Plasma Exchange for Acute Inflammatory Demyelination

How We Got Here and Where to Next?

You can view this presentation at: youtu.be/_uhlkK_8xvA

[00:00:04] **Dr. Benjamin Greenberg:** Our next speaker couldn't be with us in person and recorded a video, and before you see the video I just want to put some context to what you're about to see. So, we're celebrating the 30th anniversary of the start of this organization. It's been 30 years, and a lot has changed over 30 years. And 25 years ago, at a meeting, Brian Weinshenker presented for the first time publicly the first study of plasmapheresis in these disorders. So, it's been 25 years and what Brian's going to talk about is, is what's changed and where do we go next.

[00:00:39] And since they made the mistake of letting me have the microphone, I'll just share one story. So, when I left Baltimore and I came down to Dallas and I'm newly trained, ready to go and young and excited, and I did my first consult ever at Dallas Children's for a young man with transverse myelitis and I said, "Well, let's do plasmapheresis." They looked at me as if I had grown a second head and they said, "Why would you do that?" And I said, "Well, that's what we do." And they said, "No, no, no. We do IVIG." And I said, "Oh, come on, it'll be fun. Let's do plasmapheresis."

[00:01:15] And so for about a year, year and a half, we were doing plasmapheresis. I got accused of owning stock in plasmapheresis companies. And then we had our first six-month-old admitted with quadriplegia on a ventilator through transverse myelitis, and I said, "Let's do plasmapheresis."

[00:01:32] And I remember I'm driving away from the hospital, my phone rings and it's one of the surgeons at Children's who I've gotten to know because we needed a central line, a special IV for the plasmapheresis, and he said, "Ben, how are you doing?" I said, "Great." And he said, "Listen, we've got a good run here, you and I, all these central lines for plasmapheresis, but now you want me to put something the size of angel hair into something the size of spaghetti, are you sure you really want plasmapheresis?" And I said, "Yeah, you're going to do a great job, thanks." And I got off the phone.

[00:02:02] And he took the six-month-old and it was about a few years later that we published the series on over a hundred exchange treatments over a couple dozen children under the age of one with plasmapheresis, something that was just not being done at the time. And it's made a huge difference in how we approach these conditions, not just transverse myelitis but other conditions. And so, what Brian did 25 years ago was really fire the starting gun for all of us to think about this approach to treatment very differently, and I'm

looking forward to hearing his video on where we are now and where we're going next. So why don't we cue the video for Brian Weinshenker?

[00:02:44] **Dr. Brian Weinshenker:** Hello, everybody. My name is Brian Weinshenker. I'm a professor of neurology at the University of Virginia. I've been at the University of Virginia for the past two years. But prior to that, for 30 years, I had worked at the Mayo Clinic in Rochester, Minnesota, which is where I conducted the research that I'm going to be talking to you about today.

[00:03:10] I'll be talking to you about a very important rescue treatment that we have for patients with transverse myelitis. I know that the former name of this organization was the Transverse Myelitis Association, but in fact it's a treatment that can be used in a variety of situations for acute attacks of demyelinating disease. And we don't have enough time to cover every detail, but I'll try to talk to you about how we got here and what I see is the next challenges regarding this topic.

[00:03:53] These are my disclosures, none of which are directly related to this topic or use of plasma exchange or apheresis for acute demyelinating disease. And let me start by saying that for me this is really a trip down memory lane because I gave this talk at what I believe was the inaugural meeting of patients, physicians were part of the Transverse Myelitis Association, now the Rare Neurologic Disease Association. But although there is new names, a lot of the players were similar. Sandy Siegel was one of the leaders. Hi, Sandy. And the Johns Hopkins group at that time, Doug Kerr was the leader, were dominant players in the area of transverse myelitis and had a strong role in the association.

