Acute Treatments and Rare Neuroimmune Disorders

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[00:00:01] **Krissy Dilger:** Hello and welcome to the SRNA “Ask the Expert” podcast series. This podcast is titled, “Acute Treatments and Rare Neuroimmune Disorders.” My name is Krissy Dilger, and I moderated this podcast. 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. Our 2023 “Ask the Expert” podcast series is sponsored in part by Amgen, Alexion, AstraZeneca Rare Disease, and UCB.

[00:00:39] For this podcast, I was joined by Drs. John Chen and Elias Sotirchos. Dr. Chen is a neuro-ophthalmologist at Mayo Clinic in Rochester, Minnesota. Dr. Sotirchos is a neurologist and an assistant professor of neurology at Johns Hopkins Medicine in Baltimore, Maryland. You can view their full bios in the podcast description. Welcome and thank you both for joining me today. Can we begin just by explaining what acute treatments are and what the word acute means? Dr. Chen, if you'd like to start?

[00:01:17] **Dr. John J. Chen:** Yeah, so in terms of acute treatments I'm talking about, I think you're assuming for an acute demyelinating attack like optic neuritis, transverse myelitis. And so, typically we're going to start off with high-dose corticosteroids. The most commonly would be intravenous Methylprednisolone 1000 mg over three to five days or another option would be super high dose oral Prednisone, 1250 mg of Prednisone. And these are, we're talking about 50 mg tablets so that's 25 pills at once. And so, that's kind of the acute treatment when you have a patient with a transverse myelitis or an optic neuritis.

[00:01:55] We're trying to decrease inflammation. And then if a patient doesn't respond, then some typical things we can do are plasma exchange or less commonly IVIG. So, these are some other treatments and there's been a lot of literature, mostly retrospective studies suggesting that early steroids or early plasma exchange leads to better outcomes with these acute attacks of demyelinating disease and certainly something we need to explore in more detail. Dr. Sotirchos, any thoughts on your end?

[00:02:31] **Dr. Elias S. Sotirchos:** No, I think that you covered all the options excellent. I think that there are going to be further questions about how to use these and how to implement them and how to escalate essentially from one to the other.

[00:02:43] **Krissy Dilger:** Yes, exactly. So, those are the main ones used after an inflammatory attack. But you mentioned that steroids are typically the first step. So, Dr. Sotirchos, can you explain how steroids work in these disorders?

[00:03:02] **Dr. Elias S. Sotirchos:** Yeah, no, definitely. So, corticosteroids which are what we use here, and we use them at very high doses. So, these doses that are used are much higher than kind of typical oral Prednisone or low-dose corticosteroids that people might receive for things like eczema or other indications.

And so, these are very, very high doses through the IV. And they actually act by many, many different ways. Here, we're administering them specifically for their actions on the immune system.

[00:03:30] So, corticosteroids, our body by the way normally makes corticosteroids. Our adrenal glands make corticosteroids and people have a level that can increase with stress or other responses. And it varies actually throughout the day with our circadian rhythm. But these doses that we're giving are on the order of 100 times or more than what our adrenal glands are normally kind of making. And the goal here is that the corticosteroids can go and switch off or on different kind of pathways within inflammatory cells that are the culprits of this inflammation that is going on and causing these attacks.

[00:04:06] And it can turn a lot of these inflammatory pathways off. So, it's stopping the cells from releasing various kinds of molecules that recruit other inflammatory cells to the site of inflammation. It actually kills some inflammatory cells activating something called apoptosis, which leads to cell death of various types of white blood cells that can be active in that area. And one other thing that's important about corticosteroids is that with these super high doses and just with the way that corticosteroids can diffuse themselves throughout the body, they cross into the brain and into the spinal cord or optic nerve very nicely.

[00:04:44] So, there's something called the blood-brain barrier that kind of seals off the brain and parts of the central nervous system, and steroids are able to easily kind of diffuse through that and they get to the site where we want them to go and have them exert their action.

[00:05:02] **Krissy Dilger:** And Dr. Chen anything to add?

[00:05:04] **Dr. John J. Chen:** No, I think that's again a great explanation for it. With the ONTT, the Optic Neuritis Treatment Trial completed way back in 1980, essentially, they looked at high dose IV Methylprednisolone and as Elias was saying, we're talking about a hundredfold more physiologic than compared to placebo. So, essentially just pills with nothing.

