New Perspectives on the Diagnosis and Management of IBD

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Professor of Pediatrics
Icahn School of Medicine at Mount Sinai

Disclosures

• Grant Support:
  – Abbvie, Astra-Zeneca, Janssen

• Consultant:
  – Abbvie, Given, Janssen, Soligenix

• Honoraria/Speakers’ Bureau
  – Abbott Nutrition, Abbvie, Prometheus
OBJECTIVES

• Assess the 5-aminosalicylic acid (5-ASA) formulations utilized in IBD
• Identify patient non-adherence as a strong deterrent to favorable clinical outcomes
• Examine the efficacy and safety for existing, new, and emerging diagnostics and treatments
• Analyze individualized IBD treatments that help to optimize outcomes
• Describe the novel technological advancements to assess disease activity in IBD

Key Point 1:

IBD is a Complex Disorder that May Require a Genetically Susceptible Host with an Appropriate Environmental Trigger(s)

Pathogenesis of IBD

Key Point 2:

IBD Results from an Exaggerated Mucosal Immune Response to Commensal Microorganisms

Incidence of IBD is Increasing Dramatically Worldwide

Inflammatory Bowel Diseases

• **Chronic** intestinal inflammation from a dysregulated immune response to the enteric microbiome in a genetically predisposed host
• Today we label them as Crohn’s disease and ulcerative colitis though we recognize a host of often overlapping phenotypes
• Presenting symptoms range from mild to severe and clinical course is often unpredictable ranging from easily controlled to fulminant disease

OBJECTIVES

• Assess the 5-aminosalicylic acid (5-ASA) formulations utilized in IBD
• Identify patient non-adherence as a strong deterrent to favorable clinical outcomes
  • Examine the efficacy and safety for existing, new, and emerging diagnostics and treatments
  • Analyze individualized IBD treatments that help to optimize outcomes
  • Describe the novel technological advancements to assess disease activity in IBD
Mesalamine: Clinical Pharmacology

5-HETE = 5-hydroxyeicosatetraenoic acid; PG = prostaglandin; TX = thromboxane.

5-ASA Content of 5-ASA Preparations

<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade</th>
<th>5-ASA Content (%)</th>
<th>Usual Dosage</th>
<th>Amount of 5-ASA Delivered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfasalazine</td>
<td>Azulfidine, Azulfidine EN, Sulfazine, Sulfazine EC</td>
<td>38</td>
<td>4 g</td>
<td>1.6 g</td>
</tr>
<tr>
<td>Mesalamine</td>
<td>Apriso, Asacol HD, Canasa, Delzicol, Lialda, Pentasa, Rowasa, SfRowasa,</td>
<td>100</td>
<td>2.4-4.8 g</td>
<td>2.4-4.8 g</td>
</tr>
<tr>
<td>Balsalazide</td>
<td>Colazal, Giazo</td>
<td>35</td>
<td>3.3-6.75 g</td>
<td>1.2 g-2.4 g</td>
</tr>
<tr>
<td>Olsalazine</td>
<td>Dipentum</td>
<td>100</td>
<td>1 g</td>
<td>1 g</td>
</tr>
</tbody>
</table>

Adapted from: Ulcerative Colitis-The Complete Guide to Medical Management (Lichtenstein)

Current Therapy for Newly Diagnosed Children with Crohn’s Disease (N=1271)*

<table>
<thead>
<tr>
<th>Therapy</th>
<th>By Q1</th>
<th>By Q2</th>
<th>By Q4</th>
<th>By Q8</th>
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<tbody>
<tr>
<td>Corticosteroids</td>
<td>927 (76%)</td>
<td>943 (78%)</td>
<td>968 (83%)</td>
<td>1008 (89%)</td>
<td>1022 (93%)</td>
</tr>
<tr>
<td>6MP/Aza</td>
<td>634 (53%)</td>
<td>728 (63%)</td>
<td>807 (72%)</td>
<td>854 (81%)</td>
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</tr>
<tr>
<td>Methotrexate</td>
<td>71 (6%)</td>
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<td>141 (14%)</td>
<td>199 (24%)</td>
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</tr>
<tr>
<td>5-ASA/SASP</td>
<td>783 (64%)</td>
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<td>849 (72%)</td>
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</tr>
<tr>
<td>Infliximab</td>
<td>145 (11%)</td>
<td>202 (16%)</td>
<td>281 (22%)</td>
<td>395 (31%)</td>
<td>449 (35%)</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>2 (0.2%)</td>
<td>9 (1%)</td>
<td>18 (2%)</td>
<td>41 (5%)</td>
<td>63 (12%)</td>
</tr>
<tr>
<td>Enteral Nutrition</td>
<td>72 (6%)</td>
<td>77 (7%)</td>
<td>83 (8%)</td>
<td>96 (12%)</td>
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5ASA Maintenance in Pediatric CD: Placebo Controlled RCT

