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WHIM Syndrome Management: The First FDA Approval for Patients

Announcer:
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Dr. Tarrant:
Hi, I'm Teresa Tarrant, and I am an Allergist/Immunologist and Rheumatologist at Duke University, and I will be providing an overview today of the WHIM phase 3 trial.

To begin, I'm going to provide an overview of the medications to date that have been studied in WHIM syndrome, there have been two phase 3 trials looking at CXCR4 antagonists in the treatment of WHIM. The first is plerixafor, and then the second is mavorixafor, which we'll be discussing in detail the phase 3 of both. Both are small molecule inhibitors that specifically block signaling of the CXCR4 molecule on immune cells. The route of administration, however, differs. Plerixafor is a subcutaneous injection, whereas mavorixafor is orally bioavailable. In terms of approved indications, plerixafor is FDA approved to be used in combination with G-CSF for autologous transplantation of bone marrow cells in patients with malignancy. Mavorixafor has just received FDA approval for the treatment of WHIM syndrome. In terms of clinical studies that have been investigated, plerixafor has not only been evaluated in phase 3 trials, as well as others in WHIM, it has also been looked at in HIV infection, but was discontinued due to limited bioavailability and lack of efficacy. With respect to mavorixafor, it is FDA approved for WHIM syndrome, and it has also been investigated in Waldenstrom's macroglobulinemia, as well as it has ongoing studies in congenital neutropenia, cyclic neutropenia, as well as chronic idiopathic neutropenia.

So first to discuss the plerixafor data, there has been a phase 3 randomized quadruple-masked crossover trial looking at plerixafor versus G-CSF, which is granulocyte-colony stimulating factor, in the treatment of WHIM. To begin, the baseline demographics and characteristics of the patients were very similar. They had adolescents as well as adults represented. Female sex was slightly more biased towards female gender. And in terms of previous immunoglobulin usage, about half of the patients had been on immunoglobulin replacement. The screening absolute neutrophil count for the patients in the trial was low; it was 246, as well as the screening absolute lymphocytes several count was also low, 597. All patients included in this trial had a previously identified pathogenic CXCR4 mutation as part of inclusion criteria.

And to kind of show a schematic of the trial design, basically, patients were washed out of medications that they had had previously, and they were randomized to either receiving G-CSF or plerixafor for approximately a year, and then there was a washout period, and those patients that were in one arm switched to the other arm. So basically all patients received G-CSF or plerixafor at some point during the trial, and they were on each of the medications for 12 months, and then studied for half of a year after that. Patients, as well as investigators, were blinded to the types of treatments that they were receiving.

And what the data showed is that plerixafor increased both neutrophils and lymphocytes in the blood of WHIM participants. And so as you can see here, it's statistically significant and quite clear that patients who had previously had very low lymphocyte and neutrophil counts were able to have increased immune cells detected in their peripheral blood. In terms of the distributions of infections over a 12-

month period, on the left is kind of the pie graph of G-CSF, patients when they were on that element of the study. And then conversely, on the right, the plerixafor, when patients were on the 12 months of plerixafor, what types of infections they had. And as you can see, the majority of patients had upper airway infections. And both the distribution and the frequency of infections was not superior, meaning that plerixafor and G-CSF were beneficial, but that neither drug was found to be superior to one another, so noninferiority was demonstrated.

With respect to warts, there was improvement observed in patients on plerixafor with their warts. And if you see in the upper left corner, you can see some examples of patients over time, where they began at baseline, when they were on the G-CSF arm, and when they were on the plerixafor arm. So there were some patients that did show improvement. And subsequently, when they were on G-CSF, there was less demonstrated improvement. However, this was not perfect. There were patients who were on G-CSF who had improvement in warts, and so they kind of saw a mixed pattern. But overall, there may have been a trend towards wart improvement.

In the mavorixafor trial, which I'll be discussing more in detail in upcoming slides, there also were some changes seen in warts, but they did come and go. And what was noticed, probably more pronounced in that trial, was that new warts, or the development of new warts over time, seemed to be decreased in patients on mavorixafor.

So in general, there does appear to be a signal for warts in both plerixafor and mavorixafor, but not dramatic differences on either.

