Positioning Biologics in Crohn’s Disease

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Overview: Positioning Biologics in Crohn’s Disease

- Recognition of the natural history of Crohn’s disease
- Acceptance of the concept of disease modifying strategies
- Treating earlier
- Using objective measures of disease control
- Adoption of treat to target
The natural course of CD

Cure

Health

Subclinical Inflammation

Symptomatic Inflammation

Complications

Disability

Death

Treatment to Stop Progressive Damage in Crohn’s Disease

Bowel damage

Disease onset

Diagnosis Early disease

Inflammatory activity

Treatment to Stop Progressive Damage in Crohn’s Disease

Historical Treatment Strategies are Flawed

“Step-Up”

“Dirty Therapy”

Adapted from Pariente B, et al. Inflamm Bowel Dis 2011;17:1415–22
Evolving goals of therapy for IBD: Sustained deep remission

<table>
<thead>
<tr>
<th>Goal</th>
<th>Clinical parameters</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response</td>
<td>Improved symptoms</td>
<td>Improved QoL</td>
</tr>
<tr>
<td>Remission</td>
<td>No symptoms</td>
<td>Decreased hospitalization</td>
</tr>
<tr>
<td>Deep remission</td>
<td>Normal endoscopy</td>
<td>Avoidance of surgery</td>
</tr>
</tbody>
</table>

SUSTAINED DISEASE CONTROL

Understanding Prognosis of Crohn’s Disease
Risk Factors for Progressive Crohn’s Disease

- Age of onset <40 years
- Elevated CRP
- Initial requirement of steroids
- Perianal fistulizing disease
- Genetic markers
  - NOD2/IBD5
- Smoking
- Severe endoscopic lesions
- Stricturing, penetrating behavior
- Terminal ileum location
- Serologic markers
  - ASCA/pANCA


Update in the Treatment of Crohn’s Disease
Biologic Therapies for Inflammatory Bowel Disease

Natalizumab

Vedolizumab

Anti-integrins

\( \alpha_4\beta_1 \)

\( \alpha_4\beta_7 \)

### Where do we want to be?
**Optimal Use of Therapy for Crohn’s Disease**

- **The right time**
  - not too early, not too late
  - earlier is better but understanding of prognosis is necessary
- **The right dose**
  - not too little
  - not too much (?)
- **The right interval**
  - no breakthrough between doses
- **The right duration**
  - not too short
  - not too long (?)
- **The right efficacy: safety**
  - disease control, no AEs
- **The right cost!**

### Why aren’t we there yet?

- Existing classification system isn’t specific enough to direct therapy
  - Variations in phenotypes
  - Changing patterns over time
- Goals for management are wrong
  - Subjective, symptom-based
  - Crisis management and not chronic care!
- Therapies don’t work!
  - Inter-patient variation
  - Mechanisms don’t work
  - Wrong dosing, misunderstanding of pK issues
  - Lack of patient adherence
- There is a disconnect between patient and health-care provider
  - Lack of communication
  - Misunderstanding
  - Different expectations
Timing Does Matter

Higher Remission Rates with Adalimumab and Certolizumab with Shorter Disease Duration
Post-hoc Analyses

![Graph showing remission rates]

*\(p=0.002; \, **p=0.001; \, ^{†}p=0.014; \, ^{‡}p=0.001; \) all vs placebo

<2 years: PBO n=23, Adalimumab n=39; 2 to <5 years: PBO n=36, Adalimumab n=57; ≥5 years: PBO n=111, Adalimumab n=233

Infliximab in Children Study: REACH
Shorter Disease Duration

Median disease duration 2 years

- **Response**
- **Remission**

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>Week 10</th>
<th>Week 54 q8</th>
<th>Week 54 q12</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=99</td>
<td>88</td>
<td>64</td>
<td>33</td>
</tr>
<tr>
<td>n=66</td>
<td>50</td>
<td>56</td>
<td>24</td>
</tr>
</tbody>
</table>

Overall number of subjects n=112

Antibodies to infliximab in 3 (2.9%) patients (1 in each maintenance arm and another not randomized)


Earlier Use of Anti-TNF Biologic Therapy in Patients With CD Has Better Outcomes

- Claims data assessment
- >3700 patients all who received anti-TNF at some point

- **Continuous corticosteroid use during anti-TNF therapy**
- **CD-related Surgery during anti-TNF therapy**

*P P < 0.05 IS-to-TNF group versus other groups.

