Transcript Details

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Short Bowel Syndrome: Strategies to Reduce Dependency on Parenteral Support in Adults and Children

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Here is Dr. Valeria Cohran

Dr. Cohran:
The use of intravenous parenteral nutrition to manage chronic intestinal failure due to short bowel syndrome can have a significant impact on a patient's autonomy, self-esteem, safety, and overall quality of life. Our goal as clinicians is to help patients achieve enteral autonomy by eliminating the need for parenteral nutrition. With the approval or the introduction of GLP-2, first in 2012 for adults and later for children, this has allowed some patients who were previously unable to be successfully tapered from TPN to gain enteral autonomy.

Can GLP-2 analogs help us achieve this goal? And how successful have you been in implementing their use in patient care?

This is CME on ReachMD, and I'm Dr. Valeria Cohran.

Dr. Iyer:
And I'm Dr. Kishore Iyer.

Dr. Cohran:
Welcome, Dr. Iyer. Let's take a shot at answering some of these important questions. What does a typical patient who's dealing with intestinal failure due to short bowel syndrome, or SBS, look like? And what are they dealing with on a daily basis?

Dr. Iyer:
That's a good place to start, Dr. Cohran, because for most of us living normal lives, it's almost impossible to conceive of the near catastrophic impact of intestinal failure. We take eating and drinking as we please for granted on a daily basis. Just think of the situation where a patient has intestinal failure, a condition where the body is not able to meet its nutritional requirement through food and drink by mouth or the enteral route. The impact of the underlying disease as well as the impact and therefore the need to require intravenous supplementation on a daily basis, perhaps, is just catastrophic and far-reaching. It impacts every aspect of life.

As one patient said to me as we were confronting his recent diagnosis of intestinal failure, "It is really hard to think of one social thing we do today that does not involve food or drink." So this is a devastating disease. Of course, intravenous nutrition, parenteral nutrition, is lifesaving for certain and allows many patients to survive with excellent qualities of life. There is no escaping the continuous impact and potential risk to life even with a diagnosis of intestinal failure. Because it's an uncommon disease, many people don't recognize or do not know of somebody with intestinal failure, and that, of course, adds to the catastrophic nature of this diagnosis.

Dr. Cohran:
I would agree with you about that, Dr. Iyer. I think for the infants that I take care of, a lot of them, this is all they know. All they know is being on TPN and getting tube feedings. I think it is a big adjustment for the families who are used to or were expecting a child who could take a bottle, who would sleep at night, versus now they are concerned with children would have central lines, who have tubes in their stomach, in their small bowels, maybe stomas, so it totally changes the quality of life for these children. Those children that are older that may have a midgut volvulus, those children ate—who were "normal"—they swam, they traveled, they played contact sports, they did everything as any other child would. But after they unfortunately may get the diagnosis of short bowel syndrome from some sort of catastrophic event, they may not be able to swim; they may not be able to do contact sports. It's difficult to travel internationally or even nationally for prolonged periods of time because you always have to have your TPN. So I agree; I think it has such an impact overall on the quality of life for these patients when they develop this disease.

So, Dr. Iyer, let's focus on what's happening in the gut. There are a myriad of conditions that may lead to short bowel syndrome, but what's the common denominator here? What's the pathophysiology of short bowel syndrome?

Dr. Iyer:
When you think of intestinal failure, the majority of cases of intestinal failure are due to and are best understood by the most obvious cause leading to intestinal failure, which is anatomical loss of bowel length. And that can happen due to intrinsic intestinal disease or intestinal resection, removal of lengths of intestine for the underlying disease. So anatomical loss of bowel length is the most obvious, most common cause. Roughly two-thirds of patients—maybe 70% of patients with intestinal failure have true anatomical short bowel syndrome as their proximate diagnosis for intestinal failure. There's a smaller percentage of patients, roughly a third, about 30% of patients, who have intestinal failure due to functional disease of the intestine. The intestine is all there, but it just simply doesn't function adequately. And those patients still require parenteral nutrition, require intravenous support, and in many ways their consequences—the impact for them is very similar to that of short bowel syndrome. Notice we are saying short bowel syndrome rather than focusing on a specific diagnosis.

So the focus is very much on the loss of surface area, loss of absorptive surface area. But we have learned over the last few years that the human gastrointestinal tract is really—and I'm no endocrinologist—but may be the most complex and largest endocrine organ because there's a variety of gastrointestinal hormones that regulate the process of absorption and digestion. And of course, an exciting development in this field over the last few years has focused on improved understanding and then exploiting the knowledge of glucagon-like peptide-2 or GLP-2. So that's where we are. These are exciting times in SBS because of this new world of growth factors that has opened up.

