Immunogenicity of Biologic Agents and How to Prevent Sensitization

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Learning from the Past

• “Those who cannot remember the past are condemned to repeat it.”

• Taken from: The Life of Reason, Vol. I, Reason in Common Sense

George Santayana (1863-1952): philosopher, essayist, poet and novelist.
Infliximab
Higher Serum Antibodies is Associated with a Shortened Duration of Response in Patients with Crohn’s Disease

- Study design: prospective, cohort study
- N=125 with refractory CD
- Median follow-up: 36 mo
- Efficacy
  - Negative correlation between concentration of ATI and duration of response to infliximab ($P<0.001$)

Rheumatoid Arthritis
Combination of Infliximab and Methotrexate

Crohn’s Disease: Immunogenicity of Infliximab in ACCENT I Stratified by Dosing Regimen and Immunosuppression

Hanauer. Clinical Gastroenterology & Hepatology 2004
Crohn’s Disease: Immunogenicity of Infliximab in SONIC at Week 30*

* Patients who had 1 or more PK samples obtained after their first study agent administration were included in the analysis. PK data at Wk 30 was not available for 1 patient treated with AZA + placebo, 3 patients treated with IFX + placebo, and 4 patients treated with AZA + IFX.

Colombel JF, Sandborn WJ, NEJM 2010
## Immunogenicity of Infliximab in CD patients
### Patients With Detectable Human Anti-Human Antibodies

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Combination therapy</th>
<th>Monotherapy therapy</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colombel 2010</td>
<td>Events: 1, Total: 116</td>
<td>Events: 15, Total: 103</td>
<td>0.06 [0.01, 0.44]</td>
</tr>
<tr>
<td>Feagan 2014</td>
<td>Events: 3, Total: 63</td>
<td>Events: 13, Total: 63</td>
<td>0.23 [0.07, 0.77]</td>
</tr>
</tbody>
</table>

**Total (95% CI):**
- Events: 4, Total: 179
d- Risk Ratio: 0.14 [0.05, 0.38]

Heterogeneity: $\chi^2 = 1.40$, df = 1 ($P = 0.24$); $I^2 = 28$

Test for overall effect: $Z = 3.85$ ($P = 0.0001$)

Akobeng 2015a Cochrane review
Immunogenicity of Infliximab in UC patients

Patients With Detectable Human Anti-Human Antibodies

Akobeng 2015a Cochrane review
IV Hydrocortisone Premedication to Prevent Antibodies to Infliximab in CD: A Randomized Controlled Trial

Lessons Learned from Infliximab

• **Antibodies do matter (don’t listen to people who say they don’t!**
  – Lower or undetectable drug concentration
  – Worse clinical outcomes
  – Increased adverse events

• **Factors associated with prevention of anti-drug antibodies (sensitization) to infliximab**
  – Higher initial doses (10 mg/kg < 5 mg/kg < 3 mg/kg < 1 mg/kg)
  – Systematic dosing (systematic dosing < episodic dosing)
  – Combination therapy with azathioprine or methotrexate (combination therapy < monotherapy)
  – Pre-medications with IV steroids (pre-medications < no pre-medications)
  – Antibody construction (human < humanized < chimeric) – THIS IS A BIG REMAINING QUESTION FOR FUTURE BIOLOGIC THERAPIES
## Immunogenicity of TNF Antagonists
### Patients With Detectable Antibodies to a TNF Antagonist

<table>
<thead>
<tr>
<th>TNF Antagonist</th>
<th>Episodic Maintenance</th>
<th>Scheduled Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IMS-</td>
<td>IMS+</td>
</tr>
<tr>
<td>Infliximab¹ (CD 5 mg/kg) (CD 10 mg/kg)</td>
<td>38%</td>
<td>16%</td>
</tr>
<tr>
<td>Infliximab² (UC 5 mg/kg) (UC 10 mg/kg)</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Certolizumab³ (PRECiSE I)</td>
<td>24%</td>
<td>8%</td>
</tr>
<tr>
<td>Certolizumab⁴ (PRECiSE II)</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Adalimumab⁵ (RA, all doses)</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Adalimumab⁶ (CLASSIC II)</td>
<td>No data</td>
<td>No data</td>
</tr>
</tbody>
</table>

IMS = immunosuppressant.

AAA Formation Lowers Adalimumab Trough Serum Levels in Patients with Crohn’s Disease

- 92% of the patients with a trough serum concentration measured below the threshold for detection were positive for AAA

Karmaris Gastro 2009;137:1628–1640
Adalimumab Trough Serum Levels < 0.33 μg/mL Predicts a Lower Rate of Sustained Complete Response in Patients with Crohn’s Disease

Karmaris Gastro 2009;137:1628–1640
Immunogenicity of Vedolizumab Patients With Detectable Antibodies to Vedolizumab

<table>
<thead>
<tr>
<th>Vedolizumab 300 mg every 4 or 8 weeks</th>
<th>Patients, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Episodic Maintenance</td>
</tr>
<tr>
<td>IMS-</td>
<td>IMS+</td>
</tr>
<tr>
<td>18%</td>
<td>3%</td>
</tr>
</tbody>
</table>

IMS = immunosuppressant.

Rosario M. *Journal of Crohn’s and Colitis* 2014 (Abstract)
Immunogenicity of Vedolizumab Patients With Detectable Human Anti-Human Antibodies

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<thead>
<tr>
<th>Study or Subgroup</th>
<th>Combination Events</th>
<th>Combination Total</th>
<th>Monotherapy Events</th>
<th>Monotherapy Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feagan 2013</td>
<td>1</td>
<td>32</td>
<td>44</td>
<td>247</td>
<td>100.0%</td>
<td>0.18 [0.03, 1.23]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td>32</td>
<td></td>
<td>247</td>
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</tbody>
</table>

Heterogeneity: Not applicable
Test for overall effect: Z = 1.75 (P = 0.08)
Immunogenicity of Ustekinumab Patients With Detectable Antibodies to Ustekinumab

• Phase 2a study in Crohn’s disease
  – Of the 77 patients in population 1 and 22 patients in population 2 who had serum samples available for the assessment of anti-ustekinumab antibodies, none (0%) was positive at any time through week 54

• Phase 2b study in Crohn’s disease
  – Of 427 ustekinumab-treated patients with appropriate samples for analysis, 3 (0.7%) had positive results for antibodies to ustekinumab through week 36
  – Because most patients (81%) had undetectable serum ustekinumab levels at week 36, circulating levels of ustekinumab did not have a marked effect on the incidence of antibodies.

Conclusions

- Anti-drug antibodies to infliximab, adalimumab, certolizumab, and vedolizumab lead to loss of response

- Strategies to prevent anti-drug antibodies include: higher doses, systematic maintenance dosing, concomitant immunosuppressive therapy, and pre-medicating with intravenous steroids

- Antibody construction as a protective factor against immunogenicity (human > humanized > chimeric) is inconsistent and needs to be thoroughly evaluated with a drug tolerant assay on a case by case basis