How will new and future therapies change our management of IBD?

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Where are we at with current therapies?
Therapy is stepped up according to severity at presentation or failure at prior step.

**Disease Severity at Presentation**

**Severe**
- Aminosalicylate Oral/Topical/Combo
- Budesonide
- Corticosteroid
- Anti-TNF +/- IS
- Anti-Integrin +/- IS

**Moderate**
- Aminosalicylate Oral/Topical/Combo
- Budesonide
- Corticosteroid
- Anti-TNF +/- IS
- Anti-Integrin +/- IS

**Mild**
- Aminosalicylate Oral/Topical/Combo
- Budesonide
- Corticosteroid
- Anti-TNF +/- IS
- Anti-Integrin +/- IS

**What's New?**
- Aminosalicylate/Thiopurine/MTX
- Anti-TNF/Anti-Integrin +/- IS

**Induction**
- Aminosalicylate Oral/Topical/Combo
- Budesonide
- Corticosteroid

**Maintenance**
- Aminosalicylate Oral/Topical/Combo
- Budesonide
- Corticosteroid

Sequential Therapies for IBD
What have we learned?
What have we learned?

• IBD is Chronic & Progressive
• Symptoms do not reflect “inflammatory burden”
• Treating to biologic targets improve long-term outcomes
• The earlier the better
• Get the most out of initial therapy
• PK/PD Makes a difference
Progression of Digestive Disease Damage and Inflammatory Activity

CDAI = Crohn's disease activity index; CDEIS = Crohn's disease endoscopic index of severity; CRP = C-reactive protein

Impact of therapy will depend on degree of structural damage and speed of progression

Patients at risk:

N = 2002

Months

Cumulative probability (%)
CHARM: Early CD Shows High Levels of Remission with Adalimumab

![Graph showing remission rates for different age groups at Week 26 and Week 56](image)

- Week 26:
  - <2 years: 59\(^a\)%
  - 2 to <5 years: 40\(^a\)%
  - ≥5 years: 41\(^b\)%

- Week 56:
  - <2 years: 51\(^c\)%
  - 2 to <5 years: 44\(^d\)%
  - ≥5 years: 35\(^b\)%

\(^a\)P=0.002; \(^b\)P<0.001; \(^c\)P=0.014; \(^d\)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

CD: Comparing ACCENT I, CHARM, and PRECiSE 2 Remission Results

ACCENT I* (infliximab)

- Week 2 Response: 58.5%
- Week 30 Remission: 39.6%
- Overall Remission: 22.8%

CHARM** (adalimumab)

- Week 4 Response: 60%
- Week 26 Remission: 40%
- Overall Remission: 24%

PRECiSE 2 (certolizumab pegol)

- Week 6 Response: 64.1%
- Week 26 Remission: 47.9%
- Overall Remission: 30.7%

*5 mg/kg dose.
**Maintenance trial with 80/40 mg induction dosing. Randomized responders = CR-70 at week 4.
Week 26 remission among randomized responders on 40 mg every other week dosing.
Loss of Response to Infliximab in Crohn’s Disease: Health-Care Claims Data

- Selected patients with CD receiving infliximab maintenance therapy with an initial response
- Loss of response inferred from:
  - Upward dose adjustment
  - New drug therapy for CD
  - CD-related emergency room or inpatient visits
- Annual total health-care and CD-related costs estimated and adjusted for inflation to 2005 US dollars

Comparative Effectiveness of Infliximab and Adalimumab for Crohn's Disease

- Retrospective cohort study by using U.S. Medicare data from 2006 through 2010.
- Patients with CD who were new users of infliximab (n = 1459) or adalimumab (n = 871) after January 31, 2007.
- Primary outcome measures were disease persistence on therapy at week 26.

After 26 weeks of treatment, 49% of patients receiving infliximab remained on drug, compared with 47% of those receiving adalimumab.
At wks 8, 30 and 54, the proportion of patients achieving clinical remission increased with increasing quartiles of IFX concentrations.

