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Is Long-Term Complement Inhibition Safe and Effective in PNH?

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Dr. Broome:
Hi, I'm Dr. Catherine Broome, Associate Professor MedStar Georgetown University Lombardi Cancer Center in Washington, DC. And we're going to talk today about long-term complement inhibition in PNH, how safe is it and how effective is it?

So complement has many functions, as you will all remember. A big portion of it is related to immune surveillance and lysis of microbes. It also aids in phagocytosis and opsonization to remove not only apoptotic cells, but also to aid immune complexes in removing microbes, etc. So when we think about all of the biologic functions that complement has, we want to think about inhibiting some of these functions and what effects those may have on our patients either in the short or the long term.

So when we look overall at C5 inhibition and long-term safety, the probability of a patient experiencing 1 or more adverse events was lower as the patients were on C5 inhibition therapy than it was in the beginning, suggesting that there's no cumulative toxicity associated with the long-term administration of the C5 inhibitor eculizumab. There were some serious infections that were not fatal. And we all have to remember that related to its important role in helping us to manage and clear infections with encapsulated organisms, patients under C5 inhibition therapy need to be closely monitored throughout treatment, even if they are vaccinated.

There is the potential for the development of infection with encapsulated organisms, pneumococcus, hemophilus, and Neisseria meningitidis; 76 cases of meningococcal infection have been reported, representing an overall rate of 0.25 per 100 patient years of therapy. It's 0.24 for PNH, and 0.29 for atypical hemolytic uremic syndrome. There were 8 fatal cases of meningococcal infection by serotype B in 2, X, C, and Y in 1 each, and unknown in 3, for a rate of 0.03 per 100 patient years of therapy. All of the fatal infections occurred in patients with PNH. All 8 of those patients had received meningococcal vaccination, although not against all serotypes. So again, we need to maintain constant vigilance with regards to meningococcal infections and certainly treat our patients very early for any suspection of meningococcal infection.

As you can see here, bacterial infections, viral infections did occur. Fungal infections were quite rare. Sepsis was - also occurred but not at a high frequency. And then solid tumor rates and hematologic malignancy rates were also relatively low in patients that are on a long-term therapy.

As we look at adverse events that were reported from the ravulizumab phase 3 clinical trials, we see that total adverse events were very similar between the longer-acting preparation and the shorter-acting eculizumab. Most common side effects included headache, nausea, pharyngitis, and upper respiratory tract infections. And rates were very similar, again, between longer-acting and shorter-acting C5 inhibition.

If we look at long-term safety for C3 inhibition treatment for PNH, we can see that comparing C3 inhibition to C5 inhibition pegcetacoplan

to eculizumab, that the rates of adverse events were very similar between the 2 different complement inhibitors. The only significant differences are that pegcetacoplan, or the C3 inhibitor, is administered in a subcutaneous injection, and you did have some erythema, injection site reactions, and injection site swelling, which we're not seeing with the intravenously administered eculizumab. All other side effects were very similar between the 2 different complement inhibitors in PNH patients.

Long-term safety with regards to C3 inhibition, several trials including PADDOCK, PALOMINO, and PEGASUS, as well as PRINCE. So we have a pretty good longitudinal experience with C3 inhibition, and then we can see that the adverse events are relatively mild. There were no cases of meningitis. But remember that all of these patients are vaccinated. There were incidences of infections, but all were relatively minor and included appendicitis, biliary sepsis, breast abscess, bronchitis, some fungal skin infections, etc.

Thank you very much for joining.

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