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Project Goal: Fighting Resistance: How "Antibiotic Stewardship" is Shaping the Utilization of Antibiotics with a focus on antibiotics with new mechanisms of action in development

Project Date: 12/18/2018

Project Time: 1:00pm ET

Expert: Dr Richard Martinello - MD

Institution: Yale University

- Medical Director for Yale's Infection Prevention Department seeing approximately 2 C. Difficile cases per week.
- Oversees Hospital and System efforts to decrease healthcare associated C. Difficile and member of the System's Antibiotic Stewardship Program.
- Research interests include investigation into the epidemiology, impact and transmission of healthcare associated infections including methicillin resistant Staphylococcus aureus, Clostridium difficile and ventilator associated pneumonia.

Call Sponsor: **Summit Therapeutics**

Summit is developing new mechanism antibiotics for the treatment of serious infections. Summit's strategy focuses on developing new mechanism antibiotics:

Designed to be specific to a pathogen or infection.
Aimed at meeting the unmet needs of patients and healthcare providers.
Developed to be commercially attractive with compelling value for payors and healthcare systems.

The company's goal is to achieve commercial success by replacing the current standards of care.

Call Leader: Hi doctor, are you there?

Doctor: Yes. I am.

Call Leader: Great. Doctor, thank you very much for taking the time for this call today. I'm looking forward to hearing your thoughts on this space. For compliance purposes, I would like to confirm a few points which I'll read through and you can grant your verbal consent at the end. Okay?

Doctor: Very good.

Call Leader: Great. First, this call is being recorded and transcribed. Second, you the expert, attest that you will not disclose any confidential or material non public information. And finally, you attest that if you're a physician participating in the clinical trial, you will not discuss any information not yet in the public domain. If you're a member of the a scientific advisory board, clinical trial steering committee and/or data safety monitoring board, you will not disclose any information that is not publicly available or information that will break any confidentiality agreements by which you are bound. Do you agree to these terms?

Doctor: I agree. Yes.

Call Leader: I'll be serving as the call leader today. I too am required to keep any material non public information confidential. I attest that I will not share any material non public information or information that will break any confidentiality agreements by which I am bound. Additionally, I'd just like to note that this call is intended for informational purposes only, not investment advice. The contents of this call including any and all information provided regarding individual securities or industries do not constitute financial, legal or tax advice.

Finally, I'd just like to note this call is being sponsored by Summit Therapeutics. Summit is a clinical stage drug discovery and development company advancing innovative therapies to significantly advance the current standard of treatment for serious unmet medical needs.

Doctor, great. I really appreciate you taking the time to speak with me today. I think it's kind of an interesting time in the landscape where the media has really honed in on antibiotics and some of the resistance issues out there. I want to kind of take this conversation in two maybe three parts as you're familiar. First part, I'd like to understand really what is going on in terms of some of the resistance issues and how much of a problem is it and kind of what's going on at your institution to address these things. Secondly, I'd like to try and understand a little bit of the landscape on some new antibiotics. I don't think there's been an antibiotic with a new mechanism of action for quite some time, but really just to maybe understand the landscape and what's coming and exciting to you.

And finally, I'd like to wrap up with Summit's program with C-diff and look at their CoDIFy results and just talk to you about some of your views on that to start. But, before we get going, or maybe to get going we can start with your background. I read your bio and understanding a little bit more, your clinical experience, what involvement you have with antibiotic stewardship at Yale and just start off there before we dig into things.

Doctor: Sure. My background is that I am a board certified physician in adult and pediatric infectious diseases. I serve as our institution's director for our infection prevention program. I've been working in infectious diseases for about 18 years now and fairly clinically active too. With our antimicrobial stewardship program I help to provide oversight to that program and it's been in place, that program for a little over ten years now I'd say.

Call Leader: Okay. Great. Could you maybe talk to me a little bit about what that program's done over the last ten years, how that's changed and also just kind of what you've been experiencing from a clinical perspective on patients and their ability to be cured and treated effectively.