[00:04:55] But we had just completed a three-to-four-year clinical trial of plasma exchange for patients with acute attacks of demyelinating disease, and I was preparing to give the nature presentation of the results for the first time at the ECTRIMS Conference in Basel. But just prior to that meeting, the Transverse Myelitis Association was meeting, and I offered Sandy that I would do a preview of the results. And so, this was really the first presentation of this, what has turned out to be a very important clinical trial.

[00:05:42] Back in 1999, we had a very poor understanding of idiopathic demyelinating diseases. We really classified them entirely based on symptoms, the time course, and the severity. And some years before, basically, just trying to put together some diagram that gave some meaning based on those considerations, symptoms, severity, and time course, I came up with this diagram and you can see and I'll concentrate on transverse myelitis, many of the patients in the clinical trial had transverse myelitis. It occurred in a couple of different of these groups, most patients had mild partial transverse myelitis, maybe numbness in one limb that spread up onto the torso and that may have been their only symptom. So, it was relatively non severe, presented acutely. But we recognize that some patients with transverse myelitis would have relapses and some of those would be very severe.

[00:06:56] And a key other research in which I participated came up with the first criteria that we felt could differentiate one form of demyelinating disease, neuromyelitis optica. And in fact, we learned that most patients with relapsing myelitis, even if they didn't have optic neuritis, had neuromyelitis optica, had a separate disease. And this turned out to really dovetail with the whole story of plasma exchange because we found -- I would say, our group at Mayo Clinic discovered by Dr. Vanda Lennon, who was working on the serum of some of my patients, she discovered an antibody, which we found reacted to a protein called aquaporin-4.

[00:07:49] And this really turned the whole area of idiopathic demyelinating diseases around. We have now discovered a couple of different antibodies capable of causing acute demyelination, the major ones being to aquaporin-4 and another one to myelin oligodendrocyte glycoprotein or MOG. And this has allowed us to classify these diseases better, prognosticate, understand their pathogenesis, and maybe give some insights

into how plasma exchange was working. But this was the current state of affairs. We didn't know how to distinguish these diseases. And in this plasma exchange study, we included any patient who met the category of an idiopathic demyelinating disease.

[00:08:46] So, many people are being critical of the study and said, "Well, you included a heterogeneous group of patients." The reality is, in the late 1990s, the thinking was that all of these conditions were related and that maybe what we call neuromyelitis optica now was a severe form of MS. The differences were not appreciated. But one thing that we did appreciate is that in some patients, they would experience acute very severe attacks of disability. We recognize that most patients with demyelinating diseases, the attacks were mild and would recover on their own, but some patients would have very severe attacks that could lead to severe permanent disability. And some patients with certain syndromes, including neuromyelitis optica, commonly have these kinds of severe events.

[00:09:41] And although the majority of subsequent research in demyelinating disease very rightfully concentrated on how to prevent attacks, for those patients who were having an acute attack, their key issue was, "How do I get over this disability?" Especially those patients who had the severe attacks and did not seem to respond to the standard treatment, which was corticosteroids.

[00:10:10] What was the background knowledge of plasma exchange at the time? In fact, it had been tried in patients with demyelinating disease. As I reviewed the literature back in the mid 1990s, there had been 12 reported series, the first by Dr. Peter Dow, who was at Northwestern University. Sadly, Dr. Dow just recently died in 2021, but his obituary listed his observations with plasma exchange in demyelinating diseases as one of his key accomplishments. But these were retrospective series or small prospective series and included mainly patients with progressive forms of MS and a few patients with acute demyelinating disease. But as I reviewed the literature, it became clear that the really dramatic improvements occurred in patients who had acute attacks of demyelinating disease.

[00:11:15] In fact, there had been one previous randomized clinical trial in patients with acute attacks of MS and I would say that the results were largely negative. But it was a very complicated study. They took patients with all degrees of severity of attacks, most of them fairly mild. They treated all patients with ACTH and cyclophosphamide, and on top of that, randomized them to get plasma exchange or fake exchange, the placebo or sham exchange.