N = 122
Mesalamine for Maintenance of Medically Induced Remission in Crohn’s Disease

Risk Difference 95% CI

<table>
<thead>
<tr>
<th>Study</th>
<th>Date</th>
<th>Risk Difference</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>Thomson</td>
<td>1990</td>
<td>-0.5</td>
<td>-0.4</td>
</tr>
<tr>
<td>Pranera</td>
<td>1992</td>
<td>-0.3</td>
<td>-0.2</td>
</tr>
<tr>
<td>Brignola</td>
<td>1992</td>
<td>-0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Gendre</td>
<td>1993</td>
<td>0.2</td>
<td>0.3</td>
</tr>
<tr>
<td>Bresci</td>
<td>1994</td>
<td>0.4</td>
<td>0.5</td>
</tr>
<tr>
<td>Thomson</td>
<td>1995</td>
<td>1</td>
<td></td>
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<tr>
<td>Arba</td>
<td>1995</td>
<td>0.1</td>
<td>0.2</td>
</tr>
<tr>
<td>Modigliani</td>
<td>1996</td>
<td>0.3</td>
<td>0.4</td>
</tr>
<tr>
<td>Sutherland</td>
<td>1997</td>
<td>0.5</td>
<td>0.6</td>
</tr>
<tr>
<td>De Francisco</td>
<td>1997</td>
<td>0.7</td>
<td>0.8</td>
</tr>
<tr>
<td>Overall Studies</td>
<td>n=1371</td>
<td>Favors Treatment</td>
<td>Favors Control Group</td>
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Outcome of 5 ASA Therapy: Newly Diagnosed Pediatric UC

TABLE 1. Outcome at 1 year following initiation of 5-ASA compounds in newly diagnosed pediatric patients with ulcerative colitis by treatment group and disease severity at diagnosis (PGA)

<table>
<thead>
<tr>
<th></th>
<th>CS-free/mild-free</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PGA inactive</td>
</tr>
<tr>
<td></td>
<td>N</td>
</tr>
<tr>
<td>All patients</td>
<td>213</td>
</tr>
<tr>
<td>S-ASA only</td>
<td>98</td>
</tr>
<tr>
<td>S-ASA+CS only</td>
<td>115</td>
</tr>
</tbody>
</table>

Outcome of 5 ASA Therapy: Newly Diagnosed Pediatric UC

Only 33% were offered rectal therapy by one year

Treatment of Distal UC: Oral and Rectal Mesalamine Therapy


**Patients Reporting No Rectal Bleeding (%)**

<table>
<thead>
<tr>
<th>Time</th>
<th>Oral (2.4 g/d)</th>
<th>Rectal (4 g/d)</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Week</td>
<td>25</td>
<td>25</td>
<td>50</td>
</tr>
<tr>
<td>2 Weeks</td>
<td>25</td>
<td>25</td>
<td>50</td>
</tr>
<tr>
<td>3 Weeks</td>
<td>25</td>
<td>25</td>
<td>50</td>
</tr>
<tr>
<td>6 Weeks</td>
<td>25</td>
<td>25</td>
<td>50</td>
</tr>
</tbody>
</table>

*P<.05 vs oral alone

Slide Courtesy of the GI Health Foundation

Crohn’s and Colitis Foundation of America Survey: Primary Reasons for Nonadherence

90% of nonadherent patients “just forgot” to take their medication

N=944 nonadherent patients; some questions within the survey allowed more than 1 response per respondent.
Adherence: 5-ASA Persistency at 12 Months

Medical Event Monitoring System: MEWS Cap
### 5-ASA and 6-MP Adherence by MEMS Cap

<table>
<thead>
<tr>
<th></th>
<th>COHORT I NEWLY DX</th>
<th>COHORT II PREVIOUSLY DX</th>
<th>F</th>
<th>SIG</th>
<th>(total adherence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-ASA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-MP</td>
<td></td>
<td></td>
<td></td>
<td></td>
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### 5-ASA and 6-MP Adherence by MEMS Cap

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<th>SIG</th>
<th>(total adherence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-ASA</td>
<td>59.95</td>
<td>46.23</td>
<td>2.32</td>
<td>.13</td>
<td>53%</td>
</tr>
<tr>
<td>6-MP</td>
<td>43.25</td>
<td>60.73</td>
<td>2.26</td>
<td>.14</td>
<td>48%</td>
</tr>
</tbody>
</table>

5 ASA in IBD: Conclusions

- 5ASA is commonly used by GI community
- Evidence for efficacy in CD very limited
  - ?correct phenotype (colonic + careful monitoring)
- 40% steroid free remission at 1 yr in Peds UC
  - Role of adherence
  - ?does dose matter
  - ? Role for greater use of rectal administration