[00:05:32] And they also compare it to kind of low-dose oral Prednisone, talking about 80 mg or 1 mg per kilogram. And it's really the high dose that tends to have the benefit as opposed to a lower dose at 80 mg, which is still pretty high. That's going to be much more than you do for things like eczema. It's not enough. You want these mega-high doses of the steroids for the acute treatment.

[00:05:59] **Krissy Dilger:** You mentioned these steroids are usually administered through IV, correct? What is the difference between the IV versus oral steroids? Is there a benefit to IV steroids over oral steroids or can you expand on that, Dr. Chen?

[00:06:20] **Dr. John J. Chen:** Absolutely. Again, initially, we thought intravenous IV was the way to go because of the ONTT again, finished back in 1990s or 1990. But what we found out is it's not the route, it's actually the dose that matters. So, there's been some recent clinical trials comparing 1000 mg IV to the oral equivalent Prednisone, which is 1250 mg of oral Prednisone and there is no difference. So, it's the dose, the mega dose versus the route.

[00:06:51] The advantage of the IV is it's through an IV very easy to administer but you do need either an infusion center or some kind of mechanism to do that. The benefit of the Prednisone is you could do that at home. Again, the large disadvantage of the Prednisone is, as I mentioned earlier, the biggest tablet we've got is 50 mg tablets. That's 25 pills you're taking all at once. So, that can be hard on patients, can be hard on the stomach that kind of deal.

[00:07:18] **Krissy Dilger:** Yeah, that makes sense. And you mentioned hard on the stomach. What other side effects if any are there from an acute setting treatment of steroids? Dr. Sotirchos.

[00:07:33] **Dr. Elias S. Sotirchos:** So, steroids have a lot of potential side effects. Most of these kinds are more with long-term administration or repeated courses of steroids. Generally, for the short, at least the short courses that are used in acute relapse they're relatively safe. Steroids overall in terms of the risks associated with them so they are somewhat immunosuppressive, of course, because they are eliminating inflammatory cells. So, they can predispose to a higher risk of infection, especially with long-term use so that's one.

[00:08:04] Otherwise, steroids can increase kind of breakdown of bone. And so, they can lead to, this is more of a long-term issue to bone loss. Although sometimes with super high doses, especially in people who might be predisposed or who are elderly, or have osteopenia, so baseline that can lead to issues related to that. Other issues that steroids can cause is the stomach irritation. That's why typically steroids are administered with an acid suppression medication because they can otherwise lead potentially to ulcers in the stomach and gastric irritation otherwise.

[00:08:40] Others are especially with the high dose of the acute phase, but also with lower dose, long term, they can lead to dysregulation of blood glucose, so blood sugars. And so, especially in people who have a pre-existing history of diabetes or diabetes and they're already on medications, they can be sometimes very challenging because when you start very, very high dose steroids that can lead to significant spikes in the blood sugar. And often these patients will need to be monitored and administered more insulin than they would usually take.

[00:09:11] Or insulin even if they weren't on it previously, just in order to settle down the blood sugar from that perspective. Otherwise, long-term administration can also lead to cataracts in the eyes as well. Again, a lot of these are mostly concerned with kind of long-term administration. That's why we generally do not use steroids as much outside of relapses, especially the super high doses. We only do those for a few days at a time because of all of these side effects. And then afterwards, we try to get people on if there's an indication for it on some sort of long-term steroid-sparing medication that can take the place of steroids, but it may have a more acceptable long-term side effect profile.

[00:09:52] **Krissy Dilger:** Thank you. I am sure that's a good consideration for people to have, especially in the long-term setting but it seems like in the short-term setting it seems quite safe.

[00:10:04] **Dr. John J. Chen:** Usually safe. Again, there's some of these impossible-to-predict side effects that can happen with medications with any medication. But with steroids, you can even have strokes to the bones of your hips. But again, these are super rare but impossible to predict. Overall, we still think that the benefit outweighs the risk, but we always talk about potential risk anytime we talk about treatments.

[00:10:30] **Krissy Dilger:** Great. Thank you. So, after steroids, what would be the next step? Would you evaluate if they're working or not? Can you just explain as a clinician what you look for when you're giving those steroids to see what you're going to do next? Dr. Chen?

