

# Biologic Therapeutic Drug Monitoring

## 1. What are biologics?

Biologics are drugs that are proteins derived from living things, usually using recombinant DNA technology.<sup>1,2</sup> 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.<sup>1,3,4</sup>

## 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.<sup>3</sup>

## 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.<sup>5</sup> When a patient is experiencing a suboptimal response or loss of response, biologic monitoring is indicated to determine if treatment failure is due to pharmacokinetic insufficiency, pharmacodynamic/mechanistic mismatch or immunogenicity.<sup>5</sup> Drug and anti-drug antibody levels provide pharmacokinetic and immunogenic assessment that may be key to improving biologic response, longevity and cost-effectiveness.<sup>1</sup>

## 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 might be indicated).<sup>5</sup>

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.<sup>5</sup>

## 5. What is treatment failure?

**A:** Treatment failure may be either primary or secondary.<sup>1</sup> 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.<sup>1</sup>

## 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%.<sup>1</sup> Within a year, up to 50% of initial responders may experience a secondary loss of response.<sup>6</sup>

## 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.<sup>7</sup> 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 if that patient would be better served by a different biologic in- or out-of-class.<sup>5</sup>

**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 with time, or they may progress to increasing titers.<sup>1,7-9</sup> 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.<sup>1,8,10</sup>

**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.<sup>11,12</sup>

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

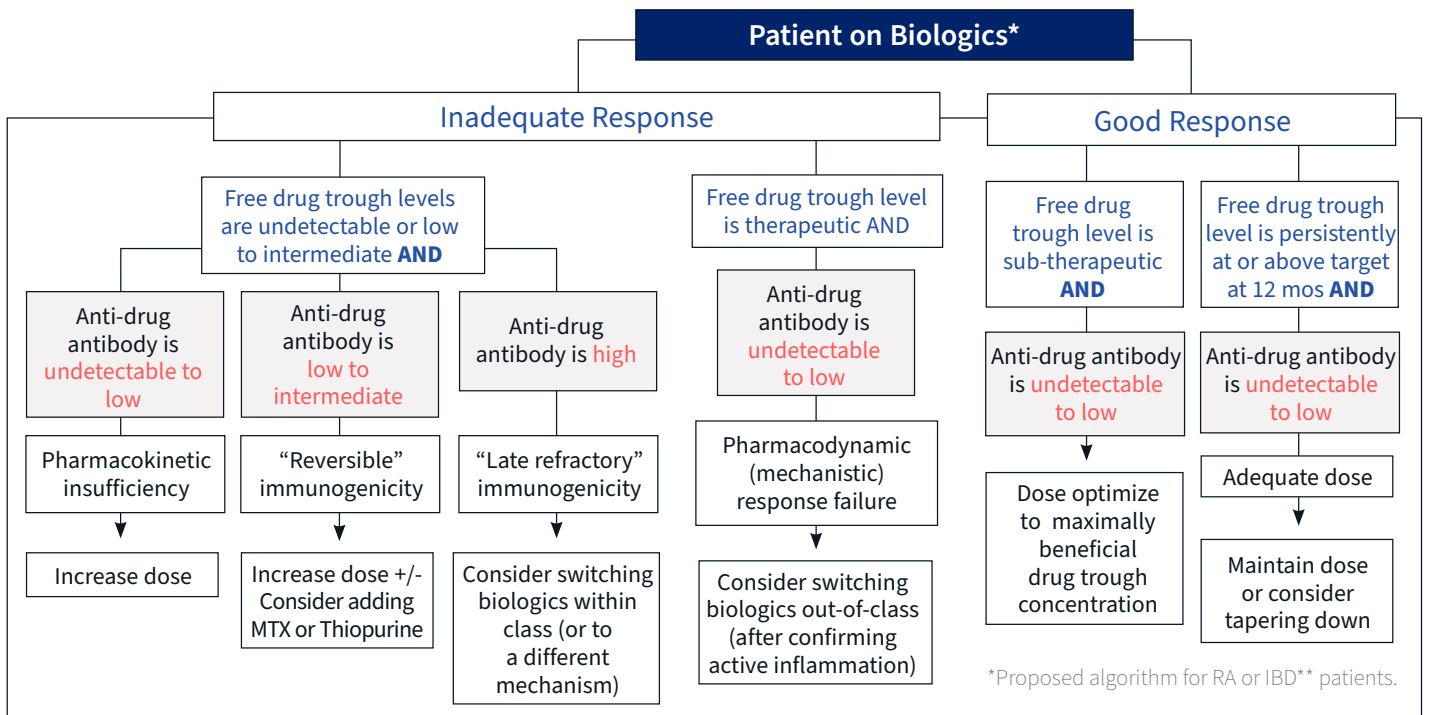
**11. How are drug-levels and anti-drug antibody results interpreted?**