[00:11:49] And what they showed in their study, and you can see the proportion of patients that improved, that over time gets better and better, when you consider all patients and compare in yellow the true exchange to the sham or fake exchange, there was essentially no difference. But when you looked at the patients with relapsing-remitting disease rather than progressive disease, I would say similarly there was very little difference, most patients recovered, even the patients who were getting the sham exchange in green, most of them recovered, and maybe there was a slight benefit of plasma exchange, but it really wasn't convincing and no one was picking up this treatment or using this treatment in their patients with acute attacks.

[00:12:43] The real inspiration to me was this work that had been reported by my senior colleague in MS at Mayo Clinic, Dr. Moses Rodriguez, who published a paper that was actually accepted without review by neurology. I found this rather shocking, but at the time the editor felt that this was a very important piece of work. He reported six consecutive patients with very severe deficits, all were paraplegic, hemiplegic or quadriplegic.

[00:13:19] Additionally, two were aphasic and two were ventilator-dependent. They were probably NMO patients. We know that acute attacks in the cervical cord can lead to ventilator dependence. So, he took the

most severe of the severe, treated them with between 6-9 plasma exchange treatments, no concomitant or confounding treatments like immunosuppression, and he found that five out of six had dramatic improvement with a change on the EDSS score, median of 4.5, a range of 0.5-6.0, and the improvement, time till he saw improvement was very rapid, significant improvement within four days.

[00:14:04] This led us to do the study that I referred to before, which was a randomized clinical trial of plasma exchange in acute CNS inflammatory demyelinating disease. It was published in the Annals of Neurology in 1999. The key design elements of this study that I think differentiated it from the Wiener study are listed here, and I think all of these were really very key. Firstly, it was randomized as Wiener's study was. It was sham controlled, so the procedure was done behind a curtain, so the patients did not know what they were receiving, the investigators didn't know what they were receiving.

[00:14:51] In fact, the machine took the blood, separated it into the plasma, and the blood cells removed the plasma. But in the case of sham, it remixed the patient's plasma with their cells, whereas in the true exchange, the patient plasma was removed and replaced with an artificial plasma. In all other respects from what the patient would see and experience, there was no difference, and it was nearly impossible for patients to know what they were receiving. And when we asked patients to guess, except for the ones who improved, who guessed they got active exchange, really it was no better than a coin toss in terms of them knowing what they received.

[00:15:37] We included patients with all types of inflammatory demyelinating diseases. As I mentioned, we didn't really have a good way of differentiating neuromyelitis optica and acute disseminated encephalomyelitis from multiple sclerosis, but we did enroll all of them, and we chose what we felt were informative patients who had a severe deficit for at least three weeks and failed corticosteroids. We weren't interested in trivial improvement.

[00:16:07] So for our outcome measure, the key definition was moderate or marked improvement. Now we had many details and scales to determine whether they met that criterion of moderate or marked improvement, but we looked for robust outcomes. And we didn't, unlike the Wiener study, use ACTH, cyclophosphamide or any other treatment. The only treatment they received was plasma exchange, real or fake, in other words, sham exchange.

[00:16:42] And a very important part of this study was - and it turned out to be very informative - was that it was a crossover study. Patients who failed after two weeks of treatment, either getting real or sham, crossed over to the other treatment. Neither the investigators nor the patients knew what they had or what they were crossing over to. All they knew is whatever they didn't get in the first two weeks, they were going to get in the next two weeks.

[00:17:10] Here were the key results. 22 patients, 11 were randomized to real and 11 to sham exchange. Of those who were randomized to real, 5 out of 11 were successes, clearly 6 did not improve. And those who got sham, we had only one success out of 11 on the sham treatment. The patients who failed crossed over, and none of the patients who crossed over from real to sham improved. Conversely, of those eight patients who failed sham exchange and crossed over, three out of the eight, and these were the most informative patients we had seen no improvement for two weeks. And as soon as they crossed over, we saw substantial moderate to marked improvement. And all patients were followed for six months.

