizumab Ustekinumab</td>
<td>Safety</td>
</tr>
</tbody>
</table>

9. Be Smart About Loss of Response

1. Confirm adherence
2. Rule out infection
3. Confirm inflammation
4. Assess drug
5. If anti-drug antibodies, take precautions on the next treatment (use combination therapy)


Can you Go Back to a Therapy That Had Worked and Stopped Working?

Circling Backwards

- If the inflammatory pathway is reactivated: YES
- If prior loss of response was due to anti-drug antibodies: NO
- After surgery:
  - Did the patient just need surgery anyway, and that was the reason for the lack of response to therapy? YES
  - Did the patient progress right through the prior therapy? NO
Novel Treatment Considerations – 1
Two Step Management

**INDUCTION** | **MAINTENANCE**
---|---
**Cytokine inhibition:**
- TNFi
- IL23
- JAKinib
| **Cellular inhibition:**
- Anti-integrin
- S1P1 receptor modulator
- Thiopurine

**Microbiota “pre-treatment”:**
- Intestinal microbiota transfer\(^1\)
- Antibiotics\(^2\)
| **Microbiota maintenance:**
- Diet
- Prebiotics
- Bacterial products
- Antibiotics?

**Surgery:**
- Ileocecectomy “curative resection”
- Diverting ileostomy

---

Novel Treatment Considerations – 2
Combination Approaches

- **Biological combinations**
- **Small molecule and biological combinations**
  - To prevent immunogenicity
  - To combine mechanisms of action
- **Antibiotics and immune suppressives**
- **Diet plus immunobiological therapies**

---
Clinical Gastroenterology and Hepatology 2019;17:406-403
Safety and Efficacy of Combination Treatment With Calcineurin Inhibitors and Vedolizumab in Patients With Refractory Inflammatory Bowel Disease
Britt Christensen,1,2,3 Peter R. Gibson,1 Dajana Mioc,1 Ruben J. Coleman,1 Sarah R. Goepfert,1 Olufemi Kassim,1 Andrea Yarur,1 Christopher R. Weber,1 Russell D. Cohen,1 and David T. Rubin2


Calcineurin Induction Therapy Followed by Maintenance on Vedolizumab in IBD

<table>
<thead>
<tr>
<th>Author/Center</th>
<th>Design</th>
<th>N</th>
<th>Week 14 Clinical Remission</th>
<th>Week 52 Clinical Remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Christensen B/UChicago CGH 2019</td>
<td>Retrospective</td>
<td>20</td>
<td>55%</td>
<td>45%</td>
</tr>
<tr>
<td>Ollech J/UChicago APT 2019</td>
<td>Retrospective</td>
<td>71</td>
<td>50%</td>
<td>43% (28% at 2 y)</td>
</tr>
<tr>
<td>Pellet G/GETAID CGH 2019</td>
<td>Retrospective</td>
<td>39</td>
<td>38%</td>
<td>--</td>
</tr>
<tr>
<td>Tarabar D/Serbia UEGW 2018</td>
<td>Prospective</td>
<td>17</td>
<td>93%</td>
<td>79%</td>
</tr>
</tbody>
</table>


The Ongoing Search for Therapeutic Biomarkers

Clinical Prediction Tools
Example: Vedolizumab Use in Crohn’s Disease

Common Predictors
- No prior bowel surgery (+ 2 points)
- No prior anti-TNF exposure (+ 3 points)
- No prior fistulizing disease (+ 2 points)
- Baseline albumin g/L (+ 0.4 points per g/L)
- Baseline CRP mg/L
  - 0-0.5 points if 3.0-10.0 mg/L
  - 3.0 points if > 10 mg/L

Low Probability of Response
(≤ 13 points)

High Probability of Response
(> 19 points)

Future of Personalized Management of IBD

Immune panel
Inflammation and response to therapy measured
Patient achieves remission
Ongoing monitoring occurs
Immune panel is repeated

New dominant pathways identified
OR Subclinical inflammation detected
Therapy changed/optimized

PK Dashboard

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