- A:**
- Drug levels are reported in units (micrograms/mL). Information on therapeutic concentrations and reference intervals is provided on the result report.
  - Anti-drug antibodies are reported with a numeric value (ng/mL) and a designation of "Undetected," "Low," "Intermediate" or "High" to facilitate clinical interpretation.
  - Furthermore, all our antibody measurements are drug-specific (e.g. anti-infliximab will not cause a false positive anti-adalimumab result) and "drug-tolerant." Drug tolerance is achieved by proprietary pretreatment of patient serum so that endogenous circulating drug does not interfere with accurate measurement of anti-drug antibodies (i.e. avoids false negatives).
  - Please contact the Biologic Monitoring Hotline at 844-225-8877 for help with patient-specific results.

**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).<sup>11,12</sup>



\*\*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 Gastroenterological Association's critical care pathways for IBD.<sup>13,14</sup>

A consensus has yet to be reached about target ranges and maximally effective concentrations.<sup>1</sup>

Optimal drug concentration is patient-specific and depends on disease and desired therapeutic endpoint.

### 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. Several published studies have shown that standard dosing without TDM leads to suboptimal biologic drug levels in about one third to one half of patients with IBD or RA.<sup>15-19</sup> This high incidence of pharmacokinetic insufficiency is corroborated by Labcorp's own clinical database of more than 50,000 patient results, which found that 20-40% of patients on infliximab and adalimumab may have sub-therapeutic drug levels in the absence of anti-drug antibodies.<sup>20</sup>

Furthermore, 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  $\geq 10$  mcg/mL) in order to achieve perianal fistular healing.<sup>21</sup>

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.<sup>13,14</sup>

### 14. Are there guidelines for biologics?

**A:** The American Gastroenterological Association (AGA) and the American College of Rheumatology (ACR) both have guidelines available.<sup>5,22</sup>

**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 comorbidities, disease activity and desired therapeutic endpoint. The table below cites some target and threshold trough levels that have been studied to date in IBD.

Biologic Drug	Proposed Trough Concentration Target Ranges or Thresholds in IBD
Adalimumab	>8 µg/mL <sup>23</sup>
Certolizumab	>20 µg/mL <sup>23</sup>
	>30 µg/mL at week 6 <sup>24</sup>
Golimumab	>4 µg/mL <sup>25</sup>
Infliximab	5–10 µg/mL <sup>13</sup>
	>10 µg/mL for perianal fistular healing <sup>21</sup>
Ustekinumab	>4.5 µg/mL <sup>26</sup> or >1.1 µg/mL <sup>27</sup>
Vedolizumab	>14 µg/mL during maintenance <sup>28</sup>
	>30 µg/mL at week 6 <sup>29</sup>

**16. What are the target ranges for trough concentrations in RA?**

**A:** Not all biologics have established target ranges in rheumatologic diseases. The table below cites trough concentrations that have been studied to date.

Biologic Drug	Trough Concentration Ranges
Adalimumab	Proposed target of 5–8 µg/mL in RA <sup>30</sup> ; 5–8 µg/mL in PA <sup>31</sup> ; 3.5–7.0 µg/mL in psoriasis <sup>32</sup>
Certolizumab	>23 µg/mL corresponded to better EULAR response rates <sup>33</sup>
Etanercept	Trough concentrations >3.1 µg/mL at 3 months predicted clinical response at 6 months in RA <sup>34</sup>
Golimumab	Higher trough levels (median 3.4 µg/mL) correspond to a greater rate of clinical response <sup>35</sup>
Infliximab	<2 µg/mL is low; >8 µg/mL is high in RA. <sup>15</sup> In rheumatoid arthritis, EULAR responders had higher median trough levels (3.6) than non-responders (0.5). <sup>36</sup>
Ustekinumab	In plaque psoriasis, median trough ustekinumab concentrations were 0.4 µg/mL at weeks 14 and 28 (ranging from undetectable to 3.6 µg/mL). <sup>37</sup> Although PASI50 responders had higher trough concentrations than non-responders in a study of 76 patients, a definitive therapeutic target range for psoriasis has yet to be established. <sup>38</sup>

**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®.<sup>39</sup>

**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.
  - Please contact the Biologic Monitoring Hotline at 844-225-8877 for help with patient-specific results.

**19. Does Labcorp's assay work for biosimilars?**

**A:** Yes. Our biologic TDM assays are appropriate for patients on biosimilars.

For Renflexis® (Organon & Co.) and Avsola™ (Amgen, Inc.) specifically, our infliximab drug and antibody assays have been validated.<sup>40</sup>

And newer biosimilars, as they become available, can easily be validated by our laboratory.

**20. Explain 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).

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