Article:
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Serum Free Light Chain (FLC) Analysis: A Guiding Light in Monoclonal Gammopathy Management.
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Guest: Dr. Ellen Jenner is head of Scientific Communications at the Binding Site Group, Limited.

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.

Immunoglobulins are produced by the body in response to foreign substances such as bacteria and viruses, in order to destroy them. They are comprised of two identical heavy chains and two identical light chains that have a constant domain and a variable domain. There are two serologically distinct light chains and they are known as kappa and lamda. These light chains can also remain in the serum unbound to the heavy chains are then known as free light chains.

Monoclonal gammopathies are a group of disorders characterized by secretion of monoclonal immunoglobulins or light chains. These disorders can be malignant such as multiple myeloma, plasma cell leukemia, and AL amyloidosis, or precursor diseases such as smoldering multiple myeloma and monoclonal gammopathy of undetermined significance, or MGUS.

A mini review titled, "Serum FLC Analysis: A Guiding Light in Monoclonal Gammopathy Management" published in the July 2017 issue of JALM discusses techniques available to screen, diagnose, and manage patients with monoclonal gammopathies focusing on serum free light chain analysis and its evolving utility. The first author of this article is Dr. Ellen Jenner, head of Scientific Communications at the Binding Site Group, Limited, and she's our guest for today's podcast.

Welcome, Dr. Jenner. First question, why are polyclonal antibodies favored over monoclonal antibodies for the detection of monoclonal-free light chains?

Dr. Ellen Jenner: So, one of the challenges associated with measuring monoclonal-free light chains is that they are polymorphic proteins. So, this means that they are very diverse molecules. And of course, this means that there can be a problem when wanting to measure the monoclonal free light

chains from one particular patient which could be genetically different from the monoclonal-free light chains from another patient.

So whilst a monoclonal antibody would be highly specific for a single epitope on one patient's monoclonal free light chain, it may not be able to detect all of the polymorphic forms of the free light chain, so for example, if an epitope is hidden or if it's simply not there on a particular monoclonal free light chain.

So, polyclonal antibodies, which are used in the reagent of the free light's assay, are able to recognize this variety of epitopes could be found on a patient's monoclonal free light chain. And we've got literature that's demonstrated over the past 15 years of the availability of the free light assay, that there have been over 16 different studies that have found that the free light's assay can correctly recognize the monoclonal free light chains actually from over 800 light chain multiple myeloma patients.

Randye Kaye: Okay. Thank you. So a serum free light chain ratio is now included in the International Myeloma Working Group's updated diagnostic criteria as a biomarker of malignancy. So, what's the rationale for this?

Dr. Ellen Jenner: So, in 2014, the International Myeloma Working Group published this new criteria for the diagnosis of myeloma. And importantly for the first time, they recommend a diagnosis could be made actually in the absence of this related end-organ damage, or CRAB symptoms that the readers should be very familiar with.

So, this diagnosis can be made providing that certain biological criteria have been met and the monoclonal free light chain levels are one such criteria. And they researched these as your biomarkers of malignancy. And these have been selected because they are able to identify a subset of patients who are at a very high risk of progression to symptomatic disease in a very short period of time. And the intention of this is to be able to intervene with these particular patients by treating them before the onset of this end-organ damage.

And some really interesting work actually by Dr. Mateos from Salamanca in Spain found that treatments of these high risk asymptomatic patients actually improve their overall survival. So, with regards to the free light chains, a highly abnormal level has been identified as one of these high-risk biomarkers. So this requires a free light chain ratio of at least 100, and at least 100 mg/l of monoclonal free light chains to meet that criteria.

And I think it's probably worth noting that these levels have actually been established using the free light's assay and this was done in the study by the Larson group from the Mayo Clinic. And they found that looking at smoldering multiple myeloma patients, if those patients had a highly abnormal free light chain ratio of greater than 100, they had an 80% risk of progression to malignant myeloma in a period of just 2 years.

And it's probably also important to note here that the free light chain assay shouldn't be looked at just in isolation in these patients when coming to this diagnosis. And it's really important to meet this diagnostic criteria, that you look at the patient's bone marrow results as well, and you look to see whether the patient has greater than 10% bone marrow plasma cells as an additional criteria.