OBJECTIVES

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- Analyze individualized IBD treatments that help to optimize outcomes
- Describe the novel technological advancements to assess disease activity in IBD
### IBD: Therapeutic Themes

- Induction therapies
- Maintenance therapies
- “Step in” is better than “step up”
- Optimization of therapy
- Treat the whole patient

### IBD: Management Goals

- Address psychosocial issues
- Identify dysplasia and detect cancer
- Improve daily functioning
- Replenish nutritional deficits
- Relieve symptoms
- Treat inflammation
- Treat complications
- Minimize treatment toxicity
- Maintain remission
## Approved Drugs for IBD

<table>
<thead>
<tr>
<th>Agent</th>
<th>Adult Approval</th>
<th>Pediatric Approval</th>
<th>Agent</th>
<th>Adult Approval</th>
<th>Pediatric Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azulfidine</td>
<td>Yes</td>
<td>“Yes”*</td>
<td>Remicade CD + UC</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Pentasa</td>
<td>Yes</td>
<td>No</td>
<td>Humira UC</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Asacol</td>
<td>Yes</td>
<td>No</td>
<td>Humira CD</td>
<td>Yes</td>
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<td>Asacol HD</td>
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<td>Cimzia CD</td>
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<td>Simponi UC</td>
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<td>Apriso</td>
<td>Yes</td>
<td>No</td>
<td>Entyvio CD</td>
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<tr>
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<td>Yes</td>
<td>No</td>
<td>Tysabri</td>
<td>Yes</td>
<td>No</td>
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<td>Colazal</td>
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<td>“Yes”</td>
<td>AZA</td>
<td>No</td>
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<td>Pred</td>
<td>“Yes”*</td>
<td>“Yes”</td>
<td>6MP</td>
<td>No</td>
<td>No</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>MTX</td>
<td>No</td>
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* Grandfathered in, minimal data

## Sequential Therapies for UC

<table>
<thead>
<tr>
<th>Disease Severity at Presentation</th>
<th>Colectomy</th>
<th>Anti-TNF</th>
<th>Anti-TNF</th>
<th>Aminosalicylate</th>
<th>Thiopurine</th>
<th>Aminosalicylate</th>
<th>Corticosteroid</th>
<th>Aminosalicylate</th>
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<td>Severe</td>
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<td>Cyclosporine</td>
<td>Thiopurine</td>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Moderate</td>
<td></td>
<td></td>
<td>Anti-TNF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td></td>
<td></td>
<td></td>
<td>Thio purine</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>Mild</td>
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Therapy is stepped up according to severity at presentation or failure at prior step. Slide Courtesy of the GI Health Foundation
Sequential Therapies for Crohn’s Disease

Disease Severity at Presentation

- Severe
- Moderate
- Mild

Step-up according to severity at presentation or failure at prior step

Natalizumab

Anti-TNF

Anti-TNF +/- Thiopurine/MTX

Induction

Maintenance

Inflammation

Structuring

Impact of Therapy Depends on Degree of Structural Damage and Velocity of Progression

Cumulative Probability (%)

Patients at risk: N = 2002 552 229 95 37

Cosnes J et al. Inflamm Bowel Dis. 2002;8:244-250.
Progressive Bowel Damage in CD

Pariente et al. Inflamm Bowel Dis 2011

GWAS Studies Have Identified over 180 Inflammatory Bowel Disease Susceptibility Loci

IBD patients may have unique signatures that predict complicated or treatment refractory disease

Clinical features: age, location, endoscopy, histology, etc.

FAMILY HISTORY
HOST GENETICS
GENE EXPRESSION
MICROBIOME
SMOKING
STRESS
NSAIDs
DIET

ENVIRONMENTAL FACTORS

GENETIC SUSCEPTIBILITY

INNATE RESPONSE

ADAPTIVE RESPONSE

SEROLOGICAL RESPONSE

BILOGICS
SURGERY
PHARMACOGENOMICS
MONITORING
ADHERENCE

ELEVEVING CLASSIFICATION
(Diabetes as the Model)

ULCERATIVE COLITIS
• Mucosal
• Continuous

CROHNS DISEASE
• Transmural
• Discontinuous
• Oral → Peri-anal

IBD 1
IBD 2
IBD 3
IBD 4
IBD 5

Indeterminate Colitis
Sequential Therapies for Crohn’s Disease

IBD: Therapeutic Themes

- Induction therapies
- Maintenance therapies
- “Step in” is better than “step up”
- Optimization of therapy
- Treat the whole patient
Predictors of Disabling Crohn’s

Referred cohort of 1128 CD patients

3 factors independently predictive disabling CD course within 5-year

- Initial requirement for steroids
  OR: 3.1  [95% CI: 2.2 – 4.4]
- Age at diagnosis below 40
  OR: 2.1  [95% CI: 1.3 – 3.6]
- Perianal disease at diagnosis
  OR: 1.8  [95% CI: 1.2 – 2.8]

Beaugerie L et al. Gastroenterology 2006;130:650-6

Consensus Predictors of Poor Outcome*

- Deep colonic ulcerations on endoscopy
- Persistent severe disease despite adequate induction therapy
- Extensive (pan-enteric) disease
- Marked growth retardation (> -2.5 height Z scores),
- Severe osteoporosis
- Stricturing or penetrating disease (B2 and/or B3 disease behavior) at onset
- Severe perianal disease

SONIC: Steroid Free Remission

All Randomized Patients (N=508)*

- AZA + placebo
- IFX + placebo
- IFX + AZA


Vedolizumab: Primary Maintenance Endpoint For Adult Crohn’s Disease

- VDZ / Placebo (n=153)
- VDZ / VDZ Q8w (n=154)
- VDZ / VDZ Q4w (n=154)

Δ=15%
p=0.01

Δ=17%
p<0.001
LOSS OF RESPONSE TO ANTI-TNF THERAPIES

Special Considerations: Biologics

- Mono vs. Combination therapy
- Dose optimization
- Immunogenicity
  - Therapeutic Drug Monitoring

Ben-Horin, Aliment Pharmacol Ther 2011;33:987
Loss of Response After Immunomodulator Withdrawal

Loss of Response after Immunomodulator Withdrawal

TL=trough levels
Drobne D et al. DDW 2011; Abstract 279

Proactive Testing in Pediatric IBD: Week 14 IFX Levels and Outcomes

(n=58)

<table>
<thead>
<tr>
<th>Week 54 Outcome (Yes v. No)</th>
<th>Median IFX Level (ug/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent Remission</td>
<td>4.7 versus 2.6*</td>
</tr>
<tr>
<td>Clinical Remission</td>
<td>3.2 versus 2.2</td>
</tr>
<tr>
<td>Clinical &amp; Laboratory Remission</td>
<td>4.2 versus 3.0</td>
</tr>
<tr>
<td>Sustained Durable Remission Week 14 to 54</td>
<td>5.5 versus 3.1*</td>
</tr>
<tr>
<td>Sustained Durable Remission Week 22 to 54</td>
<td>5.1 versus 3.0*</td>
</tr>
</tbody>
</table>

* p<0.05
Singh et al. Inflamm Bowl Disease 2014;20:1708
TREAT TO TARGET: WHAT DO WE MEAN?

- Regular assessment of disease activity using objective clinical and biologic outcome measures
- Adjust treatment if not accomplishing the goal
- Enables better outcomes in RA, hypertension, diabetes, hypercholesterolemia

Bouguen, Clin Gastroenterol Hepatol ePub 2013 Sep 10, PMID 24036054

SUGGESTED ALGORITHM

Bouguen, Clin Gastroenterol Hepatol ePub 2013 Sep 10, PMID 24036054
IS MUCOSAL HEALING ACHIEVABLE?


67 CD patients underwent 161 endoscopies

Figure 1. Cumulative probability of achieving MH.

OBJECTIVES

- Assess the 5-aminosalicylic acid (5-ASA) formulations utilized in IBD
- Identify patient non-adherence as a strong deterrent to favorable clinical outcomes
- Examine the efficacy and safety for existing, new, and emerging diagnostics and treatments
- Analyze individualized IBD treatments that help to optimize outcomes
- Describe the novel technological advancements to assess disease activity in IBD

Advances in Small Bowel Imaging

- MR Enterography (MRE)—transmural
  - No radiation
  - Time intensive (elective)
- CT Enterography (CTE)—transmural
  - Radiation
  - Rapid
- Ultrasonography (Europe)
- Video capsule endoscopy (VCE)—mucosal
  - ?monitoring
MRE: “Comb Sign”

Video Capsule Endoscopy
Summary:
Inflammatory Bowel Diseases

- Chronic intestinal inflammation from a dysregulated immune response to the enteric microbiome in a genetically predisposed host
- A family of diseases currently simplified to two umbrella terms: Crohn's disease and ulcerative colitis
- "Step in" rather than sequential therapy: best strategy to change the natural history and disabling outcomes of surgery, hospitalization, lowered QOL.
Summary:
Inflammatory Bowel Diseases

• Along with personalized approach of risk stratification, “treat to target” is emerging as a best practice.
• Therapeutic drug monitoring, optimization of therapy and tight monitoring of actual disease activity (not just symptoms) are critically important goals.
• Treatment of the whole patient will result in best overall outcomes.