Update on Biologics in Ulcerative Colitis

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Objectives

- Discuss the latest advances in the pharmacologic management of ulcerative colitis
- Describe recent key clinical trials, their results, and their application in clinical practice
- Identify the potential value of measuring serum levels and antibodies to biologics
Adalimumab
Adalimumab—
Analyses of the ULTRA 1 and 2 Trials

- Pivotal phase 3 trials for approval in ulcerative colitis (UC)
  - ULTRA 1: 8-week study
  - ULTRA-2: 52-week study

- Patients
  - Moderately to severely active UC despite concurrent or prior treatment with immunosuppressants (corticosteroids, azathioprine, 6-mercaptopurine)

- Treatments
  - Placebo
  - Adalimumab 160 mg/80 mg induction (Day 1/Day 15), 40 mg maintenance dose

- Primary end points
  - Proportion of patients achieving clinical remission at week 8 (ULTRA 1 & 2) and week 52 (ULTRA 2)

Efficacy of Adalimumab for Induction of Remission in UC

Four doses of adalimumab; endpoints measured at week 8

The intent-to-treat (ITT) population included only the 390 patients randomized after the protocol amendment

Induction and Maintenance of Clinical Remission by Adalimumab in Patients with Moderate-to-Severe Ulcerative Colitis

ADA=adalimumab

Inadequate response was defined as: Partial Mayo score (PMS) ≥Baseline PMS on 2 consecutive visits ≥14 days apart (for patients with Baseline PMS 4-7) or PMS ≥7 on 2 consecutive visits ≥14 days apart (for patients with Baseline PMS of 8 or 9)
Adalimumab for Induction and Maintenance of Remission in UC

