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Abatacept as a Mimic of Gamma Heavy Chain Disease

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Guest: Dr. David Manthei is an Assistant Professor of Pathology at the University of Michigan and Section Director of the Special Chemistry and Immunology Laboratories at Michigan Medicine.

Bob Barrett: This is a podcast from *Clinical Chemistry*, a production of the Association for Diagnostics and Laboratory Medicine. I'm Bob Barrett. As we learn more about the mechanisms responsible for causing disease, new medications that specifically target these cellular processes are regularly introduced to the market. These new therapeutics provide patients and physicians with more effective treatment tools and improve outcomes. But there's also a downside. In some cases, these new medicines may interfere with clinical laboratory tests, causing misleading results that lead to incorrect medical decisions. Although the therapeutic and safety profiles of these drugs are well established, their impacts on laboratory test methods often are not.

For the clinical laboratorian, it is essential to know which new drugs are being used for which patients, how these drugs might affect currently available test methods, and how to recognize misleading results caused by the interfering drug. Since many new drugs are brought to the market each year, staying abreast of potential interferences is a daunting task. How should laboratorians begin to approach this problem? Are there particular types of drugs that are more likely to cause interference?

A letter to the editor appearing in the August 2023 issue of *Clinical Chemistry* addresses these questions by characterizing interference caused by abatacept, a biologic used in the treatment of rheumatologic diseases. In this podcast, we are excited to talk with the letter's author. Dr. David Manthei is an Assistant Professor of Pathology at the University of Michigan. He is also Section Director of the Special Chemistry and Immunology Laboratories at Michigan Medicine. So, Dr. Manthei, let's get basic first. How can medicines or therapeutics negatively impact laboratory testing?

David Manthei: Well, that's a good and a broad question. Therapeutic agents can, I think, fall into a category of substances that can interfere with lab testing in general, and if we kind of consider those general interferences, they can be both broad or specific to an individual assay. If we think about one of the

prototypical and common interferences is in vitro hemolysis can impact different assays in different ways, but can occur because of a biproduct of how that specimen is collected or handled or other things that may have happened to that specimen. And what's one of the big parts of that is it's the movement of the intracellular components to the outside of that cell as it's being broken, and this can be the movement of something that we're actually trying to analyze itself, enzymes that may degrade other things, or things like, for example, hemoglobin being released that has a spectral interference with how tests are being done.

So there's lots of ways that an interference can have that interfering effect. In contrast, there are some substances that may be an inherent part of that patient sample and yet still cause issues with underlying components of a test or how a test functions. And I think one of the ones that over the years has gotten some kind of press is biotin interference. People may take biotin as part of supplements or for other reasons but that biotin that they're taking, if high enough doses, can impact biotin streptavidin binding, which actually can be a common linkage used in test designs of immunoassays. So along those lines, as people take therapeutic biologic agents, they can similarly be present in the actual sample collected for library testing and can lead to different types of interferences.

Bob Barrett: So why is interference caused by therapeutic drugs particularly relevant during the evaluation of multiple myeloma and related conditions?

David Manthei: I think that's a very relevant question. A normal part of our biology is the generation of a multitude of diverse immunoglobulins and their functions as part of our adaptive immune system. These antibodies typically composed of variations of heavy and light chains. For example, heavy chains typical options include IgG, IgA, IgM, IgE and IgD, whereas the light chains have the options of kappa and lambda. So the combinations of all those heavy and light chains can occur in our normal biology and they circulate and bind for antigens as part of that protective immune response.

However, in conditions like multiple myeloma and other monoclonal gammopathies, there's an overproduction of a single antibody combination from a plasma or a B-cell clone. For example, neoplastic cells could produce a single characteristic IgA lambda immunoglobulin in excess of other immunoglobulins. The detection of these single monoclonal immunoglobulins is the foundation of what we test in serum protein electrophoresis and immunofixation. So, the issue with these therapeutics is that they're designed monoclonal proteins that can be used to treat different diseases. And if these patients receiving this treatment in their serum is one

of these monoclonal proteins that are therapeutic, and are tested for monoclonal immunoglobulins looking for disease, these therapeutic agents would look the same as a neoplastic monoclonal immunoglobulin.