[00:10:52] **Dr. John J. Chen:** Yeah, so at least for us one thing going back to Optic Neuritis Treatment Trial, it was actually a little bit of surprise they found that the high dose IV steroids led to faster recovery but didn't actually change the ultimate outcome. And so, if you have a run of the male optic neuritis attack like maybe for multiple sclerosis or just something on the more mild end, those IV steroids we're looking for faster recovery or if it's mild, sometimes you can even observe even without treatment in some regards.

[00:11:24] The only drawback is you don't know which patient might have NMO or MOG. One of these words, you probably do need the steroids. So, now we're kind of leaning toward treating any severe optic neuritis attack. I think we've always treated any severe transverse myelitis attack. So, essentially, we're treating with steroids, we want to see a little bit of faster recovery and if it's severe and not responding again, we don't know if that patient might have NMO which sometimes you might need even more steroids like plasma exchange.

[00:11:54] So, if I've got a patient with really severe optic neuritis. We're talking about where they can only count fingers. We give them five days of IV steroids and they're still not turning around. That's usually where we're heading on plasma exchange because I'd like to have some response and then plasma exchange is essentially where we're hooking up the patient either through a peripheral line or a central line, taking their blood and trying to wash out the pathologic antibodies and giving them back plasma to try and get rid of those pathologic antibodies. Essentially, we'll try the steroids first usually and then go to plasma exchange if there's no response.

[00:12:32] **Krissy Dilger:** And that plasma exchange is that just in the disorders that are antibody-based like MOG and NMOSD or is that also used in transverse myelitis, ADEM that kind of thing? Dr. Sotirchos.

[00:12:48] **Dr. Elias S. Sotirchos:** That's a great question. One important issue here is that we don't really know, there haven't been really trials in general. There's really only a single what we call sham control trial where half of the patients with a severe demyelinating attack got PLEX and the other half got a sham procedure and then were crossed over to actual treatment. Generally, it is thought that it may like there's a good rationale and disorders that are associated with an underlying pathogenic auto antibody-like MOG or NMO with aquaporin-4 antibodies.

[00:13:27] However, there is literature about using plasma exchange on multiple sclerosis where at least to our knowledge there is no clear pathogenic autoantibody that's been reported. But so, in that setting, generally, I would say that this is an approach that is used regardless often of the underlying disease. And the other thing is also that when patients are coming in, especially for the first time, we often really don't know because you send these antibodies, they can sometimes take a week or two to come back.

[00:13:56] When you're making this decision to use PLEX or not, you're kind of taking into account the severity, you're taking into account whether you think it might end up being one of those conditions, but you don't really know. And I also have used plasma exchange, I mean, MS typically attacks at least are often less severe than MOG and NMO. Although we don't know if long-term MS can be associated with severe disability due to progressive disease and other underlying features, but often MS relapses can be quite severe, quite variable.

[00:14:25] And we often have used PLEX in our mind a good response from the patient. So, I would say that it can be used potentially regardless of the underlying ideology. Although I still think that we need to do more studies in order to better understand which subgroups may benefit more and also what the timing is to implement this intervention because there's a lot of variability and practice. Some people might do PLEX four weeks after the patient first came in and give the steroids a full month to see if they work.

[00:14:58] Some people might say, okay, we're going to go to PLEX day one together with the steroids. And I have to say, we don't really know is the short answer here. There's a lot of variability in how people practice. And while PLEX is generally relatively safe, it is a procedure that requires often insertion of what's called the central venous catheter, which is a catheter into one of the large veins typically in the neck. That procedure can be associated with infection, with bleeding, with severe complications very rarely. Generally, it is safe.

[00:15:36] And then the procedure itself can predispose somebody to bleeding complications, even allergic reactions can sometimes occur, and another issues, low blood pressure during the procedure. So, while it is kind of something that you could say, oh, well, let's just do it and see what happens. I mean, there are significant potential risks associated with it as well as costs and potentially having to keep somebody in the hospital for a prolonged period of time. A lot of logistical issues that go into that.

[00:16:04] **Krissy Dilger:** That makes sense. Is there anything that's known about why PLEX works on these disorders? What specifically is happening and why it works for some people and not others, Dr. Chen?

