“Benefit of Long-Term Therapeutic Plasma Exchange Treatment in a Patient with CREST Syndrome (Limited Systemic Scleroderma): A 21-year Success Story”

This is the title of a new case study that was just presented as a research poster at a medical conference over the weekend. The abstract for that poster is published in the September issue of the research journal “Transfusion”.

This will be a fairly long post, split into two sections. The first section will explain what the case study includes and its potential significance to scleroderma patients and researchers. It will also discuss limitations of the case study that must be considered as well. The second section of the post will discuss potential treatment implications.

About the Case Study Itself

For copyright reasons I can’t post the published abstract but here is a short description of the case study extracted/edited from an expanded version of the case study that is in preparation for journal submission:

“While a number of studies have shown short-term beneficial effects of plasmapheresis for treating systemic scleroderma, there have been no reports on the very long-term usage of plasmapheresis as the sole systemic treatment intervention. We report on the case of a male patient, originally diagnosed with limited systemic scleroderma in early 1990, who has been undergoing regular plasmapheresis treatments for more than 21 years, beginning in late 1993. Prior to commencing treatment, the patient exhibited symptoms including severe gastro esophageal reflux disease (GERD) with esophagitis, frequent Raynaud's attacks, reduced lung function, and chronic chilling. With the exception of mild residual Raynaud's, all of the patient's symptoms reversed after three years of regular plasmapheresis treatments and he remains in complete remission. While the typical explanation for the therapeutic benefits seen with plasmapheresis focuses on temporary reduction of circulating antibodies or other potential pathogenic factors, we propose instead an alternative explanation based on a novel disease pathogenesis model for systemic scleroderma.”

The abstract published in “Transfusion” is not very detailed since it had to be very short to be accepted for the medical conference. The actual poster presented at the conference includes much more information as well as a number of research citations. For those of you who have never seen what a research poster looks like, here is a link to the actual 42 inch x 42 inch poster that was shown at the conference: http://sclerodermainfo.org/pdf/AABB_Poster.pdf. But this is more useful – a printable version of the poster: http://sclerodermainfo.org/pdf/AABB_Poster_Handout.pdf.

(Note: A longer and significantly more detailed version of this case study has been completed and is in final review before being submitted for publication in a research journal. The longer case study has two additional co-authors with expertise in plasmapheresis and blood rheology and goes into much more detail than the poster presented at the medical conference. I can
provide a copy of the longer version of the case study report if anyone is interested. Just message me privately.)

The actual research poster may be a bit hard to understand because it uses medical jargon, so here are some of the key points to understand about this case study beyond the clinical improvement seen in the patient over time:

- The duration of this case study is very unusual. In medical research, “long-term” usually means 1 yr to at most 5 years. A 21+ year case study report is almost unheard of.

- The positive results seen in studies when plasmapheresis has been tried as a treatment for scleroderma have historically been attributed to the fact that each plasmapheresis treatment replaces more than 60% of the plasma, potentially reducing the amount of potential “bad stuff”, for example, autoantibodies, that might be circulating in the blood and causing scleroderma symptoms. Note that not all researchers are convinced that circulating antibodies are the “culprit” but many do. While this reduction in possible circulating factors may well be part or all of the reasons why plasmapheresis seems to benefit patients with scleroderma, the authors of this study are proposing an alternative hypothesis that may better explain the beneficial effects seen with plasmapheresis treatments.

- This new hypothesis is based on a significant number of research studies that have documented that almost all scleroderma patients have higher than normal blood viscosity (thickness) and that this is a result of the red blood cells clumping together abnormally (RBC aggregation). As early as 1979 researchers suggested that all symptoms seen in scleroderma appear to stem from something causing damage to the lining of small blood vessels. This case study proposes a new disease model for systemic scleroderma that is based on the idea that the early damage seen in the small blood vessels is directly triggered by these clumped red blood cells.

- This new disease model raises the possibility that most of the benefits seen in this patient may stem from the fact that plasmapheresis directly breaks apart clumped red blood cells, thereby preventing additional damage to the small blood vessels until the red blood cells clump together again, which research has shown can take six months or more to occur after a series of four plasmapheresis treatments. Because plasmapheresis treatments have been continued on a regular basis with this patient, the working assumption is that the patient’s red blood cells are generally staying disaggregated, ultimately allowing his body to heal and reverse long-standing symptoms such as GERD and even early lung damage.

Here are some issues, both pro and con, that should be considered when evaluating this case study:

On the positive side:
The length of this study suggests that at least for this patient, very long-term usage of plasmapheresis has had no harmful effects and has not lost effectiveness over time, a problem that is often seen with many drug-based treatments.

Most case studies suffer from the problem that the authors assume that because the patient improved after the treatment was implemented, the treatment must be the reason for this. However, in this case, the treatments were stopped at one point to see what would happen and later reduced in frequency for the same reason. In both cases, symptoms started to return again but were subsequently completely eliminated over time once regular treatments were resumed. While individual case studies, by their very nature, cannot be generalized to the larger patient population, when a case study does stop and start treatments as indicated above, it makes it much more likely that there is in fact a direct cause and effect relationship between the treatment and the symptom improvement seen in this particular patient.

On the negative side:

- Any case study of a single patient always runs the risk that there is something unique about this particular patient that might not occur with any other patient. Additional case studies and eventually full clinical trials are needed to determine if the results can be generalized beyond this single patient.

- This patient has anti-centromere positive limited systemic scleroderma (which is fairly common). Even if the patient is not unique and other patients with anti-centromere positive limited scleroderma might potentially see similar benefits, these results cannot be generalized to assume that this treatment approach would work equally well with other variants of scleroderma, e.g., one of the diffuse variants such as Scl-70 antibody positive diffuse scleroderma.

