TDM to the rescue in biologics boom

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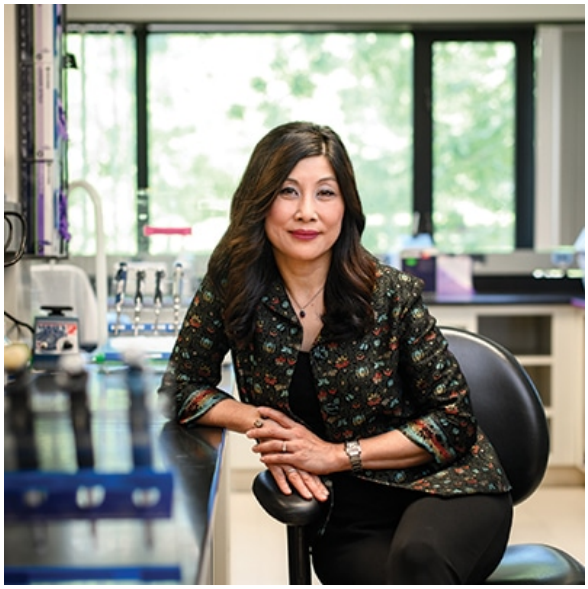
July 2019—In the early, heady days of biologic therapies, use of these drugs resembled a common military tactic of the Civil War: charge and retreat, charge and retreat, charge and retreat. The approach, though modern at the time, often proved disastrous.

Jeffry Katz, MD, recalls the excitement that greeted the arrival of anti-tumor necrosis factor-α agents, starting with infliximab (Remicade) in 1998. “What we used to do is we would give patients a drug, and we would wait for them to get sicker,” says Dr. Katz, medical director, inflammatory bowel diseases, University Hospitals Cleveland Medical Center, and professor of medicine, Case Western Reserve University School of Medicine. “And then we’d give them a stronger drug, and then we’d wait for them to get sicker. And then we’d give them our strongest drugs, or we’d send them to the operating room.” In essence, “We basically didn’t give the strongest, most effective therapies until people got more ill.”

Over time, physicians learned this approach also allowed bowel damage to occur. “And by the time we get to the best drugs, it’s often too late—nothing’s going to work at that time,” says Dr. Katz.

Little wonder that physicians are turning to a new strategy for deploying biologics: using therapeutic drug monitoring, with the aim of aggressively controlling disease and inflammation. Doing so will help prevent downstream complications, says Dr. Katz, including hospitalization, surgery, and strictures.



Dr. Jane Yang of LabCorp: “I really think TDM may be the answer to the poor longevity of biologics,” she says. (Photo courtesy of Shawn Henry)

“For the use of biologics in inflammatory bowel disease, some sort of monitoring is the standard of care at this point,” he says, “whether it’s reactive or proactive or some combination of both.”

The data to support this are far from perfect, and the best approach has yet to be determined. “We still have questions to answer,” Dr. Katz concedes, “but it’s better than flying blind, which is what we did for years with the use of infliximab and, for a while, adalimumab.”

At the very least, physicians are flying in the same direction, guided by assays for therapeutic monitoring and testing for immunogenicity. “This is one of the most rapidly growing areas in clinical immunology testing,” says

Eszter Lazar-Molnar, PhD, D(ABMLI), D(ABHI), medical director, Immunology Division, ARUP Laboratories, and director of the Histocompatibility and Immunogenetics Laboratory at the University of Utah. Within the broader biologics category, TNF antagonists—five of the parent drugs and an increasing number of biosimilars have been FDA approved—spur the majority of such testing, she says. The biggest drivers are infliximab and adalimumab (Humira), and the bulk of orders comes from gastroenterologists, though the drug is also used to treat rheumatoid arthritis.

"A huge portion of our health care dollars is being spent in specialty medicine," says Jane Yang, MD, medical science director at Esoterix specialty lab for biologic TDM of LabCorp. By 2020, she says, an estimated $400 billion could be spent on specialty drugs, accounting for just over nine percent of total national health care spending. Specialty patients represent three percent of the population, but the group accounts for 40 percent of total drug spending, she says. And of the drugs popping out of the FDA approval pipeline every year, Dr. Yang continues, roughly 70 percent are biologics. It is, she says, the fastest growing and highest grossing category of drug.