*P<.05; **P<.005

<table>
<thead>
<tr>
<th>End points</th>
<th>Placebo (n=145)</th>
<th>Adalimumab (n=150)</th>
<th>P value&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Placebo (n=101)</th>
<th>Adalimumab (n=98)</th>
<th>P value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical remission per Mayo score at week 8&lt;sup&gt;b&lt;/sup&gt;</td>
<td>16 (11.0)</td>
<td>32 (21.3)</td>
<td>.017</td>
<td>7 (6.9)</td>
<td>3 (3.0)</td>
<td>.559</td>
</tr>
<tr>
<td>Clinical remission per Mayo score at week 52&lt;sup&gt;b&lt;/sup&gt;</td>
<td>18 (12.4)</td>
<td>33 (22.0)</td>
<td>.029</td>
<td>9 (9.2)</td>
<td>10 (10.2)</td>
<td>.039</td>
</tr>
<tr>
<td>Sustained clinical remission per Mayo score at week 8 and week 52</td>
<td>9 (6.2)</td>
<td>16 (10.7)</td>
<td>.169</td>
<td>1 (1.0)</td>
<td>5 (5.1)</td>
<td>.115</td>
</tr>
<tr>
<td>Clinical response per Mayo score at week 8&lt;sup&gt;c&lt;/sup&gt;</td>
<td>56 (38.6)</td>
<td>89 (59.3)</td>
<td>&lt;.001</td>
<td>29 (28.7)</td>
<td>10 (9.9)</td>
<td>.228</td>
</tr>
<tr>
<td>Clinical response per Mayo score at week 52&lt;sup&gt;c&lt;/sup&gt;</td>
<td>35 (24.1)</td>
<td>55 (36.7)</td>
<td>.019</td>
<td>10 (9.9)</td>
<td>6 (5.9)</td>
<td>.038</td>
</tr>
<tr>
<td>Sustained clinical remission per Mayo score at week 8 and week 52</td>
<td>24 (16.6)</td>
<td>44 (29.3)</td>
<td>.009</td>
<td>6 (5.9)</td>
<td>5 (5.1)</td>
<td>.032</td>
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<tr>
<td>Mucosal healing at week 8&lt;sup&gt;d&lt;/sup&gt;</td>
<td>51 (35.2)</td>
<td>74 (49.3)</td>
<td>.014</td>
<td>27 (26.7)</td>
<td>28 (28.6)</td>
<td>.772</td>
</tr>
<tr>
<td>Mucosal healing at week 52&lt;sup&gt;d&lt;/sup&gt;</td>
<td>26 (19.3)</td>
<td>47 (31.3)</td>
<td>.018</td>
<td>10 (9.9)</td>
<td>15 (15.3)</td>
<td>.250</td>
</tr>
<tr>
<td>Sustained mucosal healing at week 8 and week 52d</td>
<td>20 (13.6)</td>
<td>36 (24.0)</td>
<td>.025</td>
<td>6 (5.9)</td>
<td>10 (10.2)</td>
<td>.269</td>
</tr>
<tr>
<td>Discontinued corticosteroid use before week 52 and achieved clinical remission at week 52&lt;sup&gt;e&lt;/sup&gt;</td>
<td>5 (6.2)</td>
<td>15 (13.6)</td>
<td>.096</td>
<td>3 (5.1)</td>
<td>5 (12.5)</td>
<td>.263</td>
</tr>
<tr>
<td>PGA ≤1 at week 8</td>
<td>63 (43.4)</td>
<td>88 (58.7)</td>
<td>.009</td>
<td>29 (28.7)</td>
<td>26 (26.5)</td>
<td>.731</td>
</tr>
<tr>
<td>SFS ≤1 at week 8</td>
<td>43 (29.7)</td>
<td>69 (46.0)</td>
<td>.004</td>
<td>27 (26.7)</td>
<td>25 (25.5)</td>
<td>.844</td>
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<tr>
<td>RBS ≤1 at week 8</td>
<td>86 (59.3)</td>
<td>116 (77.3)</td>
<td>&lt;.001</td>
<td>57 (56.4)</td>
<td>58 (59.2)</td>
<td>.695</td>
</tr>
<tr>
<td>Discontinued corticosteroid use for ≥90 days before week 52 and achieved remission at week 52&lt;sup&gt;e&lt;/sup&gt;</td>
<td>5 (6.2)</td>
<td>15 (13.6)</td>
<td>.096</td>
<td>3 (5.1)</td>
<td>5 (12.5)</td>
<td>.263</td>
</tr>
<tr>
<td>Discontinued corticosteroid use and achieved sustained clinical remission at both weeks 32 and 52&lt;sup&gt;e&lt;/sup&gt;</td>
<td>1 (1.2)</td>
<td>11 (10.0)</td>
<td>.014</td>
<td>1 (1.7)</td>
<td>4 (10.0)</td>
<td>.155</td>
</tr>
<tr>
<td>IBDQ responders at week 52</td>
<td>31 (21.4)</td>
<td>48 (32.0)</td>
<td>.039</td>
<td>9 (8.9)</td>
<td>17 (17.3)</td>
<td>.078</td>
</tr>
<tr>
<td>IBDQ responders at week 8</td>
<td>75 (51.7)</td>
<td>102 (68.0)</td>
<td>.004</td>
<td>37 (36.6)</td>
<td>42 (42.9)</td>
<td>.370</td>
</tr>
</tbody>
</table>

NOTE. Data are n (%).
IBDQ, inflammatory bowel disease questionnaire; PGA, Physician’s Global Assessment subscore; RBS, rectal bleeding subscore; SFS, stool frequency subscore.

<sup>a</sup>P values to compare adalimumab treatment group with placebo were based on \( \chi^2 \) test (or Fisher’s exact test if ≥20% of the cells had an expected cell count <5).

<sup>b</sup>Mayo score ≤2 with no individual subscore ≥1.
<sup>c</sup>Decrease from baseline in Mayo score ≥3 points and ≥30%, rectal bleeding subscore 0 or 1 or decrease from baseline ≥1 point.
<sup>d</sup>Endoscopy subscore 0 or 1.
<sup>e</sup>Among patients with baseline corticosteroid use: n=81 for placebo and n=110 for adalimumab (no prior anti-TNF); n=59 for placebo and n=40 for adalimumab (prior anti-TNF).
Conclusions

• When and where to use adalimumab in UC?
  – Anti-TNF naive
    • When infliximab vs adalimumab?
  – Inconclusive data in infliximab-experienced patients
  – Dosing not optimized
    • Dose escalation may rescue patients (ACG abstract)
Infliximab
Cyclosporine Versus Infliximab In Severe Acute Ulcerative Colitis Refractory To Intravenous Steroids: A Randomized Trial

Cys = cyclosporine; IFX = infliximab.
Cyclosporine Versus Infliximab In Severe Acute Ulcerative Colitis Refractory To Intravenous Steroids: A Randomized Trial