Clinical Implications

As soon as even a single case study like this is formally published, it increases the chances that some clinicians may be open to trying a new treatment approach with appropriate patients. In this section of the post, I want to address some issues and questions that should be considered if anyone is thinking of talking with their physicians about this as a potential treatment option.

First, I am NOT suggesting that anyone else may benefit from plasmapheresis treatments if they have early stage, anti-centromere positive limited scleroderma. This single case study is suggestive and raises the possibility that it might be beneficial to others, but it is only a first step and at a minimum several more similar case studies should be done followed by a full clinical trial if the case studies yield similar positive results.
If, however, this is something that you are interested in talking about with your physician, there are a number of background things about plasmapheresis you should know before considering this possible approach:

- (This bullet point actually applies to ALL current scleroderma treatments, not just plasmapheresis.) Until researchers develop a true cure for the root causes of scleroderma, which I believe is a long way off, ANY treatment that controls or prevents scleroderma symptoms will have to be continued indefinitely. This is true of current immunosuppressant therapies as well. Even if you are seeing good results from using an immunosuppressant drug, if you stop it, symptoms will return and the disease will continue to progress. Plasmapheresis treatments are no different.

- Plasmapheresis treatments are considered experimental when used to treat scleroderma and they are fairly expensive. However, Medicare guidelines cover plasmapheresis treatments for scleroderma for cases where the disease is life threatening and other treatments are not working (which is realistically the case currently). For this patient, his regular insurance covered the cost of treatments until he turned 65, at which point Medicare took over paying for the treatments without any objections being raised. Many (but not all) insurance companies follow Medicare guidelines and may (with a bit of pushing) ultimately be willing to cover plasmapheresis treatments as well.

- Long-term use of plasmapheresis has a very good overall safety profile. Side effects are usually minimal and are limited to the treatment period itself (blood pressure can drop during treatments, mild fatigue for up to 24 hours, pain associated with IV insertion, etc.) However, there is a limit to how many times per year standard plasmapheresis can be used without suppressing the immune system. The treatment frequency used with this patient has averaged about 16 treatments per year with no indication of any immune system suppression. It is known that weekly treatments cannot be continued indefinitely with long-term immune system suppression problems such as the inability to fight off infections, but the experts that I have talked to suggest that the protocol used for this patient (16 treatments per year) is unlikely to have any immune suppression effects.

- Plasmapheresis requires good venous access in both arms – a blood draw side and a blood return side. This particular patient has been able to continue to use normal venous access for more than 21 years with little difficulty. However, in the majority of cases, patients will require an access port to be surgically implanted, as is done with long-term dialysis patients. Having a port makes plasmapheresis very easy to do but there are definite risks associated with surgical ports that must be carefully considered as part of a decision to a long-term treatment approach like plasmapheresis.

Other Considerations
- For reasons that I won’t get into here, it is likely that plasmapheresis treatments at the frequency used in this case study (16 times per year) would not be as effective with patients with the faster-progressing diffuse variants of scleroderma. While it might slow down progression, some anecdotal reports where this has been tried with diffuse patients suggest that weekly treatments are needed to control symptoms in diffuse scleroderma patients. However, as indicated above, you cannot do standard plasmapheresis on a weekly basis without developing long-term complications because of immunosuppression.

- While it appears that many scleroderma researchers are aware of scleroderma related blood hyperviscosity, they are generally not aware of the research showing that this hyperviscosity is a result of red blood cell aggregation. In contrast, I highly doubt that most clinicians, including rheumatologists, are aware of scleroderma blood hyperviscosity (although it is apparently readily visible when doing nailbed capillary video microscopy according to one scleroderma expert that I have talked to).

I am in the process of working on obtaining funding to conduct a full clinical trial of plasmapheresis with a large group of anti-centromere positive limited scleroderma patients. In addition to a normal treatment and control group, the proposed study will also include a modified form of plasmapheresis that will help to determine if the new disease model is valid or not. This modified variant of plasmapheresis is actually less expensive and eliminates the problem of immunosuppression so if successful it may become an option for treating other variants of scleroderma in the future. The other reason for doing this study, aside from determining if this is an effective treatment for a subset of scleroderma patients, is that if the new disease model turns out to be correct, there are potential pharmaceutical treatments that may be effective as well, either in combination with reduced use of plasmapheresis or potentially by themselves. Two drugs have already been identified that may have potential as future treatments based on the new disease model as they have been shown to reduce clumping of red blood cells.

If any clinicians do decide to try plasmapheresis, I would like to propose that each case be treated as part of a pooled case study in order to learn as much as possible about whether or not this treatment option makes sense. Towards that goal, I am recommending that clinicians include some standardized basic objective measures before and during treatments so we can pool the data and have a better idea about the clinical effects of trying plasmapheresis, even before launching a full clinical trial in the future. Contact me directly for more information on this.

I can be reached at eharris@sclerodermainfo.org for more information or to obtain a copy of the longer case study.

One final note/request to anyone reading this post: most of you are probably not candidates for even considering plasmapheresis treatments for a variety of reasons, e.g., you don’t have
anti-centromere antibodies, your insurance will not pay for these treatments, your current treatments are working well, you live in a rural area where there might not be ready access to a hospital that does plasmapheresis treatments, etc. However, it is possible that your doctors may have other patients that could potentially be candidates for trying plasmapheresis. If you have a doctor that you feel would be interested in learning about this potentially important new case study, I would greatly appreciate it if you would print a copy of this post and also a copy of the research poster handout (link is above) and give this information to her/him on your next visit. I can also provide you a copy of the more detailed case study if you contact me directly.