No surprise there. "These drugs are great," says Dr. Yang. "They've really revolutionized the care of many diseases, especially now in autoimmune disease. But the disconnect is that you have these expensive drugs, and they're being dosed by standard dose, or dosing by weight. And we can certainly do better than that."

"These are miracle drugs in patients who respond," agrees Dr. Lazar-Molnar, who is also assistant professor, Department of Pathology, University of Utah.

Who respond being the key part of that sentence. "Although these are really good treatments," says Dr. Katz, "they don't work for everybody."

Some 30 percent of patients who receive a biologic are primary nonresponders, Dr. Yang says. It could be that they didn't receive the right dosage, or that they need a drug of a different mechanism. Secondary failure rate is quite high, she continues—some 50 percent of patients on a biologic are not on that drug after one year. And every year thereafter, 10 to 15 percent of patients fall off. "There's a tremendous problem with persistence," Dr. Yang says.

Failure is caused primarily by development of antidrug antibodies. "You are giving the protein drug to a patient repeatedly," says Dr. Lazar-Molnar. "It's like immunizing someone with that drug, right? So it's not a surprise that after a while they will develop antidrug antibodies."

Ten to 15 years ago, physicians who wanted to look for antidrug antibody would have to put the patient on a drug holiday because the only available antibody assays were subject to interference by circulating drug, Dr. Yang says. This may have answered their question, but it compromised treatment and contributed to immunogenicity.

"We've come a long way in being able to offer physicians better immunogenicity assays that are more sensitive and drug tolerant," Dr. Yang says. Gastroenterologists should no longer be thinking of immunogenicity as binary, she says; rather, they should use results from high-performing antibody assays the way they would a tumor marker. If a patient starts developing antidrug antibodies, it makes sense to ensure the drug level is optimized and/or to consider adding a second medication, such as methotrexate or azathioprine (Imuran), she says. "There's some evidence that you can actually reverse antidrug antibodies if they're low in titer. But if there's high-titer antidrug antibody, the patient has refractory immunogenicity, and it's likely time to switch to a different biologic."

Even more concerning, she says, is that "Once you've developed antibodies to one biologic, you need to move on to the next biologic." And—unlike with marriage—the second or third one is less effective.

"I really think TDM may be the answer to the poor longevity of biologics," says Dr. Yang. In the best-case scenario, she says, it could allow physicians to consider cotherapies where appropriate and enable patients to successfully remain on a biologic longer, with fewer complications.

Early approaches to biologics involved treating as needed or on demand, until, Dr. Katz says, "We began to see that that wasn't the best way to go about it. People would lose response or develop antibodies to the treatment. So we developed induction therapies and maintenance therapies." It has also become clear that there's a blood level-

response curve—generally, the higher the drug level, the better patients tend to do over time. “There’s sort of an optimal therapeutic window—below a certain level, they don’t seem as effective, and above a certain level they don’t seem to gain any additional effectiveness.”

Improving the longevity of these drugs also makes sense in terms of cost, says Dr. Yang, noting treatment can run to more than $30,000 per patient annually. “As great as these medications are, they’re very expensive.”

Several European studies have shown that laboratory-based management of patients on biologics, versus empirical-based management sans lab testing, saves money, Dr. Lazar-Molnar says.

But TDM in this setting poses numerous challenges. While the concept is, obviously, already familiar to laboratories, there are some differences from the traditional approach. With conventional drugs such as digoxin, say, or gentamicin, clinicians are worried about a ceiling, and the proximity of the toxic range to the therapeutic range. That’s not the case with biologics.

“These drugs have their own unique challenges for assay development,” says Dr. Lazar-Molnar. “First, you need an assay to measure drug levels, but perhaps even more importantly, you need an assay to detect antidrug antibodies that arise following treatment with these drugs. You’re measuring antibody against an antibody drug in the serum, which has a lot of antibody, a lot of immunoglobulins, in the background.” And not all antibody will be detectable in the patient who is taking the drug. “It may be bound to the drug, and not available for the assay.”