Dr. Cohran, one thing certainly we would both agree on, adult or pediatric, these are really among the most complicated patients there might be in most hospitals. At least when I see patients with intestinal failure, I'm thinking in terms of: What can I do? Are there strategies, are there opportunities here to wean this patient off the parenteral nutrition or intravenous fluid to improve his or her quality of life? And ultimately, also, have I exploited every opportunity there is to wean this patient successfully off parenteral nutrition?

Finally, if we can't wean somebody off parenteral nutrition, then our goal would be: Can we at least improve his or her quality of life significantly? Can we keep them complication-free and be able to look at a long-term survival with a good quality of life?

Dr. Cohran:
For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Valeria Cohran, and here with me today is Dr. Kishore Iyer. We're just about to discuss the role of GLP-2 analogs in treating intestinal failure in short bowel syndrome.

Now for many years, Kishore, there was really no advancement in treatment, and then several years back we had the approval of teduglutide, a GLP-2 analog. How have such agents helped us to achieve the goal of intestinal autonomy?

Dr. Iyer:
This, Val, has truly been a gamechanger in SBS-related intestinal failure. As you and I know this history quite well, but this would not be complete without acknowledging the role of Dan Drucker in Canada, who first categorized GLP-2 and its impact. It's what is called intestinotrophic effect on the intestine. And most importantly and most obviously, it increases villus height in the lining of the intestine; it increases crypt depth. And going back to the earlier analogy of the surface area of the normal intestine being that of perhaps many tennis courts, what this does in the patient with short bowel is it serves to increase the intestinal absorptive surface area. But there are some additional effects that physiologic GLP-2 has. When a healthy human being has a large meal, there is a big postprandial surge of GLP-2 levels in the blood if one were to look for it, and that presumably serves a physiologic role of absorption and digestion. But the other effects that GLP-2 has is it increases the portal blood flow; it slows down gastric emptying. So you can see if you take a physiologic view of what is GLP-2 doing, the effects of naturally occurring endogenous GLP-2 are very much to aid the process of absorption and digestion. The problem with endogenous GLP-2 is it has, unfortunately, a very, very short half-life.

Then came a recombinant glucagon-like peptide-2, recombinant GLP-2, or teduglutide, and teduglutide has now been extensively studied in international phase 3 trials.

So, to give you the highline results from the STEPS trial, approximately 60% of patients, just shy of two-thirds of patients, who were exposed to teduglutide achieved—met that primary endpoint of a 20% reduction in parenteral nutrition. There were a smaller percentage of patients who had additional decrements in parenteral nutrition, allowing some patients to get actually a few days off parenteral nutrition, so there were patients who had a 2-night reduction in parenteral nutrition; some patients came off 3 days a week. And, of course, to me, the Holy Grail of using teduglutide is whether it allows some patients to come off parenteral nutrition completely.

There is some real-world data now that tells us in the trials itself. So the STEPS trial was a 6-month trial with extension data that took it to 2 years, and certainly, some patients came off parenteral nutrition in follow-up of the STEPS trial data. In fact, we published in *Journal of Parenteral and Enteral Nutrition* in 2017 or '18 the data from patients who were weaned off parenteral nutrition completely. And out of about 134 or so patients, from memory 16 or 17 patients came off parenteral nutrition completely, so representing about—give or take—about a 15% cohort of patients who came off parenteral nutrition completely when they were treated with teduglutide. And of course over time—because this appears to be an accruing effect—over time, some more patients came off parenteral nutrition.

We published our own single-center data, much smaller cohort of patients understandably. I think we had 18 patients or so. And in our hands, 11 of the 18 patients came off parenteral nutrition completely, so that was significant, close to two-thirds of patients coming off parenteral nutrition. And what we observed in our report was that the majority of patients who came off parenteral nutrition completely had colon-in-continuity, meaning they had some small bowel that was anastomosed to the colon.

I just want to share one more recent paper. This was published by Francesca Joly and colleagues from Paris that looked at the French national experience, a larger experience, about 54 or so patients. And in their experience, about 25% of patients came off parenteral nutrition completely, and their observations were somewhat similar to us.

So, bottom line, teduglutide allows some patients to come off parenteral nutrition completely, and I think that's very exciting for what is really quite a terrible disease. And of course, I'm sure you're very excited of the pediatric trials that have just been published and its approval for pediatric use. What do you think?

