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How Antibody-Based Therapies Are Revolutionizing Its Management

Announcer:
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Dr. Piatek:
Autoimmune hemolytic anemia, or AIHA, is a collective term for several diseases differentiated by the temperature at which autoantibodies bind optimally to the patient’s red blood cells. Warm AIHA, or wAIHA, is the most common form of this disorder and represents about 70% of all AIHA cases. wAIHA can be difficult to treat, especially in the relapsed/refractory setting. There are currently no medications specifically approved to treat wAIHA. However, the treatment landscape is rapidly changing. It’s important for clinicians to gain a greater understanding of these emerging treatments, which offer the potential to greatly improve patient outcomes. Today, the focus of our discussion will be on the diagnosis as well as the current and emerging therapies for wAIHA.

This is CME on ReachMD. I’m Dr. Caroline Piatek, and I would like to welcome Dr. Irina Murakhovskaya to our conversation today.

Dr. Murakhovskaya:
Thank you, Caroline, for the invitation. And it’s a pleasure to be here.

Dr. Piatek:
So let’s begin our discussion. So, Dr. Murakhovskaya, how do you approach the diagnosis of wAIHA?

Dr. Murakhovskaya:
So as you mentioned, Caroline, autoimmune hemolytic anemia, it’s a rare, heterogenous group of antibody-mediated diseases which could be warm or cold based on the optimal binding temperature of the pathogenic antibodies. And warm autoimmune hemolytic anemia represents the majority of cases you see, in about 70% of cases. In warm autoimmune hemolytic anemia the pathogenic antibodies are directed against the erythrocyte antigens of the RH system, and they bind to those antigens at the optimal temperature of 37°. They’re most commonly of IgG subtype, and they’re typically polyclonal but occasionally can be IgA or warm-reactive IgM, either by itself or in combination with IgG. In contrast, cold autoimmune hemolytic anemia is usually mediated by an IgM and, less commonly, can be associated with an IgA.

Based on presence or absence of underlying disorder, such as malignancy or autoimmune disorder, or immune deficiency, we subdivide warm autoimmune hemolytic anemia into primary or secondary warm autoimmune hemolytic anemia. There is also a number of infections as well as medications and toxins that can be associated with warm autoimmune hemolytic anemia, but these hemolytic events are usually transient.

In terms of evaluation of patients with warm autoimmune hemolytic anemia, of course we start with a complete blood count, reticulocyte count, LDH, or lactic dehydrogenase, bilirubin, and haptoglobin to evaluate hemolysis. The next step to confirm immune nature of the

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hemolysis is to perform direct antiglobulin test, which identifies immunoglobulins and/or complement on the surface of red cells. In warm autoimmune hemolytic anemia, direct antiglobulin test is typically positive for IgG, but it can be also positive for C3d in about 50% of the cases.

In addition, to rule out all autoimmune hemolytic anemia, particularly in the cases with complement involvement, we perform cold agglutinin titer, which is typically less than 64 in warm autoimmune hemolytic anemia but can be greater than 64 in mixed cases.

In addition, we review peripheral blood smear, which reveals presence of spherocytes as well as any abnormal morphology in the lymphocytes.

Dr. Piatek:
That was a great overview. As you mentioned, the diagnosis of wAIHA is usually fairly straightforward, although there can certainly be some more challenging diagnostic scenarios.

To summarize, in a patient with hemolytic anemia, a peripheral blood smear demonstrating spherocytes and a DAT positive for IgG +/- the presence of C3 fragments would be characteristic of wAIHA.

Dr. Murakhovskaya:
So, Dr. Piatek, once wAIHA is diagnosed, what is the current standard of care for these patients?

Dr. Piatek:
I would like to just start by mentioning that there's FDA-approved medications specifically for wAIHA, and there's also limited clinical trial data published at this time to help guide our treatment options. The standard first-line therapy for wAIHA is corticosteroid therapy. This is typically given as prednisone 1 mg/kg daily. The initial response rates with steroid therapy are high, around 80%, but tapering steroids is challenging, and the long-term response rates, once steroids are tapered, are modest, around 30%.

Steroid, as you know, can be difficult to tolerate with many short- and long-term side effects, which include weight gain, changes in mood and sleep, hyperglycemia, infection, osteoporosis, and the list goes on. Rituximab, which is an anti-CD20 monoclonal antibody, can be added to steroids in the up-front setting with improved response rates at 12 and 24 months in some small studies compared to steroids alone.

Considerations for adding rituximab to the frontline setting includes severe anemia, atypical autoimmune hemolytic anemia, or Evans syndrome.

As we move into the relapsed setting, rituximab is the standard second-line therapy with overall response rates around 80%. Once a patient relapses after rituximab therapy, the next options in the third-line setting are less clear. Splenectomy remains an option but is often not pursued. The response rates with splenectomy are high, probably around 70% to 80%, but the long-term data is less clear and perhaps a third of patients will relapse after a splenectomy.

Other immunosuppression, such as azathioprine or mycophenolate, can also be considered. IVIG and erythropoietin-stimulating agents, or ESAs, can be considered as bridging therapy to help stabilize the hemoglobin. There's limited data for IVIG in wAIHA, with reported response rates around one-third of patients.

IVIG may be particularly useful in a septic patient and in an effort to avoid immunosuppressive therapy, or perhaps in the emergency setting.

Moving on to ESA therapy, this may be a helpful add-on in patients who have an inadequate bone marrow response, which is characterized by reticulocytopenia and inadequate erythropoietin level.

So just to kind of wrap things up, the management of patients with wAIHA can be very challenging with no medications currently approved for this for this indication, and with limited clinical trial data, there really is an unmet need for evidence-based treatments that are safe and effective for this patient population.