Dr. Yang advocates for tandem testing, using one assay to measure drug concentration and another to look for antidrug antibodies. “You want to expedite critical clinical decisions, as dictated by the American Gastroenterological

Association’s current guidelines, which necessitate both drug and antibody levels,” she says. Biologics are, of course, proteins, so there’s always the potential for inducing an antibody response. “And those antibodies can negatively impact drug efficacy,” she says.

Some laboratories choose reflex testing, but Dr. Yang is not a fan of this approach. “It flies in the face of what we’ve more recently seen about reversing antidrug antibodies, about adding cotherapies and optimizing drug concentrations in order to treat away lower titers and prevent their progression to high titer refractory immunogenicity.” Reflex testing might seem just as good, and cheaper, but it could mean losing an opportunity to manage early immunogenicity that could be transient and reversible.

It’s critical, she says, to know why a patient is not responding to a biologic. If there are no antibodies and the drug level is good, then the patient may have developed an infection, or they may have another disease. Or, the disease may be driven by a different mechanism, “and then you need to think about a pharmacodynamic mismatch.” On the other hand, if the drug level is low, and there are no antibodies, “then that patient likely just needs more drug.” If there are antidrug antibodies, “then you need to look at the titer.”

As many as 30 percent of patients may be subtherapeutic in the absence of any antidrug antibodies simply because they haven’t been given enough drug based on standard dosing. “We show that in our own clinical database, but it’s also shown in other studies,” Dr. Yang says. It’s true for IBD as well as rheumatoid arthritis. “Your patient may just require more drug on account of being a big male with low serum albumin and really active disease.”

From the laboratory standpoint, she says, “There’s a right way of measuring biologic drug and antidrug antibodies, and then there’s a less-informed way.”

Dr. Katz says there’s solid evidence to support use of reactive monitoring—checking drug levels if the patient is not doing well, which, depending on the result, may prompt higher dosing, use of a different drug, or switching to a different class of drug.

Some have begun to push back against the reactive only approach, however, arguing that it allows patients to

become ill before trying to figure out if the benefit of the drug is being lost. In the past two or three years, Dr. Katz says, interest in proactive monitoring has grown. Solid retrospective analyses support the idea of checking drug levels while patients appear to be doing well. Dr. Katz, who coauthored an American Gastroenterological Association technical paper on TDM for managing inflammatory bowel diseases (Vande Casteele N, et al. *Gastroenterology.* 2017;153:835–857), says that since the guideline appeared, more publications have come out supporting the idea of proactive monitoring, which clinicians are starting to adopt.

He considers this to be the major controversy in the field. "If you're going to think about proactive monitoring, when do you do it? How often do you do it?"

Most biologics have an induction dosing pattern, followed by a maintenance dosing pattern. Some data suggest that if certain drug levels aren't achieved at the end of induction and before the start of maintenance, outcomes aren't as good, he says. "So maybe you adjust your maintenance therapy to be a little more aggressive."

There are no FDA-approved assays, which complicates matters, as does the lack of standardization in the field. "No two labs are using the same technology," says Dr. Lazar-Molnar. "A result of 5 may not be an absolute 5.

Though most labs report biologic drug concentrations in micrograms per milliliter, Dr. Yang says, "it's very difficult to compare antidrug antibody levels across different labs." Some labs report antibodies in U/mL; LabCorp's Esoterix specialty lab in Calabasas, Calif., reports ng/mL. Depending on what a lab uses, a 200 may be astronomically high or in the middle of an intermediate range, she says. She and her colleagues have demonstrated an inverse relationship between free pharmacodynamically antibody unbound drug and total drug antibody to determine cut points. "For example, our lab designates anti-infliximab antibodies in excess of 1,000 ng/mL as high in titer, as almost invariably there's no free drug present in that patient," she says. A level of less than 200 is designated as a low titer as there is little or no reduction in the concomitant free drug, she adds.