Doctor: Sure. Our antimicrobial stewardship program really has two different goals to it. One goal is to really preserve the antibiotics that we have available to us to make sure that they're available to us to use in the future. And, what I mean by that is as we use antibiotics creates evolutionary pressure on the bacteria that are in our patients and within our environment and it really pushes those populations of bacteria toward becoming more resistant and selecting for bacteria that have the ability to be resistant. The more we use them, unfortunately, the more resistant bacteria become over all.

What we try to do is to really focus on antibiotics that have a more rapid ability to force bacteria to become resistant and try to preserve those. The antibiotics that we've really focused on are the broad spectrum antibiotics such as the carbapenems and then also other antibiotics such as the fluoroquinolones where bacteria can perhaps more easily become resistant.

Another focus, a second focus of our stewardship program is really to prevent and minimize the risk for our patients to develop a C-diff infection. For example, we know that drugs such as the fluoroquinolone class in addition to other broad spectrum antibiotics have more of a risk associated with them for patients developing C-diff infections. Our antimicrobial stewardship program has really spent a lot of time focusing on proper use of fluoroquinolones especially in patients with respiratory tract infections and with UTIs where there may be other options that are safer and other options including not using any antibiotics at all if the patient's situation warrants it.

I think a third goal of our antimicrobial stewardship program is really to help save money. Some of the antibiotics are more expensive than others. Oftentimes when a clinician decides to use one antibiotic or another, they may not be aware of what the cost to the patient is or the cost to hospital is and so our stewardship program helps to guide the clinician to use the most appropriate and cost effective antibiotic also. Those really are the big three goals that we have, to prevent resistance, to help prevent C-diff and then also to help minimize the cost of our antibiotics overall.

Call Leader: Okay. Great. Go ahead.

Doctor: I was just going to say that antimicrobial resistance is really an enormous problem, not only in the United States but also globally. I think those on the call are aware this is an area where we do not feel there is a lot of drug development although there are some bright spots in certain places and it's important for us to really protect the antibiotics that we have in addition to helping to support the development of new antibiotics as we're finding it more and more challenging as the years go on as our patients come in with bacteria that are causing infections and those bacteria are more and more resistant to the first line, second line antibiotics that we have.

Call Leader: Yeah. That's one of the things I wanted to understand a little bit, how the resistance and occurrence go together hand in hand and if you have that recurrence, do you see significantly more resistance or that there's a chain relationship. I guess when you're thinking about treating a patient, what's the priority and how much of an issue and burden is it when there is a recurrence. How do you think about that when treating first line at the initial point.

Doctor: I think one change that we've seen over the last ten to twenty years is really that now when we have patients who come in with serious infections, we have to choose very broad spectrum combinations often times of antibiotics to ensure that we are using antibiotics that will be active against the patient's infection. Generally then when things go well within typically one to two, two to three days, we're able to figure out what is causing the patient's infection and through the work in the microbiology lab understand more about the particular bacteria and what antibiotics are best for it. Then typically if they have two to three day time period, we'll go ahead and change the antibiotics to something much more focused on the bacteria that we have found causing the infection. Really one of the big changes that we've had is just needing to use much more broad spectrum antibiotics than we used to ten or twenty years ago.

If we pick wrong, oftentimes, if we pick the wrong antibiotics, the infection just doesn't respond in the way that we want it to and the patient's clinical condition either doesn't improve or potentially even worsens and during that time period then, hopefully that two to three day window we figure out what antibiotics are right so we can then put the person on it but we've at that point lost a few days of potential benefit to the patient and oftentimes that can be associated with bad outcomes.

Call Leader: Got it. Interesting. To a degree that's a next segway into the ridinilazole program. I want to see what your thoughts on the coDIFy results were. Your comments around moving towards more broad antibiotics versus this being a very narrow spectrum, I'd like to hear your thoughts on the general approach in this mechanism relative to kind of some of the way that you've been currently treating C-diff in patients.

Doctor: Joe, maybe I don't understand the question. Can you rephrase that?

Call Leader: I just wanted to start transition to talking about Summit's program ridinilazole and seeing what you thought of the narrow spectrum approach relative to how you're currently treating C-diff patients and what your initial impression is before we dig into any of the data or results.