[00:18:15] This shows the way we analyzed the data; this was a very innovative study with an innovative crossover. So, there were three possible outcomes. Either the patients succeeded in the first two weeks,

and they were finished, or they failed and crossed over to sham, or they failed both treatment periods, both the first two and the second two weeks. And there were two treatment assignments, active treatment first or sham treatment first.

[00:18:45] If you look at the distribution of patients, perfect. If we had a perfect treatment that was always effective, the results would have been 6, 0, 0, and 0, 6, 0. So that would have been -- sorry, it should have been 11, 0, 0, and 0, 11, 0, that would have been perfect. You could see it wasn't perfect. There were some patients who failed both treatment periods, but the distribution was clearly statistically significant. All of the patients who seem to get dramatic improvement, except for one, were receiving true exchange.

[00:19:30] Another way to summarize it is 42% of the times that the patients were getting active plasma exchange, they improved. Only 6% of the time that they were getting sham treatment. Thanks to, I would say, the media department at Mayo Clinic, which recognized this as an important and great story, good story, we got a lot of media coverage and I'm just going to show you, I think it indicates the gravitas that these results had with this video.

[00:20:07] **Charles Gibson:** And a new treatment for a terrifying illness, bringing movement to some people who are paralyzed.

[00:20:19] **Peter Jennings:** From ABC News World Headquarters in New York, this is World News Tonight with Peter Jennings. Sitting in tonight, Charles Gibson.

[00:20:28] **Charles Gibson:** Medical news, a promising study out today about a terrifying type of illness. Multiple sclerosis and central nervous disorders affect hundreds of thousands of Americans. They can lead to paralysis, slurred speech, and vision problems – and there is no cure. But today, researchers at the Mayo Clinic said they have developed a treatment that may be able to help people with the most severe cases. ABC's Jackie Judd has the details.

[00:20:54] **Jackie Judd:** This is Andrew Grant after an acute attack of multiple sclerosis. Completely helpless, unable to move.

[00:21:03] **Faith Grant:** I think the darkest moment for me was when Andy became totally immobile.

[00:21:08] **Jackie Judd:** This is Andrew Grant two years later. What happened in between was an experimental treatment called plasma exchange. Grant and 18 other victims of severely damaged nervous systems had blood removed. A machine isolated the cells and extracted the plasma, the liquid part of the blood. Plasma from healthy donors was purified until it contained just a single protein called albumin. The donor plasma and the original cells were then mixed and put back into the patients. This exchange was repeated seven times over a two-week period.

[00:21:45] **Dr. Brian Weinshenker:** We had a robust major effect in 40% of the patients. (Question to a patient) - Can you wave goodbye?

[00:21:52] **Jackie Judd:** In those who were helped, the effect was almost immediate. On day 14, Grant could get out of bed and walk with assistance. Six months later, he could walk on his own.

[00:22:03] **Andrew Grant:** When I felt my foot move and I've seen down, seen it, put a big old smile on my face.

[00:22:12] **Jackie Judd:** Doctors are not entirely sure why the treatment succeeded. An early theory is that the patient's plasma contained harmful antibodies, which allowed the disease to progress at a rapid pace, and that the replacement plasma stopped that process.

[00:22:27] **Dr. Brian Weinshenker:** I think it's just dramatic how just touching the plasma alone without doing anything to the cells can affect an immediate major recovery from a neurological disability.

[00:22:37] **Jackie Judd:** For now, doctors say this treatment is only for the most acutely affected victims who have not found relief from the traditional treatment of high doses of steroids, but it is promising. For Andrew Grant and for the other patients, life is so much better.

[00:22:53] **Andrew Grant:** Had fun?

[00:22:54] **Jackie Judd:** Jackie Judd, ABC News.

