

# What is ULTOMIRIS?

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[00:00:02] **Dr. GG deFiebre:** Hello and welcome to the SRNA "Ask the Expert" podcast series. This episode is titled, "What is ULTOMIRIS?" My name is GG deFiebre and I moderated this episode. SRNA is a nonprofit focused on support education and research of rare neuroimmune disorders. You can learn more about us on our website at [wearesrna.org](https://wearesrna.org). "Ask the Expert" is sponsored in part by Amgen; Alexion, AstraZeneca Rare Disease; and UCB.

[00:00:31] For this episode, we were pleased to be joined by Dr. Michael Levy. Dr. Michael Levy is a neuroimmunologist. He's an Associate Professor at Harvard Medical School and at Mass General, he's the Research Director of the Division of Neuroimmunology and Neuroinfectious Disease, and also the Director of the Neuroimmunology Clinic and Research Laboratory. You can view Dr. Levy's full bio in the podcast description.

[00:00:57] Thank you, Dr. Levy for joining me today to talk about the newest FDA-approved medication, Ultomiris. So do you mind just starting with what is this medication?

[00:01:08] **Dr. Michael Levy:** Yeah, Ultomiris or ravulizumab is the newest medication that was approved for neuromyelitis optica spectrum disorders. It works just like eculizumab or Solaris except instead of requiring an infusion every two weeks, it's extended to every eight weeks. It hangs around in the circulation longer, works longer. So, you need fewer infusions.

[00:01:32] **Dr. GG deFiebre:** So how does it differ from Solaris besides just that dosing timeline?

[00:01:40] **Dr. Michael Levy:** Well, it really is just about dosing. They took the Solaris molecule which is an antibody. They made four small minor mutations or changes that allow it to stay in the circulation longer. So, it's not degraded within two weeks as we currently dose Solaris, but it hangs around and so it lasts up to eight weeks or even longer in the pharmacokinetic studies, it could even hang around up to 10 weeks, but we dosed it every eight weeks in the trial. And otherwise, it works pretty much exactly the same. It blocks the complement and that has a wonderful effect on NMO in preventing relapses.

[00:02:22] So one thing to clarify though is that just like Solaris, this medication is intended only to prevent the next attack. It doesn't do anything to heal damage from previous attacks or manage symptoms. It just prevents the next attack.

[00:02:38] **Dr. GG deFiebre:** That's a great point. And so, you mentioned that it works on complement. Do you mind just talking a little bit more about how it works and what that means?

[00:02:48] **Dr. Michael Levy:** Yeah, so complement is a system in your body. It's made up of just proteins, it's not cells, and these proteins respond to bacteria. So, if you get an infection, we're going to talk about some of them that are particularly important for complement. One is called Neisseria meningitis. It's a bug, it's colonized in the nasal cavity. And if it invades into the blood, it can then get into the brain and cause a devastating meningitis.

[00:03:11] In the complement system, the system of proteins, that is designed to bind to that bacteria and destroy it, if it tries to get into the blood. That complement system is co-opted by NMO. So NMO uses that system to destroy the spinal cord, destroy optic nerve tissue. And it's there, you could see the complement deposits in the tissue from NMO attacks. And this was recognized way back, more than 20 years now, when our Mayo colleagues first showed it under the microscope. And so, the idea was, "Well, maybe if we block the complement system, we can block the damage from NMO attacks." And so, then the Phase 2 trial launched more than 10 years ago now and it showed a wonderful improvement in a small cohort of NMO patients.

[00:03:59] It was enough though to prompt the company to do the Phase 3 trial with Solaris and that proved remarkably successful, 94% reduction in relapse risk. And then that finally led to this trial because patients were complaining about every two-week infusions, it's obviously very difficult and they happen to come up with this technology to make the drug last eight weeks instead of two.

[00:04:24] **Dr. GG deFiebre:** And so, is it administered at home or in an infusion center? Is it an infusion or an injection? Do you mind just talking about how it's administered?

[00:04:33] **Dr. Michael Levy:** Yeah, it is an infusion. It's much longer than Solaris. Solaris was 35 minutes, much quicker. Now it's 2.5 hours per infusion. It is IV. It's not available Sub-Q. I wish it was a pill but it's not. It has to be given IV, but it can be given at home. It could be given anywhere. In the trial, we did a lot of infusions in the infusion center but it's not necessary. We're now doing infusions at home just like Solaris.

[00:05:02] **Dr. GG deFiebre:** So, what is the typical dosage for this medication?

[00:05:07] **Dr. Michael Levy:** It's weight based but it's weight based into classes. So, the way that we did the trials is if you were up to a certain weight and I think it was 60 kg, then you got the lowest dose which was 2,400 mg loading dose followed by 3,000 mg maintenance dose. If you were between 60 and a 100 kg, which is where most people are, then you had a 2,700 mg loading dose and a 3,300 mg maintenance dose. And if you're over 100 kg body weight, that's 212 pounds, then you have a 3,000 mg loading dose and a 3,600 mg maintenance dose. If you change your weight class, if you say you lose weight and you go under 212 pounds, then you would just drop your dose down correspondingly.