Doctor: Thank you. I think when we approach ... One of the principles of antimicrobial stewardship is really once you know the bacteria that is causing the problem, you use the most focused antibiotic possible. You want to use the most narrow spectrum antibiotic not only because often times that's the least expensive and oftentimes clinically most effective antibiotic to treat that bacteria and it's the bacteria with the particular resistance pattern but also I think over the last ten years certainly, we've come to develop a better understanding of the importance of the microbiome. The less you disrupt the microbial flora that the patient has, not only in their GI tract but their respiratory tract and their skin, the better off that patient's going to be. Choosing a narrow spectrum antibiotic whenever possible is typically the best choice for a patient.

Call Leader: Got it. Maybe just to look at the high level of the trial, they were going against Vancomycin. How often are you using that in patients now and what do you think of that as a comparative arm? I wanted to see how you thought of the actual results. The Phase two trial, did that look like a compelling set up for Phase three?

Doctor: Yeah it does. I think Vancomycin was really the right comparator. A few years ago due to some more recent trials, we've really shifted from using Flagyl, metronidazole, as our first and front line agent for C-diff to primarily using Vancomycin. Vancomycin has been used for the treatment of C-diff for many decades. I think something that we've learned over the last number of years is that especially for those with more severe now, more moderate degrees of C-diff infection, Vancomycin really has become our frontline therapy. At this point, we're really only using metronidazole for patients with the least severity of disease for C-diff. Vancomycin was really I think the right comparison drug for this trial.

Call Leader: Got it. Kind of digging into some of the results from that phase two trial, I think they were a little bit lower on patient enrollment. I want to get your thoughts, I heard the company articulate that there was a bit of a crowded environment at that point in time of the phase two trial in terms of being able to recruit patients. Has that changed and does that make sense to you?

Doctor: Yeah. I think that while it was disappointing to see how few patients were enrolled in the study, it turns out that they had a sufficient number of patients to still have a statistically significant study. What we look for first and foremost is whether or not a study achieves statistical significance which this study did.

Call Leader: Got it. And just in terms of looking at it I think we're starting the Phase three trial in early 2019. Has that patient enrollment landscape changed at all? If you're thinking about competitive options to enroll a patient, how does this program now look both moving to Phase three with positive data behind it as well as other patient options.

Doctor: I think just very simply we still see plenty of patients with C-diff. I would hope that the Phase three trial is going to be very successful enrolling as many patients as they need to.

Call Leader: Got it. And then back to your comment about still hitting statistical significance, maybe just expand a little bit on that in terms of they've met the non- inferiority well as statistically significant superiority at the ten percent level over Vanco. How compelling and surprising is that? Have you seen other options out there that you think would be like that or is this differentiating itself on a statistical basis?

Doctor: I think this drug is really differentiated in the sense of how narrow a spectrum it is. I know we'll talk about that a little bit more but this trial has achieved statistical significance and that's really what we look for. I think the caveat to that being though this still was even though it was statistically significant was a very small trial and I think that's where there will be a lot of the attention placed on the Phase three study. I think there's a lot of enthusiasm for this drug just simply based on the Phase two trial.

Call Leader: Got it. To your point on the narrowness of this, I think the company had put out a qPCR assessment of the gut microbiota after trial, at day 25. I wanted to see at a high level if that's an analysis you're familiar with, how strong a set of information that is because that is also highly significantly, high significant P value .0001. I want to see if you thought that those were the right microbes to be looking at, kind of comment on the overall approach if you've seen it before and just how much this goes beyond some of the clinical outcomes in the Phase two but really speaks to the narrowness. Am I thinking about that right?

