1. **What are biologics?**
   
   **A:** Biologics are drugs that are proteins derived from living things, usually using recombinant DNA technology.¹,² Biologics are used in the treatment of Crohn's disease, ulcerative colitis, rheumatoid arthritis, psoriatic arthritis, plaque psoriasis, ankylosing spondylitis, juvenile idiopathic arthritis, and many other diseases.³,⁴

2. **How do biologics work?**
   
   **A:** Biologics target tumor necrosis factor (TNF) and/or other specific targets that modulate the immune response to treat certain autoimmune diseases.³

3. **How should I monitor a patient on a biologic?**
   
   **A:** Biologic monitoring, also called biologic therapeutic drug monitoring (TDM), should consist of drug and anti-drug antibody levels. Both measurements are necessary because drug and anti-drug antibodies are inversely related and anti-drug antibodies may occur at any time during therapy.⁵ When a patient is experiencing a suboptimal response or loss of response, biologic monitoring is indicated to determine if treatment failure is due to mechanistic reasons, pharmacokinetic issues or immunogenicity.³ Biologic monitoring may improve the precision of therapeutic decision-making and be highly cost-effective.¹

4. **How often should I monitor a patient on a biologic?**
   
   **A:** When a patient elicits a suboptimal drug response, biologic TDM is used to detect and quantitate anti-drug antibodies (to identify low to high titer immunogenicity) and to differentiate pharmacokinetic issues (patients who may benefit from more drug) from mechanistic failure (e.g. where a non-TNF inhibitor would be indicated).³ Biologic monitoring may also be useful any time during maintenance to avoid under-treatment due to pharmacokinetic factors that can lead to sub-therapeutic drug concentrations such as male sex, low serum albumin, high adipose tissue, and high disease activity.⁵

5. **What is treatment failure?**
   
   **A:** Treatment failure can be both primary and secondary.¹ Primary treatment failure occurs early in treatment when a patient does not elicit a response to the induction therapy. Secondary treatment failure occurs when the patient loses the drug effect after an initial response and experiences disease flares during maintenance.³

6. **What are the failure rates?**
   
   **A:** Failure rates are specific to disease states and particular drugs. Primary failure rates of biologics in IBD and RA may be as high as 30-40%.³ Within a year, another up to 50% of patients experience a secondary loss of response.⁴

7. **What causes treatment failure?**
   
   **A:** Since biologics are ‘foreign’ proteins, a patient may develop antibodies to the treatment (anti-drug antibodies); this process is called immunogenicity.⁷ Primary treatment failures may be due to mechanistic or pharmacokinetic issues or poor adherence to the treatment regimen while secondary treatment failures are most often the result of the development of antibodies to the biologic drug. Since these scenarios cannot be discerned clinically, biologic monitoring is necessary to detect and quantitate anti-drug antibodies and concomitant free drug levels in order to determine if the patient will or will not benefit from more drug or a drug switch.⁵

8. **What is immunogenicity?**
   
   **A:** Immunogenicity is the development of anti-drug antibodies. All therapeutic proteins have this potential immune response which can first occur at any time during therapy, after the first exposure to years later. Anti-drug antibodies and free active drug are inversely related. Low titer antibodies may have little or no effect on drug levels or clinical outcome. In fact, they may be transient and disappear over time, or they may progress to increasing titers.¹,⁷,⁹ In contrast, high titers of antibodies are likely to be more consequential, leading to loss of drug efficacy by preventing drug binding to TNF and/or increasing drug clearance.¹,⁸,¹⁰

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Continued ➤
9. **How is immunogenicity treated?**

**A:** In the past, positivity of anti-drug antibodies at any level was an indication to switch biologic drug. Now, the American Gastroenterological Association distinguishes between low titer and high titer anti-drug antibody scenarios. Low to intermediate titer anti-drug antibodies may be treatable, by increasing drug and/or adding an immunomodulator like methotrexate or a thiopurine. In contrast, high titer anti-drug antibodies are considered refractory to reversal and necessitate a drug switch.\(^{11,12}\)

With this treatment algorithm in mind, all of LabCorp’s biologics TDM have been set to detect anti-drug antibodies with the highest sensitivity and most granular resolution of low to intermediate to high titer antibodies. High performing anti-drug antibody assays like ours have been specifically designed by immunogenicity experts in order to help physicians improve the longevity of biologics by enabling both early detection of immunogenicity and reliable monitoring of changes in titers (e.g. diminishing intermediate-range antibodies when treating with a second immunomodulator for the purpose of reversing immunogenicity).