Primary Objectives

Difference Cys vs. IFX failure rates: -6.4% (95%CI: -24.8 to 12.0%)  
P = .49

Response: D 7

Difference Cys vs. IFX: -0.3% (95%CI: -13.3 to 12.8%)  
P = .97

Cys=cyclosporine; IFX=infliximab.  
Laharie D et al. Digestive Disease Week 2011. Abstract #619
Infliximab vs Cyclosporine: Time to Colectomy

Cys=cyclosporine; IFX=infliximab.
Laharie D et al. Digestive Disease Week 2011. Abstract #619
Infliximab, Azathioprine, or Infliximab + Azathioprine for the Treatment of Moderate to Severe Ulcerative Colitis: UC Success

Randomization of Patients

<table>
<thead>
<tr>
<th>Visits</th>
<th>AZA + PBO (2.5 mg/kg) (n=79)</th>
<th>IFX (5 mg/kg) + PBO (n=78)</th>
<th>IFX+AZA (n=80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 0</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Week 2</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Week 6</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Week 8</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Week 14</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Week 16</td>
<td>○</td>
<td>○</td>
<td>○</td>
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Possible escape* (blinded)

Primary Evaluation

*Subjects not achieving ≥1 point improvement in partial Mayo score

Infliximab, Azathioprine, or Infliximab + Azathioprine for the Treatment of Moderate to Severe Ulcerative Colitis: UC Success

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
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<tbody>
<tr>
<td>Steroid-Free Remission</td>
<td>18</td>
</tr>
<tr>
<td>Infliximab</td>
<td>17</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>31</td>
</tr>
</tbody>
</table>

†Total Mayo score ≤2, with no individual subscore >1, and no steroids

Golimumumab
Unique study design of Phase 2 dose-ranging integrated with Phase 3: total of 1065 subjects randomized

Phase 2: Dose-Ranging (n=169)
- 4 arms

Prior to Dose Selection (n=122)
- 4 arms

Implement Dose Decision

Phase 3: Dose-Confirming (n=774)
- 3 arms

Phase 3 SC Maintenance Study

- Demography
  - Males (56.0%), Caucasian (82.1%) and median age of 38.0 years

- UC disease characteristics
  - Median disease duration: 4.22 years
  - Extensive disease: 42.2%
  - Median Mayo score: 8.0

- SC Induction Doses at Weeks 0 and 2:
  - Placebo (Wk 0) and Placebo (Wk 2)
  - 100 mg (Wk 0) and 50 mg (Wk 2) golimumab
  - 200 mg (Wk 0) and 100 mg (Wk 2) golimumab
  - 400 mg (Wk 0) and 200 mg (Wk 2) golimumab

Sc=subcutaneous
PURSUIT – Golimumumab for the Induction of Moderate to Severe UC

Golimumumab: A fully human monoclonal antibody against TNF-α

Adverse events of interest: One death due to peritonitis; one case of demyelination; one thyroid cancer (placebo); one colon cancer in situ (seen in screening biopsies); no serious infections

PURSUIT – Golimumumab for the Maintenance of Moderate to Severe UC

- Achieved the primary endpoint of maintenance of clinical response through Week 54, as well as other clinically meaningful outcomes
- No new safety signals were identified

Vedolizumab
α-Integrin Therapy for IBD

- Natalizumab blocks both α4β1 and α4β7 mediated trafficking, resulting in systemic effects
- Vedolizumab only targets α4β7 integrin, blocking lymphocytes trafficking to the gut

Mucosal and Inflammatory Zip Codes

Vedolizumab in UC: The GEMINI I Study

• Purpose
  – Evaluate the efficacy and safety of vedolizumab (anti-\(\alpha 4\beta 7\) integrin) in UC

• Design
  – Randomized, double-blind, placebo-controlled, 52-week phase 3 trial

• Patients
  – Mayo score \(\geq 6\) and endoscopic subscore \(\geq 2\) despite corticosteroids, purine antimetabolites, and/or TNF-\(\alpha\) antagonists
  – Patients responding after 2 induction doses of vedolizumab (weeks 0 and 2) were randomized to treatment

• Treatments
  – Vedolizumab 300 mg IV q4w
  – Vedolizumab 300 mg IV q8w
  – Placebo

• Primary end point
  – Clinical remission (Mayo score of \(\leq 2\) points and no individual subscore >1) at week 52

GEMINI I – Vedolizumab for the Treatment of UC

*P < 0.005

Vedolizumab (VDZ) is more effective than placebo as induction and maintenance therapy in patients with moderate to severely active ulcerative colitis (anti-TNF exposed and naïve patients).