Doctor: Yeah. Let me start answering this by backing up a little bit and giving a little more context. The C difficile infections are a little bit different than how we usually think of infections. Typically, when somebody gets an infection, let's say skin soft tissue infection, the bacteria gets in underneath or into the skin and causes an infection. In our bowels, it's a little bit different. Our bowels are full of different types of bacteria and other microbes and the balance of those microbes, which we refer to as our colonic microbiome, really help to protect us in the sense and they keep out bad bacteria. C-diff here is the bad bacteria. What's been found really over the last 50 years is when you take antibiotics, it disrupts your, the microbiome within your bowel, and it leaves you very vulnerable to not only picking up C-diff and having it take hold, but also then that C-diff producing toxin and making you sick. An antibiotic that both treats C-diff and also is sufficiently narrow spectrum so it minimizes the disruption to the colonic microbiome is really important and certainly something that's very novel with this drug.

With that said, with our past drugs that we've used to treat C-diff, we haven't had that opportunity. Flagyl, metronidazole, Flagyl and Vancomycin both have been very disruptive to the bowel flora. Although they may effectively treat C-diff, it leaves the patient at real high risk for that C-diff infection coming back as a recurrence. That's where this drug seems to have a really substantial leg up on Vancomycin and metronidazole.

I think the PLOS ONE study did a very nice job looking at what the diversity in the stool is. They took stool from patients who were enrolled in the clinical trial and what they did over the period of time when the patient was on either the study drug or on Vancomycin, they looked at the diversity of microbes within those patient's stool. In short, what they had found was that Vancomycin, as known, was very disruptive to the diversity of microbes in the patient's stool whereas the ridinilazole was much less so disruptive. That actually sits very well into the study findings reported in Lancet. They found many fewer recurrences associated with ridinilazole treatment than with Vancomycin.

Call Leader: Looking at that, it seems very supportive to me but it really puts data to that narrow spectrum thesis I guess if that's a fair way to analyze that.

Doctor: Yeah. Very fair.

Call Leader: And you made a comment around tolerability. Looking at the trial results, it looked like they had similar side effect profiles, I wonder if you have a comment on side effect profile and also if they are similar, how well tolerated Vanco is with these patients and do you see there being a potential for differentiation here based on that disruption to the biome, to the microbiome thesis or do you think that these drugs are reasonably well tolerated and it's more about recurrence that we should be focused on.

Doctor: Yeah. Vancomycin as was the ridinilazole are both very well tolerated. I don't think it really differentiated itself from Vancomycin better and typically it seems very similar to Vancomycin related to those adverse events. I think really what makes drugs unique is how narrow spectrum it is and how little disruption it created in the microbiome and that's then reflected on seeing fewer recurrences in patients with C-diff.

Call Leader: Before we finish the call, I want to kind of move forward into the world that we have Phase three results that are let's say similar but with more robust patient numbers. How would a drug like that be received at your institution? I have a couple specific questions around it but do you think that a recurrence number is the number that we should be really focused on? Is it the fact that the thesis of a narrow spectrum solution is playing out and if we're kind of theoretical benefits can be understood, how should we look at the phase three results? What would be the first things you focus on and then I'm going to ask you some questions about how it is actually utilized but what's the headline that's most important to you?

Doctor: I think the headline here is two fold. I think first and foremost as a clinician, what we want to see is that the patient in front of us who's sick right now that they get better from the drug that they received. The ridinilazole looked very attractive relative to Vancomycin. And, I think that that's very important and can not be understated. In fact, I hesitate to say it but because of the study size was so small, but some of the data looked like the rapidity of improvement was actually a little bit better, although I don't believe it achieved statistical significance with ridinilazole compared to Vancomycin.

A close second priority is really that of preventing recurrence. Typically, when we see recurrence, it usually occurs within a few weeks of the patient getting better and then unfortunately they backslide and they get sick again and are found to again have a C-diff. The ridinilazole was substantially better than Vancomycin in helping to prevent those recurrences. And in particular for patients who have had episodes of C-diff before, and those with more severe underlying diseases, this is really important. I think hopefully with the Phase three studies and future studies of this drug will develop a better understanding of how this drug works in those populations that at most high risk not only for severe disease but also for recurrence. But I think the findings of Phase two study are very attractive, and I think make us look forward to having this drug approved and become available for use.