[00:22:57] **Charles Gibson:** Three other points. Researchers have extended the testing beyond the original group and so far, have had the same rate of success. In order to get a better understanding of why this treatment works, researchers have saved the old plasma of the successful patients and are trying to figure out now what they may have had in common that caused the disease. And as of now, this treatment is for people only with the most severe cases, there is still much to learn. And for more on the treatment, you can log on to our website, abcnews.com.

[00:23:33] **Dr. Brian Weinshenker:** Well, it's nice to have been kind of a movie star for a couple of weeks. I will say that when this came out, it was met with a lot of controversy. And in part, I think because in spite of a lot of efforts that we made to emphasize this was for patients with acute attacks of MS, many patients who had been in wheelchairs for many years with advanced progressive MS started calling their doctors and asking for plasma exchange. And understandably, this created a big bit of a backlash, but as always, the truth eventually comes out.

[00:24:20] And one comparison that I wanted to make is the difference between the Wiener study and our study. I would say that the Wiener study, as I said, was largely negative. One might interpret it as having shown a slight benefit, but I think some key design issues, particularly the fact that we require patients to have been treated with steroids, we didn't give them any confounding treatments, we looked for very robust outcomes, and we had a crossover study. I think those were critical to the success and the fact that we found what I would say is a very convincing effect. And you'll see the importance at the end of my talk of the fact that we did this in what I consider a very convincing way because to repeat this and confirm this with another study has proven exceptionally difficult.

[00:25:25] Now since our study was published, there have been innumerable prospective and retrospective studies of apheresis. And I would say that virtually everyone that had even a fairly small but adequate sample size has confirmed that apheresis in about 50% of patients can result in major improvement. I've summarized some of the early ones there, but I filled up several slides full of studies that have confirmed at least using retrospective and prospective studies.

[00:26:09] And we've tried to look to see since not all patients respond, can we predict who's going to respond? And one of the early observations we made was that those patients who had flaccid areflexic limbs, and those are probably patients with severe axonal injury, at least I'm guessing that they are, may have neurologic deficits that cannot improve with apheresis. And that has seemed to be a fairly convincing and robust indicator of patients who might fail, those who are flaccid and areflexic.

[00:26:54] There is a classification of MS into four different categories, really two categories. The first, type 1 and type 2, and this is a category that Professor Hans Lossman and Claudia Lucchinetti have developed, have myelin targeting immunity, either macrophage-mediated or antibody-mediated with complement activation. The other two patterns, there seems to be a primary problem in the oligodendrocyte, and the myelin degenerates really as a dying-back phenomena or an oligodendrocyte degeneration.

[00:27:42] In an important study reported by my colleague, Dr. Mark Keegan, from our group that was published in The Lancet in 2005, separately Dr. Lucchinetti classified biopsies from tissue from each of these patients who are undergoing apheresis. It might not have been from the spinal cord in the case of transverse myelitis, may have been from another lesion, but it seems as if most lesions have the same pathology, according to research done by Dr. Lucchinetti. And it was clear that only patients with the type 2 pathology were responsive, whereas patients who had pattern III or pattern I were typically failures. So, this was done separate from knowledge of how the patients did, there was a separate rating by Dr. Keegan and colleagues of whether success clinically occurred and what the pathology showed, and there seemed to be an excellent correlation.

[00:28:56] There was one subsequent randomized sham study for acute attacks of multiple sclerosis that was conducted in France by Professor Bruno Brochet. It was reported in 2020. This was again a randomized sham-controlled study. This was really the first attempt to confirm using a proper randomized study. And the results were somewhat disappointing. So, there was a very slight statistical difference, especially in terms of the proportion of patients with optic neuritis who had full improvement.

[00:29:41] And looking at disability, there did seem to be some benefit of those who got plasma exchange compared to sham using an added composite functional score. But in terms of EDSS, the results were only significant at month 1 and not month 3 and 6. So, really not the same kind of robust outcome that seemed to be unequivocal that we had reported.