[00:06:06] **Dr. GG deFiebre:** What's the difference between a loading dose and a maintenance dose? Why are they different?

[00:06:12] **Dr. Michael Levy:** The loading dose, I should clarify, while the maintenance dose is every eight weeks, there's an extra loading dose. So, you would say you come in, get your first dose, a loading dose, then you'd get a second loading dose. I think it's two weeks later. And then I believe four weeks later and then after that, then you start your regular maintenance dosage.

[00:06:35] **Dr. GG deFiebre:** How much does it reduce someone's risk of relapse according to the studies that were done?

[00:06:42] **Dr. Michael Levy:** The way this study was done is they didn't have a placebo arm to compare to but what they did was they designed the trial to be just like the Solaris trial. So, they could use the placebo arm from the Solaris trial. And then nobody had to risk being in the placebo arm. When they compared it like that, there were zero attacks. And so, you could say, "Well, it was perfectly successful 100% reduction in relapse risk" but statistically, you can't do that because you didn't enroll the entire NMO population of the entire world. So, you can't be 100% sure.

[00:07:16] So, statistically, we say it's 98% reduction in relapse risk. Again, we saw no attacks. And so, I'm sure there will be eventually attacks on ravulizumab and we'll be able to calculate a more accurate reduction in risk of relapse but it's somewhere in that range of Solaris was 94% reduction in risk. This is 98%. It's somewhere in that really, really highly efficacious range.

[00:07:45] **Dr. GG deFiebre:** What are some of the side effects of this medication?

[00:07:49] **Dr. Michael Levy:** Well, the main side effect is by blocking complement, you are then vulnerable to infections that depend on complement. I mentioned *Neisseria meningitidis*. That's just one bug. There are others, *Haemophilus influenzae*, pneumococcus. These are bugs that all share in common what they have is a cell wall that's encapsulated, and the complement system evolved in humans over time to be very good at breaking open these cell walls of encapsulated organisms. And we've become dependent on our complement system for that. And so, if you're on a complement, blocking drug like Solaris or like Ultomiris, then you're more vulnerable to those types of bugs.

[00:08:38] Now we vaccinate everyone, and, in many cases, we put people on regular antibiotic dosing. So maybe penicillin every day or maybe you keep some ciprofloxacin in your medicine cabinet. So, if you get a fever, you just take that, but that's what we're aware of, is this risk for encapsulated organism infections. And we know that antibiotics work. And so, it's really a matter of figuring out the best way to prevent these specific types of infections.

[00:09:11] **Dr. GG deFiebre:** So, you mentioned vaccinations before someone starts this medication. What does someone need to do to prepare to start getting infusions?

[00:09:24] **Dr. Michael Levy:** Well, we really want everyone to get vaccinated. And vaccines are a problem in NMO because some patients have vaccine injury and that's a trigger for an NMO attack. And we recognize that. And we don't want to force people to take vaccines if they're strictly opposed, but we know that the vaccine is really helpful in preventing infections when you're on this drug. Now, another way to avoid an infection is to take a daily antibiotic. And penicillin is the easiest and you could do that with a once-a-day pill. You could also, like I said, keep your antibiotics in the medicine cabinet.

[00:10:04] We know that the infections almost always start with fever, headache, stiff neck, those are the dangerous ones, but also pneumonias that start with fever and obviously develop cough and things like that. There are ways around the vaccine, but we really want to try to get everyone vaccinated before they start taking the Ultomiris. If they don't, then you absolutely have to take antibiotics until your vaccination is up to date.

[00:10:33] **Dr. GG deFiebre:** And so, what vaccinations are people supposed to get before starting?

[00:10:38] **Dr. Michael Levy:** The meningitis one is the big one. That's the scary infection in the meninges around the brain. And that vaccine comes in two types. There's the ACYW, these are different variations of

the same meningococcus bug and then there's the Type B and those are separate vaccines. And Pfizer has a brand new one that just combines all five together. So, you can get any of those. And there are schedules for that. Some vaccines require two shots, some require three. And if you're going to be taking the two separate, then that's up to five vaccines in one year and we space them apart.

[00:11:13] And it sounds like a lot, but this is really for your safety. While you're on this drug, we know that you're vulnerable to this bug. In fact, about one out of every five kids in college has the bug in their nose and it's colonized in there, it's not causing harm. But then if you're on the drug and you come into contact with one of these people and that bug jumps into your body, then you're going to get the infection. And so that's the danger. It's not just that bug. As I said, haemophilus influenza, most of us were vaccinated as children, but vaccines wear off and you might become vulnerable to that bug. Pneumococcus is another bug.