### GEMINI I – Safety of Vedolizumab for the Treatment of UC

<table>
<thead>
<tr>
<th></th>
<th>Maintenance ITT Population</th>
<th>Safety Population</th>
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<tbody>
<tr>
<td></td>
<td>Placebo N=126</td>
<td>VDZ Q8Wks N=122</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VDZ Q4Wks N=125</td>
</tr>
<tr>
<td>Any Adverse Event (AE), %</td>
<td>84</td>
<td>82</td>
</tr>
<tr>
<td>Drug-related AE, %</td>
<td>32</td>
<td>30</td>
</tr>
<tr>
<td>AE resulting in discontinuation, %</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>Serious AEs, %</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>Serious infection AEs, %</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Deaths, n (%)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

VDZ=vedolimumab
Serum Infliximab Levels in UC
Detectable Serum Trough IFX Concentration is Associated with Higher Remission Rate and Endoscopic Improvement

- Cohort study
- N=115 with moderate to severe UC
- Follow-up time: median 13.9 months
- Efficacy
  - Detectable serum IFX was associated with
    - Higher remission rates (69% vs. 15%; \( P < .001 \))
    - Endoscopic improvement (76% vs. 28%; \( P < .001 \))
  - Undetectable serum IFX predicted an increased risk for colectomy

IFX=infliximab
Seow CH et al. *Gut* 2010;59:49-54
Presence of Detectable Trough Infliximab Levels Reduces Colectomy Rates in UC

Treatment Algorithm in IBD Patients With Clinical Symptoms (Infliximab and HACA Concentrations)

- Positive HACA
  - Change to another anti-TNF agent
  - Persistent disease
  - Change to non-anti-TNF agent

- Therapeutic IFX concentration
  - Active disease on endoscopy/radiology?
    - Yes: Change to different anti-TNF agent
    - No: Investigate alternate etiologies

- Subtherapeutic IFX concentration
  - Increase infliximab dose or frequency
  - Change to different anti-TNF agent
  - Change to non-anti-TNF agent

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*a* >12 mcg/mL at 4 weeks or detectable trough level; patients should have endoscopic or radiologic imaging

IFX=infliximab
Clinical Utility of Measuring IFX and HACA Levels in Patients with IBD

Clinical outcomes in patients with detectable HACA (n=35)*

- 6 discontinued IFX
- 3 continued same dose
- 3 proceeded to surgery
- 5 patients could not be assessed

Clinical outcomes in patients with sub-therapeutic concentrations (n=69)*

- 10 continued same dose
- 9 discontinued IFX
- 8 proceeded to surgery
- 7 patients could not be assessed

HACA=human anti-chimeric antibodies; IFX=infliximab
Novel Infliximab and Antibody-to-Infliximab Assays Are Predictive of Disease Activity in Patients with CD

- 1487 serum samples from 483 participants in 4 CD RCTs/cohorts
- Disease activity measured by CRP
- 1205 pairs of samples taken over sequential time points (trough infliximab/ATI in first sample, CRP in second sample)
- Predictors of higher CRP: ATI+, infliximab < 3 mcg/mL

ATI=antibody to infliximab; CRP=C-reactive protein; RCT=randomized controlled trial
Phase 2: Clinical Endpoints by Serum Golimumab Concentration Quartile at Week 6

- No exposure
- < 1st Quartile
- 1st and < 2nd Quartile
- 2nd and < 3rd Quartile
- 3rd Quartile

Conclusions

• Adalimumab approved for UC 9/28/12
  – “The effectiveness of Humira has not been established in patients with ulcerative colitis who have lost response to or were intolerant to TNF blockers.”

• Infliximab
  – As effective as CsA in severe IVSR UC
  – Effective in combination with azathioprine in biologic/immunomodulator naive UC

• Golimumab met primary endpoints in phase 3 trial program

• Vedolizumab met primary endpoints in phase 3 trial program
  – Different MOA
Conclusions (con’t)

• Infliximab levels/antibodies to infliximab
  – Will help with clinical decision making but dogma exceeds data
  – Especially in induction setting, more data is needed before algorithms can be adopted to guide dose escalation vs. switch
    • Is there an effective “switch” drug?
  – New assay provides more information, but is this clinically important information?