10. **When should my patient have blood drawn for drug levels and antibody tests?**

**A:**
- Prior to next dose (trough)
- Upon loss or lack of response
- After induction, during maintenance

11. **How are drug-levels and anti-drug antibody results interpreted?**

**A:**
- Drug levels are reported in units (micrograms/mL). Information on therapeutic concentrations and reference intervals is provided on the result report.
- Antibody results are reports with a numeric value (ng/mL) and a designation of “Undetected”, “Low”, “Intermediate”, or “High” with all anti-infliximab and anti-adalimumab antibody results.
- For more information, consult Dr. Chun or Dr. Yang.

**Patient on Biologics**

<table>
<thead>
<tr>
<th>Inadequate Response</th>
<th>Good Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free drug trough levels are undetectable or low to intermediate AND</td>
<td>Free drug trough level is therapeutic AND</td>
</tr>
<tr>
<td>Anti-drug antibody is undetectable to low</td>
<td>Anti-drug antibody is detectable to high</td>
</tr>
<tr>
<td>Pharmacokinetic insufficiency</td>
<td>Pharmacodynamic (mechanistic) response failure</td>
</tr>
<tr>
<td>Increase dose</td>
<td>Dose optimize to maximally beneficial drug trough concentration</td>
</tr>
<tr>
<td>“Reversible” immunogenicity</td>
<td>Adequate dose</td>
</tr>
<tr>
<td>Increase dose +/- Consider adding MTX or Thiopurine</td>
<td>Maintain dose or consider tapering down</td>
</tr>
<tr>
<td>Consider switching biologics (within class or to a different mechanism)</td>
<td>Consider switching biologics out-of-class (after confirming active inflammation)</td>
</tr>
</tbody>
</table>

**Proposed algorithm for RA or IBD** patients.

**Continued ➞**

**Though there is evidence that early titration of patients to therapeutic drug concentrations can reduce disease-associated morbidity and improve longevity of drug response, this proactive monitoring arm has yet to be included in the American Gastroenterologic Association’s critical care pathways for IBD.\(^{13,14}\)**

A consensus has yet to be reached about target ranges and maximally effective concentrations.\(^{1}\)

Optimal drug concentration is patient-specific and depends on disease and desired therapeutic endpoint.
12. How can testing drug and anti-drug levels help manage treatment failure?

A: Without measuring drug and antibody levels, it is difficult to know clinically which patients are likely to benefit from more drug versus those who need to be switched to a different biologic, either of the same or different class. Reactive biologics monitoring informs and expedites these critical clinical decisions.

If the drug level is therapeutic and antibodies are undetected, mechanistic failure is a possibility, necessitating a switch to a biologic drug of a different mechanism. If the drug level is low or undetected, then the anti-drug antibody titer needs to be evaluated. If antibodies are low in titer, then immunogenicity may be treatable by increasing drug and/or adding an immunomodulator like methotrexate or a thiopurine. If antibody titers are high, then the free drug level is almost invariably low or absent, necessitating a drug switch, usually within class (e.g. from first TNF inhibitor to another TNF inhibitor).11,12

13. How can testing drug and anti-drug levels help maximize treatment success?

A: Biologic drugs are subject to high intra- and inter-patient pharmacokinetic variability (i.e. some patients require more drug per kg than others) - measuring serum drug concentration allows for patient-specific dose optimizations. LabCorp’s clinical database of over 50,000 patient results has found that 20-40% of patients on infliximab and adalimumab may have sub-therapeutic drug levels in the absence of anti-drug antibodies.15 Biologic TDM also allows patients to benefit from what we know to date about maximally beneficial concentrations. For example, patients with severe IBD may require especially high drug levels (infliximab ≥10 mcg/mL) in order to achieve perianal fistular healing.16

Proactive use of biologic TDM has been shown to improve longevity of biologics treatment for up to 5 years and decrease disease-related hospitalizations and surgeries.13,14

14. Are there guidelines for biologics?

A: The American Gastroenterological Association (AGA) and the American College of Rheumatology both have guidelines available.5,17

15. What are the target ranges for trough concentrations in IBD?

A: Current understanding of target ranges and maximally beneficial concentrations relies on clinical data and may be evolving, especially for new biologics. It is also important to keep in mind that optimal drug concentration depends on patient-specific factors including co-morbidities, disease activity and desired therapeutic endpoint. The table below cites some target and threshold trough levels that have been studied to date in IBD.

