Positioning of Old and New Therapies in IBD

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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 ➔ Sulfasalazine

Sulfasalazine ➔ Prednisone
Personalized Therapy with Old Drugs!

Virtual Grand Rounds

The New England Journal of Medicine

Volume 289 SEPTEMBER 6, 1973 Number 10

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


GASTROENTEROLOGY 2000;118:859-866

Expression of Glucocorticoid Receptor β in Lymphocytes of Patients With Glucocorticoid-Resistant Ulcerative Colitis

MITSUNORI HONDA, FUMIKA ORIIL, TOKIYOSHI AYABE, SHINJIRO INAI, TOSHIFUMI ASHIDA, TAKESHI OBARA, and YUTAKA KOHGO

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

Modern Treatments for IBD

**Immune modification/suppression**
- 5-ASA (?)
- Steroids
- Thiopurines/methotrexate
- Anti-TNFα therapies
- Anti-integrin therapies
- Anti-IL12/23
- JAK inhibitors

**Microbiota manipulation**
- Dietary therapies (exclusion diets)
- Antibiotics
- Prebiotics
- Probiotics
- Intestinal microbiota transfer
- Bacterial derived proteins

**Surgery**
- Resection of fibrostenosis
- Resection in medically resistant disease

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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 (adalimumab¹, certolizumab pego², golimumab³, infliximab⁴)</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
- Vedolizumab (CD, UC)
- Ustekinumab (CD, UC)
- Corticosteroids
- Aminosalicylate
- Anti-TNF
- Anti-TNF/Thiopurine/MTX
- Cyclosporine/Tacrolimus
- Natalizumab
- Infliximab (UC)
- Aminosalicylate (UC)/Thiopurine (UC/CD)/MTX (CD)
- Assumption that induction dictates maintenance in all patients
- Fail first before stepping up

Doesn't suggest that de-escalation is possible

No predictive therapeutic biomarkers

1. Understand the Multiple Dimensions of Disease Control

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

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

- 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

3. Match Treatment Intensity to Inflammatory Burden

Induction therapy continues at same dose as maintenance

4. Choose Induction Therapies Wisely

- Based on disease activity and risk for bad outcomes
- Would surgery be best? (LIR!C)\(^1\)
- 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 IMMs
  - 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!**

**Virtual Grand Rounds**

### 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

![Graphs showing response to Vedolizumab and Ustekinumab](image)


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### 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 Thiopurines

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</table>
| Low (<230) | High (>5700) | 6-MMP shunter  | 1. Consider allopurinol, or  
|            |          |                                | 2. Switch agents                               |
| “Therapeutic” (>230–<400) or High (>400) | Normal range or high | Primary non-responder | 1. Assess disease  
|            |          |                                | 2. Switch agents                               |


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 IMMs...

SONIC Trial (CD)\textsuperscript{1}

Steroid-free Remission
Wk 26

<table>
<thead>
<tr>
<th>Group</th>
<th>AZA + PBO</th>
<th>IFX + PBO</th>
<th>IFX + AZA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (%)</td>
<td>30.0%</td>
<td>44.4%</td>
<td>56.8%</td>
</tr>
</tbody>
</table>

UC SUCCESS Trial\textsuperscript{2}

Steroid-free Remission
Wk 16

<table>
<thead>
<tr>
<th>Group</th>
<th>AZA</th>
<th>IFX</th>
<th>IFX + AZA</th>
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</thead>
<tbody>
<tr>
<td>Patients (%)</td>
<td>24%</td>
<td>22%</td>
<td>40%</td>
</tr>
</tbody>
</table>


...BUT, Infliximab Level is A More Important Predictor of Remission Than Combination Therapy

SONIC Post-hoc Analysis

<table>
<thead>
<tr>
<th>IFX Concentration at Week 30 (µg/mL)</th>
<th>Q1 (N=51)</th>
<th>Q2 (N=52)</th>
<th>Q3 (N=51)</th>
<th>Q4 (N=52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1: &lt;0.84 µg/mL; Q2: 0.84-2.36 µg/mL; Q3: 2.36-5.02 µg/mL; Q4 ≥5.02 µg/mL.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Virtual Grand Rounds**

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\(^1\)
- Health claims data of UC and CD\(^2,3\)

<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 Remission</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

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**Virtual Grand Rounds**

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\(^2\)

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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

![CRP Evolution](image1)

![Calprotectin Evolution](image2)


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Can You De-intensify Therapy?

Induction therapy continues at same dose as maintenance

How long?

Drug

Therapy intensity

Inflammatory burden

Time
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) Tofacitinib (UC)</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) Vedolizumab (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 Vedolizumab 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

<table>
<thead>
<tr>
<th>INDUCTION</th>
<th>MAINTENANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokine inhibition:</td>
<td>Cellular inhibition:</td>
</tr>
<tr>
<td>• TNF i</td>
<td>• Anti-integrin</td>
</tr>
<tr>
<td>• IL23</td>
<td>• S1P1 receptor modulator</td>
</tr>
<tr>
<td>• JAKinib</td>
<td>• Thiopurine</td>
</tr>
<tr>
<td>Microbiota “pre-treatment”:</td>
<td>Microbiota maintenance:</td>
</tr>
<tr>
<td>• Intestinal microbiota transfer¹</td>
<td>• Diet</td>
</tr>
<tr>
<td>• Antibiotics²</td>
<td>• Prebiotics</td>
</tr>
<tr>
<td>Surgery:</td>
<td>• Bacterial products</td>
</tr>
<tr>
<td>• Ileocectomy “curative resection”</td>
<td>• Antibiotics?</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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>
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<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></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

Virtual Grand Rounds

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