Dr. Cohran:
As with most things, unfortunately, we don't have as many trials or studies in pediatrics as we do have in adults, but last year the 24-week phase 3 study was published in children. It was a total of 59 infants, or rather children who were at least 1 year of age to 18 years of age, and at least a year after their initial surgery or insult. They were treated with 2 different doses. They were treated with either 0.025 mg/kg, 0.05 mg/kg, and they also had a standard of care group, patients that were followed similarly but of course were not receiving the actual injection. They used the same endpoints that they had used with the adults, a reduction in 20% of parenteral support, and what they found was that the patients who were receiving 0.025 mg/kg, 54% of those patients met that criteria and 69% of those patients with a 0.05 mg/kg dosage. It was definitely higher than 11% of patients who had a reduction in the standard of care group. So again, I think this is also showing us that this drug can be effective in pediatrics as has been so in adults. Out of the total of 59 children that were treated, 5 children were actually able to be liberated from TPN. The majority of these children actually had midgut—3 had midgut volvulus, 1 patient had gastroschisis, and the other patient had an intestinal atresia.

So I think that as more and more people feel comfortable with using this drug, I think that we're going to see more and more data out there in the pediatric population. And I think that hopefully we find, similar to the adults, that we are able to liberate more and more patients from TPN. And in some cases, like in this, 5 children were able to be liberated from TPN.

Dr. Iyer:
That is fascinating. I think it's in line with the adult data that we've seen so far. And certainly in adults, I think there's a challenge to us as a community to try and understand how do we use teduglutide in practice; what is its role in the multidisciplinary care of intestinal failure. I have a certain world view of this. If you look at the slide that I shared, this is in line very much with the opinion of Francesca Joly that she shared with me on how should we consider introducing teduglutide to a patient with intestinal failure. In my mind, the fundamental principles remain the same. We should optimize parenteral nutrition for the patient with SBS intestinal failure. We should make sure that the patient is optimized from a parenteral nutrition point of view. Then we should really spend time and effort with dietary education, with ensuring that these patients are compliant with what we call an SBS-compliant diet, and that's difficult. Dietary compliance is difficult to put in place. It takes time and patience but really has significant bang for the buck and for these patients.

And alongside that, we use antidiarrheals, as I discussed earlier, acid suppression we discussed earlier. And one will find that over the first few months of this care, 3 to 6 months of this care, typically patients will start to feel better about their disease—they have a better understanding—and they will in most instances start to make progress towards weaning from parenteral nutrition or at least having less

and less instability. And once you've hit a plateau, or if the patient is certainly from a nutritional and medical viewpoint deemed optimized, then that would be the time I would consider whether there's a role for teduglutide.

Look, this is my view of teduglutide. It's a very safe drug, it's a very efficacious drug, but not to ignore the fact that this is a growth factor. When it was approved by the FDA, it was approved with a REMS program in place. So physicians are obligated to ensure patients are well informed and understand the benefits, which are considerable, the risks, which are significant but manageable, and with a good discussion in place, a good understanding in place, if there are no contraindications, to start teduglutide. And there are some screening tests one has to do to ensure there are no contraindications, and that would be a colonoscopy if the patient still has a colon to rule out the presence of polyps. We do routinely an abdominal ultrasound to make sure there are no other concerns for cancer, etc. And then get ready to start teduglutide.

Dr. Cohran:
Well, this has certainly been a fascinating conversation. But before we wrap up, Dr. Iyer, can you share with our audience your one take-home message?

Dr. Iyer:
One take-home message, that's a tough one, but here is what I would say. I've perhaps used this word more than once in this 15-minute podcast, but I will say this. This is a devastating disease. There's no question about it. But these are exciting times. This era of growth factors now provides suddenly a new therapy that adds for some patients a very, very significant benefit. I have patients, even adult patients, with residual bowel length in the single digits, less than 10 centimeters of small bowel with some colon, who are managing to get off parenteral nutrition with teduglutide. So I think carefully used, a well-managed patient in a multidisciplinary program, I think suddenly there are potential opportunities that were hitherto not available. So there is a new sense of hope for many of these patients.

Dr. Cohran:
You know, I would totally agree with that, Kishore, and I think as the number of children that are actually treated with teduglutide, we too will get to the point where we have more expertise with treating children with it, with feeling comfortable with managing it. And again, I would agree with what you said. We need to optimize medical management. But I think teduglutide can definitely benefit some of our patients and help those patients go on to attain enteral autonomy.

Unfortunately, that's all the time we have today, so I want to thank our audience for listening in and thank you, Dr. Iyer, for joining me and for sharing all of your valuable insights. It was great speaking with you today. Thank you.

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