Loss of Response Over Time is Also Less Common with Shorter Duration of Disease

Clinical remission over time in ADHERE (NRI): All patients randomized to adalimumab treatment in CHARM who enrolled in ADHERE

Why Is Combination Therapy More Effective?

- Multiple mechanisms of disease control
- Reduction in anti-drug antibodies
- Elevation of serum drug levels (greater exposure)
- Other mechanisms/unknown
### Immunogenicity of Biologics with and without Concomitant Immune Modulators (IMS)

<table>
<thead>
<tr>
<th>Biologic</th>
<th>Episodic Maintenance</th>
<th>Scheduled Maintenance</th>
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<tbody>
<tr>
<td></td>
<td>IMS-</td>
<td>IMS+</td>
</tr>
<tr>
<td>Infliximab&lt;sup&gt;1&lt;/sup&gt;</td>
<td>(CD 5 mg/kg)</td>
<td>38%</td>
</tr>
<tr>
<td></td>
<td>(CD 10 mg/kg)</td>
<td></td>
</tr>
<tr>
<td>Infliximab&lt;sup&gt;2&lt;/sup&gt;</td>
<td>(UC 5 mg/kg)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(UC 10 mg/kg)</td>
<td></td>
</tr>
<tr>
<td>Certolizumab&lt;sup&gt;3&lt;/sup&gt;</td>
<td>(PRECISE I)</td>
<td></td>
</tr>
<tr>
<td>Certolizumab&lt;sup&gt;4&lt;/sup&gt;</td>
<td>(PRECISE II)</td>
<td>24%</td>
</tr>
<tr>
<td>Adalimumab&lt;sup&gt;5&lt;/sup&gt;</td>
<td>(RA, all doses)</td>
<td></td>
</tr>
<tr>
<td>Adalimumab&lt;sup&gt;6&lt;/sup&gt;</td>
<td>(CLASSIC II)</td>
<td></td>
</tr>
<tr>
<td>Golimumab&lt;sup&gt;7&lt;/sup&gt;</td>
<td>(PURSUIT)</td>
<td></td>
</tr>
<tr>
<td>Natalizumab&lt;sup&gt;8,9&lt;/sup&gt;</td>
<td>(ENACT-1&lt;sup&gt;a&lt;/sup&gt; &amp; 2&lt;sup&gt;b&lt;/sup&gt;)</td>
<td>No data</td>
</tr>
<tr>
<td>Vedolizumab&lt;sup&gt;10,11&lt;/sup&gt;</td>
<td>(GEMINI)</td>
<td>No data</td>
</tr>
<tr>
<td>Ustekinumab&lt;sup&gt;11&lt;/sup&gt;</td>
<td>(CERTIFI)</td>
<td>No data</td>
</tr>
</tbody>
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### SONIC: Corticosteroid-free clinical remission at week 26 moderate to severe Crohn’s disease

**Primary endpoint**

- **AZA + PBO**: 30.6
- **IFX + PBO**: 44.4
- **IFX + AZA**: 56.8

Proportion of patients (%)

- **NZA + PBO**: 31/169 (40.2%)
- **IFX + PBO**: 75/169 (44.4%)
- **IFX + AZA**: 96/169 (58.1%)


\[ p < 0.001 \]
\[ p = 0.022 \]
\[ p = 0.009 \]
Caveats to Combination Therapy in IBD

- Patients who develop Anti-drug antibodies with drug #1 will do so with drug #2.\(^1\) → **Use Combo**
- Elderly patients have more risks of infections.\(^2\) → **Consider NOT Using Combo**
- Emerging evidence suggests higher dose of concomitant AZA/MTX needed to gain benefit.\(^3,4\)

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\(^4\)Colman RJ and Rubin DT. ACG 2014, Abstract P1052.
Treat to Target Rheumatology: Are we ready to apply it to IBD?