Randye Kaye: Okay, thank you. I really see the importance of this. So let's talk about the current International Myeloma Working Group response criteria. It still includes urine Bence-Jones protein measurements for monitoring multiple myeloma. Should these recommendations change to favor serum free light chain measurements?

Dr. Ellen Jenner: Well, there's been really some very strong evidence emerging to support this recommendation. And there are perhaps two considerations that we should think about.

So, firstly, from a practical point of view. So I'm sure many of the readers are aware that urine samples are notoriously difficult to collect. And if you combine this with the fact that many lab protocols for looking at urine Bence-Jones proteins can be very variable, it means that results can be very inconsistent or simply, just not available to be used.

So secondly, then, from a physiological point of view, it makes sense, I guess, for free light chains to be in the urine, they must be in the serum first. So if we think about free light chain clearance, they're filtered and reabsorbed by the kidneys. So, in a healthy person, very few free light chains are going to be entering the urine. But if we think about a patient with multiple myeloma you need a very high level of monoclonal free light chains in the serum before you saturate this reabsorptive capacity of the kidney nephron so that you can detect your free light chains in the urine.

So really this is a sensitivity issue, and there have been a number of studies in the past 15 years that have actually looked at the sensitivity of serum free light chain measurements when compared to urine Bence-Jones protein. And they found that it is indeed more sensitive for the majority of patients to measure free light chains in the serum.

And one of the more recent studies published at the end of last year by Dr. Dejoie and colleagues, so from the ISM group, they used a very large trial protocol and they looked at the sensitivity of serum versus urine free light chain measurements. And they looked in over 100 light chain multiple myeloma patients, and they found that the serum free light chain measurements were indeed more sensitive both in terms of detecting the abnormality at diagnosis, but also looking at the number of patients that actually met the criteria for measurable disease to allow them to then be accurately monitored.

And not only that, but this key study went on further to understand how meaningful the two measurements were in terms of predicting patient outcome. So whilst the serum free light chain measurements following three treatment cycles did predict outcome in terms of overall survival, in contrast, urine free light chain measurements did not. So this really indicated the clinical relevance of the serum free light chain assessments and led the group to conclude that these free light chain measurements should really be the method of choice when you're assigning response in patients with light chain multiple myeloma.

Randye Kaye: Thank you. So that's a lot of evidence that those recommendations should actually change. Now, sensitive cellular molecular and imaging methods have been introduced into international myeloma working group guidelines for the detection of minimal residual disease. Is there still a role for measuring free light chains?

Dr. Ellen Jenner: So, that is an excellent question. With highly sensitive methods that of course are now available to detect MRD, the desired endpoint for any clinical trial is of course going to be to achieve an MRD negative state. But I think it's important to bear in mind that in routine practice, MRD tests are not currently accessible for all patients. So the most sensitive methods for measuring monoclonal proteins are still certainly going to continue to be important, particularly when MRD assessments aren't available, but also may have a place in guiding when your MRD assessments are required if we consider that your MRD assessments can be particularly invasive, so bone marrow biopsies, and also very complex procedures, for example, your bone marrow analysis and also your imaging studies.

So I'd certainly say that sensitive serum tests are still going to remain important. And whilst free light is a sensitive serum mark for measuring low levels of monoclonal free light chains, it's perhaps appropriate here to also mention heavy lights because this is another sensitive serum test. And this test can measure your monoclonal intact

immunoglobulins. So taken together, these two tests can provide a very sensitive measure of both your monoclonal free light chains and your monoclonal intact immunoglobulins.

And the unique aspect of the heavy lights assay is that it can separately measure both your monoclonal or your involved immunoglobulin and also, the polyclonal or uninvolved immunoglobulin levels of the same isotype.

So, the recent guidelines actually by the International Myeloma Working Group, they identified a possible role for heavy light alongside MRD assessments. And the reason that they have proposed this is in order to be able to evaluate not only your eradication of your tumor cells, which is of course a very important measurement and can be measured by your sensitive MRD techniques, but also recovery of the patient's immune functions. And this aspect of the evaluation stems really from the ability of heavy light to measure your uninvolved heavy light chain levels. So for example, measurement of your IgG lambda levels in an IgG kappa patient. And this measurement is a very interesting, very active area of research currently.

Randye Kaye: That was Dr. Ellen Jenner from the Binding Site Group talking about the JALM article, "Serum FLC Analysis: A Guiding Light in Monoclonal Gammopathy Management" 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.