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Hyperbaric Oxygen Therapy: Evaluating a Novel Approach for UC

Dr. Nandi:
More treatment options than ever have emerged for patients with ulcerative colitis, but not all developing therapies may take the form of a monoclonal antibody or a small molecule. Even more novel approaches are being studied, including the application of hyperbaric oxygen therapy. Curious to learn more?

Welcome to IBD Crosstalk for *GI Insights* on ReachMD. I'm your host, Dr. Neil Nandi. And joining me to share some of his group's pioneering research on hyperbaric oxygen therapy is Dr. Parambir Dulai. Dr. Dulai is an Associate Professor of Medicine, Director of GI Clinical Trials and Director of Precision Medicine within the Division of Gastroenterology at Northwestern University. He is an innovative physician scientist, and I am very excited to host him on the program today.

Parambir, welcome to the program.

Dr. Dulai:
Thank you so much, Neil, for having me and for bringing me on to talk about this topic, which is very close to my heart.

Dr. Nandi:
Absolutely. I know it is. You've done some great work, and I love that we are really thinking outside the box, if you will, but hopefully, outside the box becomes inside the box one day. Let's begin with some background. Can you tell us more about hyperbaric oxygen therapy and how it may play a role, the rationale behind how it may help in our inflammatory bowel disease patients?

Dr. Dulai:
Yeah, absolutely. So, hyperbaric oxygen therapy has been around for decades, and it's a mechanism through which we can deliver more oxygen to tissues that are either hypoxic or ischemic. And patients go into a chamber, the chamber gets closed, a hundred percent oxygen gets flooded in, and then they get pressurized, and that pressure drives that oxygen into the small capillaries, into areas that would maybe not see that kind of oxygen tension that we're able to create.

And I think, you know, when it relates to ulcerative colitis, one of the main reasons why we began to study this is because we have known for a very long time that hypoxia plays a critical role in the pathology dating back to Scott Plevy's work and a lot of the pioneering work around HIV-1 alpha and heme oxygenase-1, but we've never really been able to target hypoxia to treat colitis. And so the goal was really, you know, we have this treatment available, we know hypoxia is an important driver of disease development and disease progression, so why not try to link the two together to actually treat patients in practice.

Dr. Nandi:
And so, you know, you've already done some groundbreaking research. Can you give our audience a little bit more idea as to the mechanism? You know, how does this work?

Dr. Dulai:
Yeah. So there's probably three different mechanisms through which it's going to work in ulcerative colitis or the gut. One is, um, the gut has a very steep oxygen gradient when you go from the blood vessels to the epithelium, and the epithelial lining has a very, very low oxygen tension, so any small shift in that creates dramatic, sort of differences in its ability to deal with hypoxia that occurs, even small amounts of hypoxia. So the first step is probably resetting the epithelial lining's ability to deal with hypoxia or allowing it to sort of recover.

The second part is, from a lot of the diabetic foot wound literature, there's actually been good data that hyperbaric oxygen therapy

changes not only the immune cell signaling through HIV-1 alpha, but it actually prevents neutrophils from degranulating. And I think in ulcerative colitis, what we've seen and shown is that one of the main mechanisms is that it really stops those neutrophils from degranulating and causing a lot of the inflammation that we see in colitis patients.
And the third way that it really helps and I think it really drives a lot of it is it actually changes the microbiome. So the gut bacteria that we have are very oxygen-sensitive. Certain bacteria can't live in oxygen environments, and it's a completely anaerobic environment in some areas, and so, by delivering a lot of oxygen to the colon, we are actually killing off a lot of these obligate anaerobes who survive in hypoxic environments and shifting the composition towards an anti-inflammatory microbial composition.

Dr. Nandi:
So this is fascinating that there's a true mechanism for immune modulation where you're—the oxygen is actually changing the types of microbiota and influencing the immune system and ultimately affecting disease activity, but this isn't just theory. You've actually put this into practice. You have some real world study data to share. I know you guys did a phase II. How did you structure the phase II?

Dr. Dulai:
Yeah. So, so far we've had two separate phase II clinical trials. Our phase IIa clinical trial was a double-blind, sham-controlled trial. So we took the sickest of the sick. We took hospitalized ulcerative colitis patients who had acute, severe flares. They were treated with their standard of care IV steroids that we have these patients on for five days in the hospital while we wait to see if they're going to progress to needing cyclosporin or colectomy. And on the background of those IV steroids, patients were randomized to either get hyperbaric oxygen therapy one session a day at 2.4 atmospheres for a total of about five days or sham hyperbaric air where we actually put patients into the chamber, pretended we pressurized them and gave them a sham treatment. And that phase IIa clinical trial that we had, you know, we had 18 patients enrolled in that trial, and although the numbers were small, we actually saw very significant differences not only in their improvements in rectal bleeding and stool frequency scores, but their achievement of clinical remission within five days and actually prevention and avoidance of needing colectomy in the hospital.