- Shared decision-making between RA patient and doctor
- Primary goal: maximize health-related quality of life
  - Control of symptoms
  - Prevention of progressive structural damage
  - Normalization of function and social participation
- Abrogation of inflammation is the most important mean to achieve goals
- Treatment to target by measuring disease activity and adjusting therapy accordingly optimizes outcomes in RA

Challenges to Treat to Target in IBD

- What should be the target?
  - Mucosal healing? How defined?
  - Biomarkers? (CRP, fecal markers)
  - Quality of life? Other PROs?
- When do we reassess?
  - 3 months? 6 months?
  - Based on therapies?
- How do we “monitor” after achieving our target?
- Will patients, providers and payers agree to this approach?

Prevention of Post-op Crohn’s

Prevention is the Opposite of Treating to a Target
Monitoring and Early Treatment is Key
Prevention of Post-Op Recurrence in CD: The Other Side of Mucosal Healing: Monitoring for Recurrence

- Assess risk of recurrence
- Choice of initial therapy
- Colonoscopy at 3–6 months
- Assessment of endoscopic recurrence (Rutgeert's Score)

Assessment of endoscopic recurrence (Rutgeert's Score)

- Good evidence to guide therapy
- Treatment adjustment
- Follow-up

Less evidence to guide therapy: timing of treatment to re-establish control or prevent progression appears to be critical

Post-operative Endoscopic Recurrence
Infliximab vs. Placebo

- Infliximab (n=11)
- Placebo (n=13)

Infliximab vs placebo
p=0.0006

Recurrence defined as endoscopic scores of i2, i3, or i4.

**Post-operative Endoscopic Recurrence (POCER)**

**“Active” vs. “Standard”**

**Active Therapy** = Risk assessment (high/low):
- Metronidazole or Metronidazole + AZA/Adalim
- Colonoscopy at 6 m → Rx adjustment

**Standard therapy** = Metronidazole only

**Primary Endpoint:** No or mild endoscopic recurrence at 18 months

- **Active Therapy**
  - 51% (62/122)

- **Standard Therapy**
  - 33% (17/52)

De Cruz P, et al. Presented at DDW; May 21 2013. Abstract 925J.

**Infliximab vs Mesalamine for Postoperative Recurrence of CD**

**Methods:**
- Patients with endoscopic recurrence (Rutgeerts score ≥2) at 6 months received:
  - mesalamine 800 mg tid
  - infliximab 5 mg/kg bw on a maintenance basis.

**Results:** Patterns of Fecal Calprotectin in CD Patients After Surgery

Therapy Adjustments Over Time
The Concept of Disease Burden

Induction therapy continues at same dose as maintenance

Maintenance therapy decreased/de-escalated

How long?

Maintenance of remission after discontinuing IFX, (but continuing IMM) (STORI)

- Prospective study of 115 CD patients
- Combination therapy with IFX + IMM
  - > 1 year in clinical remission
  - Steroid-free remission
- IFX Stopped, but IMM continued

Close Monitoring of CRP and Fecal Calprotectin is Able to Predict Clinical Relapse in Patients with CD after Infliximab Withdrawal: A Sub-Analysis of the STORI Study

- Lead clinical relapse by 4 mo
- CRP of 6.1mg/L and calprotectin of 305mcg/g best for prediction of relapse


Summary: Positioning Biologics in Crohn’s Disease

- Endpoints of therapy moving to more objective measures
- Timing is everything- waiting too long even post-op Crohn’s disease can result in loss of control of disease progression.
- Treating earlier with effective therapy is more likely to achieve response and less likely to lose response.
- Monitoring disease and treatment success, with a focus on achieving “targets” can provide an opportunity for earlier intervention and potentially change outcomes such as surgery, hospitalization and disability.
- Adopting a “treat to target” and “monitoring” approach may lead to options for de-escalation in some patients.