The key issue that has emerged with antidrug antibody assays is the issue of drug tolerance. "Are you able to detect antibodies in the presence of circulating drug?" asks Dr. Yang. Three basic tests are available to measure drug and antidrug antibodies: ELISA, HMSA (homogeneous mobility shift assay), and ECLIA (electro-chemiluminescence immunoassay), which is the method Esoterix uses. "There's a misunderstanding out there that all ELISAs are bad and HMSAs are good," Dr. Yang says. That perception, held by some clinicians, may stem from another lab's original non-drug tolerant ELISA, which was replaced with HMSA in 2012, she says. Laboratories know, of course, that drug tolerance is not assay principal-dependent, but rather is based on, among other things, the pretreatment process of serum to remove circulating drug. Labs may have to counter these misperceptions when helping their clinical colleagues assess which test to use, she says.

Most clinicians aren't going to have fierce opinions about what type of test is used, says Dr. Katz. "The important thing is that a practitioner be comfortable with the assay their office or hospital is using, and gets used to the ranges and how people respond." That becomes a strong argument to not change assays, he says. "It gets really challenging to interpret results when you have a different company reporting results."

Drug concentrations reported in µg/mL should match up across different laboratories so that clinicians can make use of established target ranges and cutoff concentrations, Dr. Yang says, but antidrug antibody levels in general don't match up well. "It's also a matter of where the cutoff is, and how sensitive the assay is, and what you're actually measuring."

Dr. Yang says there's plenty of confusion about what the laboratory should or shouldn't be measuring. "You should be measuring free pharmacodynamically active drug," she continues. In this context, "free" means antibody unbound, because drug that is bound up to the antibody is not available to treat disease. Or, as Dr. Yang puts it, "Antidrug antibody that binds to the business end of the drug means that the drug can't bind to its target in the body to treat the disease." Dr. Yang cautions that if you're measuring total drug in the setting of a lot of antidrug antibodies, "you're going to give a very misleading result to the clinician."

At the same time, she's often asked whether results show neutralizing or nonneutralizing antibodies. That, in her

view, is moot because whether neutralizing or nonneutralizing, antibodies increase drug clearance and shorten drug half-life. “I think what’s important is that you have a very sensitive total antidrug antibody assay, and then total antidrug antibody and concomitant free drug should be interpreted together.”

It’s important to distinguish between low, intermediate, and high titer, she reiterates. “The onus is on the laboratory because you need to tell clinicians if a numeric result for the antidrug antibody is low or high in order for them to be able to follow the current AGA algorithms to direct treatment. So how well does the laboratory resolve low to high?” she asks.

If a low antidrug antibody level is 1 to 6, and 7 is higher, what does a clinician do with a result that’s 6.5? “They’re stuck between, *Am I increasing the same drug—and maybe adding methotrexate?* and *Do I need to switch drugs?*”

At her lab, the intermediate antidrug antibody range is 200 to 1,000 ng/mL. Physicians are coming to realize that at 500 or less, the antibodies can be treated away, and the patient will be monitored more frequently. At greater than 500, that approach is less successful. At 1,000 or higher, they say, “We’re done with this drug.” With the clinician able to make such choices, “Your test is working the way it should be,” says Dr. Yang—pointing physicians to very critical, very different decision arms with the best possible assay resolution. If you’re going to test, “Why not figure out the best way to do it?” she asks, and weigh long-term benefits against small savings that could prove more costly and harmful.

Dr. Yang says she still sometimes gets questions from clinicians asking whether they should be worried about toxicity. “That’s really not what you’re worried about here—it’s more the floor—you’re worried about the drug level being too low, which both undertreats the disease as well as increases the immunogenicity risk.”

Dr. Lazar-Molnar finds that the majority of clinicians’ queries concern next steps. “A lot of times we have questions about what to do with a drug level that is detected: *Is that normal? Is that in the therapeutic range?*”

Dr. Lazar-Molnar

Since such levels haven’t been completely defined, “We, as a reference lab, encourage clinicians not to base decisions on that one number that is the drug level, especially since we cannot ensure that those levels are trough levels,” Dr. Lazar-Molnar says. “You need to look at the context, at the clinical presentation.”

Another issue, says Dr. Lazar-Molnar, is that currently there are no standardized proficiency testing samples. To address this, ARUP and Mayo Clinic did a joint study comparing each lab’s infliximab assay for drug and antidrug antibody testing. The correlation was surprisingly good, she says, and based on that data, “We initiated a CAP-mediated sample exchange,” which has just begun and which involves a third lab as well. “It’s still a work in progress,” she says, adding that she would welcome CAP input in developing PT samples.