[00:11:54] Those are the top three and there might be others that we just don't know about yet, but all of them cause infections. All of them cause pneumonia and meningitis and fever. And so, we really do know what to look out for and that is the major, major, major risk with this drug.

[00:12:11] **Dr. GG deFiebre:** What ongoing monitoring should occur when someone is on this medication? Do they need to get testing for anything? Any skin checks that people have to do for any other medications?

[00:12:25] **Dr. Michael Levy:** None of those. You don't really have to get tested for anything else. We don't even have really good tests for vaccine efficacy. So, some people have thought, "Well, let me get this vaccine and then make sure that I responded well to the vaccine." We don't have really good tests for that. They are out there, but they're not widely used and we're not really sure how effective they are. Especially when you have NMO, and let's say you're on rituximab and you're going to switch. Rituximab is going to blunt your vaccine response. So even if you're on schedule for your vaccines, we don't know 100% how well the vaccines work.

[00:13:04] So with all of that uncertainty, we really do depend a lot on antibiotics. So, the monitoring really depends on you calling us if you get a fever, infection symptoms, cough, anything that's worrisome that can be one of these infections, we'll really want to start you on antibiotics right away or you can sleep easier. I can sleep easier if you just take the daily antibiotic.

[00:13:30] **Dr. GG deFiebre:** And so, if someone is pregnant, are they able to take this medication or do we know about safety in pregnancy?

[00:13:37] **Dr. Michael Levy:** We have no idea of the safety of this drug in pregnancy. The precursor, eculizumab seemed to be safe. There were no official studies, but there were no real toxicology studies either. We don't really know of anything that's harmful with Solaris and this one is probably safe too. But until we really know, then officially, we have to say we're not sure. Now with my patients personally, I would weigh the considerations. I would say, "Okay, this drug is doing really well for you. We know NMO attacks even during pregnancy. So, we don't want to stop medications during pregnancy."

[00:14:15] So that conversation would come up. "Do we continue this drug with you? Even though we don't know for certain if it's harmful to you or the baby. Or do we maybe go back to something that we know is safer in pregnancy?" For example, we have a lot of experience with rituximab, that one's not approved for NMO and there's no official study in pregnancy, but we have a lot more experience with it, a little bit more comfort with it.

[00:14:41] **Dr. GG deFiebre:** In terms of this FDA approval for the medication, is it FDA-approved? What does that mean and is it only FDA-approved for certain groups of people?

[00:14:52] **Dr. Michael Levy:** It is FDA-approved and only for certain groups of people who have the aquaporin-4 antibody. The aquaporin-4 antibody could have been tested previously. It doesn't have to be current because some people do fluctuate in their levels, and you might become negative and think that you're not eligible. That's not the case. If you tested positive in the past, you are eligible to receive the medicine according to the FDA label.

[00:15:19] And what the FDA approval does is it puts it in the index form, Copia, that insurance companies use to determine what drugs they going to pay for. They may not always want to pay for Ultomiris. They may say, "Well, here's a lower cost alternative that we want, that we prefer." But, ultimately, then with the FDA approval, it makes it much easier to appeal to insurance companies and get it covered. Also, with government insurance such as Medicare and Medicaid, they are more apt to cover this drug now that it's FDA-approved as well.

[00:15:57] **Dr. GG deFiebre:** You mentioned that this is approved in people who are aquaporin-4 positive. Do we know about the efficacy in people who are seronegative or don't test positive for this?

[00:16:08] **Dr. Michael Levy:** Unfortunately, we have no idea. We don't know if this drug works in MOG. We don't know if it works in seronegative NMO or any other condition. It's so expensive that we don't have a lot of experience just using it off label. Insurance companies are really, really picky and not likely to cover the drug unless you're aquaporin-4 positive. So, we just don't have the experience with seronegative cases at the moment.

[00:16:33] **Dr. GG deFiebre:** Anything else that I didn't ask that you think it is important to mention about this new medication?

[00:16:39] **Dr. Michael Levy:** One of the things the drug company wants you to know is that it is cheaper than Solaris. I'm sure the insurance companies would be happy about that. I believe Solaris was about \$700,000 a year and this is in the order of \$450,000 a year. So quite a bargain, almost half the cost. But NMO is a drop in the bucket for these insurance companies. They're a much smaller population than MS and other diseases. But still, for those of us who are cost conscious, this is a significant savings over Solaris.

[00:17:17] **Dr. GG deFiebre:** Thank you so much for answering these questions. I really appreciate it.

[00:17:22] **Dr. Michael Levy:** Happy to discuss it. Thank you so much.

[00:17:29] **Announcer:** Thank you to our "Ask the Expert" podcast sponsors, Amgen; Alexion, AstraZeneca Rare Disease; and UCB. Amgen is focused on the discovery, development, and commercialization of medicines that address critical needs for people impacted by rare autoimmune and severe inflammatory diseases. They apply scientific expertise and courage to bring clinically meaningful therapies to patients. Amgen believes science and compassion must work together to transform lives.

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