Transcript Details
This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: https://reachmd.com/programs/clinicians-roundtable/improving-survival-and-function-in-pediatric-tk2d/37635/

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Improving Survival and Function in Pediatric TK2d with Nucleoside Therapy

Announcer:
You're listening to *Clinician's Roundtable* on ReachMD, and this episode is supported by UCB. Here's your host, Dr. Charles Turck.

Dr. Turck:
This is *Clinician's Roundtable* on ReachMD, and I'm Dr. Charles Turck. Here with me today is Dr. Caterina Garone, who is an Associate Professor of Medical Genetics in the Department of Medical and Surgical Sciences at the Alma Mater Studiorum University of Bologna in Italy. Together, we'll be reviewing data from two posters on survival and functional outcomes in patients with thymidine kinase 2 deficiency, or TK2d for short, who received pyrimidine nucleoside or nucleotide therapy. Dr. Garone, welcome to the program.

Dr. Garone:
Thank you, and nice to meet you all.

Dr. Turck:
Now, for some background, both posters stem from a pooled analysis of several studies under the ISE and ISS frameworks. So would you start us off by walking us through the design of this integrated analysis and how it strengthens the findings we'll be discussing today?

Dr. Garone:
So thymidine kinase 2 deficiency is an ultra-rare disorder, and this challenges the design of a clinical study. So to obtain a study that had statistical power, we decided to pool data from retrospective, prospective, and early access programs for the treated patients, and we were able to analyze 82 patients. For comparison of the untreated population, we decided to analyze data from cohort studies, prospective studies, and the literature review, and we decided to analyze unique patients in a pooled dataset that comprises 93 cases.

In terms of population, we decided to analyze patients that had an age of onset of less than 12 years because this allows us to reflect the pediatric population with thymidine kinase 2 deficiency.

Dr. Turck:
Now, with that background in mind, let's zero in on the survival outcomes. The analysis showed an 87 to 95 percent reduction in mortality risk for patients treated with pyrimidine nucleoside or nucleotide therapy. What are your thoughts about the significance of those findings in the context of the natural history of TK2d?

Dr. Garone:
So to understand the survival benefit, we obtained data from multiple models, and we obtained a hazard ratio of 0.05 to 0.13. All those data were highly statistically significant with a P value less than 0.001. In the overall population, only three patients died in the treated group versus 53 patients in the untreated group. So this was very important for us to understand the long-term expectation for pediatric patients with thymidine kinase 2 deficiency when the treatment is set for those patients.

Dr. Turck:
Now, in addition to improved survival, we saw that survival time nearly doubled from 14.4 years in the untreated group to 29.2 years in the patients treated with pyrimidine nucleoside or nucleotide therapy. What are the broader implications of these findings on long-term care and related planning?

Dr. Garone:
We decided to analyze survival using a restricted mean survival time analysis, and we decided to use a 30-year span after symptom

onset. This was very important for us because it allowed us to not only understand how long patients can live after treatment, but also to extend the window for intervention and monitoring. So in other words, this gives us a chance to reflect the evolving multidisciplinary care needs over a longer disease course.

Dr. Turck:
For those just tuning in, you're listening to *Clinician's Roundtable* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Caterina Garone about how pyrimidine nucleoside or nucleotide therapy impacts survival and functional outcomes in patients with thymidine kinase 2 deficiency, or TK2d.

So, Dr. Garone, if we switch gears and focus on the functional outcomes results, nearly 84 percent of patients had lost at least one motor milestone before treatment, but only 22 percent experienced motor milestone loss after treatment. What does that tell us about this treatment's ability to change the trajectory of such a steadily progressive disease?

Dr. Garone:
So the nucleoside supplementation therapy—even when they have already lost some motor milestone—give us the opportunity to stabilize the disease, and this is why patients do not progress over the time when the treatment starts. So the percentages are very important because prior to treatment, 83 percent of patients progress in the disease course, and they continue to lose motor milestones. Instead, after treatment, we have a stabilization of the disease, so only 20 percent may lose one motor milestone.

But if we look at the group of patients that have a loss of more than four motor milestones, the percentage dropped from 40 percent to 2.2 percent. So this is very important because even in very severe patients, we have the opportunity to impact the severity of the disease by stabilizing them.

Dr. Turck:
Now, another finding was that three-quarters of patients regained at least one motor milestone after starting treatment and nearly a quarter regained four or more. How could that make us rethink what's possible in terms of reversibility or plasticity in TK2d?

Dr. Garone:
This is one of the most important lessons that we learn when we start to treat patients because the length of the disease course impacts the final outcome of the supplementation therapy. In other words, the earlier we start the treatment, the better the outcome. And if a patient starts treatment when the first sign of the disease starts, then we can have a reverse of the clinical picture of thymidine kinase 2 deficiency.

In our experience, patients that start immediately after the diagnosis—when the diagnosis was made just a few weeks or a month ago—completely regain their ability and became completely normal. Instead, when a patient had a longer disease course, they were able to regain motor milestone, but they still had some weakness. So this is very important: early diagnosis and early initiation of supplementation therapy can give us the opportunity to not only regain motor milestones, but also to reverse the disease.

Dr. Turck:
And just to bring this all together before we close, Dr. Garone, both posters showed that pyrimidine nucleoside or nucleotide therapy was generally well tolerated with few discontinuations. Given the seriousness of TK2d and the limited treatment landscape, how might that safety profile influence our treatment decision-making?

Dr. Garone:
So in the clinical studies and in our experience, the treatment is very well tolerated. The only adverse event that patients experience is diarrhea, which starts when we initiate the treatment and when we increase the doses. But then the patients are able to adapt to the treatment, and this adverse event is no longer experienced during the treatment. The second most common side effect in our study was an increase of the temperature or fever, but those were not related to the treatment itself.

Only 2 percent of patients discontinued the treatment because of an adverse event, so only 4 percent of the overall population. So in conclusion, in our opinion, the treatment is very well tolerated, is safe, and must continue in these patients considering the high level of efficacy it has in the pediatric population.

Dr. Turck:
Well, with those final comments in mind, I want to thank my guest, Dr. Caterina Garone, for joining me to discuss her research on the survival and functional outcomes in patients with thymidine kinase 2 deficiency who received pyrimidine nucleoside or nucleotide therapy. Dr. Garone, it was great having you on the program.

Dr. Garone:
Thank you.

Announcer:
This episode of *Clinician's Roundtable* was supported by UCB. To access this and other episodes in our series, visit *Clinician's Roundtable* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening!