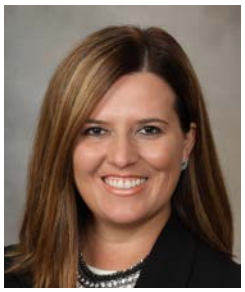

Article:
Maria Willrich.
Therapeutic Monoclonal Antibodies in the Clinical Laboratory.
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Guest: Dr. Maria Willrich is co-director of the Immunology and Mass Spectrometry Laboratories, and an Assistant Professor of Laboratory Medicine and Pathology at the Mayo Clinic at Rochester, Minnesota.

Randye Kaye: Hello, and welcome to this edition of "JALM Talk" from *The Journal of Applied Laboratory Medicine*, a publication of the American Association for Clinical Chemistry. I'm your host, Randye Kaye.

A large number of analytes in clinical laboratories are measured using antibodies in the form of immunoassays. It is well-known that these may be prone to different interferences, such as the high dose hook effect at very high analyte concentrations, human anti-mouse antibodies (HAMA), auto-antibodies such as rheumatoid factor, and also dietary supplements such as biotin.

Other methodologies such as serum protein electrophoresis and immunofixation are used to detect antibodies in patient samples in the work-up of plasma cell dyscrasias such as multiple myeloma. Therapeutic monoclonal antibodies used in the treatment of different diseases pose a new potential interference for clinical laboratories to think about when using any of these antibody-based methodologies.

A Professional Insights article titled, "Therapeutic Monoclonal Antibodies in the Clinical Laboratory" published in the November 2017 issue of JALM, discusses some of these therapies, the different ways in which therapeutic monoclonal antibodies may interfere with commonly utilized laboratory tests, and how labs can recognize the potential interference. The author of this article is Dr. Maria Willrich, co-director of the Immunology and Mass Spectrometry Laboratories, and an Assistant Professor of Laboratory Medicine and Pathology at the Mayo Clinic in Rochester, Minnesota, and she's our guest of today's podcast. Welcome, Dr. Willrich.

Here's the first question for you. Immunotherapies have been a hot topic. Can you describe what immunotherapy is?

Dr. Maria Willrich: Yes. So, immunotherapy is a type of biological therapy. It's a therapy that will use our immune system, or fragments from our immune system for instance. They are usually

artificially made, we can replicate parts of our immune system using different technologies and engineering.

So, the immunotherapies that we can talk about today a little more are the therapeutic monoclonal antibodies. They are immunoglobulins, they are antibodies that may be generated in animals or fragments of animal sequences, or they can be completely genetically engineered to have only human sequences, and target a specific molecule that is usually disregulated in a few different diseases: cancer, autoimmune disease, inflammatory states and many, many other applications.

Randye Kaye: Wow, thank you, very interesting. Now, did this new class of medications impact the clinical laboratory, and can you talk a little bit about how, if so, they did, and talk about some examples?

Dr. Maria Willrich: Yes. So, this new class of medications is definitely impacting the laboratory. I think when I moved to the States in 2012, there were maybe 30 different FDA approved medications, and they were mostly used for cancer. And now, in 2017, there are over 60 different approved therapeutic monoclonal antibodies, and they're being used more and more for chronic conditions, and patients are receiving them for the rest of their life. So, when they're being followed for some routine testing, we are getting to find some funny results or something unexpected. And a lot of times, clinicians are wondering if those could be the therapeutic monoclonal antibodies.

Randye Kaye: So, if these immunotherapies can be an interference to laboratory testing, what do we do? How can we identify them?

Dr. Maria Willrich: So, there are different ways that the therapeutic monoclonal antibodies can interfere with testing. If the patient, for instance, is diagnosed with myeloma and then eventually, during the course of the different therapies and chemotherapy, that patient is prescribed a therapeutic monoclonal antibody, we may be able to see that on the tests that the patient frequently has to monitor their disease.

So, a lot of times, we see not only that disease clone, which is also an immunoglobulin, but we are able to see the therapeutic monoclonal antibody migrating on the gel. And that can impact how we interpret that result because, let's say if a patient with multiple myeloma is responding well to therapy and eventually that original disease clone is absent but we're still seeing some positive results on the tests that the patient usually does, that can mean for someone who is unaware that that therapeutic can be interfering, that can

pose a problem, and patient may be then labeled as not responding completely to therapy.