Dr. Yang notes that trough collection is generally recommended, since target ranges are usually based on trough concentrations. Some researchers have suggested measuring stool infliximab to assess loss of drug through the gut during an IBD flare-up, says Dr. Yang. “But drug concentration at the trough is the one that is best described and understood [related to] mucosal healing.”

With adalimumab—and its longer half-life, and patients injecting themselves—some rheumatologists have become interested in obtaining random measurements. Because of its relatively long half-life of about two weeks, it may be less critical to get a perfect trough collection, she says, so a measurement taken a day or two prior to injection

may be off by less. “And that’s where I jump in and say, ‘You know, you could extrapolate what the true trough concentration would be.’”

But the targets themselves are fuzzy. “There aren’t robust data on the ideal levels across different drugs and different diseases,” says Dr. Katz. “We kind of lump everything together. We don’t have the sophistication to precisely target different levels to different types of Crohn’s disease or different types of ulcerative colitis.” It may be that there are different ideal drug levels for different conditions. For example, he says, some evidence suggests that perianal Crohn’s disease needs higher serum drug levels for optimal control compared with inflammatory luminal Crohn’s disease.

In the future, TDM might be used to determine correct drug dosage. “This is where the field is going to,” Dr. Lazar-Molnar predicts. The AGA guideline defined trough serum drug level targets for infliximab and adalimumab for patients with active disease. It’s a start, she says. “But it doesn’t cover everybody.”

Rheumatology offers even fewer answers. “What does a rheumatologist do with a lab value we give them?” asks Dr. Lazar-Molnar. “Do they make any changes based on that, or not? Because there aren’t any guidelines for rheumatology.”

Therapeutic ranges may be different in RA, Dr. Yang agrees. “Just because you can measure a drug level doesn’t mean a physician knows what to do with it. So you’re really relying on clinical studies in patients to demonstrate that a given serum concentration correlates with drug efficacy and a desired clinical outcome.”

Beyond the more pressing current clinical issues, the development of immunogenicity is an interesting research topic, says Dr. Lazar-Molnar. Not everyone develops antidrug antibodies. Pharmaceutical companies are trying to minimize non-human sequences in these antibodies, which could help address the problem, and they’re using bioinformatics tools to predict immunogenicity. “But you can never be 100 percent accurate,” she says.

Dr. Lazar-Molnar says she’d also like to see more research into the role of neutralizing versus nonneutralizing antibodies. “You would expect that neutralizing antibodies are directly inducing treatment failure because they render the drug noneffective. But based on data from other areas, we know that antibodies can form complexes even if they are nonneutralizing—they may still lead to immune complex formation and clearance of the drug. It may be cleared too soon and then become ineffective.”

Also, Dr. Lazar-Molnar says, “We cannot predict which patients will develop antibodies eventually.” Disease data may play a role in addition to the likely role of genetics. One study, she notes, looked at development of immunogenicity to infliximab in an Ashkenazi versus a Sephardic Jewish population. “Jewish Ashkenazi ethnicity was protective of antidrug antibody formation and treatment failure to infliximab,” she says. “Certainly there are some genetic determinants,” possibly related to antigen presentation, HLA type, etc. “It’s very hard to find these during the clinical trials, which tend to be done in one study population.” Moreover, she says, “You are giving these drugs to patients with autoimmune disease who are already hyper-reactive immunologically.” An immune system that is already out of balance may affect antidrug antibody formation.

More answers will be nice. But current gaps in the data aren’t necessarily a reason to wait. “Clinical labs need to be prepared that this is coming,” says Dr. Lazar-Molnar. “Immunogenicity testing will increase because therapeutic monoclonal antibodies are increasing. This is one of the largest areas in the pharma industry.”

With biologics, the stakes are high. There are many roads that feel like they should end sooner rather than later—the ones that stretch the long way across a state; the ones paved with good intentions—but biologics should not be counted among them, says Dr. Yang. “You don’t want to burn through a biologic.”

Karen Titus is CAP TODAY contributing editor and co-managing editor.