Plerixafor and G-CSF with respect to their safety data, in general, both were deemed to be safe. Bone pain was seen more so in the G-CSF group. There were also some other things, like nausea, changes in weight, injection site reaction. They were also seen and considered possibly related to one of the treatments, but there were no serious safety events noted. In terms of treatment-emergent serious events, like I said, there were not a lot of big signals. However, there were no deaths, but there was a reactive arthritis that was possibly deemed secondary to plerixafor but, you know, the good news is no deaths or hospitalizations while on either G-CSF or plerixafor. There was one reactive arthritis that could have been related to either of the drugs that was noted, so something to kind of look at there. And then dermatitis was another event that may have been secondary to plerixafor.

So in summary, with the plerixafor data, dermatitis and arthritis were seen in that arm and did lead to the discontinuation of plerixafor in 3 patients. Plerixafor was not superior to G-CSF in patients with WHIM; however, both did show a general improvement in infections overall. Together with wart regression and hematologic improvement, the infection severity results do support continued study of plerixafor as a potential treatment for WHIM syndrome. Plerixafor was noninferior to G-CSF, so both appeared to be good at treating infections and at maintaining neutrophil counts of more than 500 cells per microliter. However, plerixafor did show an improvement in maintaining lymphocyte counts, whereas G-CSF did not, and this was statistically significant. With respect to warts, there were some areas of regression seen on plerixafor in 5 of the 7 patients with major wart burdens. However, there was an up and down of wart activity and the G-CSF arm also did see some improvements.

So now to discuss the phase 3 trial of mavorixafor, another selective antagonist of CXCR4 but is an orally available medicine and is now FDA approved for the treatment of WHIM. The demographics and baseline characteristics of this trial that led to FDA approval also show that adolescents and adults were represented in the trial and a similar slight increase in female representation. In terms of previous immunoglobulin usage, again, similar to the plerixafor trial, there was about half of the patients that were on immunoglobulin replacement. And they also, like the plerixafor trial, had low absolute neutrophil counts and absolute lipocyte counts. And also, like the plerixafor trial, all patients had previously identified CXCR4 pathogenic mutations confirmed.

Here's the phase 3 mavorixafor trial design. There was a 1:1 randomization, and then basically, patients were randomized to either receive the drug or a placebo, and were studied over a year with a rollover to open-label extension.

Its primary endpoint was mean time above threshold of neutrophil counts. So if you look at the graph on the left, you can see that patients on placebo, which is the red line, have very low neutrophil counts. And those that are on mavorixafor have increased and sustained mean time above threshold of the absolute neutrophil count that is substantially increased. And that again, is analogous, a slightly different way of measuring it, but analogous to the plerixafor trial. Also, like the plerixafor trial, the mean time above threshold of lymphocyte counts is elevated. And this was also over a year period it was sustained. So basically, both CXCR4 antagonists doing a good job of increasing neutrophils and lymphocytes. And this was the primary and secondary endpoint of this specific trial.

In terms of infections, there was an overall decrease in infections, particularly if you looked at infections over time, meaning that in the beginning, like the first 6 months, if you look at the upper inset of this graph, you'll see that there were not a lot of differences between mavorixafor and placebo in the first 6 months, but that there were less infections in the mavorixafor group in the second half of the trial. And here you can see in the larger graph on the bottom of the slide, the distribution of types of infection that we're seeing in both groups.

In terms of the safety data, again, like plerixafor, no deaths, no major hospitalizations, and there were no treatment-emergent severe adverse effects that were deemed to be related to the drug. There were some severe adverse events, including infections, glioma, and

thrombocytopenia, but those were felt by the investigators to be secondary to the disease, and no discontinuations occurred on mavorixafor due to safety events.

So in summary, with mavorixafor treatment, reduced infection frequency, severity, duration, as well as a reduction in antibiotic usage. Mavorixafor showed improvement in infections over a 12-month period, but it was really more in the second half that that was seen. Mavorixafor had a well-tolerated safety profile in the patients who were taking this medication for a year. And there were no discontinuations due to treatment-emergent adverse events or serious adverse events that were felt to be drug related. Overall, mavorixafor participants had significant increases in their lymphocyte counts and neutrophil counts, and reductions in infection severity, duration, burden, and antibiotic use. And it has been approved, as I mentioned, by the FDA for the treatment of WHIM.

So that concludes our presentation today. I'd like to thank you for tuning in, and I hope you learned something today.

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