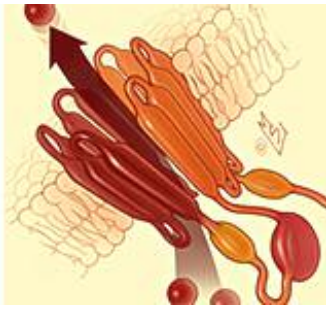

INTERVIEW WITH DR. PATRICK FLUME: TRANSCRIPT

DR. PETER MOGAYZEL: I'm Dr. Peter Mogayzel from the Johns Hopkins University School of Medicine and one of *e*Cystic Fibrosis Review program directors. I am speaking with Dr. Patrick Flume from the Medical University of South Carolina. Dr. Flume presented the data on the Continuous Alternating Therapy trial for inhaled antibiotics at the most recent NACSE meeting. Patrick, thank you for joining me today.

DR. PATRICK FLUME: I'm happy to be here.

DR. PETER MOGAYZEL: Let's start with the basics: what's the rationale for using inhaled antibiotics for Pseudomonas treatment?

DR. PATRICK FLUME: Inhaled antibiotics have become the standard of care for the treatment of our patients. Years ago, when we didn't have many therapies, some brave souls tried inhaled antibiotics, the science was put to the test, and eventually antibiotics were developed that were proved to be effective. Essentially the notion is that we're trying to suppress the infection so we can get good clinical benefit, in this case usually improvement in lung function and reduction in exacerbations.

DR. PETER MOGAYZEL: What are the typical antibiotics that are used and how does one use them in clinical practice?

DR. PATRICK FLUME: Two antibiotics are FDA approved, and there we also use some antibiotics off label. Inhaled tobramycin, affectionately known as tobi, was the first drug that was approved for aerosol use. Inhaled aztreonam, also known by the trade name Cayston, is also approved. Both of those drugs went through the standard approval process through the FDA, and both were developed using a regimen of using the medications either twice or three times a day per their label for a month of 28 days, and then taking a month off. Other medications, typically intravenous formulations, have been nebulized for the treating patients.

DR. PETER MOGAYZEL: So Patrick, many physicians find that the use of antibiotics every other month is not adequate for their patients, and I think a number of them are using different strategies, including using antibiotics continuously. Can you comment on that?

DR. PATRICK FLUME: Yes, the studies that were done initially were based upon a month on/month off regimen, and there's a lot of history to that, probably more than we could talk about right now, but that was the regimen that went through approval process. Our patients tended to like the month on medication but had trouble on the month off medication. And even during the trials, although lung function would improve during treatment, it often regressed to the previous baseline when they came off therapy, and there was still a steady progression of lung function decline, as well as frequent exacerbations. As clinicians we're looking for ways to try for further improvement, and while the initial notion about month on/month off was trying not select out resistant bugs, we've since learned that that probably isn't the most relevant issue, and so people have moved toward a continuous form of therapy.

With continuous inhaled antibiotics, meaning keeping the patient on some kind of suppressive therapy every day with no time off, there's a couple of different strategies. One is using one medication continuously, for example, inhaled tobramycin every day. The other is to go with a rotation using antibiotic A for a month and then switch to antibiotic B for a month, then continue that rotation. That's what we mean by continuous alternating therapy, or we use the

affectionate acronym CAT therapy. This has been an evolving process because clinicians have been trying to take care of their patients

So when we designed a trial to test whether continuous antibiotics would be beneficial, we thought about which strategy we would use, whether we would go with a single drug or to go with CAT therapy. We chose to go with CAT therapy based on one of the studies done in the development of inhaled aztreonam in which patients started with a month of inhaled tobramycin, sort of a tobramycin run-in, and then they were randomized to either inhaled aztreonam or a placebo. Those who were on inhaled aztreonam saw additional improvements in their lung function. That added weight to the notion that it might be preferable to rotate the antibiotics.

That was the CAT trial in which everyone received inhaled tobramycin every other month and in in between they were randomized to receive either inhaled aztreonam or placebo for three cycles.

DR. PETER MOGAYZEL: What were the challenges in undertaking this trial?

DR. PATRICK FLUME: We had a very difficult time with enrollment. When we designed the study our intention was to reduce the frequency of exacerbation; that was our primary endpoint. But to do that, we had to enroll a fair number of patients. Our planned sample size was about 250 patients, but as we started enrolling patients we were having a tough time and had to keep of recalibrating because enrollment was falling way behind our expected schedule. When we reached out to investigators to find out why they had such a hard time enrolling patients, a number of reasons emerged, but one stood out: they already had patients on a CAT regimen of rotating antibiotics, and they had ethical issues with taking them off that regimen in which a patient might get a placebo on the interim month. So despite a long attempt to recruit, we ended up only enrolling 88 patients who were randomized to either the CAT therapy or the usual single antibiotic therapy.