Dr. Murakhovskaya:
Thank you for this wonderful summary, Dr. Piatek. It sounds like we're still far away from optimal therapy for a warm autoimmune hemolytic anemia despite some options in a first- and second-line setting.

Dr. Piatek:
For those of you just tuning in, you're listening to ReachMD. I'm Dr. Caroline Piatek, and today Dr. Irina Murakhovskaya and I are talking about therapeutic approaches to warm autoimmune hemolytic anemia. We're just about to delve further into emerging therapies for this disorder.

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Dr. Murakhovskaya, can you tell us a little bit about the exciting investigational agents for the treatment of wAIHA?

Dr. Murakhovskaya:
There is a number of therapies that are currently in development. I'll just briefly touch upon a few of them.

So starting with non-antibody approaches for warm autoimmune hemolytic anemia, they include fostamatinib, which is a SYK inhibitor. SYK is involved in phagocytosis of the antibody-coated red blood cells. And the fostamatinib has been studied in phase 2 and phase 3 studies in warm autoimmune hemolytic anemia with encouraging results in phase 2 study, which did not confirm in the phase 3 trial.

Rilzabrutinib is a reversible covalent BTK inhibitor, which also inhibits phagocytosis through interaction with the SYK pathway and is being currently evaluated in warm autoimmune hemolytic anemia in a phase 2 study.

Parsaclisib is a PI3K kinase inhibitor, which has been evaluated in a phase 2 study in patients with warm autoimmune hemolytic anemia with favorable responses seen. However, the phase 3 study has been halted since the drug development has been discontinued by the company.

Bortezomib is a proteasome inhibitor and has been evaluated in retrospective case series, case reports, and small prospective studies in patients with warm autoimmune hemolytic anemia, with responses seen in a significant proportion of patients.

Sirolimus is a mTOR inhibitor, which regulates T cell proliferation and demonstrated significant responses in retrospective as well as prospective studies.

But moving to monoclonal antibody therapies, daratumumab is a monoclonal antibody, which it targets CD38 on antibody-secreting plasma cells as well as activated T cells, and the responses in have been demonstrated in warm autoimmune hemolytic anemia in case series as well as case reports.

Since there is approximately 50% of patients with warm autoimmune hemolytic anemia that have complement involvement, complement inhibitors, such as eclizumab and pegcetacoplan, have been evaluated in warm autoimmune hemolytic anemia with preliminary data showing efficacy in patients with evidence of complement involvement; however, the final data have not been published yet.

Moving on to nipocalimab. Nipocalimab is an anti-FcRn monoclonal antibody. FcRn is required for physiologic recirculation of IgG, which results in extension of biologic half-life of IgG1, IgG2, and IgG4 to approximately 23 days. Blockade of the FcRn receptor results in shortening of IgG half-life and lowering of IgG levels, both pathologic as well as normal IgG levels, to about 10% of normal levels. The benefit of this drug is that it does not inhibit the normal IgG production. The trial evaluating efficacy of nipocalimab in warm autoimmune hemolytic anemia, has recently completed its accrual. We're looking forward to results of this trial since nipocalimab already demonstrated efficacy in myasthenia gravis.

Another very exciting indication for nipocalimab is treatment of hemolytic disease of fetus and newborn, and this was evaluated in UNITY trial, which is a phase 2, multicenter, open-label trial, which evaluated use of nipocalimab in women and fetuses at high risk of hemolytic disease of fetus and newborn. And the results of the study has been reported and revealed that nipocalimab treatment significantly delayed or prevented fetal anemia or need for fetal transfusion compared to historic benchmarks in pregnancies of high risk of early-onset hemolytic disease of fetus and newborn. And that was a basis for breakthrough designation for this indication for nipocalimab, which was granted in February of 2024.

Dr. Piatek:
That was a great overview of emerging therapies for wAIHA. We certainly look forward to the results of these clinical trials. In the meantime, it's important to consider enrolling patients with wAIHA into clinical trials as we and our patients look for better treatment options in this difficult-to-treat disease.

Dr. Murakhovskaya:
Dr. Piatek, we would be remiss in not discussing potentially emerging therapeutic approaches in wAIHA in emergency settings. Which do you find most interesting?

Dr. Piatek:
in the emergency setting, usual options are transfusion and high-dose steroids. IVIG and plasma pheresis may also be considered. As you mentioned earlier, there may be some role of complement inhibition in patients whose DAT is positive for C3 fragments. Anti-complement therapy provides rapid complement inhibition and control of hemolysis and in complement-mediated diseases, such as PNH [paroxysmal nocturnal hemoglobinuria] and cold agglutinin disease. In wAIHA, which is partially complement mediated, complement inhibitors could also be useful here. ESA therapy, which we talked about a little bit earlier, can also be helpful in patients who have inadequate response to the anemia, so this is manifested by reticulocytopenia, and the ESA therapy helps to stimulate red

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blood cell production. And then lastly, the FcRn inhibitor, nipocalimab, which we were discussing a little bit earlier, also has the potential to induce a quick response by rapidly reducing serum IgG autoantibodies, which was demonstrated in the myasthenia data.

Dr. Murakhovskaya:
That's very interesting. That potentially would be able to spare our patients much more morbid procedures such as plasma exchange and would allow us to achieve a rapid improvement in hemoglobin.

Dr. Piatek:
And that's all the time we have today. So I just wanted to thank the audience for listening, and I also want to thank Dr. Irina Murakhovskaya for sharing her expertise and insight with us today. It was great speaking with you.

Dr. Murakhovskaya:
Thank you and goodbye.

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