[00:16:22] **Dr. John J. Chen:** Yeah, it's hard to know exactly how it works. Again, the easy answer is it's removing pathologic antibodies but as Dr. Sotirchos said, it seems to work for multiple sclerosis as well, which isn't thought to be primarily an antibody immunity process. So, it's probably had multiple ways that plasma exchange is helping but certainly, it does seem to. There's unfortunately one randomized clinical trial that shows that it worked.

[00:16:54] But we've got a lot of retrospective observational studies suggesting that early plasma exchange leads to much better outcomes. Again, the exact mechanisms are still a little unclear, but it seems to be associated with better outcomes. I think we really do need more randomized clinical data to kind of prove that it truly works. One in what settings, what diseases and the timing I think are all critical to kind of getting a better understanding of how plasma exchange works.

[00:17:28] **Krissy Dilger:** Thank you. And so, after you decide we're going to administer plasma exchange or not, I guess what would be the next step? Is there IVIG or anything else? And how do you evaluate I guess how the patient is doing? Dr. Chen.

[00:17:49] **Dr. John J. Chen:** Yeah, usually with plasma exchange we're going to give them five treatments or seven treatments every other day. That's kind of the standard treatment. To me, that's usually our biggest gun. So, usually after plasma exchange, I wait and see how they do. Occasionally, you can add on IVIG acute treatment with IVIG as well to see if that might help some more. But it's hard to know if that's truly helping or if that's just a plasma exchange that's kind of taking more time to have an effect. Again, usually in a setting of severe optic neuritis it's going to be IV steroids, then plasma exchange or sometimes both together if it's very severe and I'm really suspicious of NMO and then I'm going to give it time and hopefully they turn around, but certainly acute IVIG treatment is certainly an option in some patients too.

[00:18:47] **Krissy Dilger:** Dr. Sotirchos anything to add?

[00:18:50] **Dr. Elias S. Sotirchos:** No, I agree completely. I think that it's always very uncomfortable as a clinician to see that you've done steroids and PLEX and patient is not improving. I mean, we know that with longer time out from the optic neuritis potentially. Again, and optic neuritis can recover like slowly on its own as well. Like that's what the Optic Neuritis Treatment Trial showed us that even the people who didn't get there eventually at a year out were kind of similar to the people who got steroids.

[00:19:20] So, while there's this temptation to kind of throw everything at the patient and try to solve it as best you can in the situation, I think we have to be aware of the risks associated with kind of escalating to more and more sometimes where the temptation to let's do another pulse of steroids. And again, steroids, as I said, relatively safe, but you can have complications including rare complications that Dr. Chen mentioned. So, I think that this potential of doing more can have harms. I mean, the IVIG question I think is interesting.

[00:19:52] It's one of those things that there's not clear evidence to necessarily support doing PLEX and then doing IVIG afterwards. The only situation where I may consider that is in patients where I'm suspicious or known to have MOG antibody disease. It is there I might start the IVIG and then actually continue it as a maintenance treatment for relapse prevention potentially. So, I might try to get a dose loaded after the PLEX in order to kind of and then plan with the plan though to continue it then as a maintenance treatment in a patient.

[00:20:30] **Krissy Dilger:** In terms of timeline for acute treatments, is there a specific time cut-off where you would say we're not going to administer any more treatments it's been too far from the attack? Do you have to look for markers of inflammation still? What's the process for that? Dr. Sotirchos?

[00:20:54] **Dr. Elias S. Sotirchos:** Yeah, it's a great question and I think it's difficult sometimes. I mean, sometimes I do use some information for whether there is ongoing inflammation or activity that could kind of help guide me for whether in rare cases to do maybe a second round of steroids or something like that. Like situations where I might consider that is if let's say the patient had an initial improvement, but then worsened again. Then you could argue that maybe this is kind of a second relapse or a worsening of the player rather than kind of the natural history of worsening and then getting better after treatment.

[00:21:33] So, in that situation where I'm kind of convinced that there's been kind of a setback, it might consider like retreating or escalating or something like that as you mentioned. So, that's from a clinical perspective I would say. From a kind of para-clinical perspective of trying to use tests or markers or things like that. I mean, generally, things that might aid is kind of a repeat MRI for example, but I have to say the enhancement often can persist even with a kind of just a normal attack which is improving.