And that first phase II that we did was quite promising, and that led us to embark on a second phase IIb clinical trial where we wanted to really confirm the efficacy that we were seeing and start to get a sense of the durability of effect. So in the second phase II that we did we had a similar approach. It was hospitalized ulcerative colitis patients who got their background IV steroids, and in those first five days they were given hyperbaric oxygen therapy for either three or five days to see if we had a superiority or a comparability in those sessions to make it maybe a little bit more practical to administer with just three sessions. And so, what we saw there similarly was that almost 80 percent of patients had a response by day three with improvements in rectal bleeding and stool frequency with nearly complete resolution of rectal bleeding, but five days was really needed to optimize that response and get them to a point where they were in full clinical remission.

Dr. Nandi:
For those just tuning in, you're listening to *GI Insights*' IBD Crosstalk on ReachMD. I'm Dr. Neil Nandi, and I'm speaking with Dr. Parambir Dulai about his innovative research on hyperbaric oxygen therapy for ulcerative colitis.

Now, Parambir, we've just had you review the phase IIa and IIb results. I don't think you can get a better controlled study than that, sham controlled study with some very good response, and you shared several months, at least three months of good durability, cwhich is an opportunity—If the patients stop bleeding, then they have opportunities to see—and avoid colectomy, then they have an opportunity together, patient and physician, to decide what's the next step in treatment. So let me ask you: What do you have planned next? How durable beyond three months is this effect?

Dr. Dulai:
Yeah. I mean, it's a great question, and I agree with you. I think the big paradigm shift that we're hoping for is right now in the hospital you have two to three options to rescue these patients—, cyclosporin or colectomy So the hope is that by bridging these people through this hospitalization, getting them out and getting them on to effective therapies, you can maintain some of that durability. Our hope now though is that we are looking—we're in the process of planning a large phase III clinical trial across 18 centers in the U.S. for nearly 130 patients to A) sort of confirm in a really well-powered clinical trial that this works, B) try to get FDA approval if we do have that efficacy data, but C) we're going to be looking out to a year to see how well these patients do and whether we've not only treated the acute disease but really changed the natural history of the disease for these patients by modulating the microbiome, some of these hypoxia pathways, and changing their ability to respond and adapt to other treatments.

Dr. Nandi:
Very exciting, and I love that you are trying to push this to a larger multisite trial. For clinicians listening to this, you know, there are many number of patients who would benefit from this study. How can they find out about how to enroll patients into your trial?

Dr. Dulai:

Yeah. So, you know, we're in the process of planning it with the NIH, and we should hear by the end of July about timing and start. And what our plan is, is at Northwestern we're going to launch a website for this so that people have a sense of their nearest institute that has access to enrollment in the clinical trial. But one important thing, Neil, is that these chambers are already out there. There are over 1,300 hospital-based hyperbaric chambers in the community, often in rural locations, and I don't know if providers really need to be waiting that long to consider integrating some of this into practice. Although we are going to work to generate more evidence, I think the evidence is pretty strong for some of these places to start to think about this now.

Dr. Nandi:
All right. Very good. I think this is extremely exciting. And like we said, this is at current time in 2022 still out of the box, but the needle is moving, and hopefully, this exciting data will pan out for some even greater durability so it's inside the box and part of our armamentarium. Before we close, Parambir, are there any other insights about hyperbaric oxygen therapy or your trial that you want to impress upon our clinicians who are listening in?

Dr. Dulai:
One thing that I'd like to just sort of, you know, have people walk away from is to start thinking outside the box with some of these treatments and being more accepting to what we've typically not been very accepting of because we're starting to put real science behind it. And one of the big things that we really pushed for is a lot of immune microbe sequencing, and the phase III study is going to really solidify not only how hyperbaric oxygen therapy works with some of these things but probably getting into some underpinnings of mechanism of disease as well. So we're really optimistic that some of the research we're doing here is going to help change the way we think about this, and I just want physicians and clinicians to start to, you know, maybe be a little bit more open and optimistic about some of these things that are considered sort of naturopathic or natural therapies.

Dr. Nandi:
Absolutely. Dr. Dulai, thank you so much for coming on our program and really sharing this exciting, research and plan for the phase III. We really, really appreciate it. It was great speaking with you today.

Dr. Dulai:
Thank you so much for having me and for taking the time.

Dr. Nandi:
For ReachMD's IBD Crosstalk, I'm Dr. Neil Nandi. To access this and other episodes in this series, please visit reachmd.com/gi-insights where you can be Part of the Knowledge. Until next time, thanks for listening.