Did they improve? The reality is that they kind of did. Look at the primary endpoint, the rate of exacerbations was actually numerically lower in the patients who were on the rotational CAT therapy compared to those who were alternating with placebo. The problem is, we were so underpowered that we can't say that it was done with statistical significance. Nonetheless, there was about a 25 percent reduction in the exacerbations overall, and that was the same no matter what subgroup we looked at. When we looked at the time to the first protocol — the time to exacerbation of the hospitalization rate — those, too, were in favor of patients who were on a CAT therapy regimen as opposed to those on the placebo regimen. Again, that is not statistically significant because we were so underpowered.

DR. PETER MOGAYZEL: These results certainly suggest that CAT therapy could be valuable for some patients. How do you think practitioners should look at this data; how should they incorporate it into their practices?

DR. PATRICK FLUME: I think that if physicians look at the data and believe they need to do something more for a patient who is having frequent exacerbations, they will likely see these data as a positive, meaning it would support their notion that continuous therapy would help their patient, and go with the rotational approach. I would feel much better about that if we could say yes, without doubt statistically significant differences were seen, but we realize this was a real challenge in designing and conducting a study like this when basic care of these patients was already evolving. While we were designing this study, physicians were already moving toward a CAT type regimen for their patients. So I think most of those folks will look at this study as confirming their hypotheses.

DR. PETER MOGAYZEL: Were there any concerns in the study with adverse events or other things we should think about when comparing this to the traditional month on/month off approach for antibiotic use?

DR. PATRICK FLUME: If you eliminate the exacerbation aspect, the side effect profiles were essentially identical and were typical of what you see in aerosolized antibiotic trials with cough or airway irritation, and so forth. So there was no difference in safety between the two groups. I think it's perfectly safe moving toward that regimen.

DR. PETER MOGAYZEL: And when you think about design of future trials for antibiotics or other therapies

where you're comparing something new to what may be coming a standard approach, are there any lessons to be learned from this?

DR. PATRICK FLUME: I think there's a huge message. If I have a new antibiotic that I want to develop for treating cystic fibrosis and as a clinician I think we need more options because our patients either can't tolerate some of these medicines or they feel the effect is not as robust as it once was, they're definitely looking for newer medications. But we're in a much different era now. When these other two drugs were developed, it was possible to do a placebo controlled trial over a long period of time and tease out these benefits. Nobody thinks that's ethical anymore because if you have a patient with Pseudomonas you don't want them to go three to six months without any aerosolized antibiotic. I already can't do a simple placebo controlled trial like that.

An intriguing approach would be do the CAT regimen, testing my drug on the interim months and showing that it is indeed still better than the placebo, but as we learned from this trial, we had a hard time enrolling patients in that. I'm not sure I could convince docs to do otherwise now; they've already adopted that protocol.

So you move into an area where if you have a new drug, you have to go toe to toe with a direct comparison against a drug. The challenges with that approach, however, depend on how that drug is delivered because if you look at just, say, tobramycin and aztreonam, they are delivered or recommended to be delivered in different devices. So when you are thinking about blinding your patients and investigators to the treatment arm they're on, it's tougher to do that because you can't use the same device and just blind them to the drug.

The same with the treatment regimen because tobramycin is recommended as a twice a day and aztreonam as a three times a day. So there are some real logistical issues about conducting a true blinded study that would rise to the level of evidence that you want to bring to the FDA.

DR. PETER MOGAYZEL: You brought up a number of challenges, and I agree with you entirely that we do need more antibiotics to be able to treat patients. I think this is going to be something that the community will have to struggle with to figure out the best approach to getting these therapies approved.

DR. PATRICK FLUME: A key issue for clinicians is, if they believe in CAT therapy, they're expecting or are already getting pushback from the payers because it's an off label approach to the typical regimen and payers obviously would rather not spend more money on inhaled antibiotics. But I'm hopeful that the evidence we had in the CAT trial is confirmatory enough that payers would realize the benefit for those particular patients for whom it's been prescribed.

DR. PETER MOGAYZEL: I think you're right. This is absolutely a challenge to demonstrate efficacy of medications in a real world setting so we can know they work and will be effective and safe and insurers will feel that they are appropriate to be reimbursed.

Well, Patrick, thank you for taking the time to talk with me about inhaled antibiotics and the CAT trial, I hope that this has been beneficial to the listeners and I want to thank you again for joining me.

DR. PATRICK FLUME: Oh, it's my pleasure, thank you.