<table>
<thead>
<tr>
<th>IFX Conc. (% patients)</th>
<th>1st Quartile</th>
<th>2nd Quartile</th>
<th>3rd Quartile</th>
<th>4th Quartile</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 8</td>
<td>26.3% (&lt;21.3µg/mL)</td>
<td>37.9% (e21.3-&lt;33µg/mL)</td>
<td>43.9% (e33-&lt;47.9µg/mL)</td>
<td>43.1% (&gt;47.9µg/mL)</td>
<td>P=0.0504</td>
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<tr>
<td>Week 30</td>
<td>14.6% (&lt;0.11µg/mL)</td>
<td>25.5% (e0.11-&lt;2.4µg/mL)</td>
<td>59.6% (e2.4-&lt;6.8µg/mL)</td>
<td>52.1% (&gt;6.8µg/mL)</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>Week 54</td>
<td>21.1% (&lt;1.4µg/mL)</td>
<td>55.0% (e1.4-&lt;3.6µg/mL)</td>
<td>79.0% (e3.6-&lt;8.1µg/mL)</td>
<td>60.0% (&gt;8.1µg/mL)</td>
<td>P=0.0066</td>
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</table>
### ACCENT I: Week 54 Sustained Clinical Outcome and Week 14 Serum Infliximab Level in CD

<table>
<thead>
<tr>
<th>Sustained Clinical Outcome</th>
<th>&lt;3.5 μg/mL Week 14 Serum IFX Level</th>
<th>≥3.5 μg/mL Week 14 Serum IFX Level</th>
<th>P-value*</th>
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<tbody>
<tr>
<td>Subjects included in analysis</td>
<td>96</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>Subjects with sustained response</td>
<td>17 (17.7%)</td>
<td>20 (39.2%)</td>
<td>0.0042</td>
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<tr>
<td>Subjects without sustained response</td>
<td>79 (82.3%)</td>
<td>31 (60.8%)</td>
<td></td>
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</table>


*Chi-square test
Vedolizumab Trough Levels Also Correlate with Response to Therapy: UC Week 6

4-week Response According to Prior Therapy with Anti-TNF from Adalimumab CLASSIC vs GAIN studies

![Bar chart showing response rates for CLASSIC (TNF Naïve) and GAIN (Prior TNF Rx) studies with Placebo and Adalimumab 160/80mg treatments.]

Hanauer, S. et al. Gastroenterol. 2006;130:323–33
Vedolizumab for Ulcerative Colitis: Maintenance at Week 52 by TNFα Antagonist Failure

Prior Anti-TNF Antagonist Exposure (n=149)

- VDZ/PBO: 10.6%
- VDZ/VDZ Q8W: 36.0%
- VDZ/VDZ Q4W: 40.4%

Patients Without TNF Antagonist Exposure (n=224)

- Clinical Remission: 19.1%
- Durable Clinical Response: 65.3%

Vedolizumab in Crohn’s Disease
Clinical Remission at Week 6 and 10

Clinical Remission at Week 6

<table>
<thead>
<tr>
<th></th>
<th>Overall population</th>
<th>Failure</th>
<th>Naïve</th>
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</thead>
<tbody>
<tr>
<td>Patients, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>12.1</td>
<td>19.1</td>
<td>12</td>
</tr>
<tr>
<td>P=0.04</td>
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<tr>
<td></td>
<td>31.4</td>
<td>12</td>
<td>16</td>
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Clinical Remission at Week 10

<table>
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<th></th>
<th>Overall population</th>
<th>Failure</th>
<th>Naïve</th>
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<tr>
<td>Patients, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>12.1</td>
<td>26.6</td>
<td>13</td>
</tr>
<tr>
<td>P=0.001</td>
<td>12.1</td>
<td>13</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>35.3</td>
<td>13</td>
<td>16</td>
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</table>

Mean Δ% vs placebo (95% CI)

<table>
<thead>
<tr>
<th></th>
<th>Overall population</th>
<th>Failure</th>
<th>Naïve</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Δ%</td>
<td>3.0</td>
<td>6.9</td>
<td>19.2</td>
</tr>
<tr>
<td>95% CI</td>
<td>(-4.5, 10.5)</td>
<td>(0.1, 13.8)</td>
<td>(3.3, 35.0)</td>
</tr>
</tbody>
</table>

PBO=placebo; VDZ=vedolizumab
Indications for Biologics

• (1998) Infliximab
  – Moderate to Severe CD/UC Not Responding to Conventional Agents
• Adalimumab
  – Moderate to Severe CD/UC Not Responding to Conventional Agents
• Certolizumab
  – Moderate to Severe CD Not Responding to Conventional Agents
• Natalizumab
  – Moderate to Severe CD Not Responding to Conventional Agents and Anti-TNFs
• Vedolizumab
  – Moderate to Severe CD/UC Not Responding to Conventional Agents or Anti-TNFS