<table>
<thead>
<tr>
<th>Biologic Drug</th>
<th>Proposed Trough Concentration Target Ranges or Thresholds in IBD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>&gt; 8 μg/mL18</td>
</tr>
<tr>
<td>Certolizumab</td>
<td>&gt; 20 μg/mL18</td>
</tr>
<tr>
<td></td>
<td>&gt; 30 μg/mL at week 619</td>
</tr>
<tr>
<td>Golimumab</td>
<td>&gt; 4 μg/mL20</td>
</tr>
<tr>
<td>Infliximab</td>
<td>5 – 10 μg/mL13</td>
</tr>
<tr>
<td></td>
<td>&gt; 10 μg/mL for perianal fistular healing16</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>&gt; 4.5 μg/mL21 or &gt; 1.1 μg/mL22</td>
</tr>
<tr>
<td>Vedolizumab</td>
<td>&gt; 14 μg/mL during maintenance23</td>
</tr>
<tr>
<td></td>
<td>&gt; 30 μg/mL at week 624</td>
</tr>
</tbody>
</table>

Continued ➤
16. What are the target ranges for trough concentrations in RA?
A: Target ranges have yet to be established in rheumatic diseases. The table below cites some trough concentrations that have been studied to date.

<table>
<thead>
<tr>
<th>Biologic Drug</th>
<th>Trough Concentration Ranges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>5 - 8 μg/mL in RA; 5 – 8 μg/mL in PA; 3.5 – 7.0 μg/mL in psoriasis</td>
</tr>
<tr>
<td>Certolizumab</td>
<td>&gt;23 μg/mL corresponded to better EULAR response rates</td>
</tr>
<tr>
<td>Etanercept</td>
<td>rough concentrations &gt; 3.1 μg/mL at 3 months predicted clinical response at 6 months in RA</td>
</tr>
<tr>
<td>Infliximab</td>
<td>&lt;2 μg/mL is low; &gt;8 μg/mL is high in RA</td>
</tr>
</tbody>
</table>

17. Can I use drug levels from lab-to-lab interchangeably?
A: Yes, most labs report in micrograms/mL (μg/mL). Published data shows that LabCorp’s values match Janssen and landmark clinical studies for Remicade.

18. How are LabCorp units different from other laboratories’ units?
A: • For drug levels, we use the same units (micrograms/mL)
• For antibodies, we report in nanograms/mL (ng/mL) and designate (see above). Other labs may use U/mL.
• Dr. Chun or Dr. Yang can help with patient-specific results.

19. Does LabCorp’s assay work for biosimilars?
A: Yes. Our infliximab assays have been validated for Renflexis and Inflectra.

20. LabCorp’s expertise in Biologic Monitoring
A: LabCorp’s biologics monitoring assays were developed and are performed at the LabCorp specialty lab, Esoterix, in Calabasas, CA. Esoterix has the following accreditations/certifications/licenses: ISO 15189, CAP, CLIA, NY, FL, CA, RI, PA, MD licensure.

21. Do the assays offered by LabCorp meet FDA guidance?
A: Assays performed at Esoterix meet and surpass FDA guidance documents for industry including:
• Bioanalytical Method Validation (2013)
• Assay Development & Validation for Immunogenicity Testing of Therapeutic Protein Products (2016)

22. Can LabCorp’s assays detect both low- and high-titer antibodies?
A: Yes. LabCorp’s anti-drug antibody assays are designed to reliably detect low to high titer antibodies with best-in-class resolution and sensitivity. All positive anti-drug antibody results are subject to a confirmatory test.

23. How drug tolerant are LabCorp’s antibody assays?
A: LabCorp’s anti-drug antibody assays are drug-tolerant to drug levels in excess of therapeutic ranges (i.e. the presence of drug in the serum does not interfere with the detection of anti-drug antibodies).
References