[00:30:16] But the problems were substantial in this study. They had intended on recruiting twice as many patients, so recruitment was very incomplete. And what became very clear is the majority of physicians participating in the study were unwilling to randomize many of their patients, especially the most severe patients in this study. So, the patients who were included had relatively modest disability. It only included patients with MS and not patients with neuromyelitis optica and certain inflammatory disease subtypes that have the highest rate of poor response. And what they observed, similar to the Wiener study, was a very high rate of spontaneous recovery. Many of the patients who were receiving sham recovered very well. They had a less robust primary outcome, and this was not a crossover study.

[00:31:19] So, their conclusion was the study did not establish a difference of at least moderate improvement. They did point out the lack of power and the unexpectedly good outcome in the control group. So, it left me at least looking at this study rather disappointed. The study was published in the Journal of Clinical Apheresis. Probably has not received a lot of attention, at least I don't know of many colleagues who are aware of this study, but this was an opportunity to confirm it.

[00:32:00] And so this brings me really to the end of my talk and the question of, where do we go next? What has happened is I have stayed relatively conservative and recommend apheresis after a trial of corticosteroids. I don't believe that we need to wait two weeks. Typically, I wait three or four days to see if there is some clear evidence that the patient is responding, but many colleagues based on retrospective data actually, in a sense low-quality, unconvincing data have suggested that we should be treating patients from day one, and in fact, some would say you should treat with apheresis before corticosteroid. So, I don't know whether that's right or wrong, but I have stayed fairly conservative in my recommendations at this point. I think it's a point up for debate.

[00:33:00] We have some new agents that are very promising. We have ways, because the biggest problem with apheresis is the cumbersome nature of the procedure and risk of sepsis and the need for lines. We have a way of doing essentially a chemical plasma exchange with drugs that are inhibitors of the neonatal Fc receptor that fairly rapidly remove the immunoglobulin from the circulation. But even though they do this rapidly, the kinetics are not such that it is a substantial competitor of plasma exchange and make it a credible acute rescue treatment.

[00:33:41] So, at this point I think this is a promising form of treatment that can be used in many situations where we currently use apheresis, but as an acute rescue treatment, I'm somewhat skeptical that it's going to be as effective. Certainly, there are other effectors of injury and inflammatory pathways that are activated by antibodies binding with their target antigen complement activation. We have complement inhibitors. We have some antibodies for some diseases that are being explored, like aquaporumab, which binds to the aquaporin-4 with high avidity and could potentially block pathogenic antibodies from binding and causing all the downstream effector mechanisms like complement activation. We have inhibitors of other downstream effector mechanisms.

[00:34:43] Do we have enough data based on the study we conducted to champion plasma exchange and even suggest it? Or do we need further randomized studies? I think the trial design is critical, but when you do a good job and make a study very convincing and people see it with their own eyes in treating certain patients, it becomes very difficult to mount another randomized trial, especially in the same informative way that we did in waiting three weeks before we randomized patients. We did that in our clinical trial because people weren't using plasma exchange, and we felt that we had to choose a very informative population.

[00:35:33] But can we mount a similar trial again? You've seen one attempt in that Brochet study that was published in the Journal of Clinical Apheresis to repeat the experiments. And I would say that the results are equivocal, and I think one can argue that if you cannot do it well to confirm or refute the results, should you be doing it at all?

[00:36:04] So, I've taken you down my trip in memory lane. It's certainly been an interesting journey for me with plasma exchange and I think it's led us to a general interest in antibody-mediated diseases in the central nervous system and how we can exploit rapid removal of antibodies as a treatment. I am, of course, very gratified with each individual patient that I've treated with plasma exchange who's responded to see this. I think people have been convinced one patient at a time because it is a very dramatic benefit that we can see in some patients.

[00:36:48] So, thank you very much for indulging me and allowing me to give this talk. I'm very sorry that I could not be with you tonight. I gather that some of my colleagues are going be able to take some questions, and I wish you a very good meeting. Thank you.