Duration of Disease in Clinical Trials Now 6-10 years
What are we seeing from next-gen therapies?
Next Generation Therapies

• Late disease (8-9 years)
• Complicated disease
• Steroid-Refractory
• Multi-drug Resistant
• Inadequate development of PK/PD
• Absent Biomarkers
UNITI-1 & UNITI-2

Clinical Remission Through Week 8 with Ustekinumab

UNITI-1
anti-TNF refractory

UNITI-2
failed prior conventional therapy (primarily anti-TNF naïve)

Proportion of Subjects (%)

0 10 20 30 40 50 60 70

Weeks

0 3 6 8

Disease Duration 10 years

Disease Duration 6 Years

All p-values <0.05 except 130 mg dose at Week 3 in both studies

Subjects who had a prohibited Crohn's disease-related surgery or had prohibited concomitant medication changes prior to designated analysis time point are considered not to be in 70-point response, regardless of their CDAI score. Subjects who had insufficient data to calculate the CDAI score at designated analysis endpoint are considered not to be in clinical remission.


*Weight-range based UST doses approximating 6 mg/kg: 260 mg (weight ≤55 kg), 390 mg (weight >55 mg and ≤85 kg), 520 mg (weight >85 kg).
• Treat earlier in course (before complications)
• Insure “Complete response”
• Combination Therapy
• Utilize PK/PD
• Utilize TDM
**Efficacy/Positioning**

- “Early”
- “Mild-Moderate UC”
- Induction & Maintenance
- “Safe”
- ~50% Efficacy
- Relatively Cost-Effective

**Therapeutic Gaps/Opportunities**

- “Crohn’s”
- “Moderate-Severe”
- Pill-Burden
- Rectal Applications
- ~50% Efficacy
- Relative Cost (generics?)
Corticosteroids

Efficacy/Positioning

• “Moderate-Severe”
• “Early or Late”
• Rescue therapy for everything
• ~80% Efficacy
• Low cost

Therapeutic Gaps/Opportunities

• Safety, Safety, Safety
• Steroid-Dependence
• “Maintenance”
Immunomodulators

**Efficacy/Positioning**
- Steroid-sparing (Maintenance)
- Combination Therapy with Biologics
- ~40% Efficacy
- Cost-Effective

**Therapeutic Gaps/Opportunities**
- Induction (without steroids)
- Improved Efficacy
- Safety
Anti-TNF Biologics

Efficacy/Positioning
• “Late Disease”
• “Moderate-Severe”
  – After steroids, IM’s
  – Complicated disease
• ~30% Long-term efficacy
• Relatively safe
• Cost, cost, cost

Therapeutic Gaps/Opportunities
• “Early Disease”
• “First-Line”
• Enhanced efficacy
  – TDM
• Oral delivery
• Biosimilars
Anti-Integrins

Efficacy/Positioning
• Very late
• “Moderate-Severe”
• ~30-40% Efficacy
• “Safe”
• Cost, cost, cost

Therapeutic Gaps/Positioning
• Early Disease
• “Mild-Moderate”
• Improved Onset of Action
• Oral delivery
• Cost
Current Indications & Consequences for Biologics

**Indications**
- Moderate-Severe Disease
- Not Responding to Conventional Agents (or Anti-TNF agents)

**Consequences**
- Steroid-Refractory/Steroid-Dependent
  - No benefit & all risks
- Long-disease duration
  - Least likely to respond
    - Refractory disease
    - Transmural complications
- <50% Remission rates for “next generation agents”
Redefining Disease Severity in IBD

Impact on Patient
- Symptoms
- QOL
- Disability

Inflammatory Burden
- CRP
- Mucosal lesions
- Disease extent

Complicated Disease Course
- Bowel damage
- Resection
- Perianal disease
- EIMs
What do we need & What should we expect?

Needs
• Treatment of “early disease”
• Enhanced Inductive/Maintenance
• Biomarkers
• Improved cost-effectiveness
• Improved development pathways
  – Regulatory
  – Pharmaceutical
  – Patient availability for early disease

Near term expectations
• Continued “late-disease” development
• Marginal improvements in efficacy (due to “late-disease” development)
• Potential “Game Changers”
  – Mongerson???????
I always use the newest medicine first...Before it’s effectiveness wears off

Sir William Osler