Call Leader: When I think about trying to, you come from more of a financial perspective modeling the addressable population or patients, I guess what it gets priced at is a separate conversation but if we assume some form of branded pricing in a world where there are generics, do those two points alone make it compelling to you to use in patients first line or second line or how would you think about segmenting out C-diff patients that you're seeing in your institution. Part of that I want to tie back to your comment around thinking about price for the total procedure and recurrence is having the burden on patients and things. I'm just trying to think about really patient selection in a world where the Phase three trial shows a lot of the information or shows the result that you just described.

Doctor: I think the results from the Phase two trial, if they are upheld in a Phase three study and the data that becomes available in the course of its licensure, I think does make it very attractive as a first line agent. Joe, as you were saying what's going to be so important is pricing because when hospital or an insurer decides how it's appropriate to use this drug versus Vancomycin, a lot of that's going to come down to pricing because there are, especially for first, episodes of first disease with C-diff, there's a lot of similarities between these two drugs. Probably the benefit will be greater in the treatment of persons who are high risk to have recurrence or are experiencing their first or further recurrences. I think that pricing piece is going to be really important.

Call Leader: Got it. When a patient does have a recurrence even in a first line, after first line cure, can maybe just walk me through a little bit on the cost side and what's done. Are they just given another course of antibiotics and hope for the best or are they admitted sometimes? I'm just trying to understand both the payer's perspective as well as the patient's what that really looks like.

Doctor: The hospitalization is really determined by the severity of the patient's disease. Generally the paradigm we typically follow for treatment of recurrent C-diff is we'll just really use the same drug that we used the first time which in the past has really focused on metronidazole and more recently Vancomycin. Of course FMT, fecal microbiota transplant, has become much more popular in use. I think at our institution and other institutions its use continues to grow and we know that some of the commercial stool banks are making more convenient products that are really helping to decrease the barriers to using FMT.

I think we'll as time goes on continue to see that being more and more attractive option for the treatment of patients. And I think, and I should say that mostly while its use is part of treatment but the benefit of FMT is really one of helping to prevent further recurrences. This drug can even be I suspect one way I would think of it is pairing it with FMT if recurrence continued to be a problem. My hope would be that in using ridinilazole that it would actually help to prevent those recurrences and hopefully then avoid the need for FMT.

Call Leader: Got it. I was thinking as you were saying that that essentially one of the benefits of using a first line would be not having to rebuild the gut microbiome. Would that be a logical way to essentially think about that?

Doctor: Yes.

Call Leader: Okay. I think I've walked through most of my questions. When you're thinking about the Phase three results, is there a number? I think you've looked at the trial design roughly, is there a number that we should be looking for on the difference between recurrence and, you know between Vanco and this drug that is really exciting or could you maybe give me a very good result and a home run result or is it really just the meeting of statistical significance that you think is going to differentiate it?

Doctor: I think achieving that statistical significance is really important. Generally what is chosen is when they're designing the study is trying to figure out what would be clinically relevant. Generally we'd say if there was a 10, 20, 30% chance difference between the two, that is something I think would be useful from a clinical perspective. Probably at least 20% difference would be, assuming you achieved statistical significance would be very convincing.

Call Leader: Okay. Great. Is there anything else you think I should be asking about on this before I ask my last question? Are there other aspects of either the delivering clinical side or trial results that are interesting to you that we haven't discussed, having reviewed all the documents or data?

Doctor: No. I think we've more or less covered everything.

Call Leader: Okay. Great. I ask this question on almost all my calls, on a scale of one to ten, ten being very excited, how excited are you for this approach, this drug based on what we know so far?

Doctor: Yeah. I would probably say an eight to nine.

Call Leader: To get up to a ten, would that just be replicating with more patients or is there something else that you'd like to see?

Doctor: I also serve on our hospital PNT committee so I would like to see it come in at a competitive price point.

Call Leader: That's a fair answer. Let me just double check one more time if we didn't forget any last questions. I think that's everything that we had. Yeah. Those are all mine. I really appreciate you walking me through this. We'll look forward to the Phase three results.

Doctor: Very good. Thank you so much.

Call Leader: Thank you. Bye bye.

Doctor: Take care, bye.

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