[00:22:03] And so, it's difficult to kind of put a lot of weight on that. But let's say that the lesion looks worse, or it's expanded especially in the spinal cord, or you have a new area that's enhancing that wasn't enhancing previously, one might argue there that maybe there is kind of some process that is still present that maybe I need to intervene upon separately. And then there could be very rare cases. This is not very typical with transverse myelitis where patients are having kind of these stuttering courses and worsening and multiple enhancing spinal cord. And one last option that we didn't mention previously and very rarely we may use.

[00:22:40] And I would say that even for this the data is certainly not there would be something called IV Cyclophosphamide, but that is also a kind of a treatment with even more risks than the ones that we've already discussed. That would be really mainly considered for transverse myelitis that is severe and worsening but there is evidence that I mean that can cause a whole host of side effects. It can completely suppress the kind of bone marrow production of white blood cells for months and severely immunosuppress someone.

[00:23:08] And even some literature that it can affect neural precursor cells in the central nervous system and affect the healing process as well. So, that's something that I generally do not use. Although I know that some people may use that and historically, it was used somewhat in refractory cases of transverse myelitis.

[00:23:28] **Krissy Dilger:** Got it. Thank you.

[00:23:30] **Dr. John J. Chen:** And in terms of, how late is too late? It's always a good question. We recently did a multi-center international study where we looked at and this is retrospective about 400 optic neuritis attacks treated with plasma exchange. And as all these observational studies suggest earlier is better, but we did have some patients that were treated one month out, six weeks out and some patients still had what looked like an improvement of a response to it even as late as a month, six weeks.

[00:24:10] So, if you've got a patient with a bad bout of optic neuritis or transverse myelitis and you're seeing them now, six weeks later or a month later, can you do plasma exchange and maybe potentially squeeze a little bit more improvement out? I'd say probably chances are it's not going to come back to normal but maybe it might prove. And then we're looking at three months out, then the chance of the recovery from plasma exchange is made pretty low. I know pretty unlikely, and six months would be a definite no.

[00:24:32] So, I think certainly within six weeks I would probably consider doing plasma exchange if they haven't recovered with IV steroids. Obviously, some of the studies are suggesting that the earlier the better, but it's hard to know is that the natural history of disease or is the plasma exchange truly helping.

[00:24:49] **Krissy Dilger:** Got it. Thank you. And when we're talking about these treatments, are there any age considerations, both sides of the spectrum too young, too old for any of these? Dr. Chen.

[00:25:05] **Dr. John J. Chen:** For plasma exchange a lot of it has to do with access to the veins. And so, in an adult who's very healthy sometimes we can actually do it through a peripheral vein instead of requiring that central vein through central vein access which increases the risk of the procedures. That certainly weighs in. Otherwise, there are some very young oral patients that can get plasma exchange. It's access to the venous system. So, it makes it a little bit trickier.

[00:25:34] Whereas with IVIG, that's typically going to be just through the peripheral IV. So, sometimes in kids will lean more toward IVIG just to avoid having to worry about access through the central vein for the PLEX. But certainly, there's a lot of centers that do a lot of PLEX even in young kids.

[00:25:54] **Krissy Dilger:** Thank you. And steroids are safe for all ages?

[00:26:00] **Dr. John J. Chen:** That's a good question too. So, with kids obviously, they're growing and a lot of changes their bone development. So, we want to limit that as much as possible in children. We also want to be weight-based because 1000 mg in a 25-year-old kid is going to be a lot of steroids. So, it's going to be weight-based when you're young. And then when you're older there's a little bit more slightly higher risks of steroids as well.

[00:26:30] And so, again, it's certainly a consideration a little bit something more we might talk about, but we'll still do it at all age ranges, there's just a little bit higher risk at the low end and the high end. At low end for kind of development. High end for maybe a cardiovascular kind of reasons.

[00:26:53] **Krissy Dilger:** Thank you. So, these are the main treatments that we've gone through and you kind of touched on research that looking forward might give us some more ideas into how these treatments work, who we should use them on, when time frames, which diseases all of that. Dr. Sotirchos, would you mind talking a little bit about that? There's anything in the pipeline or anything that you're looking forward to in that realm?

[00:27:27] **Dr. Elias S. Sotirchos:** And I think that there's always interest in many different kinds of neuroprotective or remyelinating therapies to be studied. I think that the pipeline, I mean, there are many kinds of agents that have been proposed and studies that we've been aware of, including studies that unfortunately failed or studies that have shown encouraging results. One example of a failed study was a drug called Opicinumab that targets a factor called LINGO-1. It was actually tested in a clinical trial in optic neuritis to see this actually targets a target that might be inhibitory to remyelination.