So, there are a few techniques that the laboratory can use to mitigate that interference. And there's at least two different methods, one is by trying to bind that therapeutic monoclonal with an antibody within another antibody against that drug, what we call the antidrug antibodies (ADAs), and that would shift that positive identification pattern to somewhere else where we know that if that was indeed a therapeutic protein or a therapeutic monoclonal antibody, that's where it would be, we know the shift would happen and that would prove it. And we also can make use of mass spectrometry. If we know that accurate molecular mass of that specific therapeutic monoclonal antibody, we are able to then find it in a patient. If that accurate molecular mass is found, we're able to say, "Hey, this was that therapeutic monoclonal antibody," for instance.

So, we do have a few ways to mitigate that interference.

Randye Kaye: Wow, there's so much to it. Now, are there reasons why a clinician would like to measure the amount of immunotherapies in circulation?

Dr. Maria Willrich: Yes. So, for some of those therapeutic monoclonal antibodies that are used more routinely, I would like to highlight especially the gastroenterology practice, patients with inflammatory bowel disease, they have been benefitting from the use of therapeutic monoclonal antibodies quite a bit. And the goal of a GI physician is to keep the patients on those drugs for as long as possible because once patients start failing therapy with drugs, they can need surgery, actually. So, they may go to a round of abdominal surgeries once they have failed all the possible therapeutic medications that would keep them in remission. And there are a series of studies that have correlated the levels of those biologics, the levels of these therapeutic monoclonal antibodies, with better outcomes for those patients.

So, a clinician will try to monitor the levels of those immunotherapies in circulation in patient serum and try to keep them above certain thresholds by adjusting the therapy, so something very similar to what's done in toxicology, for instance, and in therapeutic drug monitoring, when we're doing that monitoring with small molecules, that's also happening now for these immunotherapies.

And patients may lose response to therapy over time. You know, these immunotherapies, there are large molecules and we say that they are immunogenic, or they have the capability of eliciting an immune response, and we actually

may develop an autoantibody against this therapeutic drug. So, it can become quite complex. And in the laboratory, we were asked, I would say in the last decade, to start developing assays to then measure the amount of immunotherapy that is in circulation, and also to assess if the patient has developed an immune response to those therapeutic monoclonal antibodies.

So, there are panels of tests, or we can also perform them in a reflex approach, but usually a combination of tests by measuring the concentration of these drugs and the assessment of antidrug antibodies, that's becoming very common especially in the GI environment, assessing patients with inflammatory bowel disease.

Randye Kaye: Okay, thank you. So, it's important to measure, it's important to keep monitoring and monitor the efficacy, and that makes a lot of sense. Any other advice, what advice would you offer to fellow laboratorians who are facing challenges with immunotherapies?

Dr. Maria Willrich: Well, the field is very new, so I think when talking to a clinician, it's very important to ask questions: What are they looking for? Is this a case that the patient is experiencing a loss of response to therapy? Are they looking to understand if that result that they are receiving is real, if the monoclonal antibody is actually an interference? So, it's very important to get the clinical context of what the clinician is actually looking for.

And more than that, it's also important to ask, when was that sample drawn? Is that immediately after an infusion of the drug, when we would expect to have very high concentrations of that therapeutic monoclonal antibody on board? Or was that last infusion received about a month ago? So, asking a lot of questions is very important. And if you are seeing something abnormal, something suspicious, also talk to the reference laboratory performing the test.

I do think that one of the main weaknesses in reference laboratories is that we don't know the entire story behind the sample when it's sent to us. So, giving that clinical context also to the reference lab performing the test will help a lot to interpret the results better.

And I think, also keep your eyes open for the presence of these therapeutic monoclonal antibodies in samples. I've been getting calls and clinicians questioning results, at least a couple of times a month. So, I think, it will become more and more common.

And I think that last but not least, learn more about the field. AACC has been on top of this game and has published

a few articles in many different journals. The [AACC] Annual [Scientific] Meeting has also put together several educational sessions on the topic every year, so they can definitely help us become more aware and more familiar with this new field.

Randye Kaye: That was Dr. Maria Willrich from the Mayo Clinic talking about the JALM Professional Insights article, “Therapeutic Monoclonal Antibodies in the Clinical Laboratory” for this podcast. Thanks for tuning in for “JALM Talk.” See you next time and don’t forget to submit something for us to talk about.