Anti-drug Antibodies.  So What?

K. A. Papp  MD, PhD

Probity Medical Research
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Because


Clinical development of onercept, a tumor necrosis factor binding protein, in psoriasis.

Papp K¹.
Mostly Because

- Altered effectiveness
Factors Impacting Immunogenicity
Immunogenicity of biologics

- HAMA: Mouse (75% Human)
- HACA: Chimeric (95% Human)
- HAHA: Humanised (99.9% Human)
- HAHA: Human (100% Human)
Remember
A gnawing concern

66% of individuals not exposed to CHO-HCP express antibodies

Xue L, Johnson R, Borovits B. Prevalence and isotypic complexity … AAPS J 2010
Target

Neutralizing

Evil ADA

Non-Neutralizing

Neutralizing

Semi-Evil ADA
Drug Intolerant
Drug Tolerant
<table>
<thead>
<tr>
<th>Drug</th>
<th>Peak Cmax</th>
<th>Steady State Trough</th>
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<tbody>
<tr>
<td>Secukinumab 300mg</td>
<td>27.3 ± 9.5 µg/mL</td>
<td>34.4 ± 16.6 µg/mL</td>
</tr>
<tr>
<td>Ixekizumab</td>
<td>10.5 ± 4.16 µg/mL</td>
<td>3.63 ± 2.33 µg/mL</td>
</tr>
<tr>
<td>Adalimumab 40 mg eow</td>
<td></td>
<td>5 µg/mL</td>
</tr>
<tr>
<td>Ustekinumab 90 mg</td>
<td>6.1 ± 3.6 µg/mL</td>
<td>0.47 µg/mL - 0.49 µg/mL</td>
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</table>
A Highly Sensitive and Drug-Tolerant Anti-Drug Antibody Screening Assay for Ixekizumab Using Affinity Capture Elution

Talia M. Muram¹, John H. Sloan¹, Jana S. Chain¹, Wendy J. Komocsar¹, Bruce I. Meiklejohn¹, Andrew Blauvelt², Kim Papp³, Michael P. Heffernan¹, Yue-Wei Qian¹, and Robert J. Konrad¹

¹Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN;
²Oregon Medical Research Center, Portland, OR;
³Probity Medical Research, Waterloo, Ontario, Canada
**Drug Tolerance Comparison**

Ixekizumab MSD Bridging Assay vs. ACE Assay

ACE provides a significantly improved drug tolerance over the MSD bridging assay.

Affinity-purified anti-ixekizumab antibody from monkeys or humans was spiked into normal human serum at a concentration of 500 ng/mL. Samples were also spiked with concentrations of ixekizumab ranging from 0.1-500 μg/mL and analyzed on the ACE and MSD bridging assays. Results are shown as the mean ± SEM (n=2). The MSD bridging assay reports in ECL units (ECLU), while the ACE assay generates an OD450 readout.

ACE=Affinity Capture Elution; ECL=Enhanced Chemiluminescence; MSD=MesoScale Discovery; OD=Optical Density.

Summary of the Two ADA Assays

♦ Affinity Capture Elution (ACE) assay

• Advantages\(^1\)
  – High sensitivity
  – Robust and reproducible
  – Excellent drug tolerance

• Disadvantages
  – Higher degree of complexity

♦ MesoScale Discovery (MSD) – bridging format

• Advantages\(^2\)
  – High sensitivity
  – Robust and reproducible\(^3\)
  – Reduced complexity

• Disadvantages
  – Lower drug tolerance\(^4\)

So what?