[00:28:13] And so, the thought was that if we could enhance remyelination and optic neuritis that that might lead to a better outcome. Again, these studies have been relatively small. It was a phase two study. Some may say that maybe the time from onset may have been a little bit too long potentially for the drug to work. And there are some concerns that maybe that interfered the outcome. But I think that I've seen other things mentioned, like there's a study of a gold nanoparticle treatment, not necessarily in acute optic neuritis, but I think they have a trial on both acute neuritis and chronic optic neuropathy.

[00:28:50] So, there are a variety of things that we have seen in the pipeline and things that have been proposed. Nothing that is currently to my knowledge and at least a very advanced phase of development in phase three. But I think that one thing in my mind that is important is that we have all these treatments as we mentioned previously, and we still don't know how to use them actually. And so, like we keep coming back to these data, we really keep quoting a single randomized controlled trial from the early 1990s to kind of support everything that we're discussing about steroids and optic neuritis.

[00:29:24] Transverse myelitis we don't really have treatment... even that it's like a basic study like that is good quality and large in order to support what we're doing. There was an attempt to do an IVIG trial once in the UK and unfortunately, there was issues with the recruitment that led to that trial not being actually completed. Unfortunately, they were only able to recruit a handful of patients. And so, my focus in terms of, I mean, right now, and this is a study that we're discussing with Dr. Chen and designing together is to potentially see how we can better understand how to use the treatments that we have now and ways to optimize their treatment.

[00:30:04] One other thing that we didn't mention about plasma exchange is that while we bring it up, it's not really that easily accessible to everyone. Generally, plasma exchange is going to be performed at large tertiary referral centers. It's not something that's going to be very easily accessible to everybody even across the United States, even less so in developing kind of countries. And so, I think that we need to understand better when to implement these approaches, how to implement these approaches in order to kind of be better able to treat.

[00:30:39] **Krissy Dilger:** Thank you. Dr. Chen, anything you'd like to add?

[00:30:43] **Dr. John J. Chen:** Yeah, I completely agree. Just trying to get a better handle on plasma exchange I think is very important in terms of timing and which patients would benefit. There's a lot of saying in neurology and ophthalmology that time is brain, time is vision. And again, this is all based on retrospective studies suggesting that early plasma exchange is better. But again, it's not randomized. And the problem is if you've got a patient who comes in with pretty bad vision, count fingers vision, even without treatment they may recover. So, if you gave them plasma exchange early on, did they recover because they would have recovered anyway, or is the plasma exchange is what turned them around?

[00:31:21] We've all seen enough cases of plasma exchange really having miraculous recovery. So, we do truly think it helps but until we have a randomized trial proving it it's hard to know. Again, going back to the 80s and early 90s when we did the Optic Neuritis Treatment Trial, I think the vast majority of people would have thought that IV steroids significantly led to better outcomes. And surprisingly, it really didn't, all it did was speed up recovery. And so, if we have a treatment like plasma exchange that we think works, but is actually potentially a little more, it is more aggressive than IV steroids, we want to know it works, prove that it works before we're administering it to a larger and larger number of patients.

[00:31:57] And yet, it's being used more. We actually recently looked at a large national database and at least for optic neuritis, it's gone up and up and up in terms of its usage fivefold over the past 10 years in terms of

usage for optic neuritis. So, it's being used even without the evidence, we just need the evidence to prove it works or if it doesn't work to actually only use it for patients that need it like a patient with NMO.

[00:32:33] **Krissy Dilger:** Thank you so much. That's all the questions I have for you. I really appreciate you joining and sharing your knowledge and expertise and dedicating your time to this. I hope some of this research we talked about would go forward in the future and we can regroup again not too long from now and talk about the new knowledge we have.

[00:32:59] **Dr. John J. Chen:** Wonderful. Well, thanks so much. It's a pleasure to talk to you today.

[00:33:03] **Krissy Dilger:** Thanks.

[00:33:04] **Dr. Elias S. Sotirchos:** Thank you so much. It was a pleasure to join.

[00:33:08] **Krissy Dilger:** Thank you to our 2023 “Ask the Expert” podcast series 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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