So, the impact in myeloma is potentially increased beyond any generic conditions that maybe treated by these therapeutics, as some therapeutic monoclonal proteins, for example, IgG kappas, like daratumumab, are commonly used to treat this very disease that involves the detection and monitoring of monoclonal proteins. And if that patient's disease-causing monoclonal protein is the same type, for example, an IgG kappa, as that therapeutic protein, it raises the possibility of confusion, especially at low levels of disease.

Bob Barrett: Doctor, interference due to therapeutic monoclonal antibodies has been documented before. What is different in your report and why isn't this commonly reported?

David Manthei: So, there's a little bit of difference of therapeutic monoclonal proteins and therapeutic agents in general. So, in contrast to therapeutic monoclonal antibodies, which like other antibodies have heavy and light chain components, abatacept is a fusion protein that has part of a heavy chain from IgG, but no antigen binding Fab portion or light chains of an immunoglobulin. And this is by design to have the functional effect of the drug bind, its target, whereas the Fc portion, or that kind of stem portion of immunoglobulin, stabilizes its presence in the circulation.

Instead, the extracellular portion of abatacept is from CTLA-4, and it's the effector portion that binds and blocks antigen presenting cells as part of the autoimmune disease process that they're typically used to treat, for example, rheumatoid arthritis. In contrast to typical therapeutic monoclonals, which would show restrictions by our lab testing to both the IgG heavy chain and the kappa light chain on immunofixation for our typical therapeutic monoclonals, this type of fusion structure doesn't have those light chains associated with the heavy chain. As such, only the heavy chain shows a restriction by our testing.

Now, if this is not due to a therapeutic molecule, as we presume in the case of abatacept, these findings would be seen in rare cases like gamma heavy chain disease, which if the true cause, could be appropriate for a patient to seek specialist evaluation for any of the potential causes for that finding. And these fusion therapeutics may not be as commonly seen as the monoclonal proteins, but even when utilized, they may be administered by different routes than we typically think about. For example, some of these fusion proteins are eyedrops. You can imagine that would not be something that is going to be into the blood circulation

because of where it's actually being applied. Whereas some drugs like abatacept, may be administered either by intravenous infusion or by subcutaneous injection. So even the route of a particular drug may impact the ability to see it in the blood. The case that we described in this report were from intravenous infusions of the medicine, and so thereby we were more likely to actually detect concentrations that were present.

Bob Barrett: Well, finally, Dr. Manthei, what lessons can our listeners take away from this work?

David Manthei: Well, I think that in the high level, this is just another example of how therapeutics can be mistaken for inherent protein and adds additional caution when we're looking at new findings. I think that historically, a lot of the therapeutic agents that we've been potentially concerned with are typically IgG kappa agents because that's what a lot of therapeutic monoclonals have been designed to be. There are others, for example, some IgG lambdas that are in development and in use, but are often not either at concentrations or in the kind of diseases that we would be monitoring with this type of process.

However, it adds caution that anything that you see that's a little bit atypical may raise that question of what the underlying cause could be, and I think as a rule of thumb, if there's any odd or rare finding, if you have any ability to correlate with additional patient information, it can be useful, which was, in this instance, the manner by which the association was seen. And furthermore, I was fortunate to be able to communicate with the clinician directly and were able to discuss the findings and in the end, able to provide reassurance that the patient didn't need to have a specialist referral because we could associate this finding with the known medication that they were taking.

Bob Barrett: That was Dr. David Manthei from the University of Michigan. He wrote a letter to the editor describing interference with clinical laboratory testing by recumbent biologic therapeutics in the August 2023 issue of *Clinical Chemistry*, and he's been our guest for this podcast on that topic. I'm Bob Barrett. Thanks for listening.